Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

Preparation of Condensed *N*-Heterocycles *via* Chemoselective Benzylic C-H Activations and Preparation of Alkenylmagnesium Reagents, Allylic Zinc Reagents and their Applications in Organic Synthesis

von

Hongjun Ren

aus

Jiangsu, China

München, 2006

Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs.3 bzw. 4 der Promotionsordnung vom 01. August 2003 von Professor Dr. P. Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

München, am 16.November, 2006

Hongjun Ren

Dissertation eingereicht am 16.November, 2006

1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Thomas Lindel

Mündliche Prüfung am 18.December.2006

This work was carried out under the guidance of Prof. Knochel at the Fakultät für Chemie und Pharmazie der Ludwig-Maximilians-Universität, München from Aug. 2003 to Oct. 2006.

I would like to thank my supervisor, Prof. Dr. Paul Knochel, for giving me the opportunity of doing my Ph.D. in his group, for his invaluable support and kindness through this time, and for his guidance in the course of scientific research presented here.

I am also very grateful to Prof. Dr. Thomas Lindel for agreeing to be my "Zweitgutachter", as well as Prof. Dr. K. Karaghiosoff, Prof. Dr. M. Heuschmann, Prof. Dr. H. R. Pfaendler, and Prof. Dr. H. Zipse for the interest shown in this manuscript by accepting to be referees.

I thank Miss Xixi Jia, Dr. Srinivas Reddy Dubbaka, Dr. Vicente del Amo, Guilaume Dunet for the careful correction of this manuscript.

I would like to thank the Ludwig-Maximilians-Universität for financial support.

Special thanks to Prof. Dr. Liuzhu Gong, Dr. Pradipta Sinha, Guilaume Dunet, Zhuo Li, Tobias Thaler, Maximilian Dochnahl for the happiest time we spent together in the lab.

I would like to thank all past and present co-workers I have met in the Knochel's group for their brief or lasting friendships. I especially thank Dr. Xiaoyin Yang, Wenwei Lin, Murthy Narasimha Cheemala, Ching-Yuan Liu, Simon Matthe, Andrei Gavryshin, Ralf Klötzing and Arkady Krasovskiy for their kindness and consideration in my study in Munich. I also thank Dr. Lutz Ackermann, Sylvie Perrone, Oliver Baron, Nadège Boudet, Darunee Soorukram, Armin Stoll, Christina Despotopoulou, Felix Kopp, Dr. Giuliano Clososki, Marc Mosrin and Christian Rauhut for the nice time we had together.

I would also like to thank Vladimir Malakov, Beatrix Cammelade, Simon Matthe and Yulia Tsvik for their help in organizing everyday life in the lab, as well as the analytical team, Dr. D. Stephenson, Dr. C. Dubler, Dr. W. Spahl, B. Tschuk, I. Brück, H. Schulz and G. Käser for their invaluable help. Especially, I thank Dr. Peter Mayer for measuring X-ray structures.

Finally I would like to thank my family and my teachers in China for their love and great support, as well as all of my friends in China, USA and Germany for their friendship and consideration through my Ph.D.--**Thank you very much**!

Parts of this Ph. D. thesis have been published:

1) Chemoselective Benzylic C-H Activations for the Preparation of Condensed *N*-Heterocycles
   Hongjun Ren, Paul Knochel* *Angew. Chem., Int. Ed.* **2006**, *45***,** 3462;

2) Magnesiated Unsaturated Silylated Cyanohydrins as Synthetic Equivalents of Aromatic and Heterocyclic Grignard Reagents Bearing a Ketone or an Aldehyde
   Ching-Yuan Liu, **Hongjun Ren**, and Paul Knochel* *Org. Lett*. **2006**, *8*, 617;

3) Regioselective Functionalization of Trisubstituted Pyridines Using a Bromine-Magnesium Exchange
   Hongjun Ren, Paul Knochel* *Chem. Comm.* **2006**, 726;

4) Stereoselective Preparation of Functionalized Acyclic Alkenylmagnesium Reagents Using *i*-PrMgCl·LiCl
   Hongjun Ren, Arkady Krasovskiy and Paul Knochel* *Org. Lett*. **2004**, *6*, 4215;

5) Preparation of Cyclic Alkenylmagnesium Reagents *via* an Iodine/Magnesium Exchange
   Hongjun Ren, Arkady Krasovskiy and Paul Knochel* *Chem. Comm.* **2005**, 543;

6) Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using Trisubstituted Allylic Zinc Reagents
   Hongjun Ren and Paul Knochel*, manuscript in preparation;

7) Chemoselective Benzylic sp3 C-H Bond activation and Domino C-H Activation for Preparation of Condensed *N*-Heterocycles
   Hongjun Ren, Zhuo Li and Paul Knochel*, manuscript in preparation.

To my parents, sister
and my girl friend
with love.

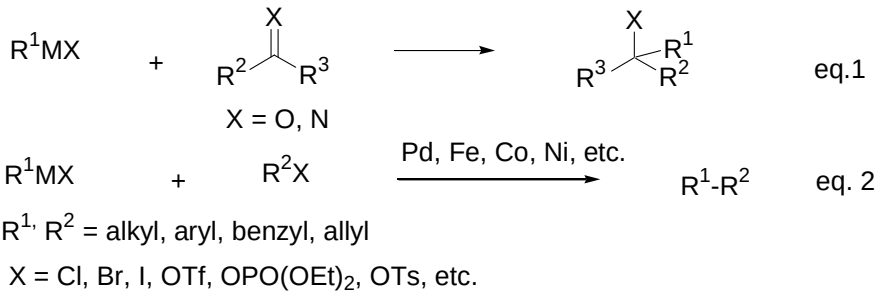
ABBREVIATIONS

1	Ac	acetyl	2	AcOH	acetic acid
3	Ar	aryl	4	Bn	benzyl
5	Boc	*tert*-butoxycarbonyl	6	br.	broad
7	calcd.	calculated	8	CH_2Cl_2	dichloromethane
9	Cy	cyclohexyl	10	d	double
11	dec.	decomposition	12	DMAP	4-dimethylaminopyridine
13	DME	1,2-dimethoxyethane	14	DMF	*N*,*N*-dimethylformamide
15	DMSO	dimethyl sulfoxide	16	equiv.	equivalent
17	EI	electron-impact	18	Et	ethyl
19	FAB	fast-atom bombardment	20	FG	functional group
21	GC	gas chromatography	22	h	hour
23	HMPT	hexamethylphosphorous triamide	24	HRMS	high resolution mass spectroscopy
25	*n*-Bu	*n*-butyl	26	*i*-Pr	isopropyl
27	IR	infra-red	28	*J*	coupling constant (NMR)
29	LG	leaving group	30	M	molarity
31	*m*	meta	32	m	multiplet
33	Me	methyl	34	Met	metal
35	min	minute	36	mol.	mole
37	mp.	melting point	38	MS	mass spectroscopy
39	NBS	*N*-bromosuccinimide	40	NMR	nuclear magnetic resonance
41	Nu	nucleophile	42	*o*	ortho
43	*p*	para	44	Pent	pentyl
45	PG	protecting group	46	Ph	phenyl
47	Piv	pivaloyl	48	q	quartet
49	rt	room temperature	50	s	singlet
51	t	triplet	52	*t*-Bu	*tert*-butyl
53	TBS	*tert*-butyldimethylsilyl	54	TES	triethylsilyl
55	Tf	triflate	56	TFA	trifluoroacetic acid
57	tfp	*tri*-(2-furyl)phosphine	58	THF	tetrahydrofuran
59	TLC	thin layer chromatography	60	TMS	trimethylsilyl
61	TP	typical procedure	62	Ts	4-toluenesulfonyl

THEORETICAL PART

1. Overview

Carbon-carbon bond formation reactions are one of the most important processes in chemistry as they represent the key step for building more complex molecules from simple precursors. The addition of organometallic reagents to electrophiles, such as aldehydes or ketones, is a versatile method for the carbon-carbon bond formation (eq. 1, Scheme 1). In this area, main group organometallics, such as lithium, magnesium, boron and aluminum reagents have played a major role since the Grignard reagents were first used more than one hundred years ago.[1] In addition, in the past 30 years, a wide variety of cross-coupling methodologies using organometallic reagents have been developed and these cross-coupling reactions have emerged among the most powerful and useful synthetic tools for the C-C bond formation (eq. 2, Scheme 1).[2] Therefore developing methods to prepare the functionalized organometallic reagents, such as Grignard and organozinc reagents, becomes more important.



Scheme 1. Carbon-carbon formation from organometallic reagents.

1.1 C-H bond activation [3]

Recently, reactions that can substitute one preactivated species, such as halides, with a simple arene have appeared. These processes have been described as C-H bond activations, C-H bond functionalization or direct arylation.[4]

---

[1] a) *Handbook of Functionalized Organometallics*, Ed.: P. Knochel, Wiley-VCH, Weinheim, **2005**; b) *Main Group Metals in Organic Synthesis***,** Ed.: H. Yamamoto and K. Oshima, Wiley-VCH, Weinheim, **2004**; c) G. S. Silverman, P. E. Eds Rakita, *Handbook of Grignard Reagents*; Marcel Dekker: **1996**; d) Richey, Jr. H. G., Ed. *Grignard Reagents: New developments*; Wiley, New York: **1999**; e) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; f) *Organolithiums: Selectivity for Synthesis*, Ed.: J. Clayden, Elsevier Science/Pergamon, Amsterdam, **2003**.

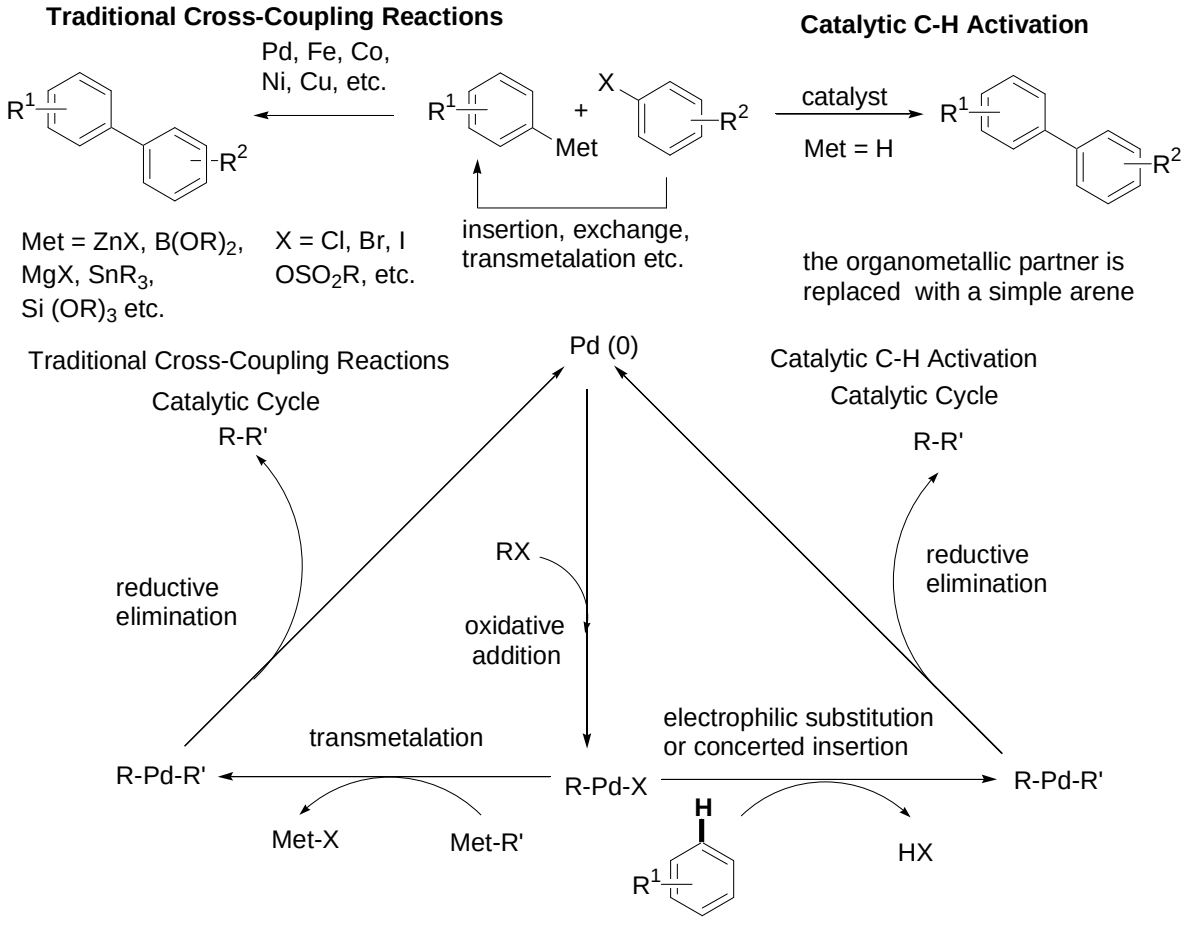
[2] For reviews on this topic, see a) *Metal-catalyzed Cross-coupling Reactions*; F. Diederich, P. J. Stang, Eds. Wiley-VCH: New York, 1998; b) J. Hassa, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; c) Metal-Catalyzed Cross-Coupling Reactions, 2nd ed. (Eds: A. de Meijere, F. Diederich), wiley-VCH, Weinheim, **2004**; d) *Palladium Reagents and Catalysts*, Ed.: J. Tsuji, John Wiley & Sons, Ltd, **2004.**

[3] *Handbook of C-H Transformations: Application in Organic Synthesis, Vol. 1 and Vol 2* (Ed.: G. Dyker), Willey-VCH, Weinheim, **2005**.

[4] L-C. Campeau, K. Fagnou, *Chem. Comm.* **2006**, 1253.

1.1.1 Intermolecular arylation reaction

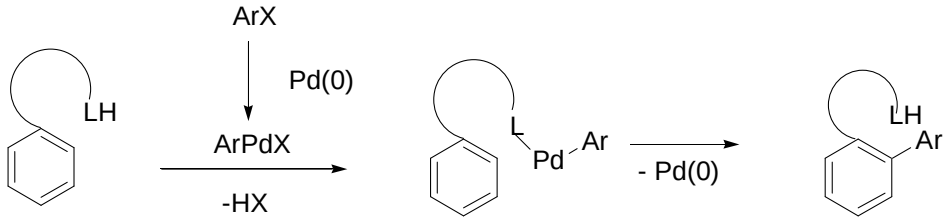
Transition metal-catalyzed cross-coupling reactions are well recognized to be one of the most powerful methods for carbon-carbon bond formation. The palladium-catalyzed coupling of aryl halides or their synthetic equivalents (such as triflates, tosylates) with arylmetals is very often employed in the synthesis of biaryl molecules. The prevalence of these reactions is illustrated by the many processes involving palladium that bear the names of those who discovered them, including the Kumada-Corriu, Mirozoki-Heck, Stille, Suzuki-Miyaura, Sonogashira, Hiyama and Negishi reactions.[2] Recently, the direct arylation of electron-rich heteroaromatic rings has begun to replace these more traditional techniques in specific cases. In the direct arylation reactions, one of the preactivated arenes is substituted with a simple arene, whereas in traditional cross coupling reactions, dual preactivated arenes are necessary (Scheme 2).



Scheme 2. Cross-coupling methods for preparation of biaryl molecules.

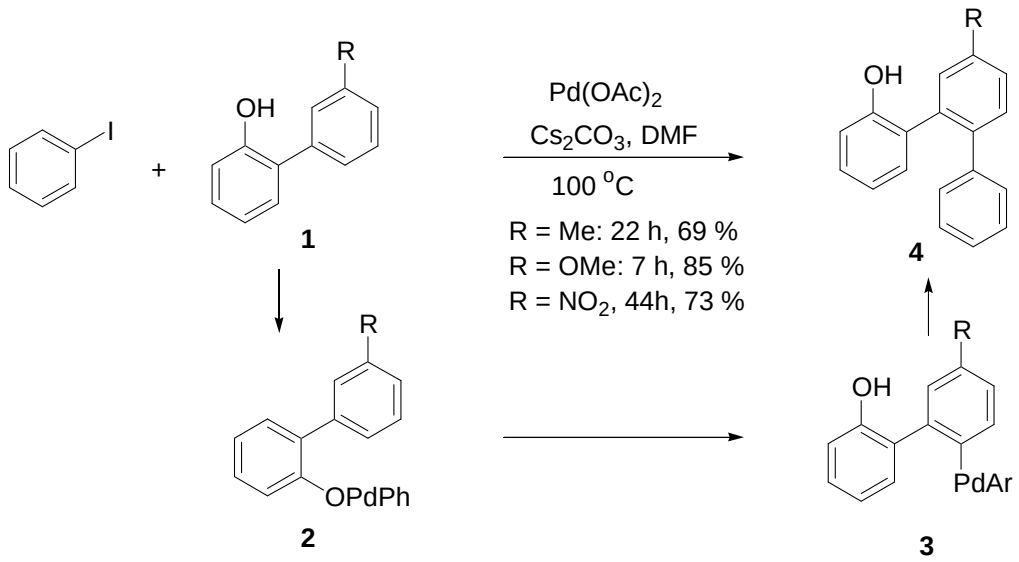
Appropriately functionalized aromatic substrates such as phenols and aromatic carbonyl compounds have been found to undergo a regioselectively intermolecular arylation upon

treatment with aryl halides in the presence of transition metal catalysts such as Pd, Rh and Ru salts recently.[5] A general catalytic sequence with a palladium catalyst is outlined in Scheme 3. The coordination of a given functional group to a metal centre is determinant for an effective coupling by C-H bond cleavage. Obviously the reaction has a significant advantage since the stoichiometric metalation of aromatic substrates is not required.



Scheme 3. Pd-catalyzed and coordination assisted intermolecular aryl-aryl coupling *via* C-H cleavage.

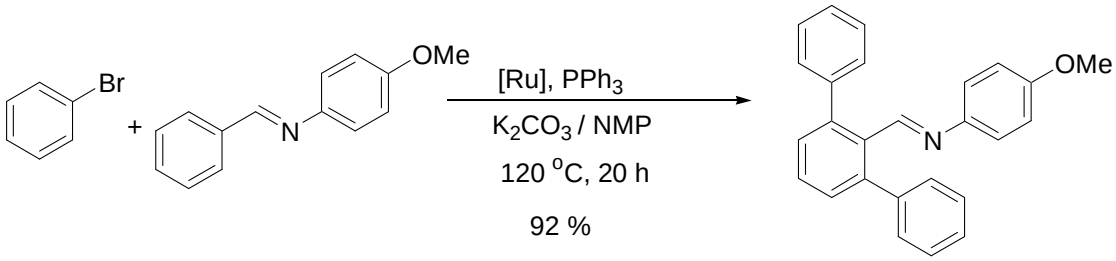
Arylation of 2-phenylphenols **1** with aryl iodides is one of the first examples to proceed according to the sequence given in Scheme 4.[6] Oxidative addition of Pd(0) to iodobenzene results in PhPdI, which coordinates with the phenolic oxygen forming the intermediate **2**. Through C-H activation, the diarylpalladium intermediate **3** is formed and it affords the product **4** after a reductive elimination. The use of a relatively strong inorganic base, such as Cs_2CO_3, is important for a smooth coupling.



Scheme 4. Pd-catalyzed regioselective arylation of 2-phenylphenols.

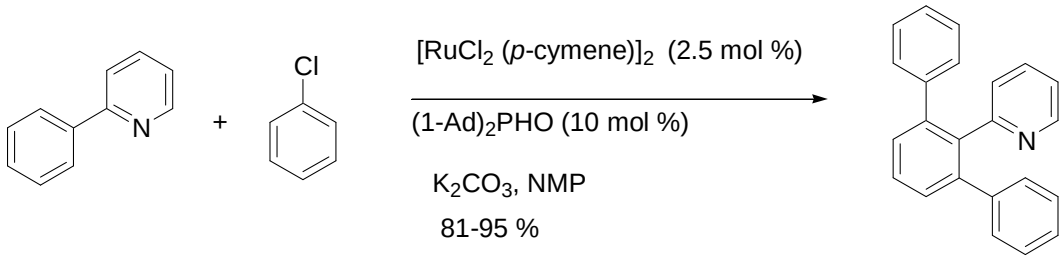
[5] a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; b) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211.
[6] a) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1740; b) T. Satoh, J. Inoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1567.

Benzylidene anilines, formed from benzaldehydes and anilines, have been found to undergo *ortho* arylation effectively when a ruthenium catalyst such as $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ is used in the presence of K_2CO_3 as base.[7] A polar solvent such as NMP is necessary. In this reaction, the substrates have no acidic hydrogens and thus *ortho*-metalation seems to occur *via* coordination of the neutral nitrogen to the metal centre (Scheme 5).



Scheme 5. Ru-catalyzed arylation of benzylidene anilines.

Arylation of pyridines through C-H bond activation using aryl chlorides is achieved by using the air-stable, electron-rich phosphine oxides as preligands in the presence of ruthenium. The catalytic system derived from a sterically-hindered adamantyl-substituted phosphine oxide has proved to be highly efficient, tolerating a number of important functional groups (Scheme 6).[8]



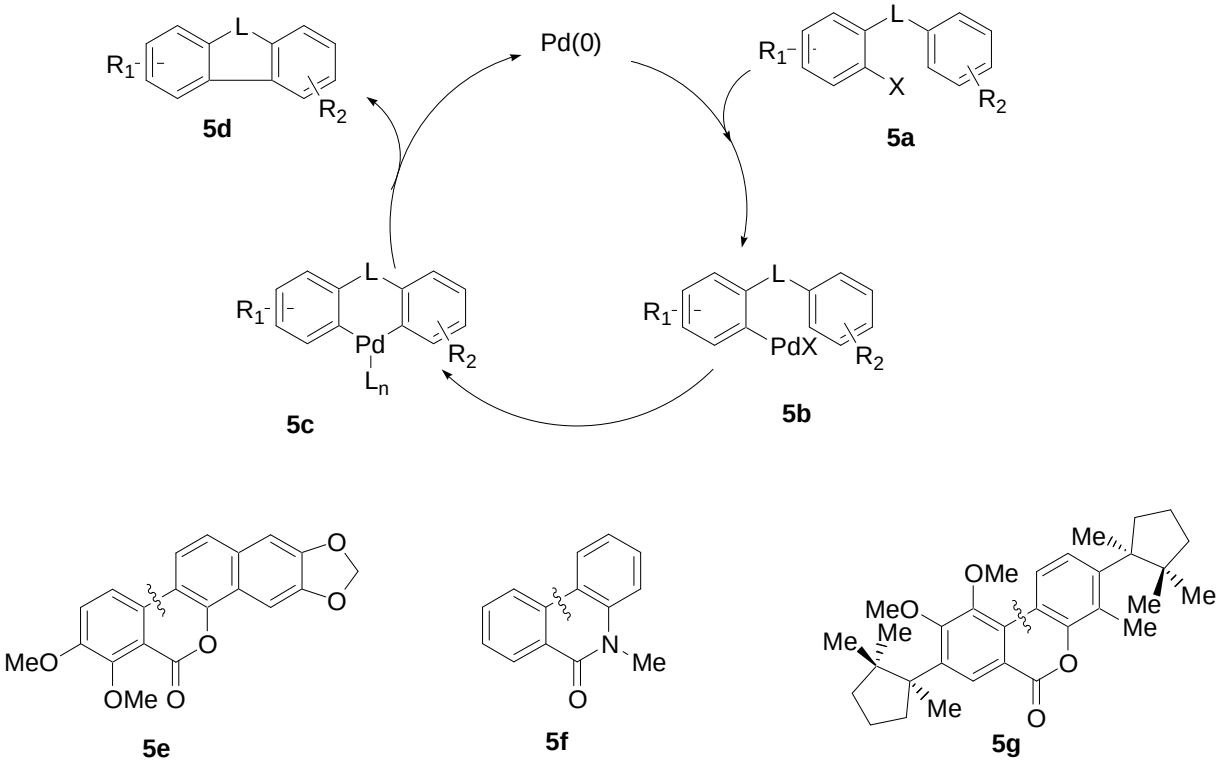
Scheme 6. Ru-catalyzed arylation of pyridines through C-H bond activation.

1.1.2 Intramolecular C-C bond formation *via* C-H activation

Palladium catalyzed C-H activation is a powerful tool for the syntheses of biaryls from tethered aryl halide and triflate substrates of type **5a** (Scheme 7). From a mechanistic point of view, the cyclization proceeds through the oxidative addition of Pd(0) to the aryl halides or triflates to give σ-arylpalladium intermediate like **5b**. Electrophilic attack on the aromatic or heteroaromatic ring leads to diarylpalladium species **5c**, which after reductive elimination of

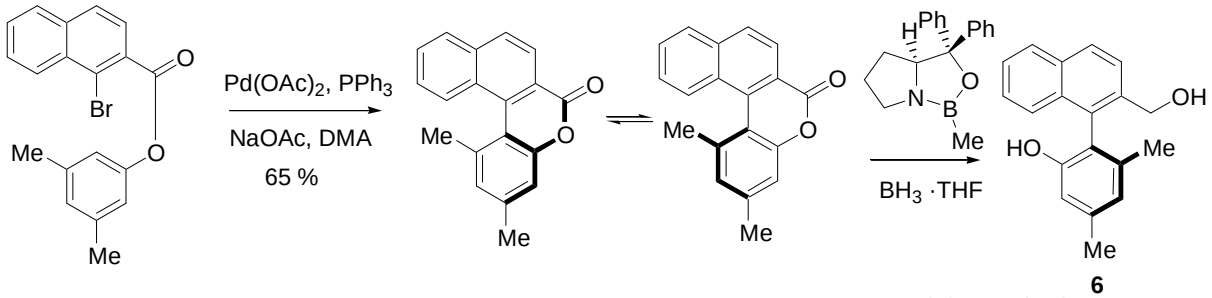
[7] S. Qi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783.
[8] a) L. Ackermann, J. Spatz, C. J. Gschrei, R. Born, A. Althammer, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622; b) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123.

Pd(0), afford heterocycles **5d** (Scheme 7). This technique has proved to be useful in the synthesis of six-membered heterocycles such as **5e**[9], **5f**[10] and **5g**[11].



Scheme 7. Intramolecular biaryl bond formation and its application in the total synthesis of nature products.

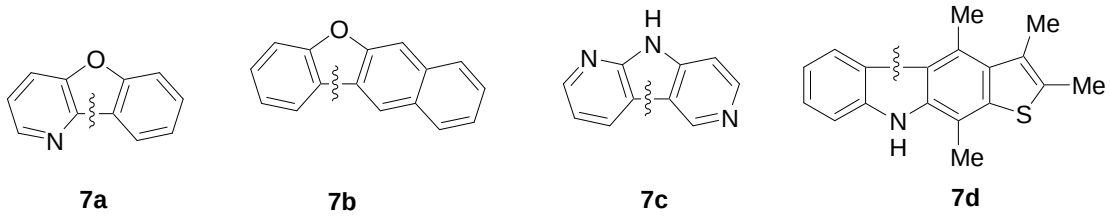
Combining this coupling method with an asymmetric reduction reaction, the enantiomerically pure axially chiral biaryl alcohol **6** can be easily prepared (Scheme 8). [12]



Scheme 8. Preparation of chiral biaryl alcohol.

[9] T. Harayama, H. Yasuda, *Heterocycles* **1997**, *46*, 61.
[10] T. Harayama, T. Akiyama, H. Akamatsu, K. Kawano, H. Abe, Y. Takeuchi, *Synthesis* **2001**, 444.
[11] G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft, J. Connolly, *J. Am. Chem. Soc.* **2000**, *122*, 9127.
[12] a) G. Bringmann, M. Breuning, P. Henschel, J. Hinrichs, *Organic Synthesis*, **2003**, *79*, 72; b) G. Bringmann, J. Hinrichs; J. Kraus, A. Wuzik, T. Schulz, *J. Org. Chem*. **2000**, *65*, 2517.

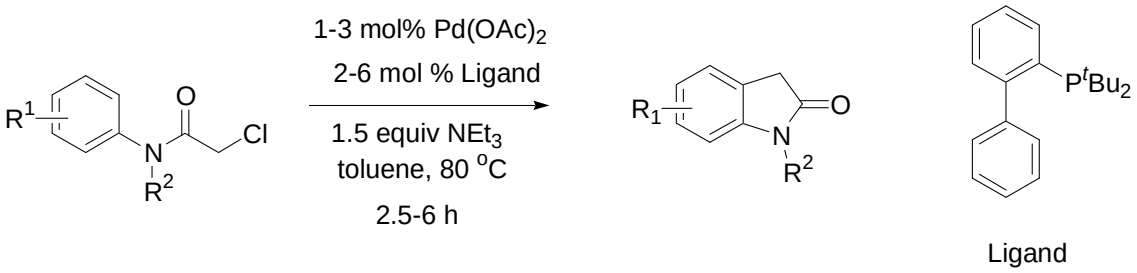
Five-membered rings are also readily synthesized using this coupling method, enabling the production of dibenzo[b,d]fused heterocycles such as dibenzofurans **7a** [13] and **7b**[14], carbazoles **7c**[15] and **7d**[16] (Scheme 7, L = O, NR respectively) and related compounds.



7a **7b** **7c** **7d**

Scheme 9. Some important structures of dibenzofurans and carbazoles.

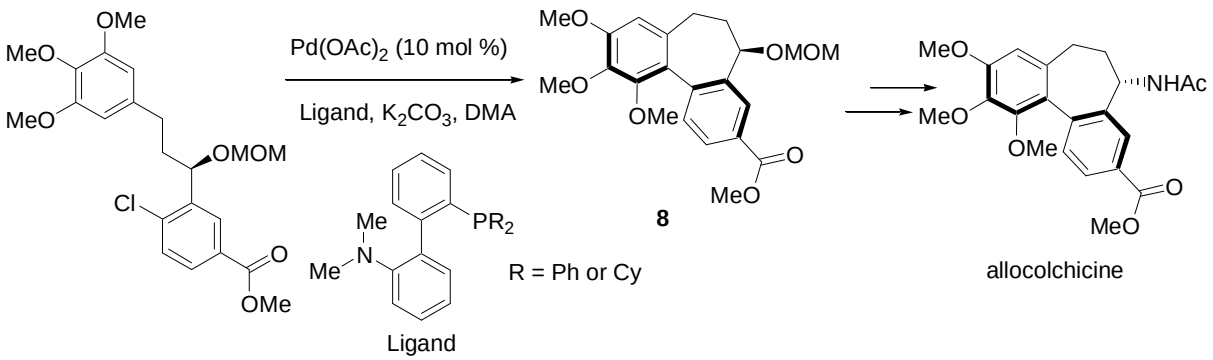
Using this type of intramolecular palladium-catalyzed C-H functionalization, substituted oxindoles can be prepared from α-chloroacetanilides in 78-97% yield (Scheme 10).[17]



Scheme 10. Preparation of oxindoles *via* C-H activation.

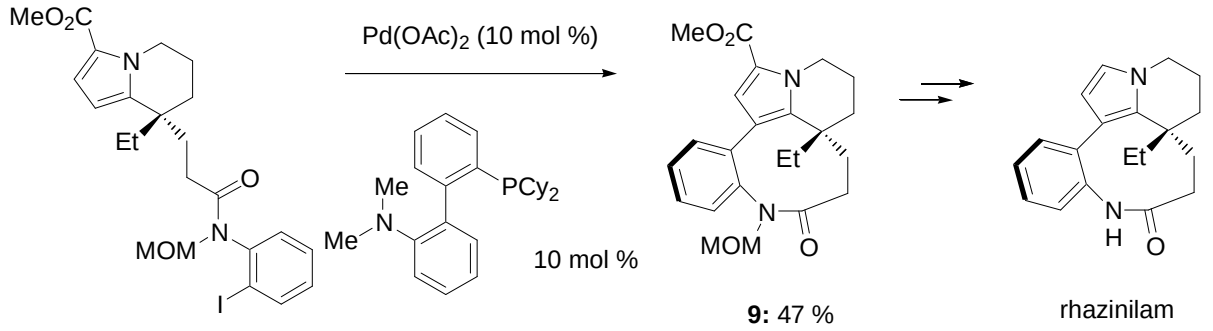
Formation of seven-membered rings *via* direct arylation is a more challenging task due to the ring strain.[18] Recently, Fagnou reported an approach to synthesize allocolchicine with the direct intramolecular coupling of an aryl chloride as the key step in the construction of the biphenyl derivative **8** (Scheme 11).[19]

[13] W. S. Yue, J. J. Li, *Org. Lett*. **2002**, *4*, 2201.
[14] J.-Q. Wang, R. G. Harvey, *Tetrahedron* **2002**, *58*, 5927.
[15] T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemiere, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett* **2003**, 615.
[16] I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2003**, *59*, 3737.
[17] E. J. Hennessy, S. L. Buchward, *J. Am. Chem. Soc*. **2003**, *125*, 12084.
[18] a) L. –C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc*. **2004**, *126*, 9186; b) M. Lafrance, N. Blaquiere, K. Fagnou, *Chem. Commun*. **2004**, *24*, 2874 ; c) for examples with heterocyclic arene coupling partners, see : C. C. Hhughes, D. Trauner, *Anger. Chem., Int. Ed*. **2002**, *41*, 1569 and C. C. Hhughes, D. Trauner, *Tetrahedron* **2004**, *60*, 9675.
[19] M. Leblanc, K. Fagnou, *Org. Lett.* **2005**, *7*, 2849.



Scheme 11. Fagnou's approach to allocolchicine by C-H activation reaction.

Using Fagnou's method, Trauner [20] developed a highly efficient synthesis of rhazinilam featuring the formation of a strained nine-membered ring **9** through intramolecular coupling of an unactivated pyrrole (Scheme 12).



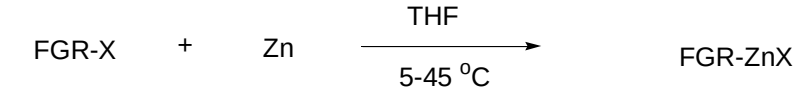
Scheme 12. Trauner's approach to strained nine-membered ring.

1.2. Preparation of organozinc and organomagnesium reagents

1.2.1. Direct insertion of zinc or magnesium into organic halides

The direct insertion of zinc dust into organic halides is the most general method for the preparation of functionalized organozinc halides. Functional groups such as an ester, ether, acetate, ketone, cyano, halide, primary and second amino, amide, sulfoxide, sulfide, sulfone and boronic acid can be present during the formation of the alkylzinc halides.[21] However, the preparation of arylzinc iodides in THF from aryl iodides can only be achieved by using highly activated zinc powder (Rieke Zn)[22] or requiring the presence of electron-withdrawing groups in the *ortho*- position of the aryl iodides, as well as by elevated temperatures (Scheme 13).[23]

[20] A. L. Bowie, Jr., C. C. Hughes, D. Trauner, *Org. Lett.* **2005**, *7*, 5207.
[21] *Handbook of Functionalized Organometallics: Applications in Synthesis*, Ed.: P. Knochel, Wiley-VCH, Weinheim, **2005**.
[22] a) *Organozinc Reagents*, Editors: P. Knochel, P. Jones, Oxford University press, New York, **1999**; b) R. D. Rieke, P. T. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; c) R. T. Arnold, S. T. Kulenovic, *Synth. Commun.* **1977**, *7*, 223.
[23] R. Ikegami, A. Koresawa, T. Shibata, K. Takagi, *J. Org. Chem.* **2003**, *68*, 2195.



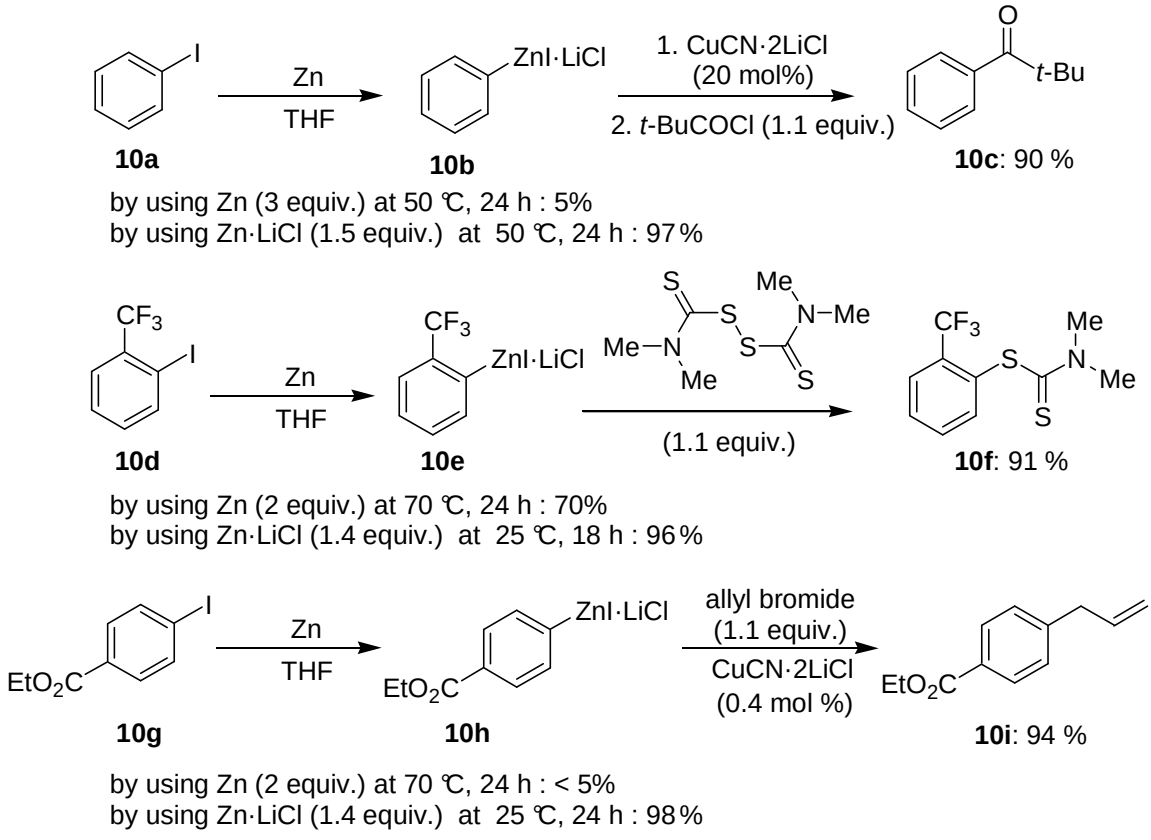
X = I, Br;

FG = CO_2R, CN, halide, $(RCO)_2N$, $(TMS)_2N$, RCONH, $(RO)_3Si$, RSO, RSO_2

R = alkyl, aryl, benzyl, allyl

Scheme 13. Preparation of functionalized organozinc reagents by zinc insertion.

Recently, P. Knochel and co-workers have reported a new protocol for the preparation of functionalized aryl- and alkyl-zinc compounds using commercially available Zn powder and LiCl (1:1) in THF under very mild conditions (Scheme 14).[24]

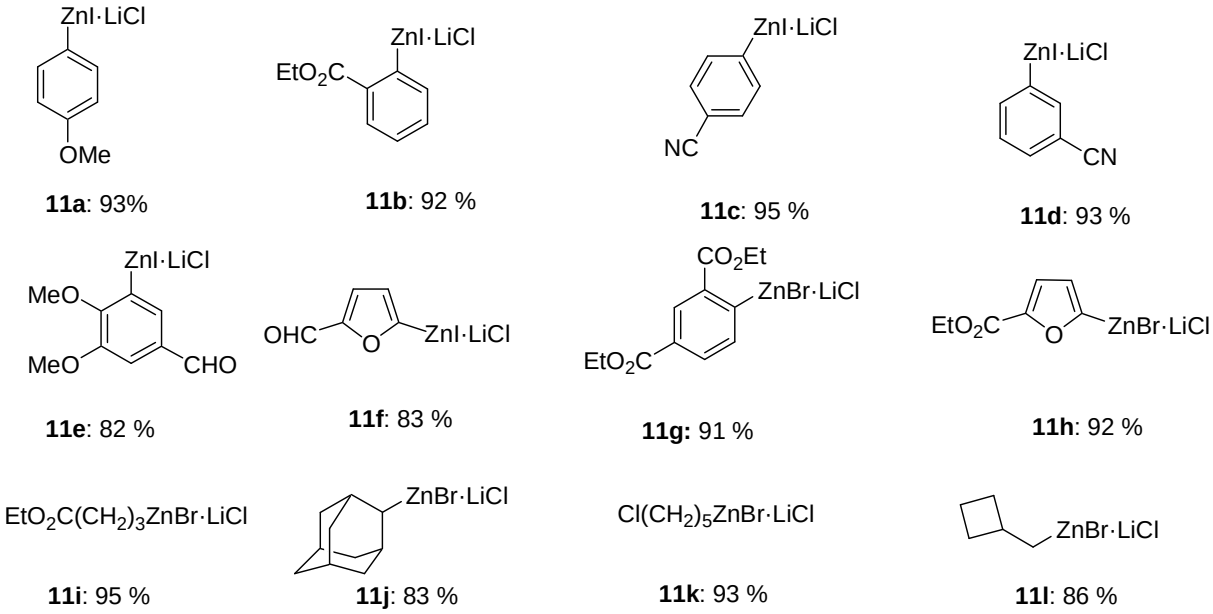


Scheme 14. Insertion of Zn into aryl iodides with and without LiCl.

A broad range of functionalized arylzinc iodides **11a-11f** (Scheme 15) bearing an active functional group such as aldehyde, ester, nitrile or amide have been easily obtained with excellent yields (92-95%). Furthermore, in the case of activated aryl and heteroaryl compounds, the insertion of Zn into C-Br bond is also possible (**11g**, **11h**). Interestingly, the

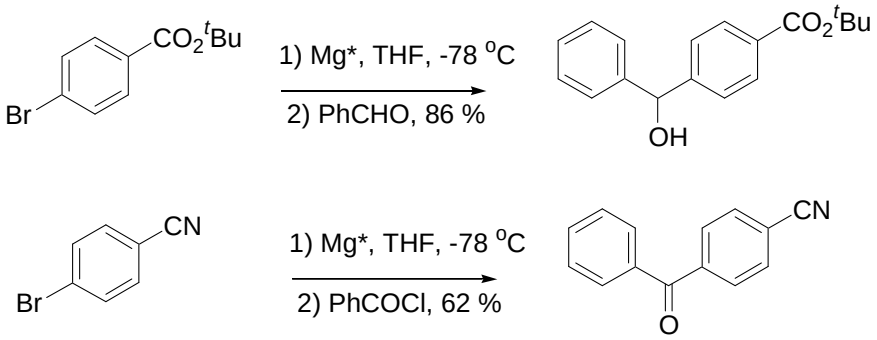
[24] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

unactivated primary alkyl bromides can also be converted to the corresponding alkylzinc reagents in the presence of Zn·LiCl (**11i-11l**, Scheme 15).[25]



Scheme 15. Preparation of functionalized organozinc halides using Zn·LiCl.

However, for organomagnesium reagents, only simple Grignard reagents can be prepared *via* the direct insertion reaction due to the high reductive reactivity of magnesium towards many functional groups. Using highly active magnesium (such as Rieke Magnesium), the direct insertion of Mg into aryl bromide substrates containing a nitrile, ester or chloride group has been successfully achieved at very low temperature (Scheme 16).[26]

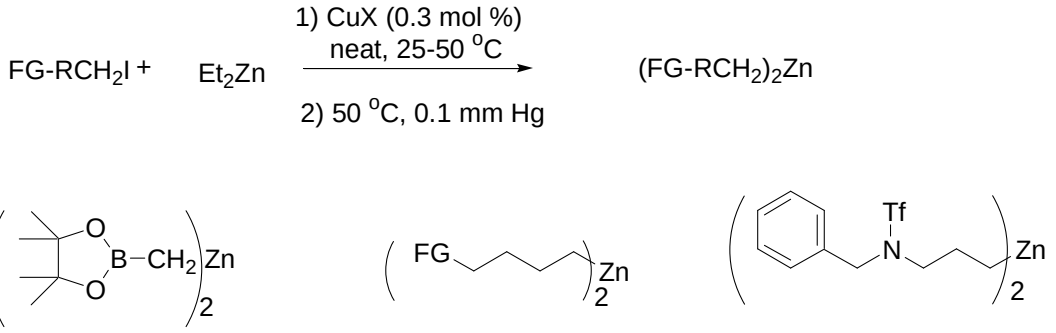


Scheme 16. Preparation of functionalized Grignard reagents using Rieke Magnesium.

1.2.2 Halogen/zinc or halogen/magnesium exchange reaction

[25] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
[26] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; c) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; d) R. D. Rieke, T. –J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *54*, 4323; e) R. D. Rieke, M. S. Sell, T. Chen, J. D. Brown, M. V. Hansan, in *Active Metals*, A. Fuerstner, Ed., Wiley-VCH, Weinheim, **1995**.

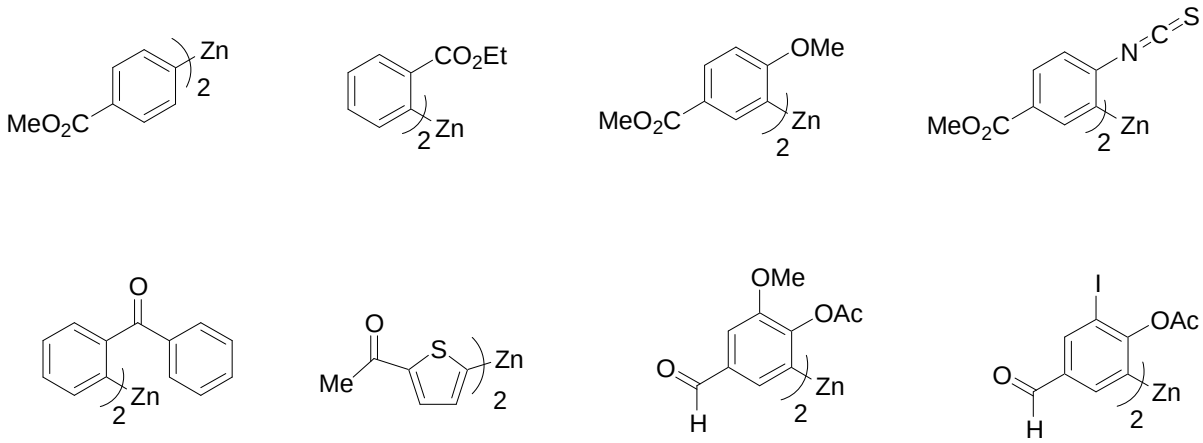
On the other hand, the halogen-metal exchange reaction has been found to be the best way to prepare highly functionalized reagents of considerable synthetic utility. The iodine-zinc exchange reaction is a practical way for preparing polyfunctional diorganozincs (scheme 17). This method provides the general access to functionalized dialkylzincs[27] such as **12a**-**c**, but failed in the case of aromatic iodides.[28]



12a **12b** **12c**

Scheme 17. Preparation of polyfunctional dialkylzincs using halogen-metal exchange reaction.

In 2004, P. Knochel and co-workers found that Li(acac) can accelerate the exchange reaction dramatically. The mild reaction conditions allow its compatibility with a range of sensitive functionalities such as an aldehyde, ketone and isothiocyanate (Scheme 18).[29]

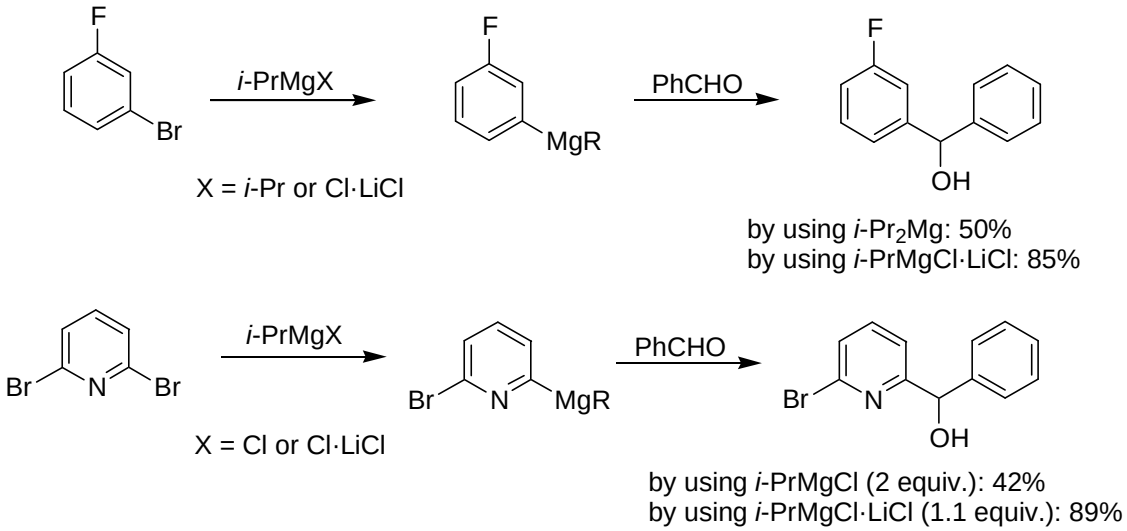


Scheme 18. Preparation of polyfunctional diarylzinc reagents in the presence of Li(acac).

P. Knochel and co-workers have also shown that highly functionalized aryl- and heteroaryl-magnesium halides can be readily prepared by using an iodine-magnesium exchange

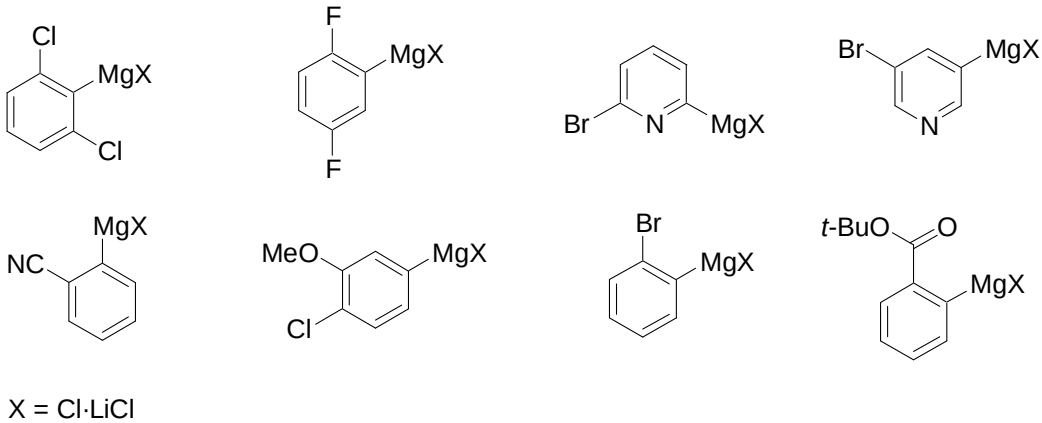
[27] L. Micouin, P. Knochel, *Synlett* **1997**, 327.
[28] For a cobalt-catalyzed synthesis of organozinc reagents with zinc metal, see: H. Fillon, C. Gosmini, J. Perichon, *J. Am. Chem. Soc.* **2003**, *125*, 3867.
[29] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

reaction.[30] *i*-PrMgX (X = Cl, Br) was found to be the most convenient exchange reagent. Recently, a super exchange reagent *i*-PrMgCl·LiCl has been developed for preparing organomagnesium reagents under milder conditions.[31] With this new reagent, the preparation of the organomagnesium reagents obtained *via* the bromine-magnesium exchange reaction became also possible (Scheme 19).



Scheme 19. Br/Mg exchange reactions in the presence of LiCl.

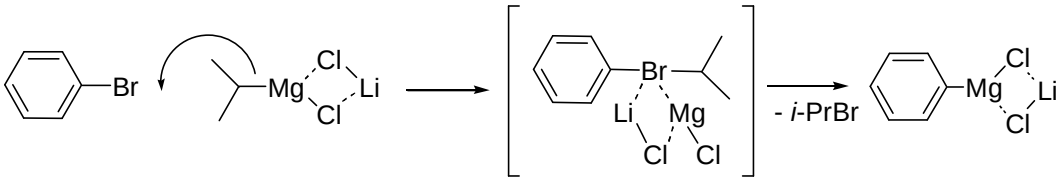
Various aryl bromides with fluoro-, chloro-, methoxy and *tert*-butyl ester group were readily converted into the corresponding magnesium reagents at room temperature using *i*-PrMgCl·LiCl (Scheme 20).



Scheme 20. Preparation of Grignard reagents *via* Br/Mg exchange reaction using *i*-PrMgCl·LiCl.

[30] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed*. **1998**, *37*, 1701; b) G. Varchi, A. E. Jensen, W. D.ohle, A. Ricci, P. Knochel, *Synlett* **2001**, 477; c)
[31] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333.

Although the mechanism of the process is not elucidated, it is believed that the role of lithium chloride is to activate *i*-PrMgCl by increasing the nucleophilic character of the isopropyl group through the formation of magnesiate species of type **13**, leading to the ate-intermediate of type **14** and finally to the organomagnesium species PhMgCl·LiCl **15** (Scheme 21).



13 **14** **15**

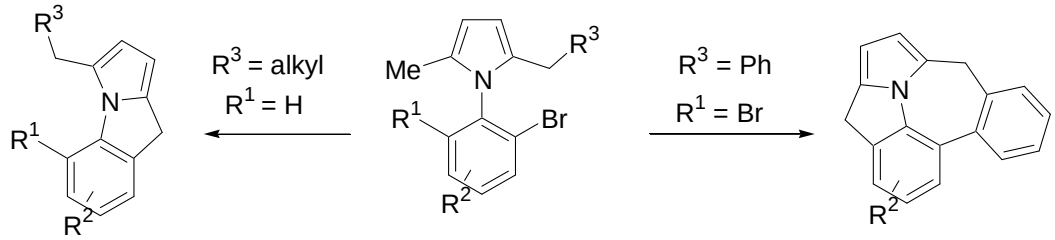
Scheme 21. Lithium chloride activates *i*-PrMgCl *via* the complex **13**.

2. Objectives

Due to the utility of complex polycyclic heterocycles as potential pharmaceuticals, the first project involved the development of new methods to construct polycyclic heterocycles using C-H activation reactions. The objectives for this work are:

☺: The development of a catalytic system for the construction of polycyclic heterocycles;

☺: The extension of this catalytic system to domino reactions.

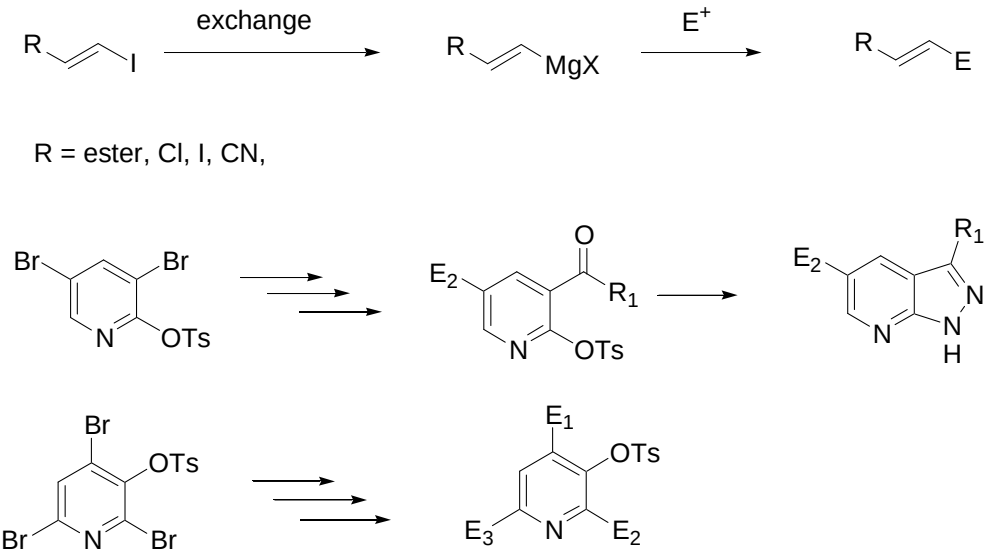


Scheme 22. Proposed synthesis of polycyclic heterocycles *via* C-H activation.

Due to the expanded applications of organomagnesium reagents in organic synthesis, the second objective involves:

☺: Access to stereoselectively prepared functionalized alkenyl organomagnesium reagents *via* I/Mg exchange reaction using *i*-PrMgCl·LiCl,

☺ Access to regioselectively prepared polyfunctional pyridylmagnesium reagents *via* a Br/Mg exchange reaction using *i*-PrMgCl·LiCl.

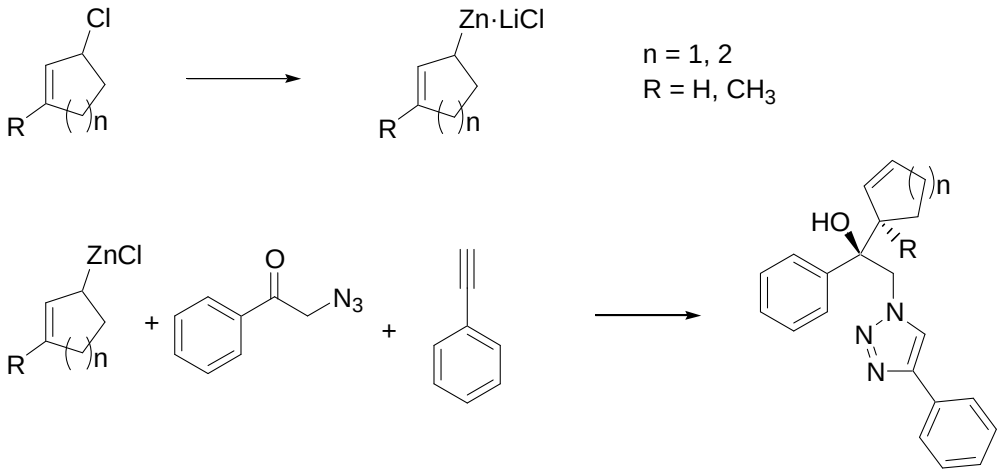


Scheme 23. Development of new methods to prepare alkenylmagnesium and pyridylmagnesium reagents *via* I/Mg or Br/Mg exchange.

As previously mentioned, numerous organozinc reagents, such as aryl and alkylzinc halides, bearing active functional groups can all be prepared using a zinc insertion or a I/zinc exchange. However there are not too many effective methods to prepare allylic zinc reagents due to the special properties of the allylic system. Hence the third objective of this work is:

☺: To access the preparation of cycloallylic zinc reagents from readily available allylic substrates;

☺: The synthesis of complex compounds using these types of allylic zinc reagents.



Scheme 24. Development of new methods to prepare allylic zinc reagents and their applications in organic synthesis.

3. Preparation of Condensed *N*-Heterocycles by Chemoselective Benzylic C-H Activations

3.1. Introduction: a catalytic approach for the functionalization of sp^3 C-H bond

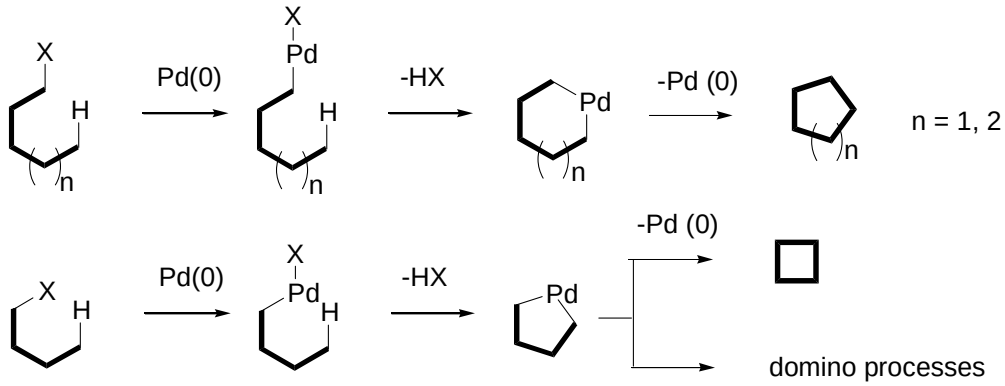
The development of methodologies for the direct functionalization of relatively unreactive C-H bonds has now become a major research topic.[32] C-H bond functionalization represents a chemical process of broad synthetic potential, since such methodology facilitates the direct formation of C-C and C-Z bonds (Z = O, N, B, Si, etc.) without utilizing prefunctionalized C-X bonds (X = halogens, OTf, etc.). Although pioneering studies on the activation of C-H bonds by stoichiometric amounts of transition-metal complexes occurred in the early 1960s, it was not until 20 years later that catalytic reactions involving the cleavage of C-H bonds were achieved.[32a]

The high-energy barrier of C-H bond cleavage is lowered when preceeded *via* cyclometalation, which is initiated by precoordination of the metal complex to a carbon or heteroatom in the molecule. This precoordination directs the metal centre to the vicinity of the C-H bond to be broken. Among the transition metals, it was shown that palladium(0) is particularly suitable for this process, since the precoordination step can arise from the oxidative insertion into carbon-halogen bond, for instance also observed in the cross coupling reactions. A sequence of oxidative addition and cyclopalladation is a straightforward way for assembling palladacycyles. The starting materials for this purpose have to fulfil two structural requirements: 1) a carbon-halogen bond (or alternatively a carbon-triflate bond) at a position, where a β-hydrogen elimination is prohibited in the subsequent step after oxidative addition (that is of course true for aryl halides) and 2) a carbon-hydrogen bond (either sp^3- or sp^2-centered) has to be in an appreciable distance from the halide. Thus, 7-membered, 6-membered and 5-membered palladacycles are regularly generated as reactive intermediates as outlined in Scheme 25.[33]

---

[32] Recent reviews: a) F. Fakjuchi, N. Chatani, *Adv. Synth. Catal***. 2003**, *345*, 1077; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev*. **2002**, *102*, 1731; c) S. Ma, Z. Gu, *Angew. Chem. Int. Ed*. **2005**, *44*, 7512; d) M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed*. **2006**, *45*, 1683.

[33] *Handbook of C-H Transformations: Application in Organic Synthesis, Vol. 1 and Vol 2* (Ed.: G. Dyker), Willey-VCH, Weinheim, **2005**.



Scheme 25. Palladacycles and their ring-size-dependent reactivity (general pictogram).

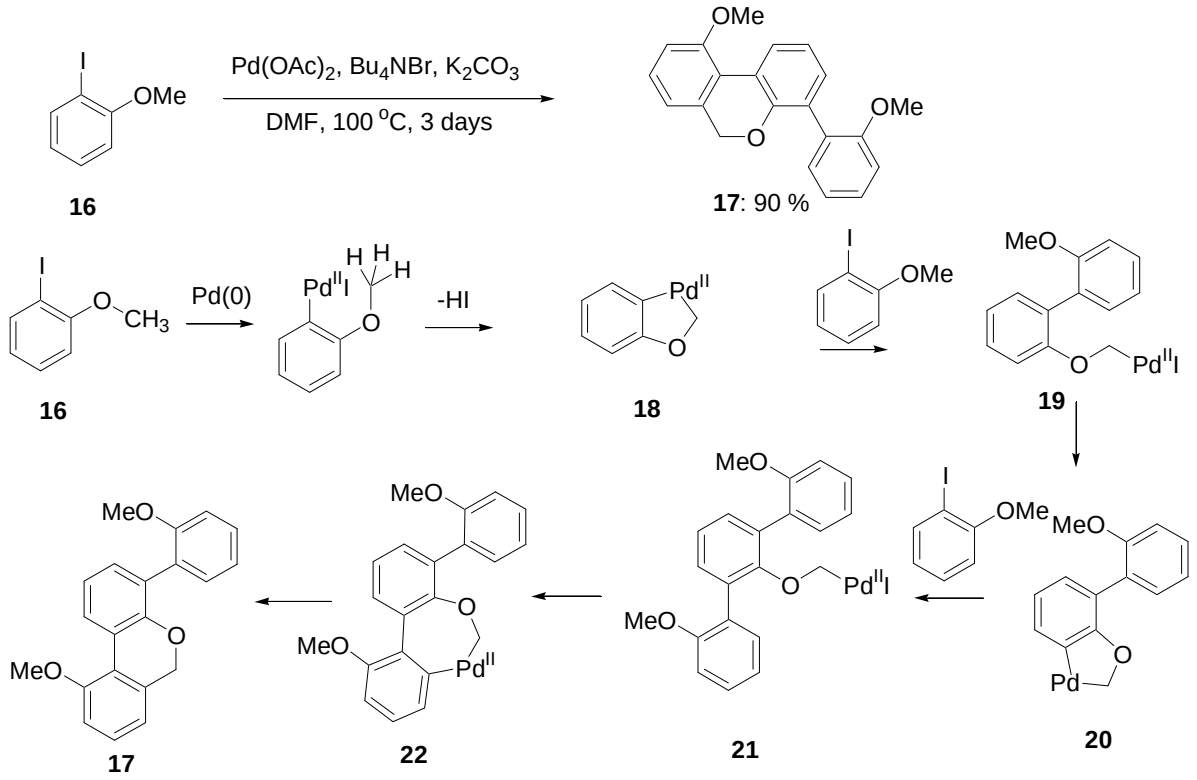
7-Membered and 6-membered palladacycles readily undergo reductive elimination to give 6-membered and 5-membered rings as final products, whereas the similar process to give 4-membered carbocycles from 5-membered palladacycles is less feasible, although not completed ruled out, and restricted to special cases.

A number of intramolecular arylations that proceed by catalytic C-H activation of arenes have been described (See the overview).[34] However, fewer cases have been reported regarding catalytic activation of sp^3 C-H bonds through cyclometalation.

Among those few cases, Dyker[35] reported the preparation of polycycles through a methoxy C-H activation. The homo-coupling of three equivalents of 2-iodoanisole **16** generated the terphenyl **17** in an excellent yield (Scheme 26). The reaction proceeded through the palladacyclic intermediate **18** formed by direct C-H activation of the methoxyl group, followed by addition of a second equivalent of **16** and reductive elimination to form the intermediate **19**. A second cyclometallation led to paladacycle **20**, which reacted with the third equivalent **16** to give intermediate **21**. After another cyclometallation step (formation of the intermediate **22**) the domino process was completed by reductive elimination, which simultaneously freed the active catalyst.

[34] a) M. Catellani, E. Motti, S. Ghelli, *Chem. Commun*. **2000**, 2003; b) L-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186; c) L. –C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581; d) M. Parisien, D. Valette, K. Fagnou, *J. Org. Chem*. **2005**, *70*, 7578; e) L-C. Campeau, P. Thansandote, K. Fagnou, *Org. Lett.* **2005**, *127*, 1857;

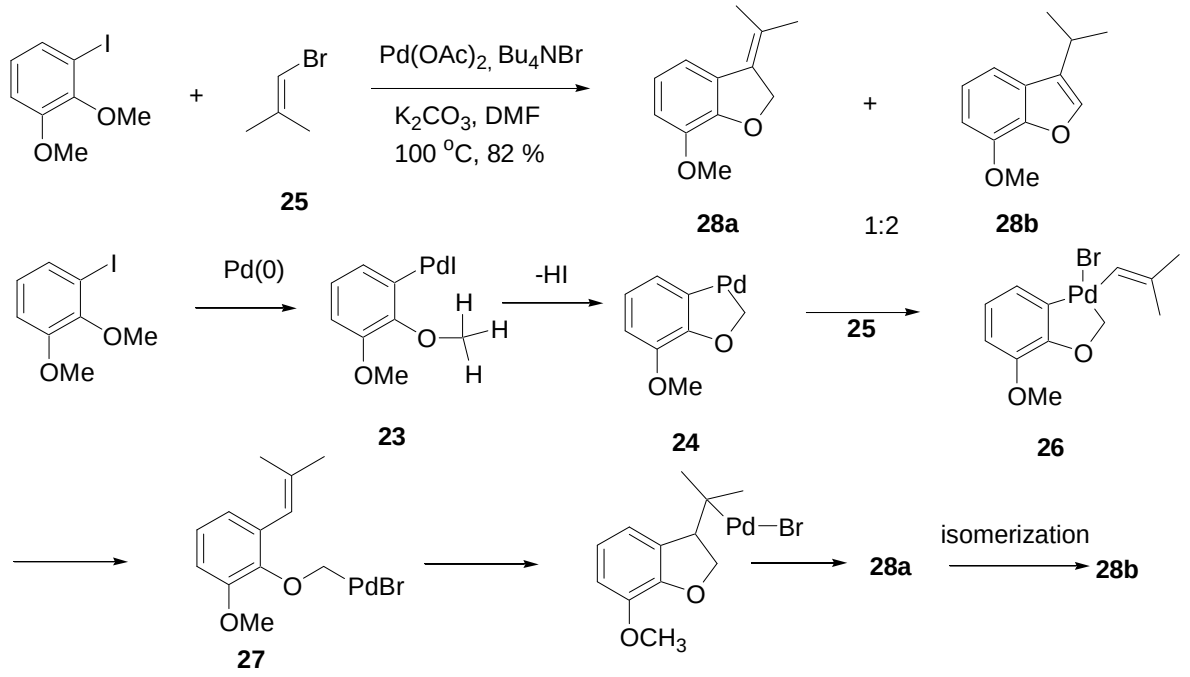
[35] a) G. Dyker, *Angew. Chem*. **1992**, 104, 1079; *Angew. Chem. Int. Ed*. **1992**, *31*, 1023; b) G. Dyker, *Chem. Ber*. **1994**, *127*, 739.



Scheme 26. Dyker's C-H activation at methoxy groups.

Dyker also reported a similar C-H activation of the *ortho*-methoxy group of intermediate **23** to form a palladacyclic intermediate **24**.[36] The intermediate **24** may then react with vinylbromide **25** to afford the palladium(IV) intermediate **26**, which would form the palladium intermediate **27** after reductive elimination. The following intramolecular carbopalladation followed by *β*-hydride elimination would provide the product **28a**, which, upon isomerisation, produced **28b** (Scheme 27).

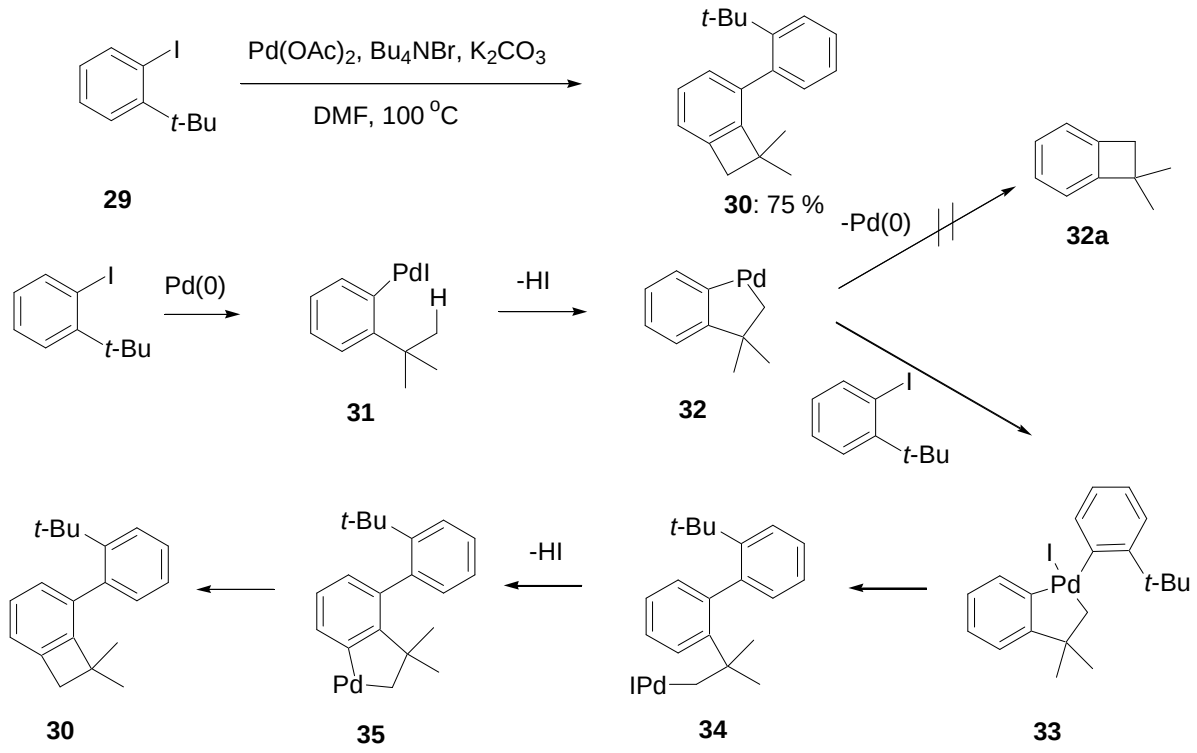
[36] G. Dyker, *J. Org. Chem*. **1993**, *58*, 6426;



Scheme 27. Dyker's C-H transformation at methoxy groups.

This type of C-H transformation is also feasible at the notoriously unreactive *t*-butyl group, as outlined in Scheme **28**, to prepare benzocyclobutane.[37] The reaction might proceed by the direct C-H activation of intermediate **31**, forming a palladacyclic intermediate **32**, which may undergo oxidative addition with iodobene **29** to afford intermediate **33**. Subsequent reductive elimination would lead to **34**, which would undergo another C-H insertion and HI elimination to afford **35**. Product **30** may be formed by reductive elimination of **35**. The formation of compound **32a** by reductive elimination of **32** was not observed probably because the formation of the four-membered ring is slower than the oxidative addition to another iodobenzene **29** (Scheme 28).

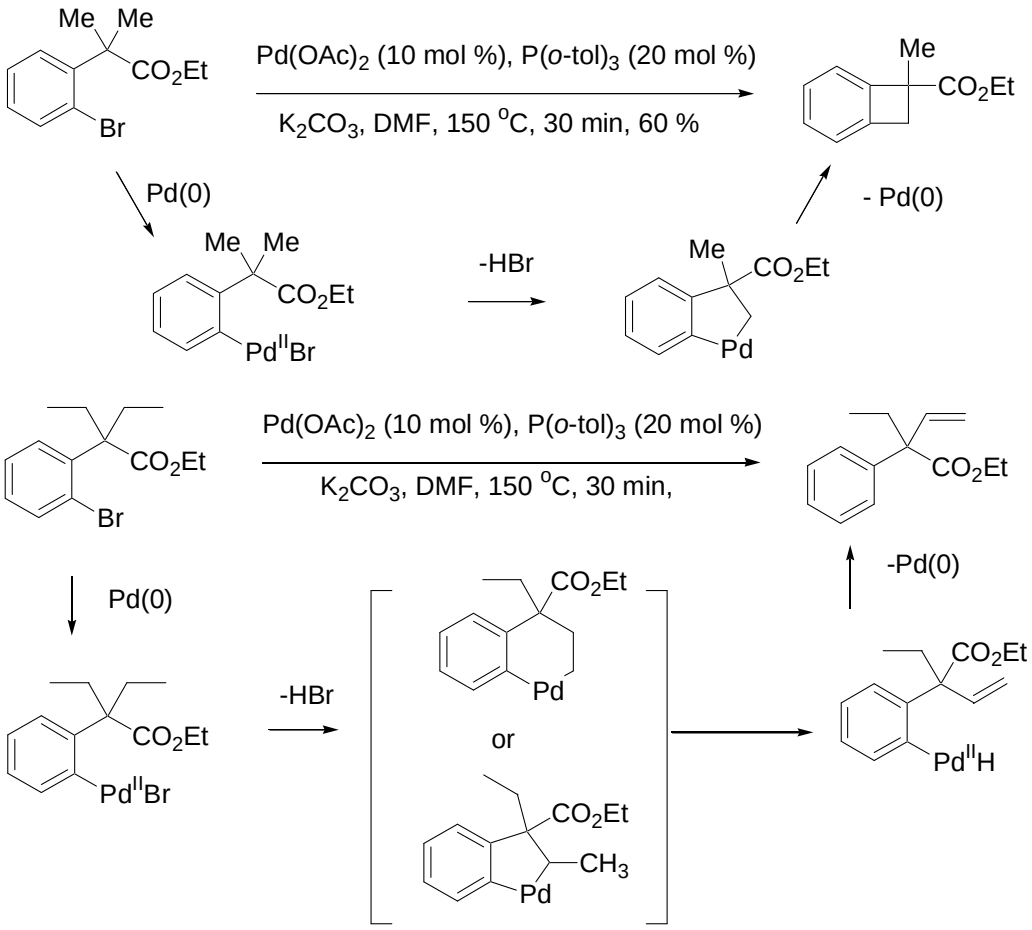
[37] G. Dyker, *Angew. Chem*. **1994**, *106*, 117; *Angew. Chem. Int. Ed*. **1994**, *33*, 103.



Scheme 28. C-H transformation at unreactive *t*-butyl group.

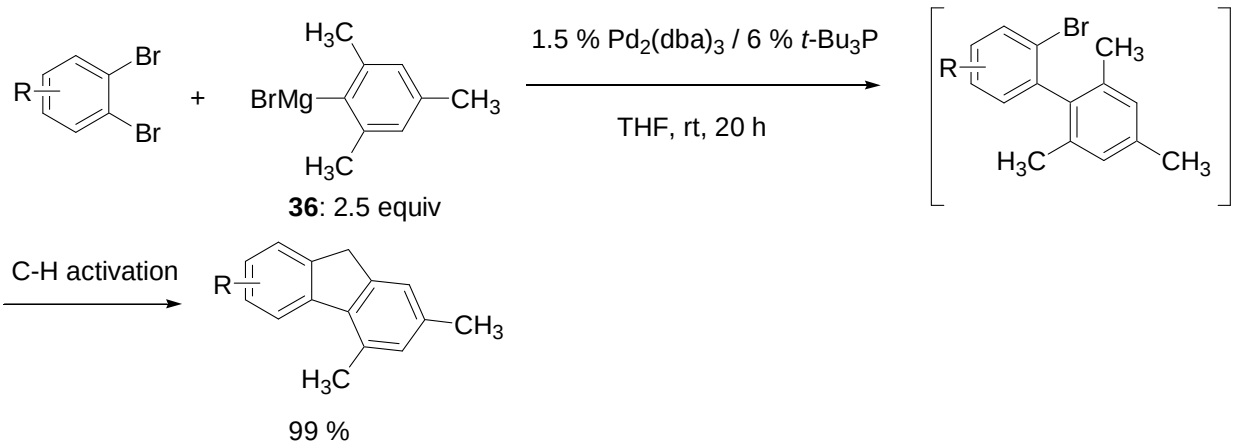
Recently, Baudoin reported a Pd-catalyzed C-H activation of *gem*-dialkyl groups on bromo- and iodobenzene to give olefins or benzylcyclobutenes as are shown in Scheme 29.[38]

[38] O. Baudoin, A. Herrbach, F. Guéritte, *Angew. Chem. Int. Ed*. **2003** *42*, 5736.



Scheme 29. Pd-catalyzed formation of olefins and benzocyclobutenes.

Q. Hu has also developed a new type of Pd-catalyzed annulative tandem reaction of 1, 2-dibromobenenes with hindered Grignard reagents **36** based on a Pd-catalyzed cross-coupling reaction and sp^3 C-H bond activation strategy (Scheme 30).[39]



Scheme 30. Pd-catalyzed annulative tandem reaction of dibromobenzenes with Grignard reagents.

[39] C. Dong, Q. Hu, *Angew. Chem. Int. Ed.* **2006**, *45*, 2289.

3.2. Design of the starting materials for the preparation of polycyclic heterocycles *via* C-H activation

Polycyclic heterocycles of type **37** are found in various alkaloids such as mytomicine C and (-)-(S)-tylophorine. The mytomicine family is a group of metabolites isolated from *Streptomices* that has attracted much attention due to their potent antitumoral and antibacterial activity (Figure 1).[40] (-)-(S)-Tylophorine and its analogs are phenanthroindolizidine alkaloids, many of which have been isolated from plants of the family asclepiadaceae, including members of the genus *Tylophora* that are found in India and Southeast Asia.[41] These compounds have been the targets of synthesis, modification, and antitumor evaluation in many research groups.[42]

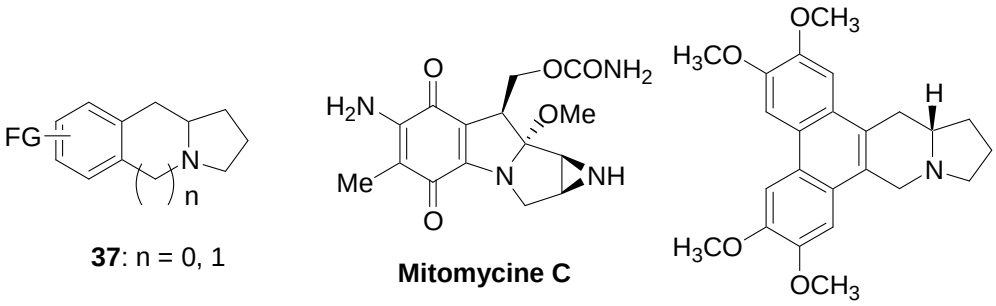


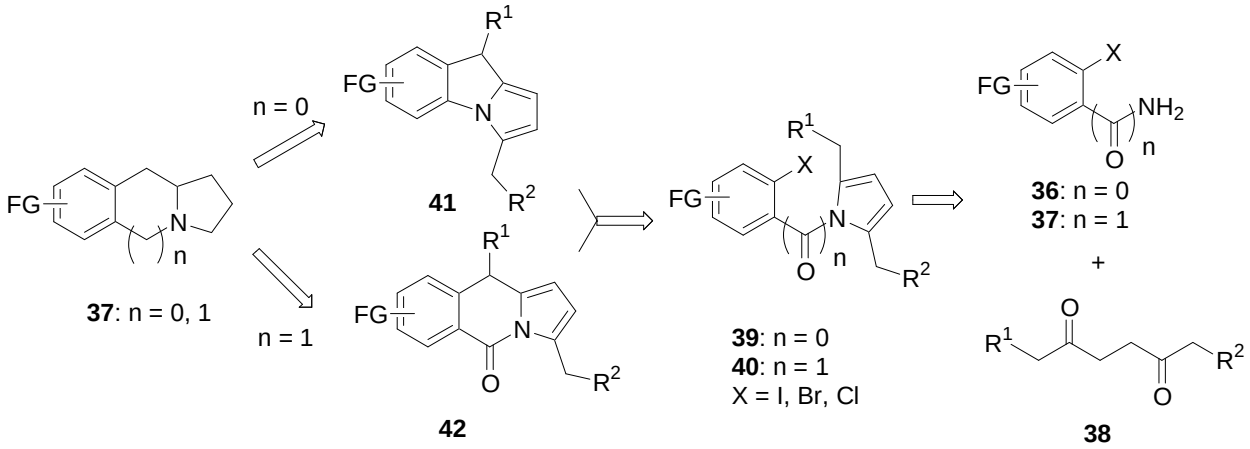
Figure 1. Structures of mitomycine C and (-)-tylophorine.

The preparation of complex polycyclic heterocycles (such as mitomycine C and (-)-tylophorine) is an important synthetic goal due to the application of these molecules as potential pharmaceuticals.[43] One of the most efficient approaches for preparing polycyclic molecules is to use domino- reactions.[44] Especially attractive are such reaction sequences which involve C-H activation reactions[45] since such reactions tolerate the presence of

[40] W. A. Remers, R. T. In. Dorr, *Alkaloides: Chemical and Biological Perspective*; S. W. Pelletier, Ed.; John Wiley & Sons: New York, **1998**; Vol. *6*, pp. 1-74.
[41] A.N. Ratnagiriswaran, K. Venkatachalam, Indian *J. Me. Res*. **1935**, *22*, 433.
[42] a) K. N. Rao, R. K. Bhattacharya, S. R. Venkatachalam, *Cancer Lett*. **1998**, *128*, 183; b) E. Gellert, R. Rudzats, *J. Med. Chem*. **1964**, *7*, 361; c) W. Gao, W. Lam, S. Zhong, C. Kaczmarek, D. C. Baker, Y.-C. Cheng, *Cancer Research* **2004**, *64*, 678.
[43] a) T.L. Gilchrist, *Heterocyclic Chemistry*, Longman, **1998**; b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles* Wiley-VCH, **2003**.
[44] a) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem*. **2004**, *76*, 1967; b) A. de Meijere, P. von Zezschwitz, S. Bräse, *Acc. Chem. Res*. **2005**, *38*, 413; c) A. Padwa, *Pure Appl. Chem*. **2003**, *75*, 47; d) B. Breit, *Chem. Eur. J*. **2000**, *6*, 1519; e) S. Ikeda, *Acc. Chem. Res*. **2000**, *33*, 511.
[45] a) F. Kakiuchi, S. Murai, Activation of C-H bonds: catalytic reactions *Top. Organomet. Chem.* **1999**, *3*, 47; b) G. Dyker, *Angew. Chem. Int. Ed.* **1999**, *38*, 1699; c) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879; d) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev*. **2002**, *102*, 1731; e) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res*. **2001**, *34*, 633; f) C.-J. Li, *Acc. Chem. Res*. **2002**, *35*, 533; g) S. Ma, Z. Gu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7512.

additional functionalities in the substrate. A range of Ru-[46] Rh-[47] Pt-[48] and Pd-[49] catalyzed C-H activations for heterocycle synthesis has recently been described.

We envisioned that the polycyclic system **37** could be assembled through a palladium catalyzed intramolecular C-H activation reaction. From the retrosynthetic analysis of **37**, we propose that a C-H activation of *N*-arylpyrrole **39** and **40** would afford heterocycles of type of **41** and **42** respectively. *N*-arylpyrrole derivatives of type of **41** are readily available from 2-halogen-anilines **39** and 1,4-diketones **38** (Scheme 31).



Scheme 31. The retrosynthetic analysis for the formation of polycyclic molecules **37**.

[46] a) C. S. Yi, S. Y. Yun, I. A. Guzei, *J. Am. Chem. Soc.* **2005**, *127*, 5782; b) C. S. Yi, S. Y. Yun, *J. Am. Chem. Soc.* **2005**, *127*, 17000; c) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935; d) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; e) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123

[47] a) B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556; b) R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 7192; c) K. L. Tan, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, *123*, 2685; d) K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman, A. J. Souers, *Org. Lett.* **2003**, *5*, 2131; e) K. L. Tan, S. Park, J. A. Ellman, R. G. Bergman, *J. Org. Chem.* **2004**, *69*, 7329; f) H. M. L. Davies, Q. Jin, P. Ren, A. Y. Kovalevsky, *J. Org. Chem.* **2002**, *67*, 4165; g) R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, *123*, 9692.

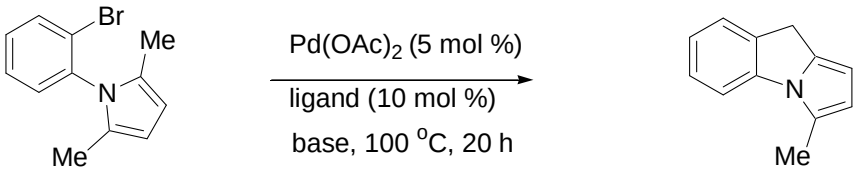
[48] a) J. A. Johnson, N. Li, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 6900; b) J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2000**, *122*, 6321.

[49] a) B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 13372; b) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856; c) J. L. Portscheller, H. C. Malinakova, *Org. Lett.* **2002**, *4*, 3679; d) Q. Huang, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460; e) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084; f) D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657; g) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; h) V. G. Zaitsev, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 4156; i) O. Daugulis, V. G. Zaitsev, *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; j) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586; k) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; l) M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506; m) C. Bour, J. Suffert, *Org. Lett.* **2005**, *7*, 653; n) L. -C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186; o) L. –C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, *J. Am. Chem. Soc.* **2006**, *128*, 581; p) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002,** *124*, 5286.

3.3 Optimization of the reaction conditions

The first experiments were performed with *N*-(2-bromophenyl)-2,5-dimethylpyrrole **39a** with $Pd(OAc)_2$ (5 mol%) and various ligands in toluene in the presence of a base for scavenging resulting HBr was performed (100 ^oC, 20 h, Table 1). Preliminary experiments showed that polar solvents such as DMF led to complex reaction mixtures, whereas apolar solvents such as toluene gave much better results. Strongly chelating ligands such as dppe or dppp did not lead to the formation of *9H*-pyrrolo[1,2-a]indole **41a**, however PPh_3 (10 mol%) led to **41a** with 45% conversion after 20 h at 100 ^oC (see entries 1-3 of Table 1). By replacing K_2CO_3 by Cs_2CO_3 (1.2 equiv), the conversion increased to 73% (entry 4). Sterically hindered ligands such as *o*-Tol_3P or *o*-$Furyl_3P$ led to mediocre conversions (entries 5 and 6), but *m*-Tol_3P afforded 27% conversion in the presence of K_2CO_3 and 100% conversion by using Cs_2CO_3. The best result was obtained with *p*-Tol_3P in the presence of Cs_2CO_3, giving 100% conversion at 110 ^oC within 12 h (compare entries 7, 8, 9 and 10). Interestingly, a conversion of 67% was observed by using the hindered phosphine 2-dicyclohexylphosphino-2'-*(N,N*-dimethylamino) biphenyl[50] (entry 11).

Table 1. Pd-catalyzed cyclization of the pyrrole derivative **39a** leading to the tricyclic heterocycle **41a**.

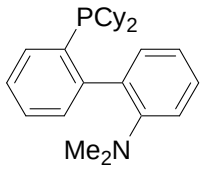


39a **41a**

Entry	Ligand	Base	Conversion (%)[a]
1	dppe	Cs_2CO_3	0
2	dppp	Cs_2CO_3	0
3	PPh_3	K_2CO_3	45
4	PPh_3	Cs_2CO_3	73
5	*o*-Tol_3P	Cs_2CO_3	0
6	*o*-$Furyl_3P$	Cs_2CO_3	8

[50] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998,** *120*, 9722.

Table 1 (continued)

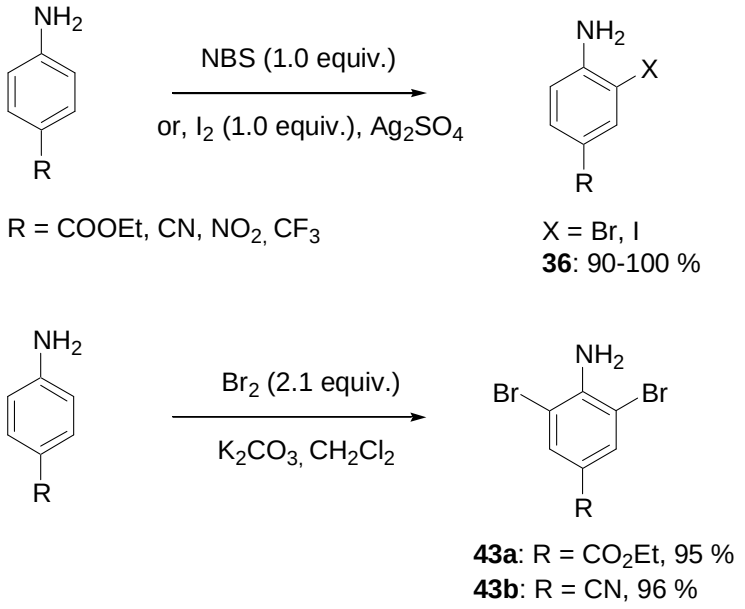
7	*m*-Tol_3P	K_2CO_3	27
8	*m*-Tol_3P	Cs_2CO_3	100
9	*p*-Tol_3P	K_2CO_3	15
10	*p*-Tol_3P	Cs_2CO_3	100[b]
11		Cs_2CO_3	67

[a] The conversion was determined by GC analysis of hydrolyzed reaction aliquots; [b] Conversion after 12 h at 110 ^oC.

3.4 Preparation of the bromo or iodo-*N*-arylpyrrole derivatives

The starting materials, bromo or iodo-*N*-arylpyrrole derivatives, were prepared by the reaction of bromo- or iodo-anilines with 1,4-dicarbonyl compounds (Paal-Knorr Synthesis) in the presence of catalytic amount of $TsOH{\cdot}H_2O$.[51] Bromo or iodo-anilines were prepared from the corresponding anilines, which reacted with NBS[52] (1.0 equiv) or iodine (1.0 equiv in the presence of 1.0 equiv of Ag_2SO_4),[53] affording the monobromo or iodo-anilines **39** in 90% to 100% yields (Scheme 32). Treatment of 4-amino-benzoic acid ethyl ester or 4-amino-benzonitrile with Br_2 (2.1 equiv) resulted in the dibromoaniline **43a** and **43b**, which were obtained in 95-96% yield (Scheme 32).

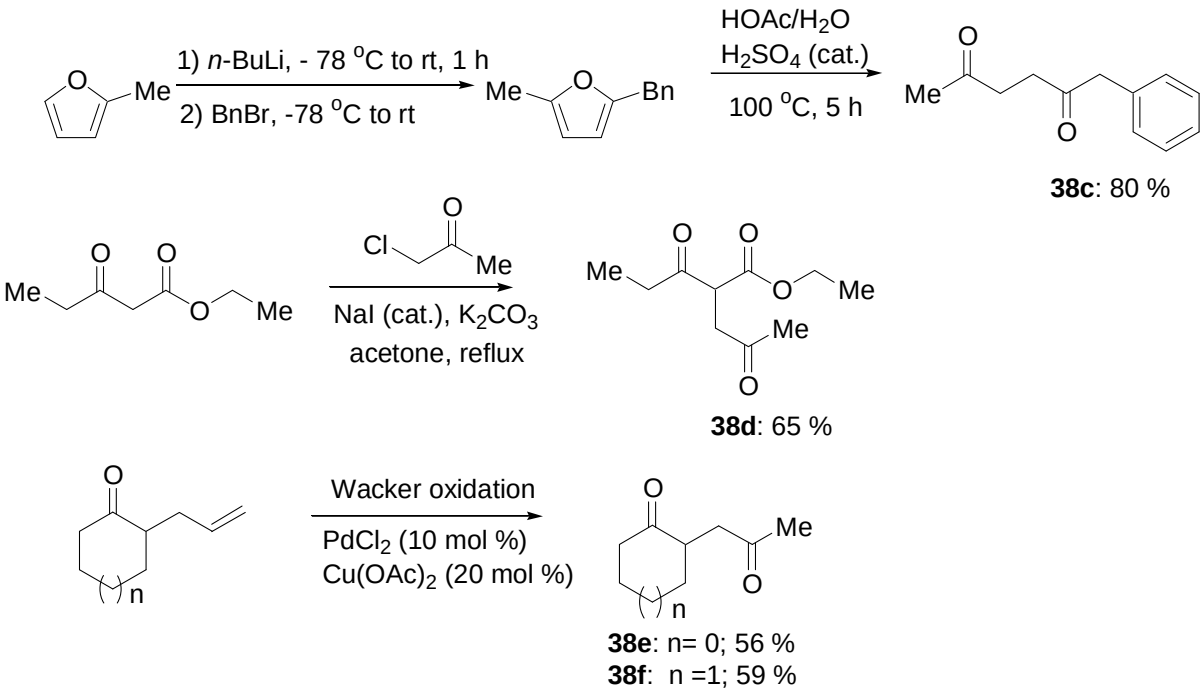
[51] L. Knorr, *Chem. Ber*., **1884**, *17*, 1635.
[52] T. Yoshito, U. Naoto, K. Kazuya, N. Atsushi, A. Kiyomi, A. Shunji, S. Motohiro, H. Keiji, N. Koichiro, *J. Am. Chem. Soc*. **2002**, *124*, 5350.
[53] C. Liu, P. Knochel, *Org. Lett*. **2005**, *7*, 2543.



Scheme 32. Preparation of monobromo, iodo and dibromoanilines.

Only few 1,4-dicarbonyl compounds are commercially available, such as hexane-2,5-dione **38a** and 1-phenylpentane-1,4-dione **38b**. Further 1,4-dicarbonyl compounds were prepared through various methods according to the literatures as shown in Scheme 33. Thus, benzylation of the methylfuran anion derived from methylfuran with *n*-BuLi, followed by acidic hydrolysis of the furan function, provided phenyl-hexane-2,5-dione **38c** in 80%.[54] The dione **38d** was prepared from ethyl 3-oxopentanoate and 1-chloropropan-2-one in the presence of NaI in 65% yield.[55] The palladium(II)-catalyzed oxidation (Wacker Oxidation) of the 2-allylcyclohexanone and 2-allylcyclopentanone resulted in the formation of diones **38e** and **38f** in 56-59% yield.[56]

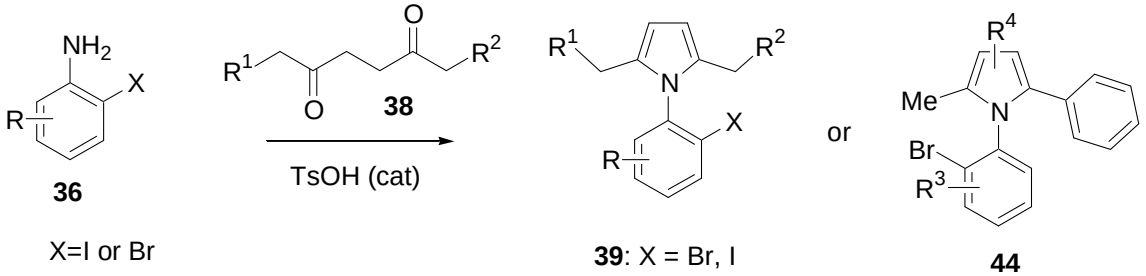
[54] M. Mondal, N. P. Argade, *Tetrahedron Lett*. **2004**, 5695.
[55] P. Chiu, M. P. Sannes, *Tetrahedron* **1990**, *46*, 3439.
[56] T. Mitsudome, T. Umerani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed*. **2006**, *45*, 481.



Scheme 33: Preparation of 1,4-dicarbonyl compounds.

With these anilines and 1,4-dicarbonyl compounds, various functionalized *N*-substituted pyrroles were smoothy obtained in good to excellent yields by the use of the Paal-Knorr reaction (Table 2). From table **2**, we can see that the bromoanilines always give good yields but iodoanilines give meager yields. This may be due to the fact that the iodopyrrole derivatives are less stable than the bromo ones.

Table 2. Preparation of the monobromo or monoiodo-*N*-arylpyrrole derivatives **39** and **44**.



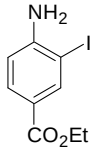
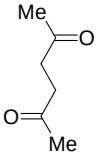
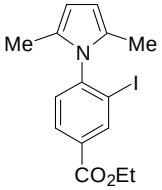
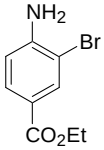
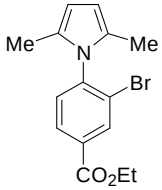
entry	aniline	dione	pyrrole[a] (%)	entry	aniline	dione	pyrrole[a] (%)
							
1	**36a**	**38a**	**39b**: 40	2	**36b**	**38a**	**39c**: 87

Table 2 (continued)

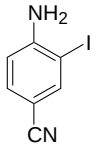
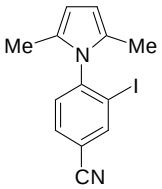
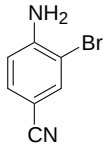
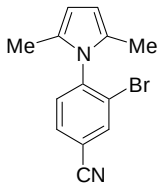
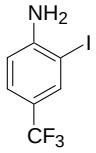
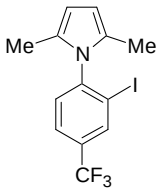
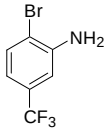
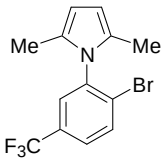
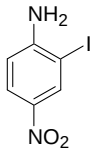
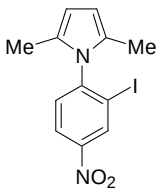
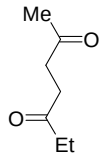
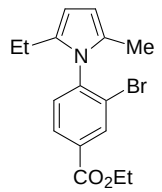
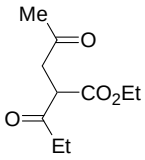
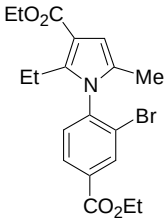
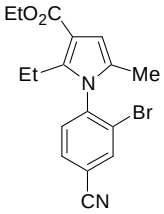
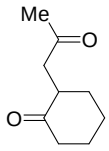
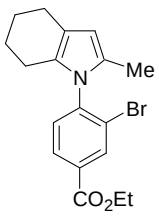
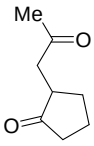
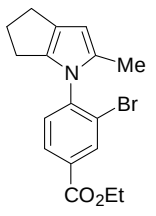
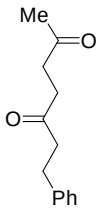
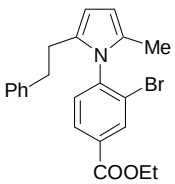
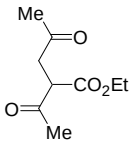
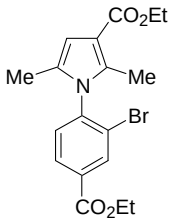
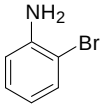
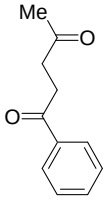
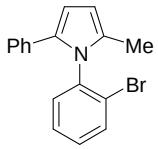
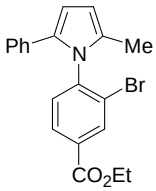
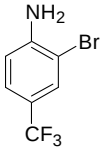
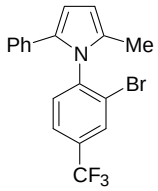
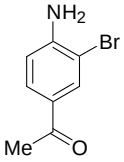
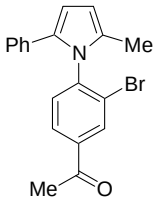
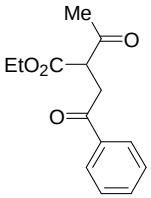
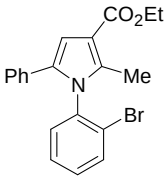
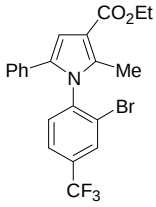
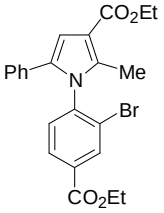
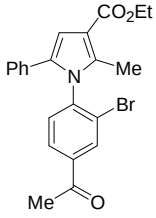
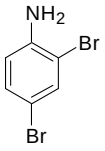
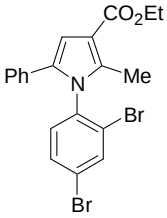
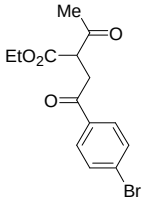
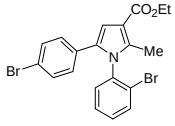
							
3	**36c**	**38a**	**39d**: 48	4	**36d**	**38a**	**39e:** 94
							
5	**36e**	**38a**	**39f**: 50	6	**36f**	**38a**	**39g**: 82
							
7	**36g**	**38a**	**39l**: 45	8	**36b**	**38c**	**39n**: 80
							
9	**36b**	**38d**	**39o**: 83	10	**36d**	**38d**	**39p**: 80
							
11	**36b**	**38e**	**39q**: 72	12	**36b**	**38f**	**39r**: 70
							
13	**36b**	**38g**	**39s**: 75	14	**36b**	**38h**	**39t**: 81

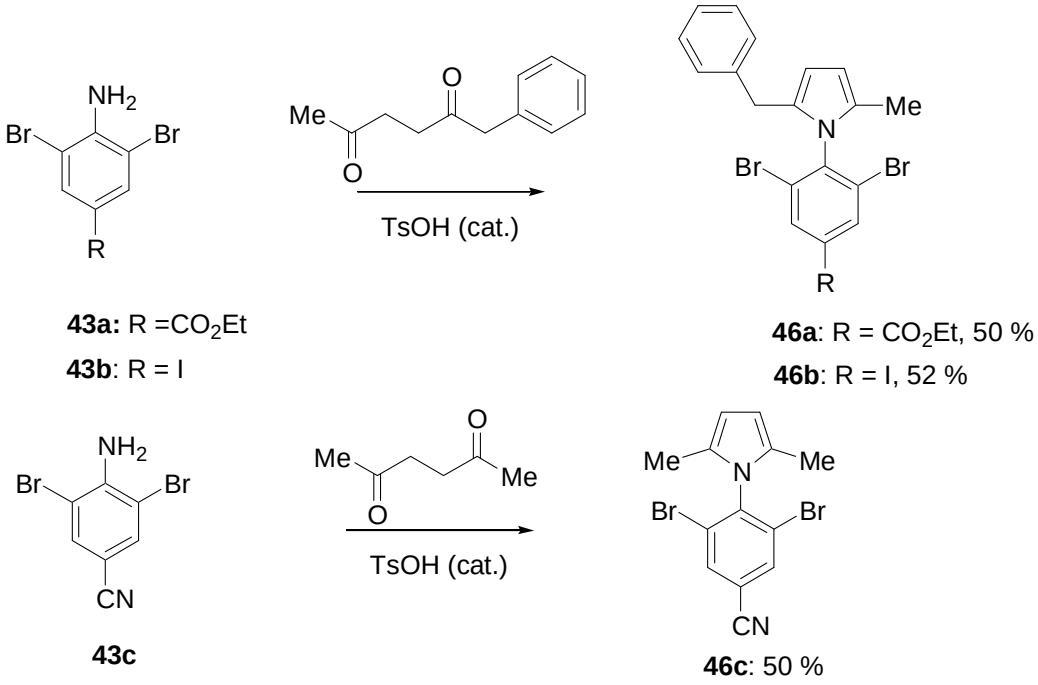
Table 2 (continued)

							
15	**36h**	**38b**	**44a**: 95	16	**36b**	**38b**	**44b**: 89
							
17	**36f**	**38b**	**44c**: 81	18	**36i**	**38b**	**44d**: 75
							
19	**36h**	**38i**	**44e**: 90	20	**36f**	**38i**	**44f**: 82
							
21	**36b**	**38i**	**44g**: 72	22	**36i**	**38i**	**44h**: 85
							
23	**36j**	**38i**	**44j**: 83	24	**36h**	**38j**	**44k**: 81

[a]: Isolated yield of analytically pure product.

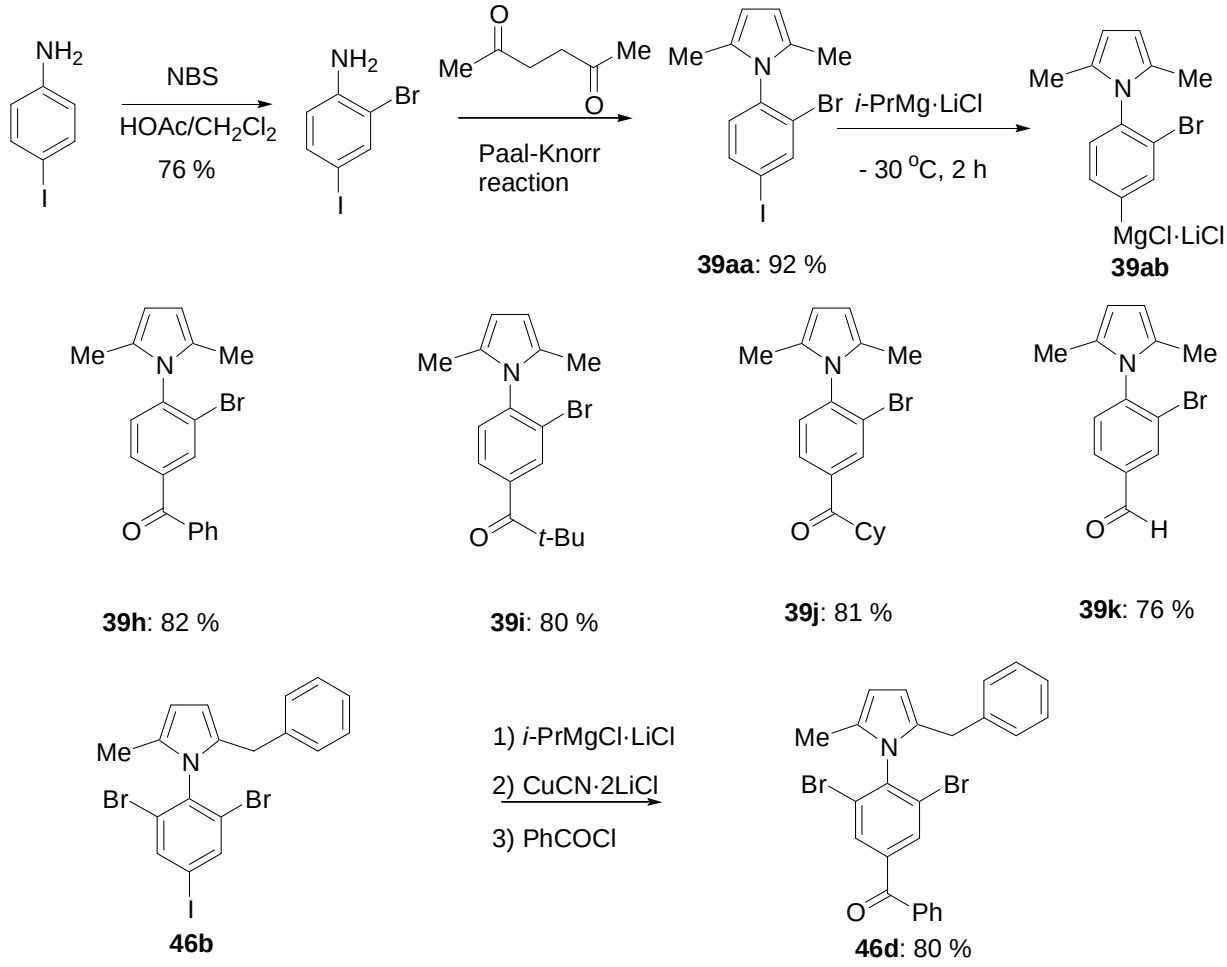
Dibromo-*N*-arylpyrrole derivatives can also be prepared from dibromo-anilines with a 1,4-dicarbonyl compound using the same procedure, but they cost much more time and require an excess of 1,4-dicarbonyl compounds due to the hinderance of the products and increased formation of the byproduct of furans, which come from the 1,4-dicarbonyl compounds. Thus, treatment of dibromoaniline **43a** and *p*-iodo-dibromoaniline **43b** with hexane-2,5-dione **38c** in

the presence of TsOH·H_2O (2 mol %) provided the dibromoarylpyrrole **46a** respectively in 45% yield and **46b** in 52% yield (Scheme 34). The 2,5-symmetrically substituted dibromoarylpyrrole **46c** can also be obtained in 50% yield from the dibromoaniline **43c.**



Scheme 34. Preparation of 2,5-symmetrical and unsymmetrical dibromoarylpyrroles**.**

Functionalized mono- or dibromo-*N*-arylpyrrole derivatives also can be prepared from the corresponding iodo compound using an I/Mg exchange. Thus, by treating the iodo-*N*-arylpyrrole **39aa** with *i*-PrMg·LiCl at -30 ^{o}C for 2 h, the corresponding Grignard reagent **39ab** was obtained. After transmetalation with CuCN·2LiCl, the Grignard reagent **39ab** reacted with various acid chlorides providing ketones. The ketones of **39h-j** were obtained in 80-82% yields according to this method. Furthermore, the Grignard **39ab** can also be directly trapped with dry DMF, providing the aldehyde **39k** in 76% yield. Similarly, a selective I/Mg exchange of iodo-dibromo-*N*-arylpyrrole **46b** leads to the Grignard **46c**. After transmetalation with CuCN·2LiCl and reaction with benzoyl chloride, resulted in the formation of dibromo-*N*-arylpyrrole **46d** in 80% yield (Scheme 35).



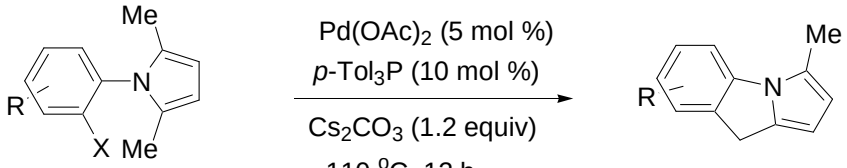
Scheme 35. Preparation of functionalized mono- or dibromo-*N*-arylpyrrole derivatives *via* I/Mg exchange.

3.5 Scope of the C-H activation reaction and preparation of functionalized *9H*-pyrrolo[1,2-a]indoles

A broad range of *9H*-pyrrolo[1,2-a]indoles of type **41** can be prepared from the corresponding iodo or bromo-*N*-arylpyrrole derivatives under optimized reaction conditions (Table 3). The 2-iodo- and 2-bromo-*N*-arylpyrrole derivatives **39b** and **39c** undergo smoothly the ring closure, providing the tricyclic product **41b** respectively in 81% and 83% yield, showing that the use of aryl iodides or bromides leads to similar results (entries 1 and 2 of Table 2). The ester function is well tolerated in this ring closure. The cyano-substituted iodide **39d** and bromide **39e** also furnished the expected product **41c** in respectively 70% and 60% yield (entries 3 and 4) under the standard conditions. Trifluoromethyl-substituted substrates, which, may be of interest for the preparation of pharmaceutically relevant heterocycles, react readily and lead to the tricyclic products **41d** (77%) and **41e** (65%) (entries 5 and 6). Ketone and

aldehyde functions are also well tolerated. For example, the ketone derivatives **39h-j** are readily converted to the tricyclic products **41f-h** in 55-61% yield (entries 7-9). Even an aldehyde function is tolerated in this ring closure process. Hence, heating the aldehyde **39k** in the presence of $Pd(OAc)_2$ afforded the tricyclic compound **41i** in 55% yield. Only a nitro-substituent was complicated the reaction and furnished the *9H*-pyrrolo[1,2-a]indole **41j** in only 33% yield (entry 11). With a strong electron donor such as NH_2 as substituent, no ring closure was observed (entry 12).

Table 3. Preparation of *9H*-pyrrolo[1,2-a]indoles of type **41** from an *N*-arylpyrroles of type **39**



39 **41:** 33-86%

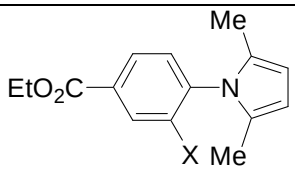
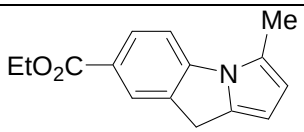
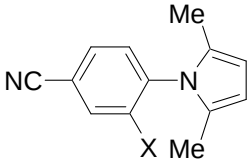
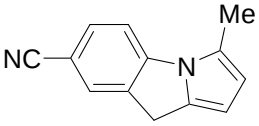
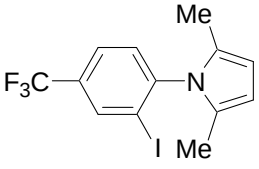
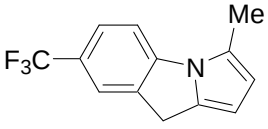
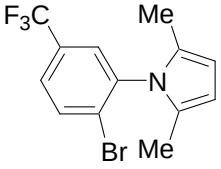
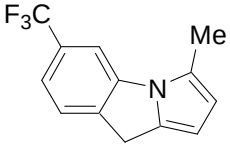
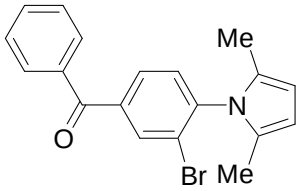
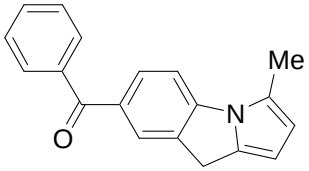
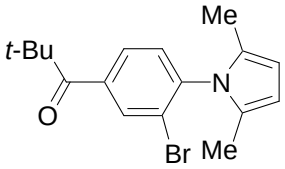
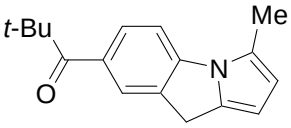
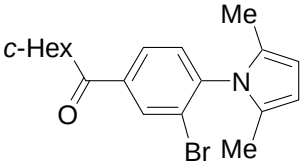
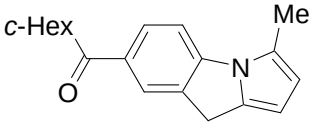
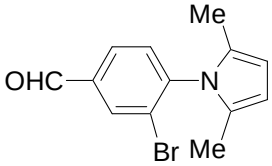
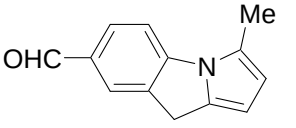
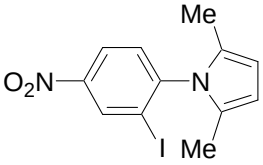
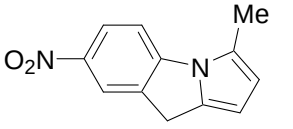
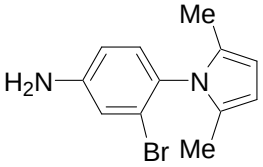
Entry	Pyrrole of type **39**	Product of type **41**	Yield [%][a]
			
1	**39b**: X = I	**41b**	86
2	**39c**: X = Br		83
			
3	**39d**: X = I	**41c**	70
4	**39e**: X = Br		60
			
5	**39f**	**41d**	77
			
6	**39g**	**41e**	65

Table 3 (continued)

			
7	**39h**	**41f**	61
			
8	**39i**	**41g**	66
			
9	**39j**	**41h**	69
			
10	**39k**	**41i**	55
			
11	**39l**	**41j**	33
			
12	**39m**		0

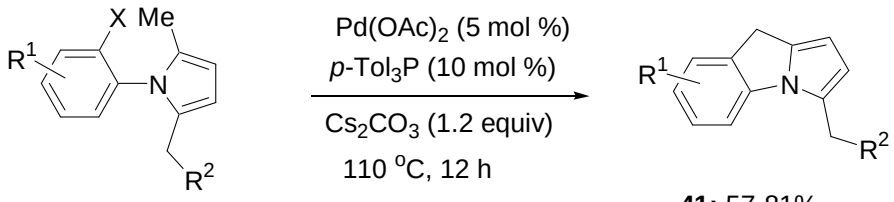
[a] Isolated yield of analytically pure products.

Regioselective C-H activations have only been scarcely studied.[57] Remarkably, when a 2,5-unsymmetrical substrates like 2-ethyl-5-methyl-arylpyrrole **39n** was treated with $Pd(OAc)_2$,

[57] a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 653; b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005,** *127*, 7330; c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004,** *126*, 9542; d) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004,** *126*, 2300.e) Buchwald, S. L.; Henneessy, E. J. *J. Am. Chem. Soc.* **2003,** *125*, 12084.

only the activation on the methyl group was observed and the tricyclic compound **41a** was obtained in 75% yield (entry 1 of Table 4). Muti-substituted pyrroles also led to excellent selectivities. With an ester-substituted pyrrole ring, the selective C-H activation provided the polyfunctionalized tricyclic compounds **41l** and **41m** in 80-81% yield (entries 2 and 3). Tetracyclic compounds can also be prepared using this C-H activation method. Thus, 2-methyl-4,5,6,7-tetrahydro-*1H*-indole derivate **39q** and 2-methyl-1,4,5,6-tetrahydro-cyclopenta[b]pyrrole derivate **39r** undergo a selective C-H activation, providing the tetracyclic compounds **41n** (64% yield) and **41o** (60% yield) under the standard conditions (entries 4 and 5). Even for the substrate **39s**, which has much more active hydrogen in the structure, the selective C-H activation of the methyl group resulted in the formation of the product **41p** in 57% yield (entry 6). The substitution on *N*-arylpyrrole also affects the regioselectivity of the ring closure. For example, a ratio of **41q**:**41r** of 2:1 was obtained from the reaction of 2,5-dimethyl-3-ethoxycarbonyl phenylpyrrole derivative **39t** (entry 7). This may result from an activation (acidification) of the proximity methyl group by the ester group. The structure of **41q** was determined by H-H NOESY NMR analysis (See experimental part).

Table 4. Chemoselective preparation of *9H*-pyrrolo[1, 2-a]indoles of type **41** from pyrroles of type **39**.



39 **41:** 57-81%

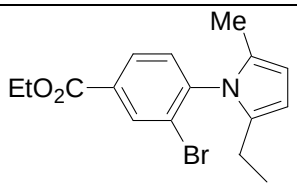
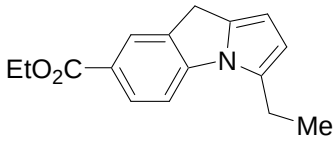
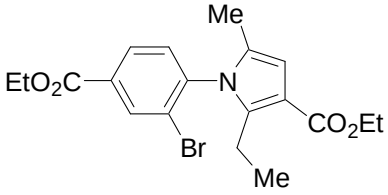
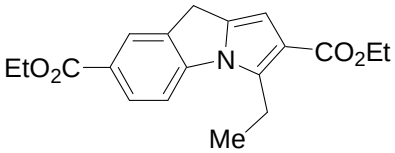
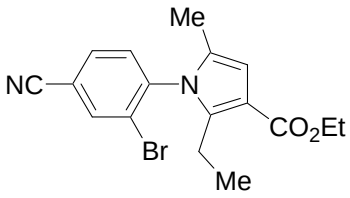
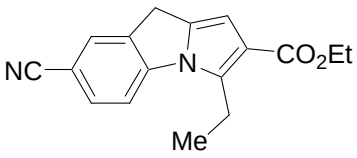
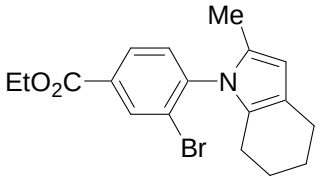
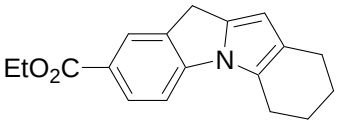
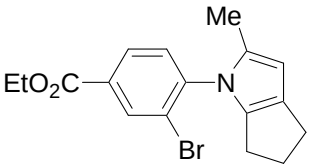
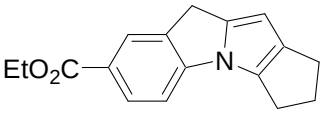
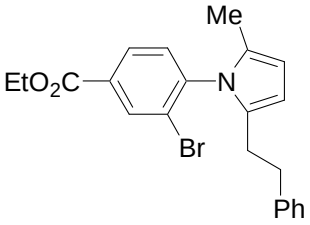
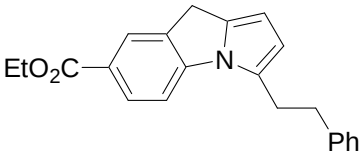
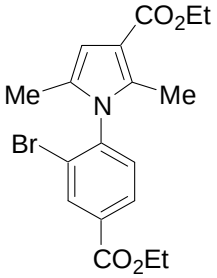
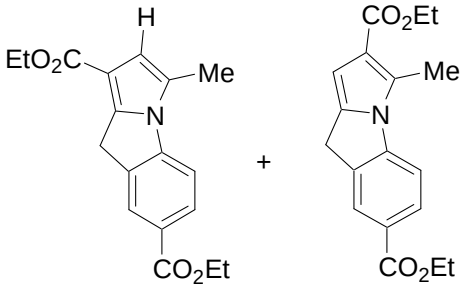
entry	Pyrrole of type **39**	Product of type **41**	Yield [%][a]
1	 **39a**	 **41a**	75
2	 **39b**	 **41b**	80

Table 4 (continued)

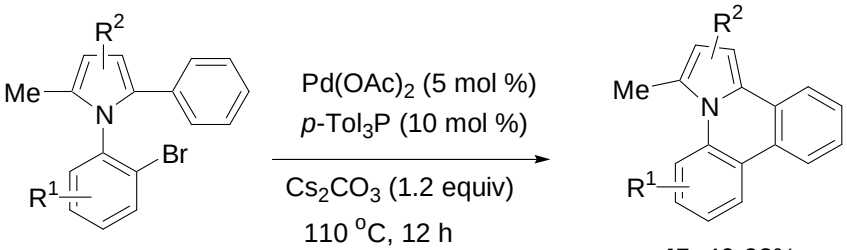
			
3	**39c**	**41c**	81
			
4	**39d**	**41d**	64
			
5	**39e**	**41e**	60
			
6	**39f**	**41f**	57
			
7	**39g**	**41q** : **41r** = 2 :1	80

[a] Isolated yield of analytically pure product.

In the case of 2-phenyl-5-methyl-arylpyrrole derivates, the activation of the phenyl group was found to be much faster than that of the methyl group and leads to the pyrrolo[1,2-f]phenanthridine ring system. Thus, the *N*-arylpyrrole derivative **44a** preferentially undergoes a chemoselective activation of the phenyl ring over the methyl substituent, leading to the

pyrrolo[1,2-f]phenanthridine derivative **45a** in 93% yield (entry 1 of Table 5). The ester function is well tolerated in this ring closure. The ester substituent on both the arene and pyrrole groups gives good yields (83-86%; entries 2, 5, 6 and 7). Moreover, the trifluoromethyl-substituted bromides **44c** and **44f** furnished the expected products **45c** and **45f** in 85-86% yield (entries 3 and 6). Even a ketone is tolerated and ketones **44d** and **44g** lead to the products **45d** and **45g** in 46-61% yield (entries 4 and 8). The pyrrole **45i**, bearing a hydroxyl group in the benzylic position, also gave the desired product **45i** in 53% yield (entry 9).

Table 5. Preparation of pyrrolo[1,2-f]phenanthridines of type **45** from pyrroles of type **44**



44 **45**: 46-93%

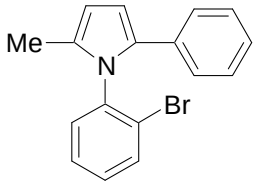
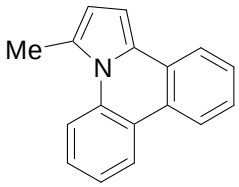
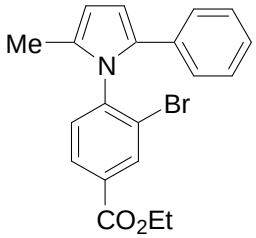
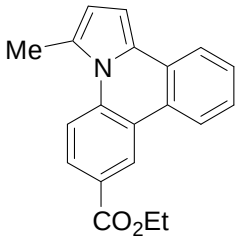
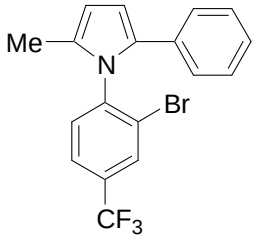
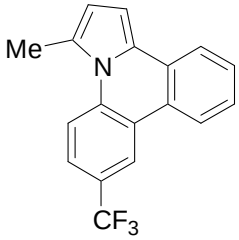
entry	Aniline	Product	Yield
			
1	**44a**	**45a**	93
			
2	**44b**	**45b**	85
			
3	**44c**	**45c**	85

Table 5 (continued)

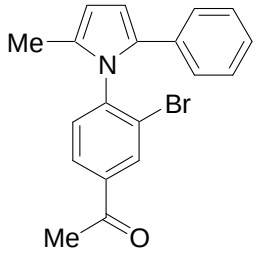
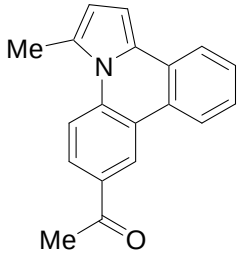
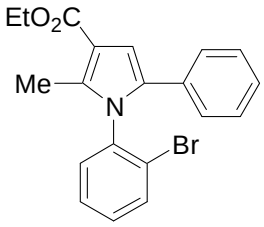
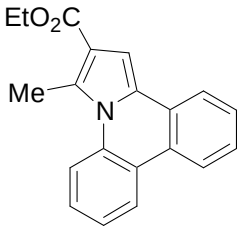
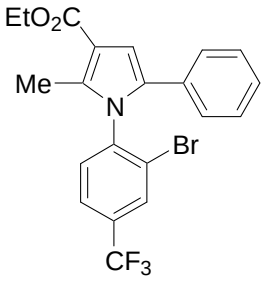
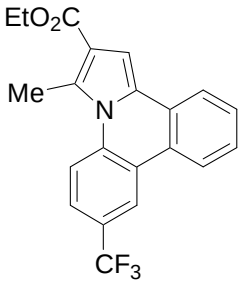
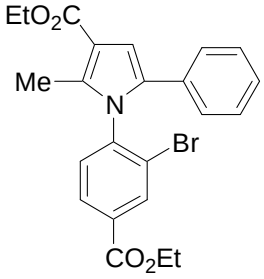
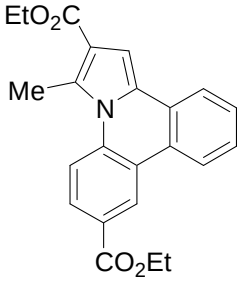
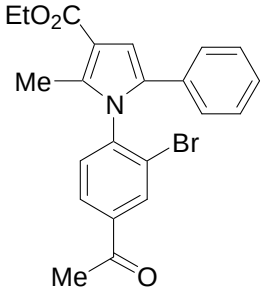
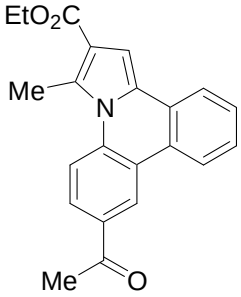
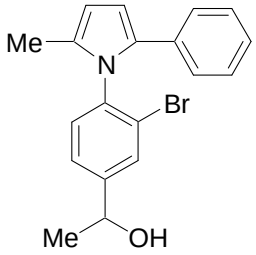
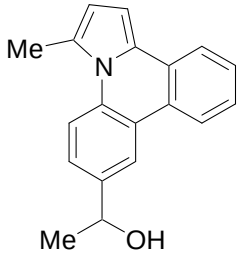
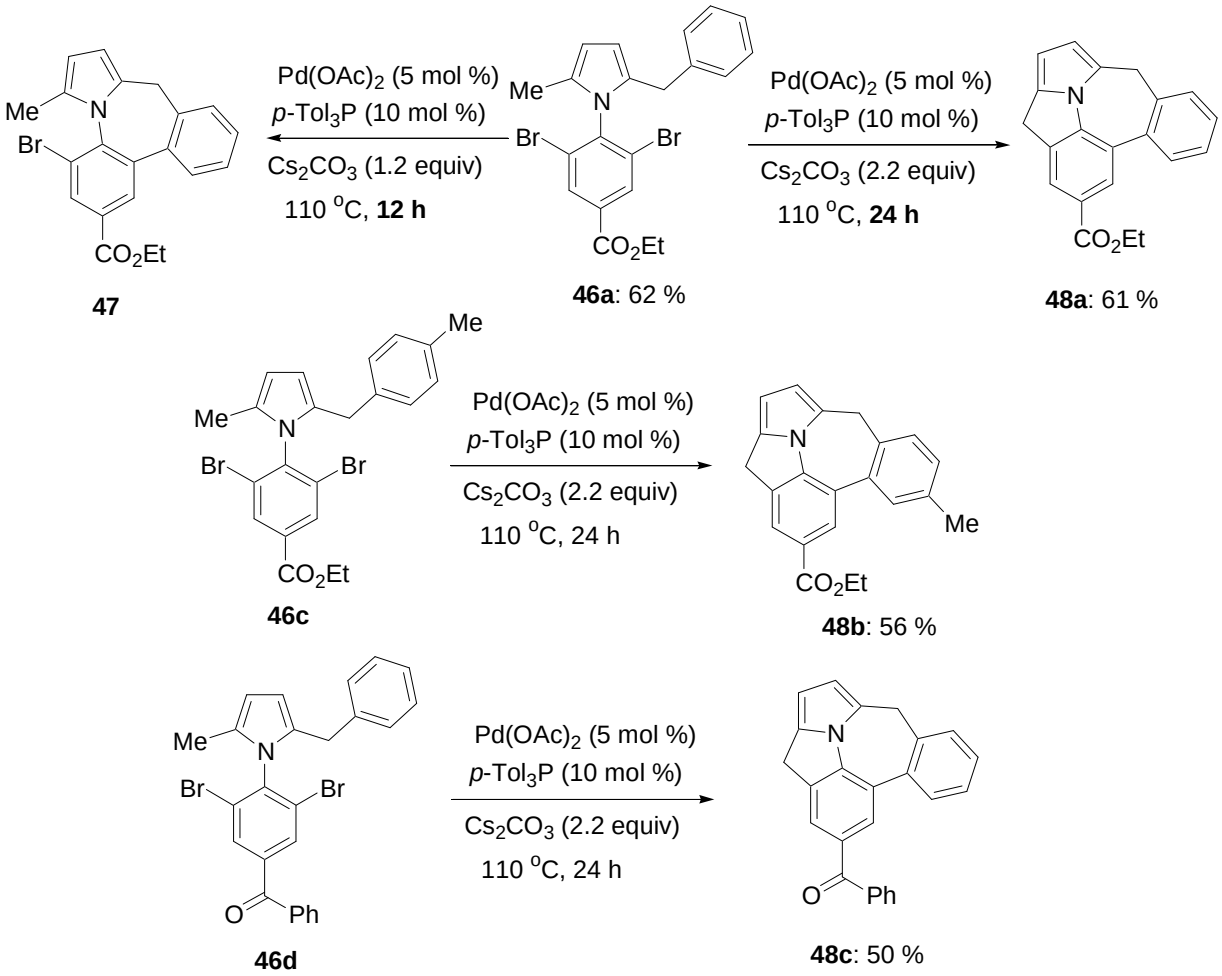
4	 **44d**	 **45d**	61
5	 **44e**	 **45e**	83
6	 **44f**	 **45f**	86
7	 **44g**	 **45g**	84
8	 **44h**	 **45h**	46

Table 5 (continued)

9	 **44i**	 **45i**	53

[a]: Isolated yield of analytically pure product.

In the case of the 2,5-unsymmetrically substituted dibromo derivatives **46**, an interesting stepwise cyclization is observed. Only the benzylic substituent is activated leading to the 7-membered ring (**47**, 62%). Forcing reaction conditions (110 ^{o}C, 24 h) lead to a second cyclization with the formation of the pentacyclic compound **48a** in 61% yield (Scheme 36). Under the same conditions, the pentaheterocyclic compounds **48b** and **48c** are obtained from the corresponding dibromo compounds **46c** and **46d** in 50-56% yield. These condensed heterocyclic compounds are difficult to obtain *via* conventional cross-coupling methods.



Scheme 36. Preparation condensed heterocyclic compounds *via* domino C-H activation reactions.

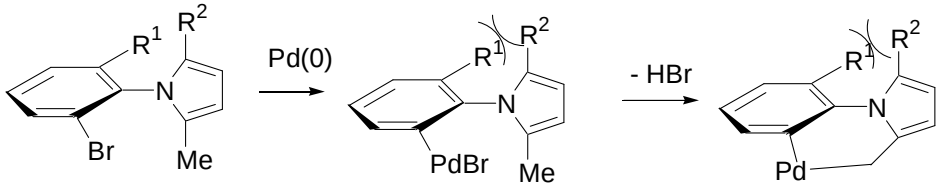
3.6 Mechanistic investigations

Several mechanisms have been proposed for direct arylation reactions, including an electrophilic palladation pathway,[58] a carbopalladation (Heck-type) pathway [59]or a direct C-H activation pathway.[60] All of these processes involve the formation of palladacycles. In our case, the two rings (the aryl ring and pyrrole) are not coplanar; a rotation has to take place leading to an increased repulsion between the substituents R^1 and R^2. Hence the formation of palladacycle **49** is greatly affected by the nature of the groups R^1 and R^2 (Scheme 37).

[58] a) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005,** *127*, 8050. b) D. Trauner, C. C. Hughes, *Angew. Chem., Int. Ed.* **2002**, *41***,** 1569. c) R. S. Shue, *J. Am. Chem. Soc.* **1971,** *93*, 7116. d) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003,** *125*, 12084.

[59] M. Toyata, A. Ilangovan, R. Okamoto, T. Masaki, M. Arakawa, M. Ihara, *Org. Lett.* **2002**, *4*, 4293.

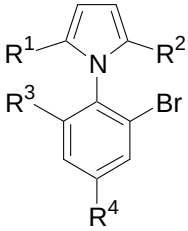
[60] a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003,** *125*, 12084; b) J. Cámpora, E. Gutiérrez-Puebla, J. A. López, A. Monge, P. Palma, D. del Río, E. Carmona, *Angew. Chem., Int. Ed.* **2001**, *40***,** 3641. c) J. Cámpora, J. A. López, P. Palma, E. Spillner, E. Carmona, *Angew. Chem., Int. Ed.* **1999**, 38, 147.



49

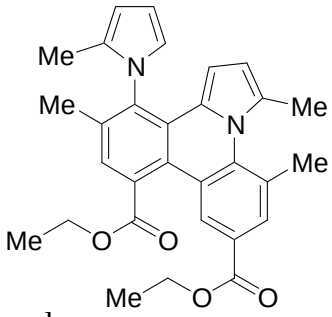
Scheme 37. Formation of palladacycles affected by the substituents R^1 and R^2.

In order to probe the mechanism, various substituted 2-bromo-*N*-arylpyrrole derivatives were investigated under the standard conditions and the results were summarized in Scheme 38. These results showed that the nature of the groups R^1 and R^2 greatly affect the reaction. Interestingly, when substrate **39w** was involved in this reaction, a complex heterocycle **50** was obtained in 85% but failed of substrate **39u**.



entry		R^1	R^2	R^3	R^4	Result
1	**39u**	Me	H	H	H	a
2	**39c**	Me	Me	H	CO_2Et	b
3	**39n**	Me	Et	H	CO_2Et	b
4	**39v**	Et	Et	H	CO_2Et	a
5	**39w**	Me	H	Me	CO_2Et	c
6	**39x**	Me	Me	Me	CO_2Et	a
7	**46c**	Me	Me	Br	CO_2Et	a

a: No desired product; b: C-H activation reaction is observed;
c: Provides a complex compound (**50**).



50: 85 %

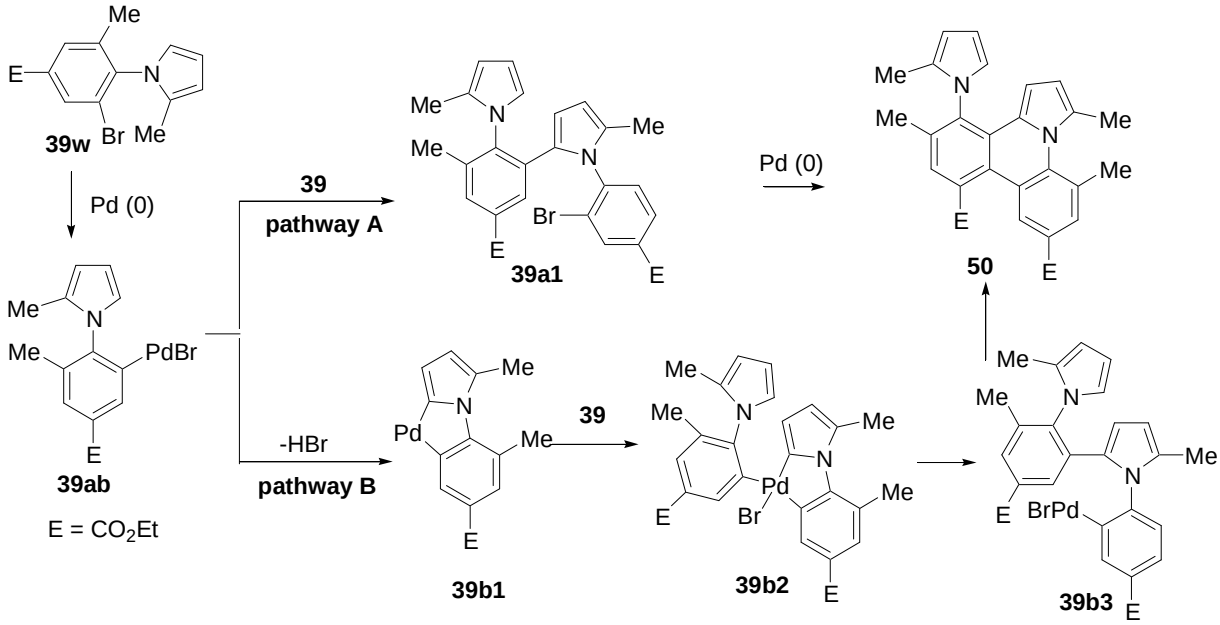
Scheme 38. Summary of the results with different R^1 and R^2 groups.

Two plausible mechanisms can be envisioned for the formation of **50**. Once the intermediate **39ab** is formed through oxidative addition, there are two possible pathways in which the reaction can further proceed. In the first pathway, the intermediate **39ab** reacts with another molecule of 2-bromo-*N*-arylpyrrole derivative **39** to form the intermediate **39a1** in a Heck-like type reaction. **39a1** would give the product **50** after an intramolecular arylation in the presence of Pd(0) (pathway A). Alternatively, the reaction may proceed *via* the direct C-H activation of intermediate **39ab**, forming a palladacyclic intermediate **39b1**[61], which may undergo oxidative addition with **39** to afford the intermediate **39b2**[62]. Subsequent reductive

[61] a). M. A.Campo, R. C. Larock, *J. Am. Chem. Soc.* **2002,** *124*, 14326. b) Q. Huang, M. A. Campo, T. Yao, Q. Tian, R. C. Larock, *J. Org. Chem.* **2004**, *69*, 8251. c) G. Karig, , M.-T. Moon, N. Thasana, T. Gallagher, *Org. Lett.* **2002**, *4*, 3115. d) Q. Tian, R. C. Larock, *Org. Lett.* **2000**, *2*, 3329. e) R. C.Larock, Q. Tian, *J. Org. Chem.* **2001**, *66*, 7372.

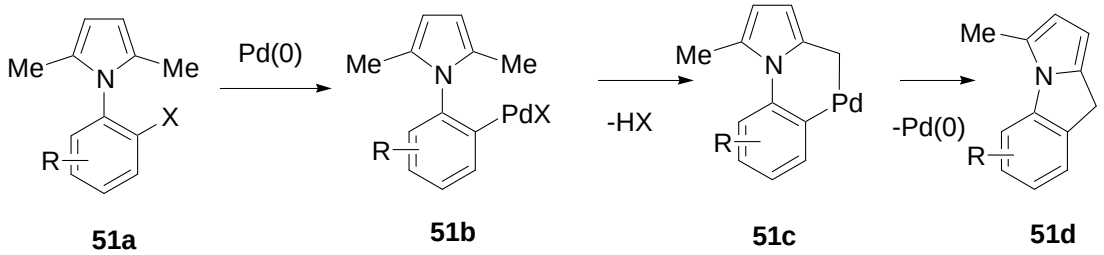
[62] Ref. for palladium (IV) complex: a) A. J. Canty, J. Patel, T. Rodemann, J. H. Ryan, B. W. Skelton, A. H. White, *Oranometallics* **2004**, *33*, 3466. b) M. Lautens, J.-F. Paquin, S. Piguel, M. Dahlmann, *J. Org. Chem.* **2001**, *66*, 8127. c) M. Lautens, S. Piguel, *Angew. Chem., Int. Ed.* **2000**, *39***,** 1045. d) M. Lautens, J.-F. Paquin, S. Piguel, M. Dahlmann, *J. Org. Chem.* **2002**, *67*, 3972. e) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem., Int. Ed.* **1997**, *69***,** 119.

elimination would lead to **39b3**, which will give the product **50** after an intramolecular arylation (pathway B) (Scheme 39).



Scheme 39. The plausible mechanisms for the formation of **50**.

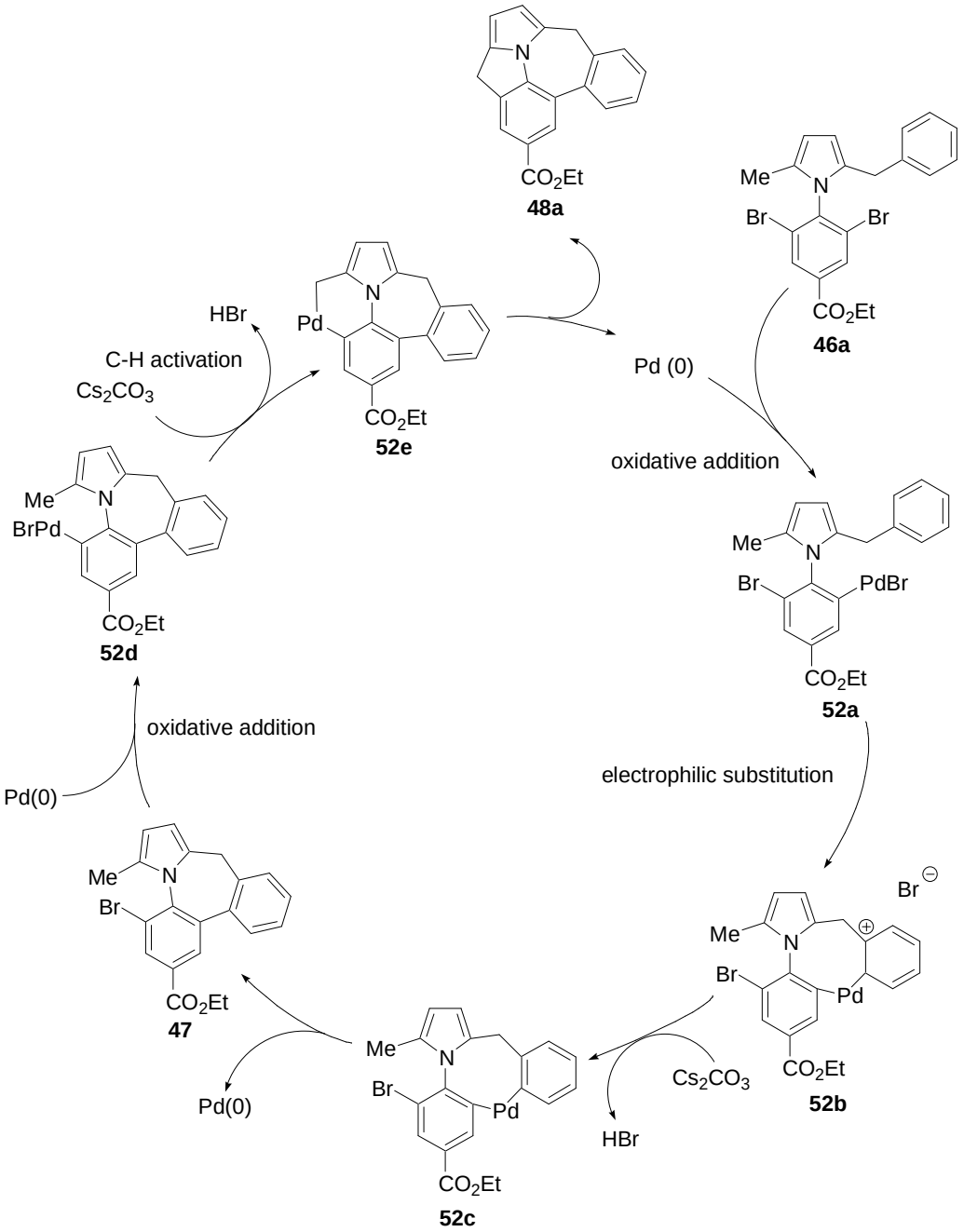
Our results show that the activation of a methyl substituent is not an easy process and that the reaction is hampered by steric hindrance. These considerations led us to propose the following tentative mechanism for the cyclization reaction. The *N*-(2-haloaryl)pyrrole derivative **51a** first undergoes an oxidative addition of Pd(0) generated *in situ*, leading to the Pd(II) species **51b** (Scheme 40). Concomitant C-H activation and HX elimination provides the palladacycle **51c**, which, after reductive elimination, yields the *9H*-pyrrolo [1,2-a] indole **51d**.



Scheme 40. Tentative mechanistic pathway for the ring closure.

On this basis, we suggest a plausible reaction mechanism for the domino C-H activation preparation of pentacyclic compounds **48a-c**. The process is most likely initiated by an oxidative addition of Pd(0) to the dibromoarylpyrrole **46a**, resulting in the Pd(II)-species **52a**. The formation of the carbon-carbon bond may proceed *via* an electrophilic aromatic substitution to give 8-membered palladacycle **52c**, which then undergoes a reductive elimination affording the product **47** and regenerates the Pd(0)-species. The Pd(0)-insertion

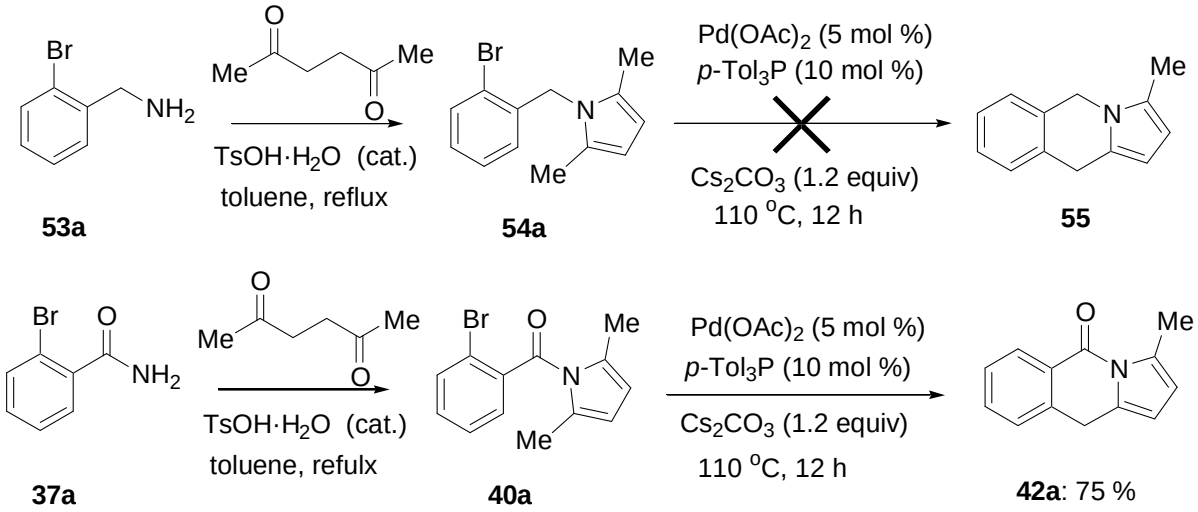
into the C-Br bond of the aryl bromide **47** results in the formation of the Pd(II)-species **52d**. Concomitant C-H activation and HX elimination provides the palladacycle **52e**, which leads to the pentacyclic compound **48a** after reductive elimination (Scheme 41).



Scheme 41. A plausible reaction mechanism for the preparation of pentacyclic compounds *via* domino C-H activation.

3.7 Extending the C-H activation reaction

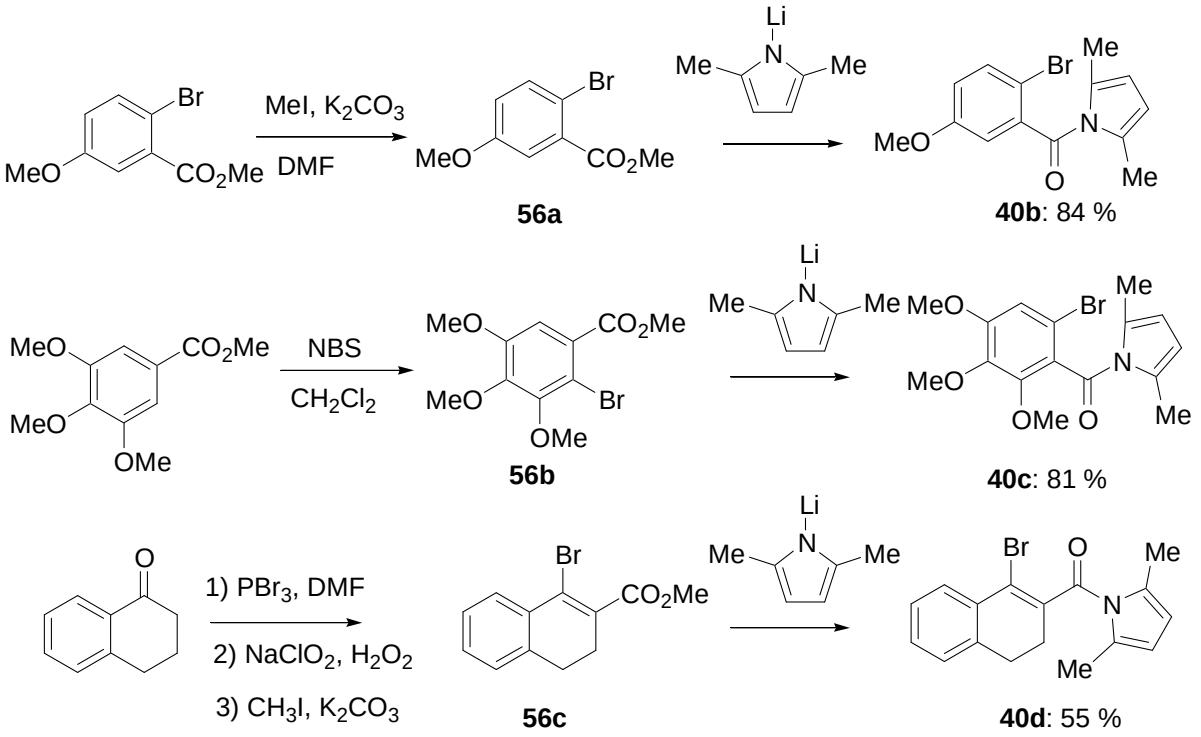
We have then focused our attention on the formation of 6-membered ring synthesis. Initially, we focused on the compound **54a**, since it can be easily prepared from the (2-bromophenyl) methanamine **53a**. Once we had the starting material **54a** in hand, we tried the reaction using the standard conditions. Unfortunately, the product **55** could not be observed. Interestingly, when heating the compound **40a** under the standard conditions, the ring closure product **42a** smoothly formed in 75% yield (Scheme 42).



Scheme 42. Formation of 6-membered ring through a Pd-catalyzed C-H activation.

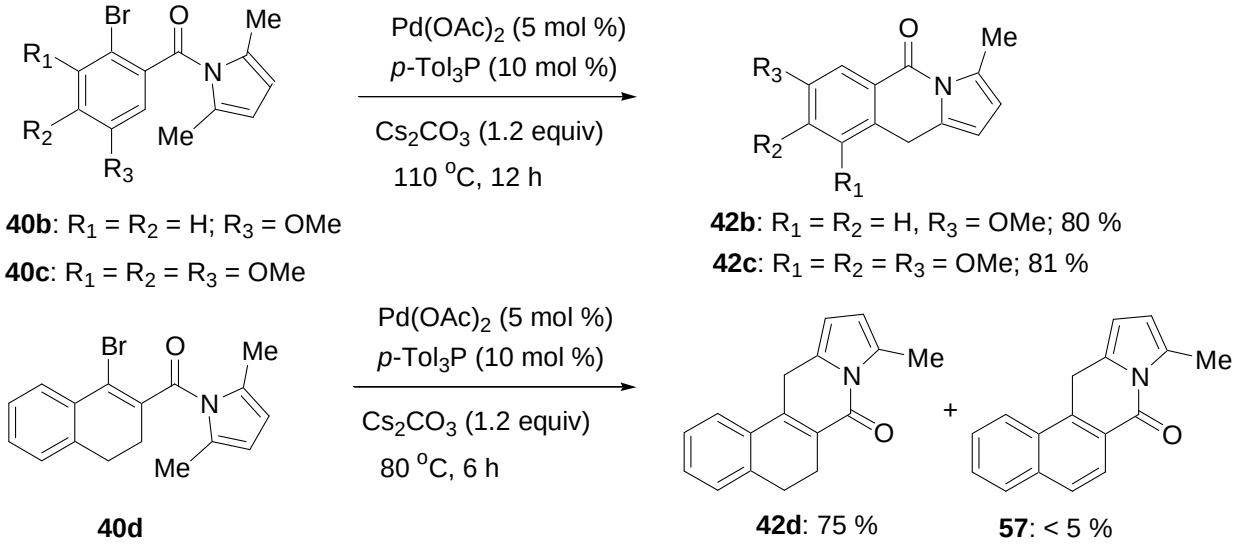
In order to investigate the scope of this type of reaction, several *N*-acyl-2,5-pyrrole derivatives **40b-d** were prepared from the corresponding methyl ester and the lithium amide of 2,5-dimethyl-*1H*-pyrrole. Thus, treatment of 2-bromo-5-methoxybenzoic acid methyl ester **56a**[63] and 2-bromo-3,4,5-trimethoxy-benzoic acid methyl ester **56b** with lithium amide of 2,5-dimethyl-*1H*-pyrrole (which was generated from 2,5-dimethyl-*1H*-pyrrole and *n*-BuLi), a substitution reaction occurred and provided the *N*-acylpyrroles **40b** and **40c** in 81-84% yield. The cycloalkenyl derivative **40d** was obtained by this method starting from 1-bromo-3,4-*2H*-naphthalene-2-carboxylic acid methyl **56c**[64], which was obtained from α-tetralone in 3 steps (Scheme 43).

[63] S. Ozaki, M. Adachi, S. Sekiya, R. Kamikawa, *J. Org. Chem.* **2003**, *68*, 4586.
[64] T. L. Gilchrist, M. A. M. Healy, *Tetrahedron* **1993**, *49*, 2543.



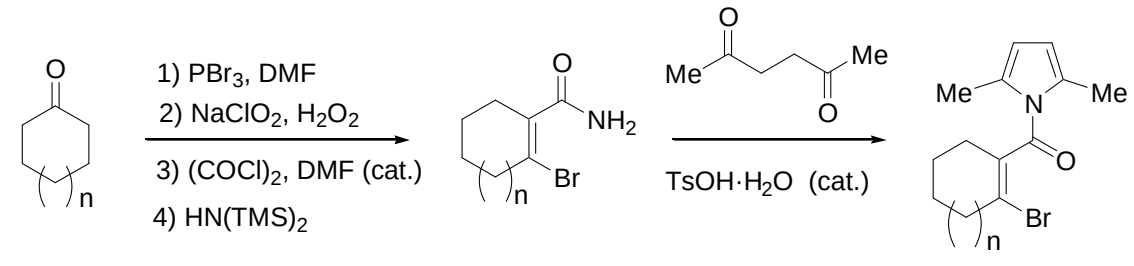
Scheme 43. Preparation of *N*-acyl-2,5-pyrrole derivatives.

Remarkably, under the standard conditions, the readily available amides **40b** and **40c** were both converted into the pyrrolo[1,2-b]isoquinolines **42b-c** in 75-81% yield. For the substrate **40d**, milder conditions can be used. Thus, the amide **40d** was heated in the presence of $Pd(OAc)_2$ (5 mmol%) at 80 ^oC for 5 h affording heterocycle **42d** in 79% yield. The oxidized naphthyl derivative **57** was also present in the crude reaction mixture (less than 5% as shown by ^1H-NMR analysis; Scheme 44).



Scheme 44. Preparation of pyrrolo[1,2-b]isoquinolines.

Cycloalkenyl *N*-acylpyrroles undergo also the desired ring closure. The starting materials were prepared as shown in Scheme 45 from cyclic ketones **58a-c**. Thus, the 2-bromo-cyclohex-1-enecarboxylic acid amide **59b** was obtained in 4 steps according to the literature. [65] Treatment of 2-bromocyclohex-1-enecarboxamide **59b** with hexane-2,5-dione in the presence of $TsOH \cdot H_2O$ (2 mol %) provided the *N*-acylpyrrolamide **60b** in 79% yield. The *N*-acylpyrrolamide **60a** and **60c** were prepared from the same procedure in 40-81% yields (Scheme 45).



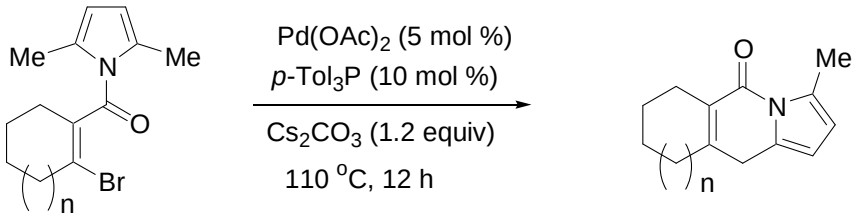
58a: n = 0
58b: n = 1
58c: n = 2

59a: n = 0
59b: n = 1
59c: n = 2

60a: n = 0; 40%
60b: n = 1; 79 %
60c: n = 2; 81%

Scheme 45. Preparation of non-aromatic *N*-acylpyrroles **60a-c.**

The *N*-acylpyrrolamides **60a-c** were all converted to the tricyclic compounds **61a-c** under the usual conditions in 74-85% yield (Scheme 46).



60a: n = 0
60b: n = 1
60c: n = 2

61a: n = 0; 80%
61b: n = 1; 85%
61c: n = 2; 74%

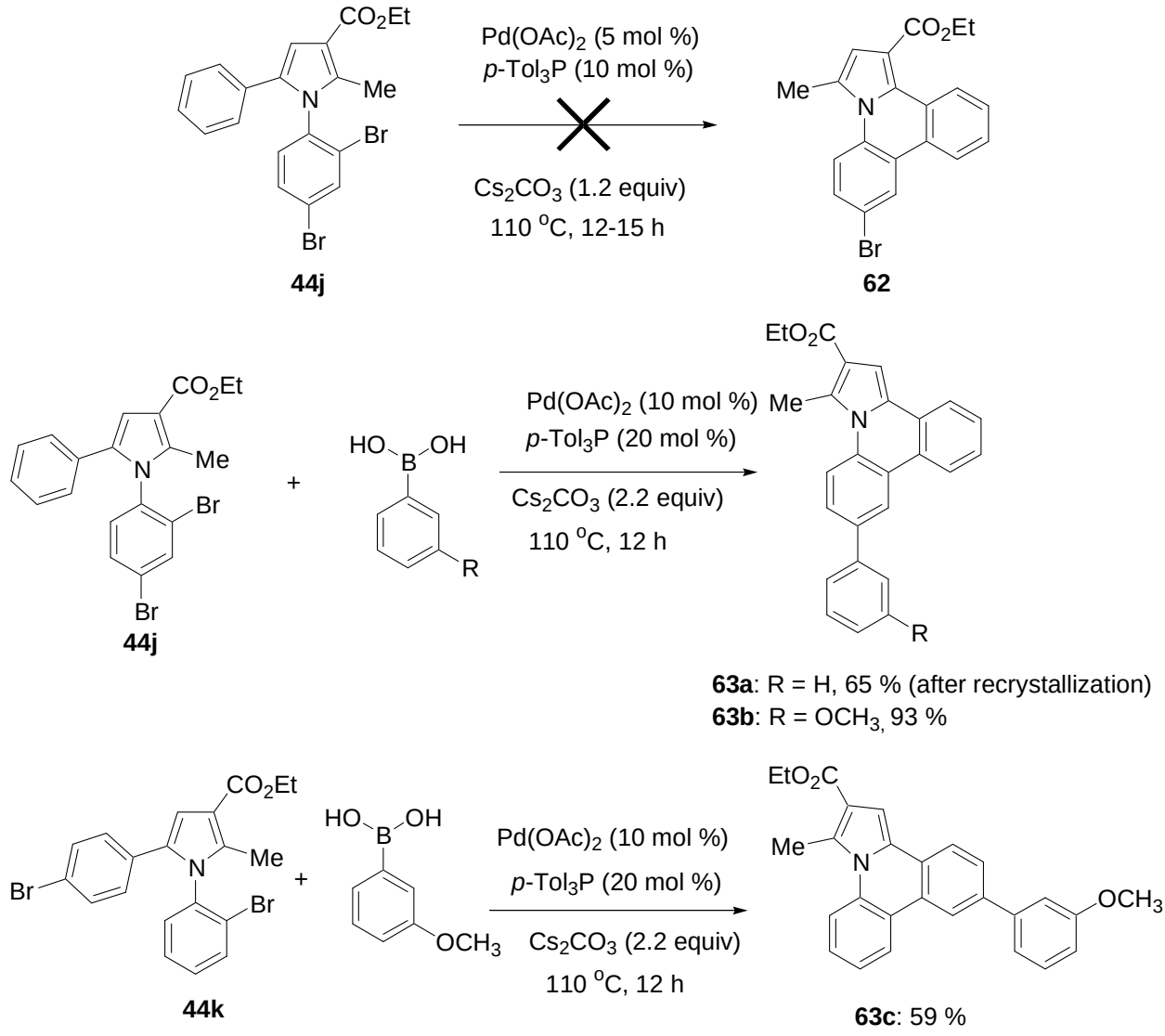
Scheme 46. Preparation of tricyclic heterocycles starting from non-aromatic *N*-acylpyrroles.

3.8 Tandem reactions involving a Suzuki cross-coupling and a C-H activation

We have also investigated the performance of C-H activation reactions in conjunction with Suzuki cross-couplings. The dibromoaryl pyrrole **44j** when treated with $Pd(OAc)_2$ in toluene did not give the desired C-H activation product **62**. However when dibromoarylpyrrole **44j** was treated with phenylboronic acid (1.1 equiv) in the presence of $Pd(OAc)_2$ (10 mol%) and

[65] K. Ohe, K. Miki, T. Yokoi, F. Nishino, S. Uemura, *Organometallics*, **2000**, *19*, 5525.

p-Tol_3P (20 mol%), the domino Suzuki cross-coupling and C-H activation product **63a** was obtained in 65% yield (after recrystallization). The amount of phenylboronic acid used in this reaction is important. If an excess of phenylboronic acid (2.0 equiv) was used, the double Suzuki cross-coupling product was formed instead of **63a**. If 0.9 equiv was used, the mono-Suzuki cross-coupling compound and starting material **44j** was obtained without any trace of **63a**. When 3-methyloxyl benzeneboronic acid was used, the cross-coupling and C-H activation compound **63b** was obtained in 89% yield. Interestingly, when the dibromo substrate **44k** was treated with 3-methyloxyl benzeneboronic acid under these conditions, it also afforded the desired product **63c** in 59% yield (Scheme 47).



Scheme 47. Domino-reactions involving a Suzuki cross-coupling and a C-H activation.

3.9 Conclusion

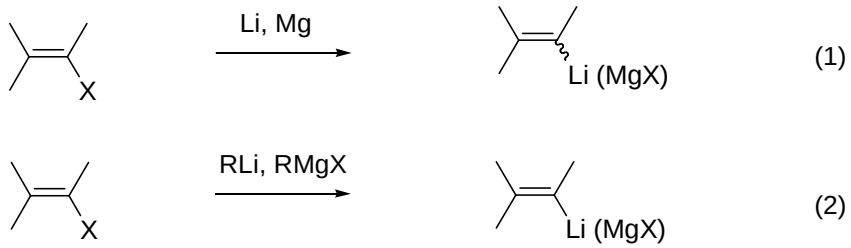
In conclusion, we have established a new type of C-H activation reaction catalyzed by $Pd(OAc)_2$ and *p*-Tol_3P for the construction of complex condensed *N*-heterocycles. The key step of this ring closure is a chemoselective intramolecular C-H activation of a methyl group at position 2 of a pyrrole ring. We also expended this reaction to domino reactions to prepare complex *N*-heterocycles in one pot.

4. Preparation of Functionalized Alkenylmagnesium Reagents and Polysubstituted Pyridylmagnesium Reagents Using *i*-PrMgCl•LiCl

4.1 Introduction

Organomagnesium reagents are key organometallic intermediates for organic synthesis.[66,67] The stereoselective preparation of functionalized alkenylmagnesium reagents is an important synthestic task, since these reagents are frequently used in organic chemistry. Due to the expanded applications of alkenylmagnesium reagents in organic synthesis, numerious methods were developed for their preparation.

A standard preparation of magnesium reagents is the direct insertion of magnesium into an organic halide.[66,68] However, this method is not suitable for the preparation of functionalized organomagnesium compounds due to competitive reduction of several important functional groups. [69] Furthermore, the Mg-insertion into alkenyl iodides or bromides is not stereoselective and provides an *E/Z*-mixture of alkenylmagnesium reagents (eq. 1, Scheme 48).[70] An important and highly useful synthetic reaction for the preparation of vinylmetals is a metal-halogen exchange since the corresponding alkenyl lhalides are convenient and easily available synthons (eq. 2, Scheme 48).[71]

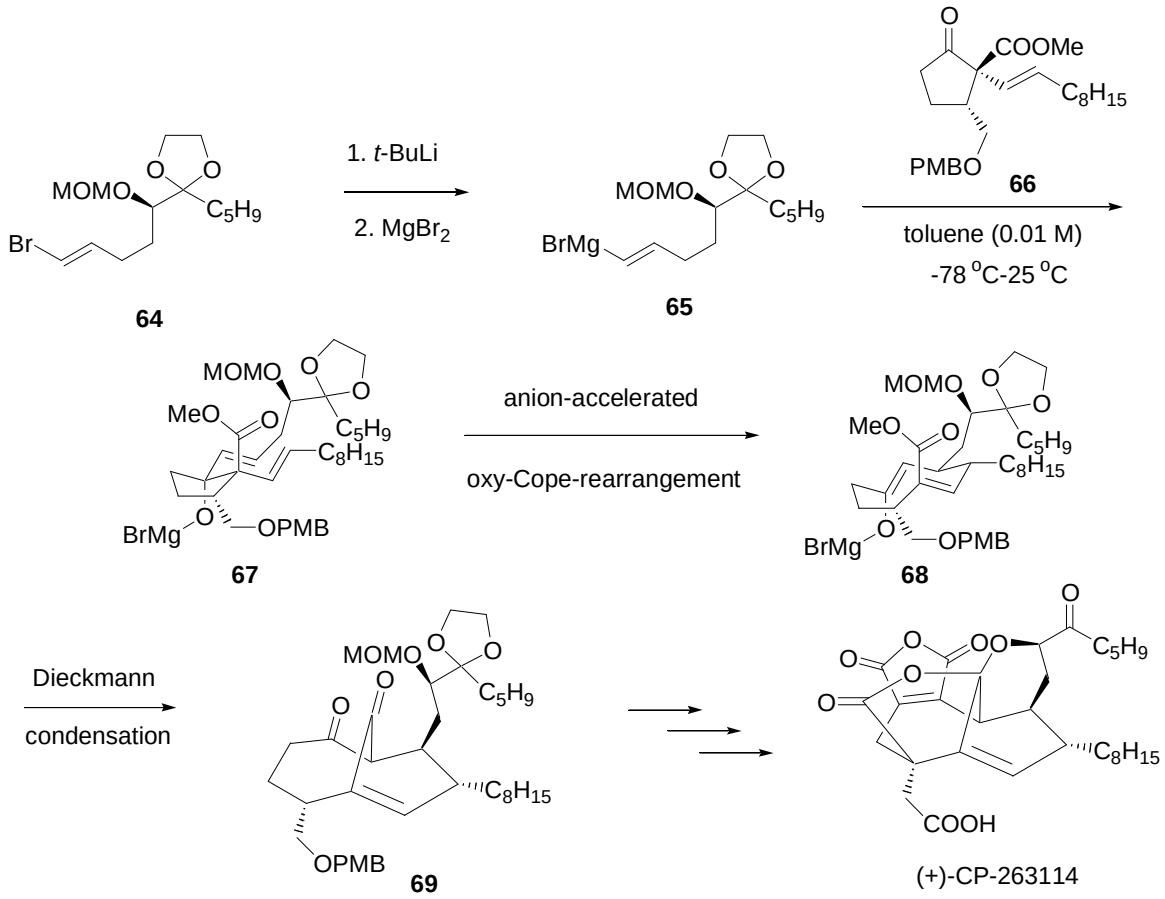


Scheme 48. The methods for the preparation of vinylmetals.

The alkenyl organiomagnesium reagents have become a type of valuable reagents in total synthesis because of their unique properties. Recently, Professor Shair and his group at

[66] (a) G. S. Silverman,. P. E. Eds Rakita, *Handbook of Grignard* Reagents; Marcel Dekker: **1996**. (b) Richey, Jr. H. G., Ed. *Grignard Reagents: New developments*; Wiley, New York: **1999**. (c) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[67] For recent application see: (a) A. Klos, G. R. Heintzelman, S. M. Weinreb, *J. Org. Chem.* **1997**, *62*, 3758. (b) D. F. Taber, J. H. Green, J. M. Geremia, *J. Org. Chem.* **1997**, *62*, 9342. (c) Y. Hayashi, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **1998**, *39*, 63. (d) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333. (e) N. M. Heron, J. A Adams, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 6205. (f) A. F. Houri, Z. Xa, D. A Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943. (g) F. F. Fleming, V Gudipati, O. W. Steward,. *Org.Lett.* **2002**, *4*, 659. (h) F. F. Fleming, Z. Zhang, Q. Wang, O. W. Steward, *Org.Lett.* **2002**, *4*, 2493.
[68] The use of activated magnesium (Rieke-magnesium) has an especially broad reaction scope: (a) R. D. Rieke, H. Xiong, *J. Org. Chem.* **1991**, *56*, 3109. (b) R. D. Rieke, *Science* **1989**, *246*, 1260.
[69] (a) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674. (b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1610.
[70] P.;Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 4431.
[71] C. E. Tucker, T. N. Majid, P. Knochel, , *J. Am. Chem. Soc.* **1992**, *114*, 3983.

Harvard University completed the the synthesis of (+)-CP263114 [72]using a clever cascade sequence initiated by the addition of vinyl Grignard **65** to the ketone **66**. The vinyl Grignard **65** was synthesized by Br/Li exchange on the vinylbromide **64** followed by transmetalation with $MgBr_2$. With this event proceeding **67**, the stage was set for a subsequent anion-accelerated oxy-Cope rearrangement *via* a chair-like transition state to generate an eight-membered ring in the formation of **68**, which gave rise to the complete [4.3.1]bicycle of the CP-molecule **69** in a terminating Dickmann condensation (Scheme 49).



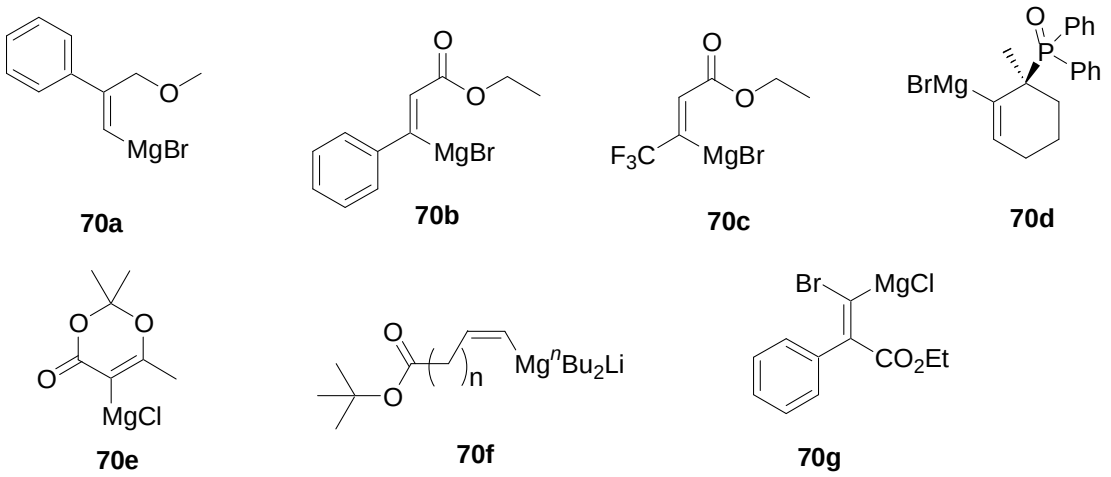
64 **65** **66** **67** **68** **69** (+)-CP-263114

Scheme 49. Shair's route to CP molecule using an alkenyl magnesium reagent.

Alkenyl iodides react with *i*-PrMgBr, *i*-PrMgCl, *i*-Pr_2Mg or *n*-Bu_3MgLi, leading to the corresponding alkenylmagnesium halides after an I/Mg exchange. This exchange reaction is slower than similar one using aryl iodides, which implies that either the use of more reactive reagents or the presence of chelating groups would be advantageous. A lot of functionalized alkenylmagnesium reagents have been prepared from the corresponding alkenyl iodides using an I/Mg exchange, such as the alkenylmagnesium bromide **70a** (*i*-PrMgBr, THF, -70 °C, 12

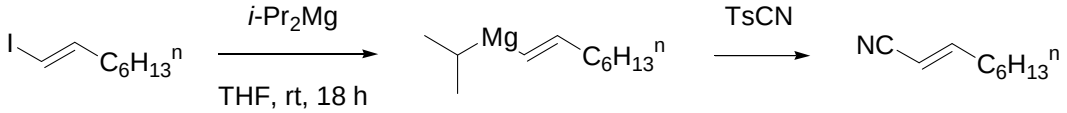
[72] a) C. Chem, M. E. Layton, S. M. Sheehan, M. D. Shair, *J. Am. Chem. Soc*. **2000**, *122*, 7424; (b) C. Chem, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc*. **1998**, *120*, 10784.

h), **70b** (*i*-PrMgBr, THF, -20 °C, 30 min)[73], **70c** (*i*-PrMgBr, THF, -20 °C, 30 min)[74], **70d** (*i*-PrMgBr, THF, -30 °C, 15 min)[75], **70e** (*i*-PrMgCl, THF, -30 °C, 30 min),[76] **70f** (*i*-Pr^{n}Bu$_2$MgLi, 0 °C, 1 h)[77] and **70g** (*i*-PrMgCl, ether, -50 °C, 15 min)[78](Scheme 50).



Scheme 50: The functctionalized alkenylmagnesium reagents generated from an I/Mg exchange.

For substrates without any chelating or electron-withdrawing groups, such as (*E*)-1-iodo-oct-1-ene **71a**, more reactive reagents are needed. Recently, our group have shown that an I/Mg-exchange using *i*-Pr$_2$Mg leads stereoselectively to alkenylmagnesium reagents **72a** (Scheme 51).[79] Unfortunately, the relatively high temperature for performing this reaction (25 °C) precludes the presence of functional groups. Only substrates bearing a chelating oxygen atom at the appropriate position undergo the I/Mg-exchange at low temperature.

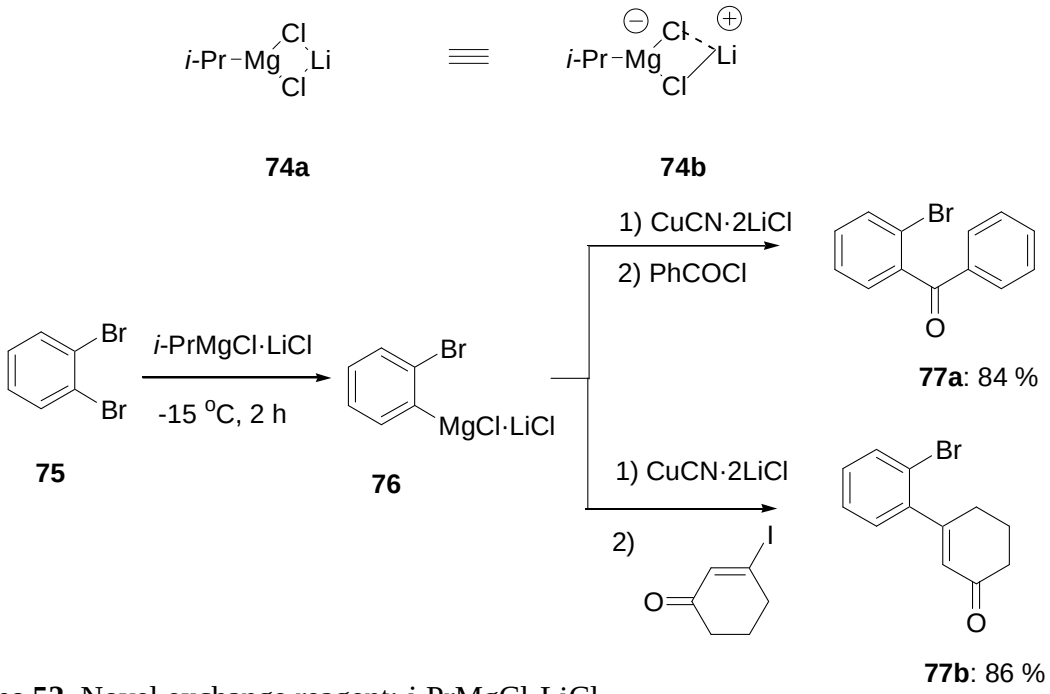


Scheme 51. *E*-iodooctene undergoes the exchange reaction at room temperature.

Recently, our group have found that the complex *i*-PrMgCl·LiCl (**74a**) exhibits a dramatically increased reactivity compared to *i*-PrMgCl or *i*-Pr$_2$Mg for performing halogen-magnesium exchange reactions.[80] This may be explained by the structure **74b** of this reagent, which

[73] I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun*. **2001**, 2068.
[74] J. Thibonnet, A. Duchene, J.-L. Parrain, M. Abarbri, *J. Org. Chem*. **2004**, *69*, 4262.
[75] Dissertation, Matthias Lotz LMU, Munich (Germany), 2002.
[76] V. A. Vu, L. Bérillon, P. Knochel, *Tetrahedron Lett*. **2001**, *42*, 6847.
[77] A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem*. **2001**, *66*, 4333.
[78] V. A. Vu, I. Marek, P. Knochel, *Synthesis*, **2003**, 1797.
[79] M. Rottländer, L Boymond, G. Cahiez, P. Knochel, *J. Org. Chem*. **1999**, *64*, 1080.
[80] A. Krasovskiy, P. Knochel, *Angew. Chem., Int. Ed. Engl*. **2004**, *43*, 3333.

displays an extra negative charge at the magnesium center enhancing the nucleophilic properties of the *i*-Pr group (Scheme 52). The generation of *ortho*-bromophenylmagnesium reagents **76** can be achieved conveniently with this type of reagent. Thus, the reaction of 1,2-dibromobenzene **75** with *i*-PrMgCl·LiCl was completed within 2 h at -15 °C, leading to the Grignard reagent **76**. The Grignard reagent **76** was transmetalated with CuCN·2LiCl and further reacted with PhCOCl and 3-iodo-2-cyclohexen-1-one, providing the products **77a** and **77b** in 84% and 86% yield respectively (Scheme 52)[76].



Scheme 52. Novel exchange reagent: *i*-PrMgCl·LiCl.

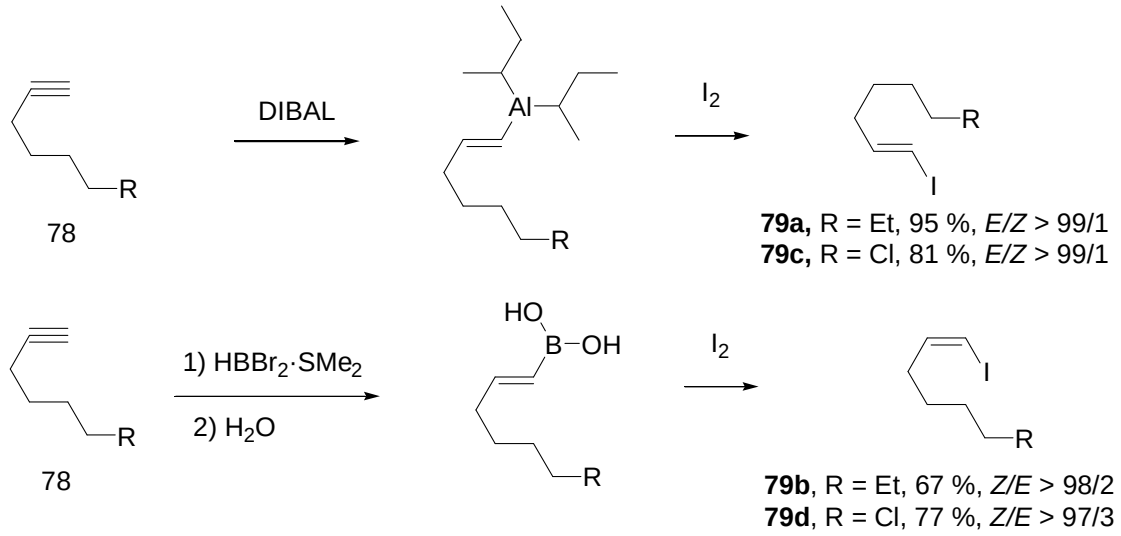
4.2 Extension of the usage of *i*-PrMgCl•LiCl in the preparation of alkenylmagnesium reagents and synthetic applications

4.2.1 Stereoselective preparation of acyclic vinyl iodides

Alkenyl iodides, which are important starting materials in organic synthesis, are usually prepared by sequential reactions on alkynes, i.e., hydrometalations of alkynes with various metal hydrides, followed by iodolysis. 1-Iodo-1-alkenes can be prepared conveniently *via* hydrometalations of alkynes in an *anti-Markovnikov* fashion. Thus, the *E* isomers of **79a** and **79c** were obtained in good yields (95% and 81% respectively) and excellent stereoselectivity (E/Z > 99/1) from their corresponding alkynes using DIBAL.[81] The *Z* isomers of **79b** and **79d**

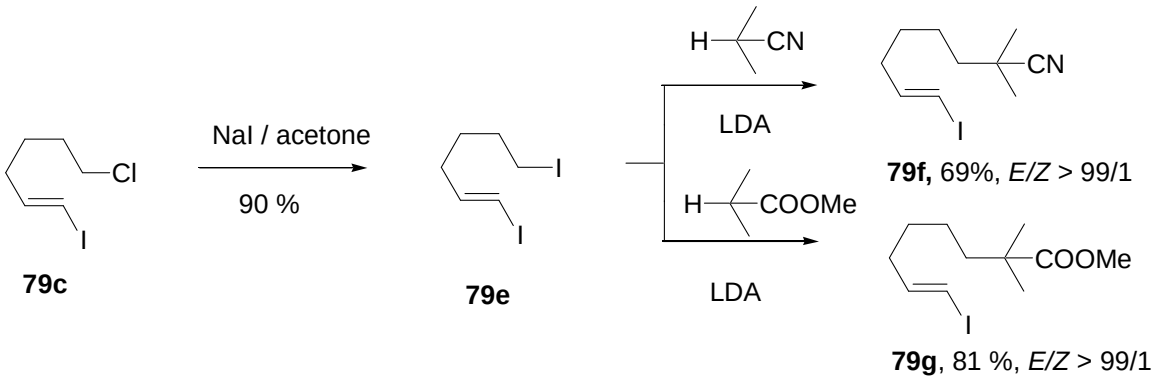
[81] B. M. Trost, M. T. Rudd, *Org.Lett.* **2003**, *5*, 4599.

can be prepared from the alkynes using Brown's method[82] (Scheme 53) respectively in yields of 67% and 77%.



Scheme 53. Steroselective preparation of terminal vinyl iodides.

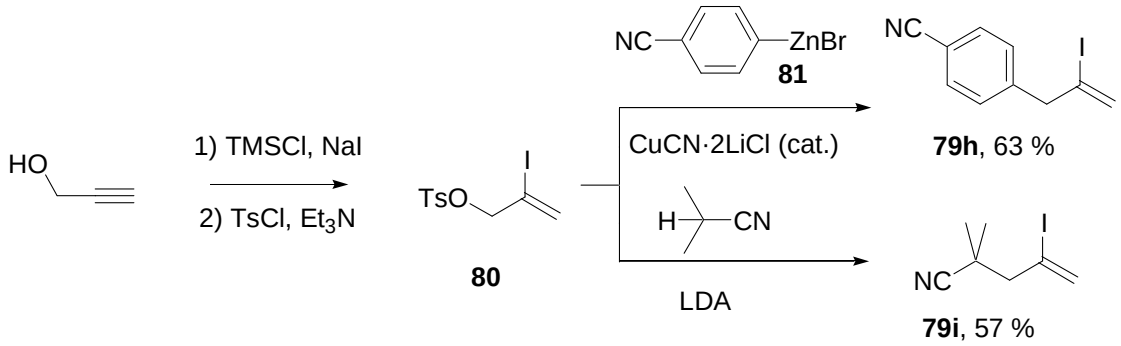
Interestingly, treatment of 6-chloro-1-iodo-hex-1-ene **79c** with NaI resulted in 6-iodo-1-iodo-hex-1-ene **79e**, which can then be converted to some other functionalized alkenyl iodides through reaction with nucleophilic carbons. Thus the exposure of iodide **79e** to lithium isobutyronitrile (formed by deprotonation of isobutyronitrile with LDA) led to the desired carbon-carbon bond formation. This reaction took place smoothly and gave rise to functionalized alkenyl iodide **79f** in 69% yield. The alkenyl iodide **79g** was obtained *via* the same procedure in 81% yield (Scheme 54).



Scheme 54. Preparation of functionalized terminal vinyl iodides.

[82] H. C. Brown, C. Subrahmanyam, T. Hamaoka, N. Ravindran, D. H. Bowman, S. Misumi, M. K. Unni, V. Somayaji, N. G. Bhat, *J. Org. Chem*. **1989**, *54*, 6068.

Internal alkenyl iodides, such as **79h** and **79i**, can be prepared from toluene-4-sulfonic acid 2-iodo-allyl ester **80**[83], obtained from prop-2-yn-1-ol in two steps. Treatment of the iodide **80** with the zinc reagent **81** in the presence of catalytic amounts of CuCN·2LiCl afforded the alkenyl **79h** in 63% yield. Exposure of the iodide **80** to lithium isobutyronitrile, which was formed by deprotonation of isobutyronitrile with LDA, provided the functionalized alkenyl iodide **79i** in 57% yield (Scheme 55).



Scheme 55. Preparation of functionalized internal vinyl iodides.

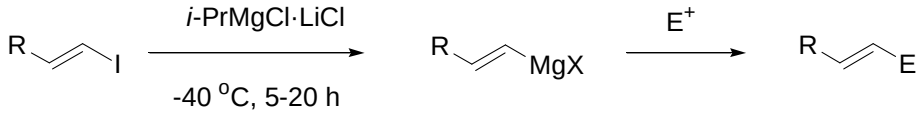
4.2.2 Stereoselective Preparation of Functionalized Acyclic Alkenylmagnesium Reagents Using *i*-PrMgCl•LiCl

With the reagent *i*-PrMgCl·LiCl **74a**, the I/Mg-exchange of alkenyl iodide **79a** proceeded at -25 °C or lower. This considerably enhances the functional group compatibility and allows conversion of a variety of functionalized alkenyl iodides of type **79** to the corresponding Grignard species **82** with retention of the double bond configuration. The reaction with various electrophiles provides polyfunctional alkenes of type **83** with good yields and excellent stereoselectivity (table 7). Thus, the reaction of (*E*)-1-iodo-oct-1-ene (**79a**; *E: Z* = 99:1) with *i*-PrMgCl·LiCl (1.1 equiv) at –40 °C gives the corresponding alkenylmagnesium reagent **82a** which reacts with various electrophiles (aldehyde, DMF or PhSSPh) providing the expected products **83a-c** with an excellent stereoselectivity (*E: Z* = 99:1, entries 1-3 of Table 7). Similarly, (*Z*)-1-iodo-oct-1-ene **79b** (*E:Z* = 2:98) furnishes the corresponding *Z*-alkenylmagnesium chloride **82b**, which after reaction with an aldehyde or a disulfide, leads to the *cis*-products **83d** and **83e** in 69-70% yields (entries 4 and 5). The mild reaction conditions required for the I/Mg-exchange allow the preparation of functionalized alkenylmagnesium compounds bearing a chloride (**82c** and **82d**; entries 6 and 7), an iodide (**82e**, entry 8), a

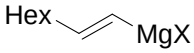
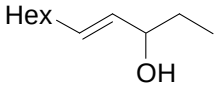
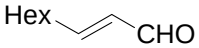
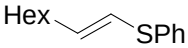
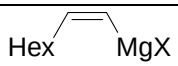
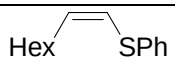
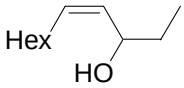
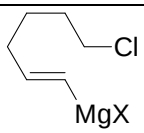
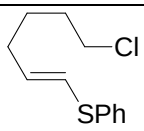
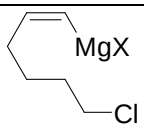
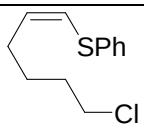
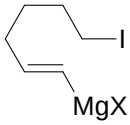
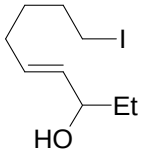
[83] I. Shinji; K. Takao; I. Yasutaka; O. Masaya. *Synthesis* **1988**, 366.

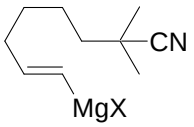
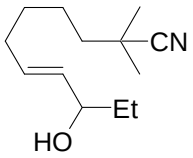
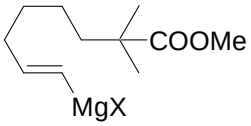
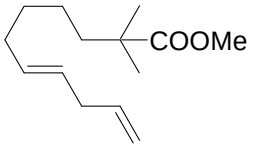
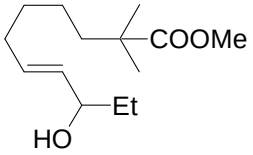
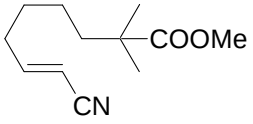
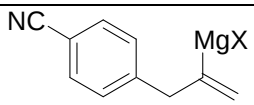
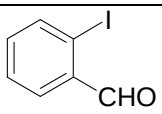
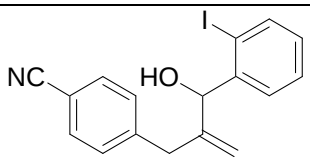
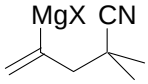
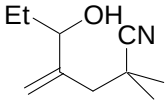
cyanide (entries 9, 13 and 14) or an ester (entries 10-12). The expected products **83f-n** were all obtained in satisfactory to good yields.

Table 6. Products of type **83** obtained by the reaction of polyfunctional alkenylmagnesium reagents with *i*-PrMgCl·LiCl.



79 **82** **83**

entry	Grignard reagent[a]	electrophile	Product of type 83	Isolated yield (%)[b] (E/Z)
1[c]	 **82a**	EtCHO	 **83a**	82 (99:1)
2[c]	**82a**	DMF	 **83b**	71 (99:1)
3[c]	**82a**	PhSSPh	 **83c**	70 (99:1)
4[d]	 **82b**	PhSSPh	 **83d**	69 (2:98)
5[d]	**82b**	EtCHO	 **83e**	70 (2:98)
6[c]	 **82c**	PhSSPh	 **83f**	75 (99:1)
7[d]	 **82d**	PhSSPh	 **83g**	81 (3:97)
8[c]	 **82e**	EtCHO	 **83h**	84 (99:1)

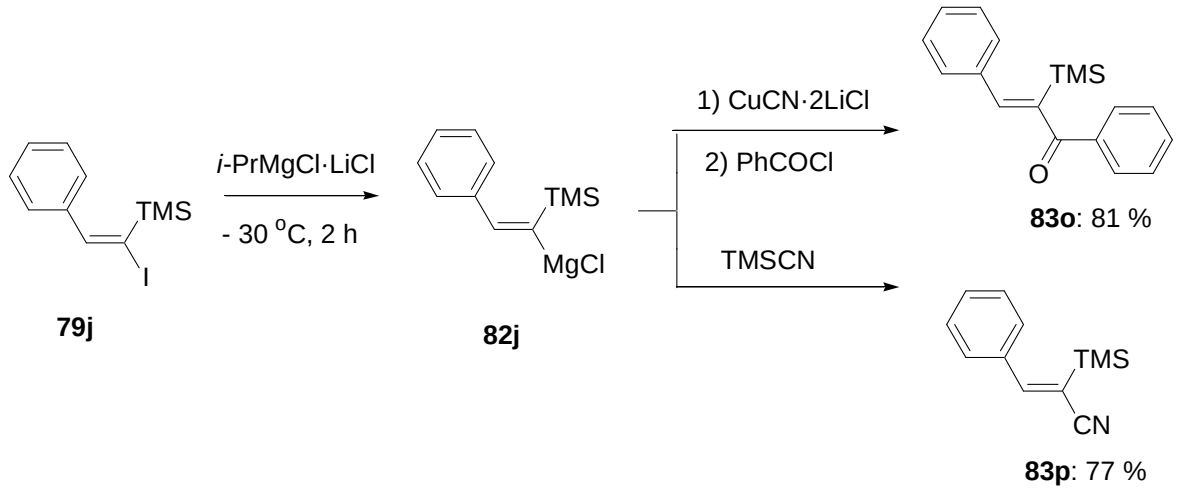
9[c]	 **82f**	EtCHO	 **83i**	77 (99:1)
10[e]	 **82g**	Allyl bromide	 **83j**	71 (98:2)
11[e]	**82g**	EtCHO	 **83k**	82 (99:1)
12[e]	**82g**	TsCN	 **83l**	75 (99:1)
13[f]	 **82h**		 **83m**	91
14[c]	 **82i**	EtCHO	 **83n**	70

[a] X = Cl·LiCl. [b] Isolated yield of analytically pure product. [c] The exchange was performed at -40 °C for 7 h. [d] The exchange was performed at -40 °C for 40 h. [e] The exchange was performed at -40 °C for 12 h. [f] The exchange was performed at -40 °C for 5 h.

Interestingly, the Grignard reagent **82j** was obtained in excellent yield with retention of the double bond configuration when (1-iodo-2-phenyl-vinyl)-trimethyl-silane **79j** [84]was treated with *i*-PrMgCl·LiCl at -30 °C. This type of Grignard reagent can be converted to its corresponding copper reagent, which, if trapped with PhCOCl, provided the ketone **83o** in

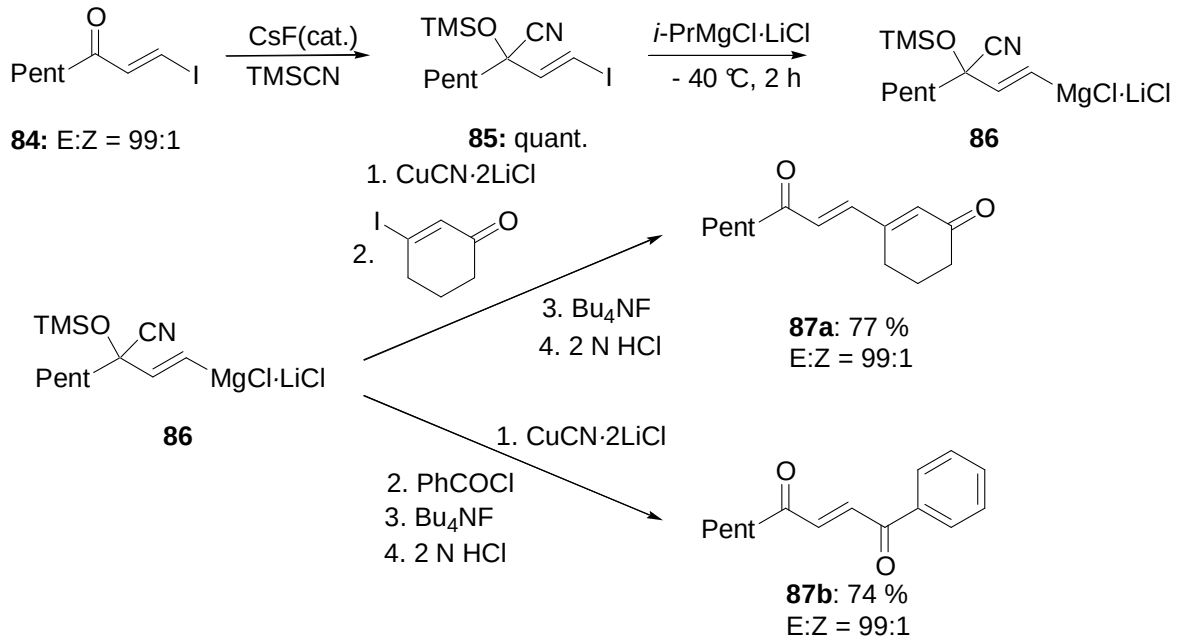
[84] E. Negishi, T. Takahashi, *J. Am. Chem. Soc*. **1986**, *108*, 3402.

81% yield. In addition, this type of Grignard can be directly trapped with electrophiles, such as TsCN, to furnish the nitrile compound **83p** in 77% yield (Scheme 56).



Scheme 56. Preparation of Grignard reagent **82j** *via* an I/Mg exchange.

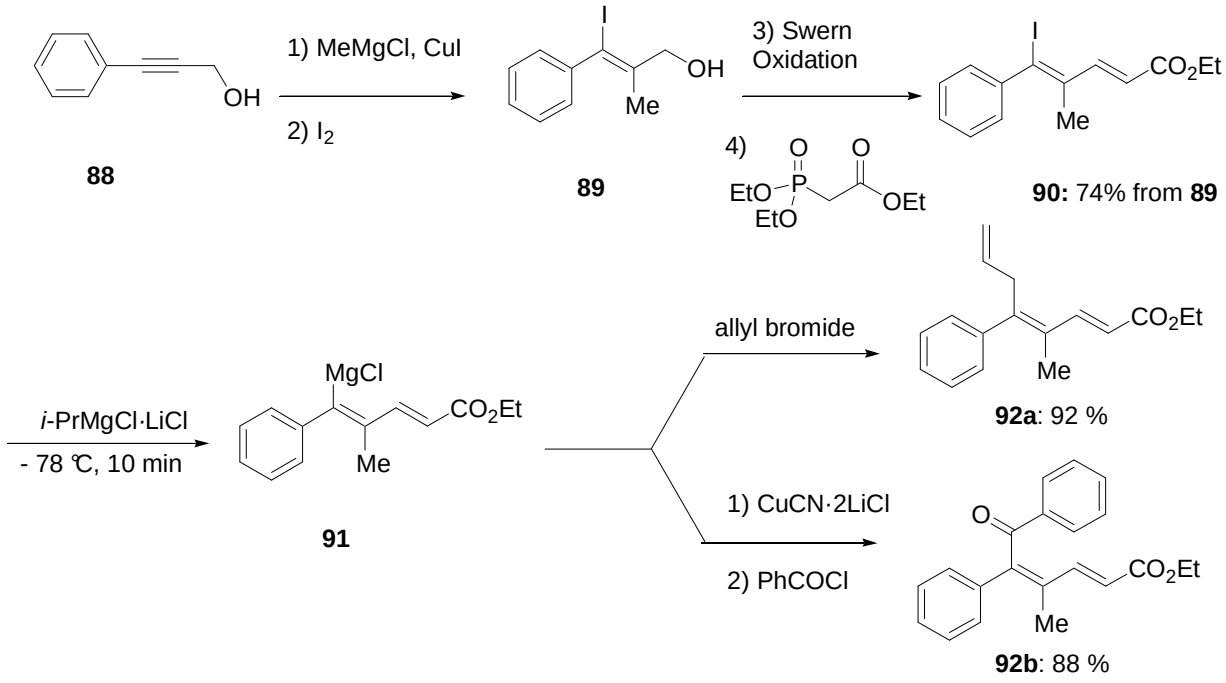
Although a ketone group is usually [85] not compatible with the presence of a carbon-magnesium bond, we have found that the corresponding silylated cyanohydrin derivative **85** of 1-iodo-oct-1-en-3-one **84**[86] can be readily converted into its corresponding magnesium species **86**. After transmetalation with CuCN·2LiCl, it reacted with 3-iodocyclohexane or benzoyl chloride leading to the unsaturated diketones **87a** and **87b** in 77% and 74% yields after deprotection of the intermediate cyanohydrin derivatives with Bu_4NF and HCl (2 M in H_2O) (Scheme 57).



Scheme 57. Synthesis of unsaturated diketones **87a** and **87b**.

[85] For exceptions, see: F.F. Kneisel, P. Knochel, *Synlett* **2002**, 1799.
[86] The silylated cyanohydrin **85** was *in situ* prepared from 1-iodo-oct-1-en-3-one **84** by addition TMSCN in the presence of catalytical amounts of CsF in dry CH_3CN. Ref: S. S Kim, G. Rajagopal, D. H. Song, *J. Organomet. Chem.* **2004**, *689*, 1734.

This method can be extended to the preparation of functionalized dienic Grignard reagents. The diene iodide **90**, which was easily prepared from 3-phenyl-prop-2-yn-1-ol **88** in 4 steps, was treated with *i*-PrMgCl·LiCl (1.1 eq) and the exchange reaction took place, providing its corresponding dienic magnesium reagent **91.** The exchange was very fast and it was completed at -78 ^{o}C within 10 min! The dienic magnesium reagent **91** could be trapped with different electrophiles. Treatment of the Grignard reagent **91** with allyl bromide in the presence of CuCN·2LiCl (1 mol %) afforded the diene compound **92a** in 92% yield. The diene species can be converted to the unsaturated ketone **92b** in 88% yield *via* transmetalation with CuCN·2LiCl and subsequent reaction with benzoyl chloride (Scheme 58).



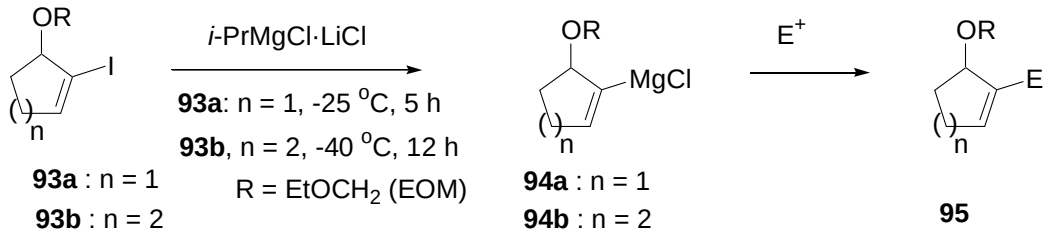
Scheme 58. Preparation of the functionalized dienic Grignard reagent **91**.

4.2.3 Preparation of Cyclic Alkenylmagnesium Reagents *via* an Iodine/Magnesium Exchange

Our group has demonstrated that chiral 2-iodocycloalkenyl alcohol derivatives of type **93** readily undergo substitution reactions with zinc-copper reagents (when OR is a leaving group), giving chiral cycloalkene derivatives with good to excellent *ee*.[87] Now we have found that *i*-PrMgCl·LiCl reagents react at low temperature with **93a** (-25 °C, 5 h) and **93b** (-40 °C, 12 h) to give the corresponding alkenylmagnesium species **94a** and **94b**. Reaction with various

[87] a) M. I. Calaza, X. Yang, D.Soorukram, P. Knochel, *Org. Lett*. **2004**, *6*, 529. b) M. I Calaza, E. Hupe, P. Knochel, *Org. Lett*. **2003**, *5*, 1059; c) G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun*. **2003**, 396; d) F. Kneisel, P. Knochel, *Synlett*, **2002**, 1799.

electrophiles (E^+) provides the corresponding chiral products **95a-i** in good to excellent yields (see Table 8 and Scheme 59).



93a : n = 1
93b : n = 2

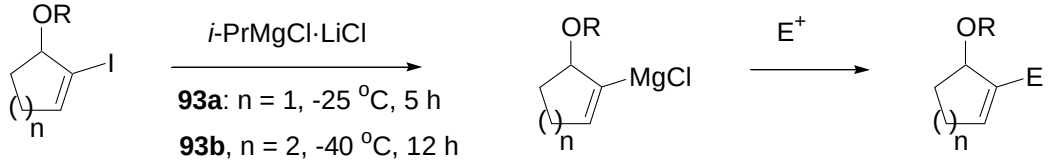
94a : n = 1
94b : n = 2

95

Scheme 59. Preparation of cyclic alkenylmagnesium reagents *via* an I/Mg exchange.

Thus, the allylation of **94a** with allyl bromide proceeds readily in the presence of copper additives, leading to the protected cyclopentanol **95a** in 91% yield (entry 1 of Table 8). Similarly, the reaction of the cyclohexenol derivative **94b** with allyl bromide furnishes the allylated product **95g** in 81% yield (entry 7). All reactions proceed with complete retention of chirality (proved for allyl cyclohexenol derivative **95j**). Diphenyl disulfide reacts with **94a** and **94b,** providing the thioethers **95b** and **95h** in 81-82% yields (entries 2 and 8). After transmetalation with CuCN·2LiCl, an addition-elimination reaction with 3-iodo-2-cyclohexen-1-one leads to the dienone **95c** in 61% yield (entry 3). Aldehydes like benzaldehyde lead to 1, 3-diol derivatives such as **95d** (89%) and **95i** (84%) as a mixture of diastereomers (for **95d**: dr = 66: 34; for **95i**: dr = 80: 20). The acylation of the copper derivative of **94a** proceeds in moderate yields, affording the unsaturated enone **95e** in 53% yield (entry 5). The opening of *N*-tosylaziridine[88] provides the amino-alcohol derivative **95f** in 63% yield (entry 6).

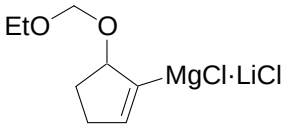
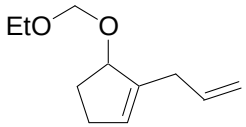
Table 7: 2-Magnesium cycloalkenol derivatives and their reaction with electrophiles.



93a : n = 1
93b : n = 2

94a : n = 1
94b : n = 2

95

Entry	Grignard reagent	Electrophile	Product of type **95**	Yield (%)[a]
1	 **94a**	Allyl bromide	 **95a**	91

[88] (a) D. Enders, C. F. Janeck, J. Runsink, *Synlett*, **2000**, 641. (b) A. N. Vedernikov, K. G. Caulton, *Org. Lett.* **2003**, 5, 2591.

Table 7 (continued)

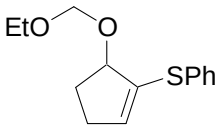
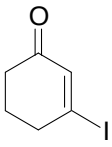
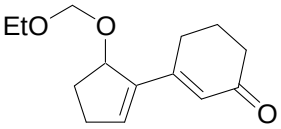
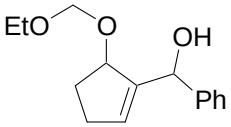
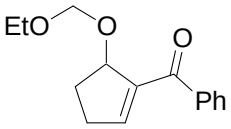
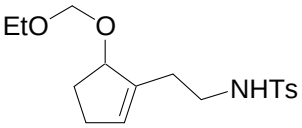
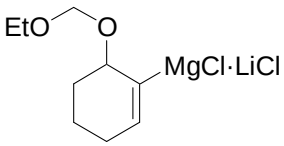
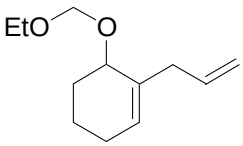
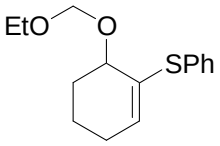
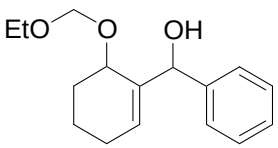
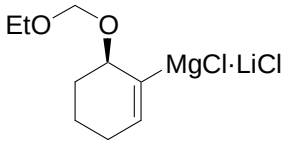
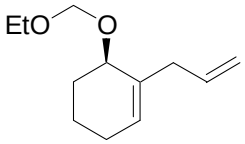
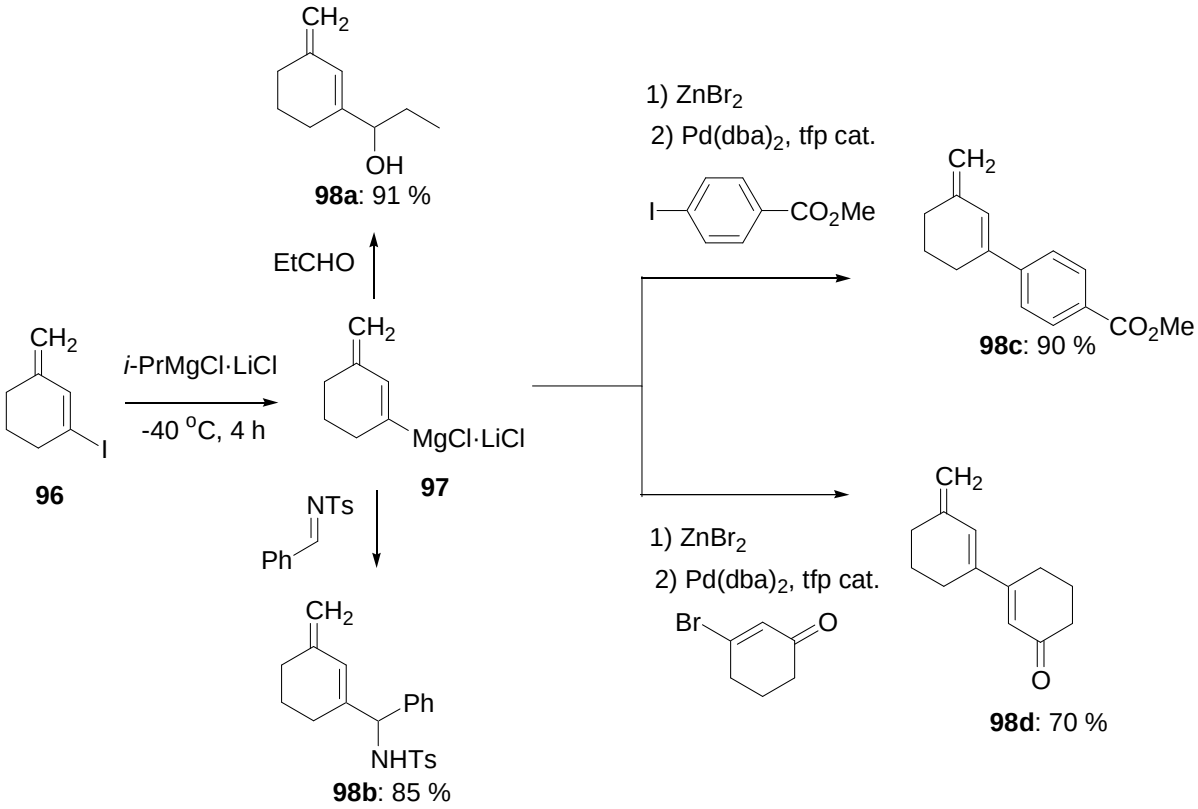
2	**94a**	PhSSPh	 **95b**	82
3	**94a**		 **95c**	61
4	**94a**	PhCHO	 **95d**	89
5	**94a**	PhCOCl	 **95e**	53
6	**94a**		 **95f**	63
7	 **94b**	Allyl bromide	 **95g**	81
8	**94b**	PhSSPh	 **95h**	80
9	**94b**	PhCHO	 **95i**	84

Table 7 (continued)

10		Allyl bromide		82
	94c		**95j**	

[a]: isolated yields of analytically pure products.

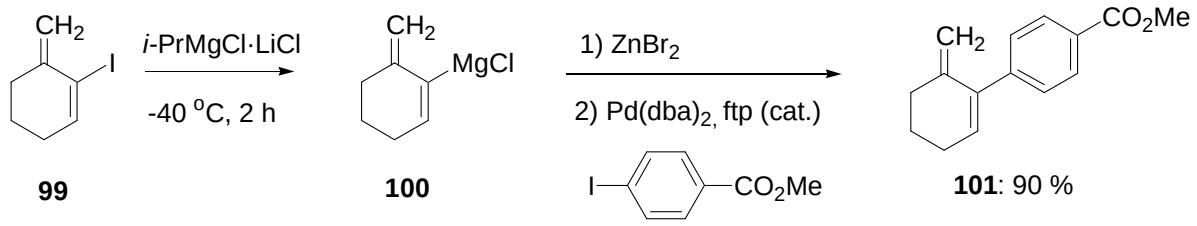
Interestingly, this approach can be extended to the cyclic exo-methylene dienes **96** and **99**.[89] The iododiene **96** is converted smoothly to the corresponding magnesium derivative **97** (-40 °C, 4 h) in high yield. Its reaction with propionaldehyde furnishes the dienic alcohol **98a** in 91% yield. Its addition to *N*-tosylbenzaldimine gives the diene sulfonamide **98b** in 85% yield. After transmetalation with $ZnBr_2$, a Negishi cross-coupling reaction with methyl 4-iodobenzoate or 3-bromocyclohexenone in the presence of $Pd(dba)_2$ (5 mol%) and tri(2-furyl)phosphine (tfp, 10 mol%) provides the aryl-substituted diene **98c** in 90% yield and the conjugated trienone **98d** in 70% yield respectively (Scheme 60).



Scheme 60: The reaction of dienic Grignard reagent **97** with different electrophiles.

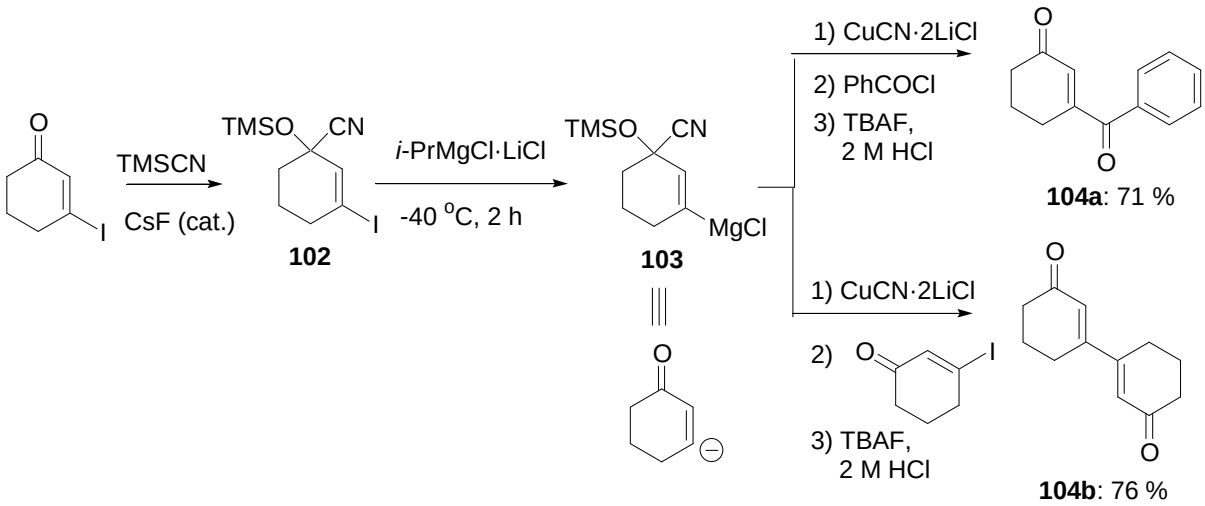
[89] These dienes are readily obtained by the Wittig-olefination of 3-iodo- and 2-iodo-cyclohexenone with $CH_2=PPh_3$ (rt, 12 h) respectively in variable yields (84% for **96** and 10% for **99**).

A similar behaviour is observed from the diene **99**. Its reaction with *i*-PrMgCl·LiCl (- 40 °C , 4 h) provides the corresponding dienic Grignard reagent **100,** which undergoes a Pd-catalyzed cross-coupling with methyl 4-iodobenzoate after transmetalation with $ZnBr_2$, leading to the expected product **101** in 90% yield (Scheme 61).



Scheme 61. Negishi cross-coupling reaction of dienic Grignard reagents **100**.

Because of the mild reaction conditions, this exchange strategy can also be employed in generating *β*-acylvinyl anion equivalents. The reaction of silylated cyanohydrin **102** with *i*-PrMgCl·LiCl (-40 °C, 2 h) provides the intermediate alkenylmagnesium reagent **103**, which, after transmetalation with CuCN·2 LiCl, allows a smooth acylation with benzoyl chloride or cross-coupling with 3-iodo-cyclohex-2-enone, leading to the dione **104a** in 71% yield and dione **104b** in 76% yield after removal of the protecting group (Scheme 62).



Scheme 62. Generate *β*-acylvinyl anion equivalents *via* an I/Mg exchange.

4.3 Regioselective Functionalization of Dibromo and Tribromo Pyridines *via* a Br/Mg Exchange

The functionalization of heterocycles using organolithium or organomagnesium intermediates has attracted a lot of attention in recent years.[90] Direct metalation[91]and halogen-magnesium exchange[92] reactions have been used in the preparation of mono- and di-substituted pyridines. Herein, we wish to report a selective stepwise magnesiation of 3, 5-dibromo-2-tosyloxypyridine allowing the preparation of polyfunctional trisubstituted pyridines *via* a regioselective bromine-magnesium exchange reaction. [93] In the course of preliminary experiments we have noticed that 2-bromo-3-tosyloxypyridine **105**[94] undergoes a very fast bromine-magnesium exchange due to the inductive effect of the tosyloxy group. Thus, the bromopyridine **105** reacts with *i*-PrMgCl·LiCl at -30 ^{o}C within 7 h, providing the corresponding pyridylmagnesium reagent **106** in more than 95% yield. The Grignard reagent **106** reacts with various electrophiles like DMF or propionaldehyde, leading to the expected products **107a** (88%) and **107b** (85%) (Scheme 63).

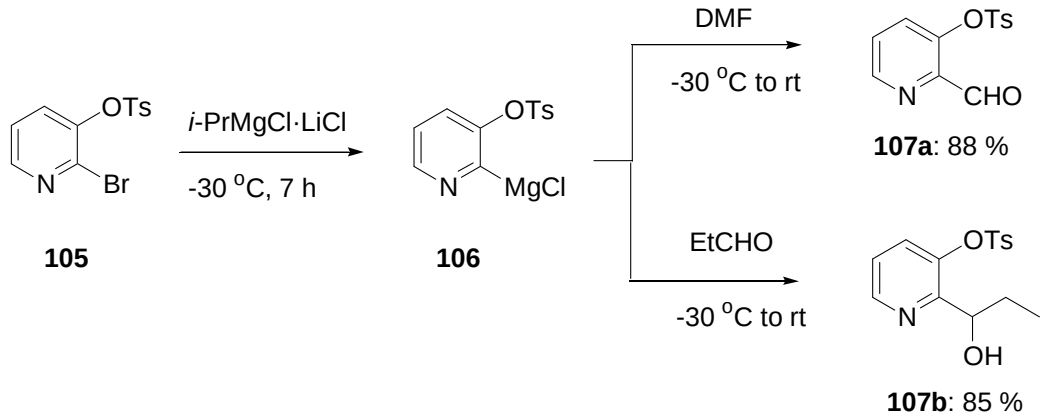
[90] (a) J. Clayden, Organolithiums: Selectivity for Synthesis. Tetrahedron Organic Chemistry Series, Pergamon, **2002**, Vol 23. (b) T. L. Gilchrist, Heterocyclic Chemistry, Longman, **1998**. (c) T Eicher; S. Hauptmann, The Chemistry of Heterocycles, Wiley-VCH, 2003.

[91] (a) G. Karig, J. A. Spencer and T. Gallagher, *Org. Lett*. **2001**, **3**, 835; (b) E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Heterocycles*, **1999**, *50*, 215; (c) K. C. Nicolaou, Y. He, F. Roschangar, N. P. King, D. Vourloumis and T. Li., *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 84; (d) F. Mongin, F. Trécourt and G. Quéguiner, *Tetrahedron Lett*., **1999**, *40*, 5483; (e) F. Mongin, A. –S. Rebstock, F. Trécourt, G. Quéguiner and F. Marsais, *J. Org. Chem.*, **2004**, ***69***, 6766; (f) H. Awad, F. Mongin, F. Trécourt, G. Quéguiner and F. Marsais, *Tetrahedron Lett*., **2004**, *45*, 7873

[92] (a) L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez and P. Knochel, *Synlett*, **1998**, 1359; (b) F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Quéguiner, *Tetrahedron Lett*., **1999**, *40*, 4339; (c) F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Quéguiner, *Tetrahedron*, **2000**, *56*, 1349; (d) V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel and G. Quéguiner, *Synlett*, **2002**, 1008; (e) J. J. Song, N. K. Yee, Z. Tan, J. Xu, S. R. Kapadia and C. H. Senanayake, *Org. Lett*., **2004**, *6*, 4905; (f) Á. Meana, J. F. Rodríguez, M. A. Sanz-Tejedor and J. L. García-Ruano, *Synlett* **2003**, 1678.

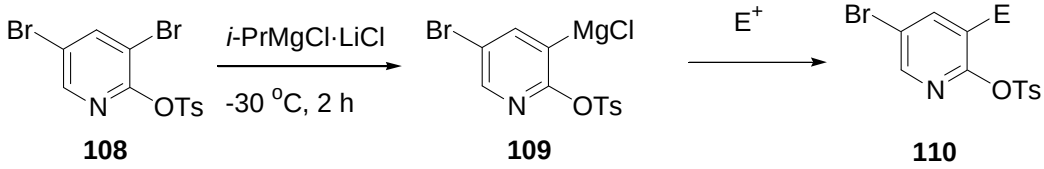
[93] For the regioselective functionalization of heterocycles using organometallics, see: (a) C. Stock, F. Höfer and T. Bach, *Synlett*, **2005**, 511; (b) S. Schröter, C. Stock and T. Bach, *Tetrahedron*, **2005**, *61*, 2245; (c) A. Spiess, G. Heckmann and T. Bach, . *Synlett*, **2004**, 131; (d) L. Green, B. Chauder and V. Snieckus, *J. Heterocyclic Chem.*, **1999**, *36*, 1453; (f) A. C. Kinsman and V. Snieckus, *Tetrahedron Lett*., **1999**, *40*, 2453.

[94] 2-Bromo-3-tosyloxypyridine (**105**) and 3,5-bromo-2-tosyloxypyri- dine (**108**) were prepared according to the literature: J. Mathieu and A. Marsura, *Synth. Commun.*, **2003**, *33*, 409.



Scheme 63. Preparation of pyridylmagnesium reagent **106** *via* Br/Mg exchange.

The exceptional activity of *i*-PrMgCl·LiCl for performing a Br/Mg-exchange, combined with the strong electron-withdrawing effect of the OTs-group, is responsible for this fast exchange reaction. We have extended this exchange reaction to 3,5-dibromo-2-tosyloxypyridine **108** and have found that the bromine substituent in position 3 undergoes a Br/Mg-exchange with 99:1 regioselectivity, showing the strong influence of the tosyloxy group. In this case, the exchange is even faster due to the inductive effect of the bromine atom in position 5 leading to the corresponding magnesium reagent **109** at -30 °C within 2 h. The reaction of the pyridylmagnesium reagent **109** with various electrophiles leads to polyfunctional trisubstituted pyridines of type **110** with high yields (Scheme 64 and Table 9).

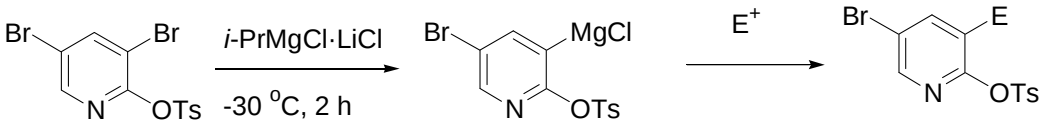


Scheme 64. Exchange reaction on 3,5-dibromo-2-tosyloxypyridine.

Thus, the trapping of Grignard reagent **109** with DMF affords the pyridylaldehyde **110a** in 88% yield (entry 1 of table 9). The addition of propionaldehyde to **109** leads to the pyridyl alcohol **110b** in 87% yield (entry 2). The reaction of **109** with acid chlorides proceeds well if the Grignard reagent has been transmetalated to the corresponding copper derivative through a reaction with CuCN·2LiCl. Under these conditions, the ketones **110c** (89%), **110d** (83%) and **110e** (75%) are obtained (entries 3-5). In the presence of catalytic amounts of CuCN·2LiCl (2 mol%) the allylation of **109** proceeds smoothly, affording the allylated product **110f** in 93% yield (entry 6). A CuCN·2LiCl mediated cross-coupling with 3-iodo-2-cyclohexenone, which occurs *via* an addition-elimination mechanism, provides the pyridyl

enone **110g** in 84% yield (entry 7). Finally, the direct reaction of **109** with tosyl cyanide gives the cyano derivate **110h** in 71% yield (entry 8).

Table 8. Products of type **110** obtained by the reaction of the Grignard reagent **109** with various electrophiles.



108 **109** **110**

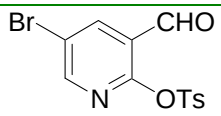
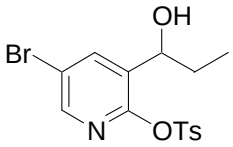
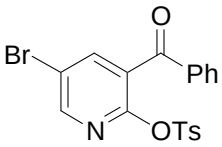
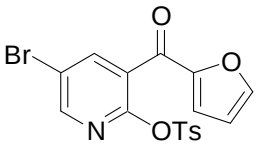
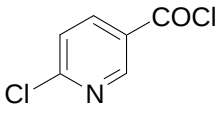
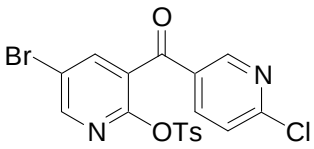
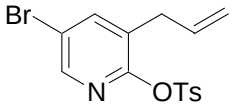
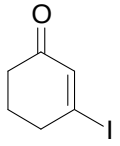
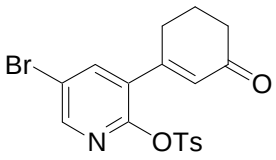
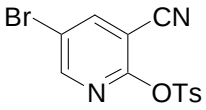
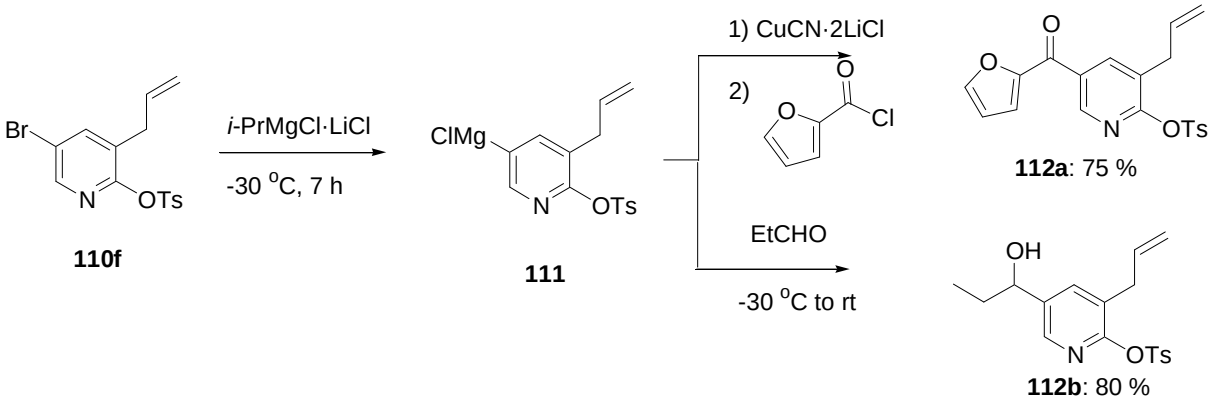
Entry	Electrophile	Product of type **110**	Isolated yield (%)[a]
1	DMF	 **110a**	88
2	EtCHO	 **110b**	87
3[b]	PhCOCl	 **110c**	89
4[b]	2-FurylCOCl	 **110d**	83
5[b]		 **110e**	75
6[c]	Allyl bromide	 **110f**	93

Table 8 (continued)

7[b]		 **110g**	84
8	TsCN	 **110h**	71

[a] Yield of analytically pure products. [b] The Grignard reagent has been transmetalated to the corresponding copper reagent with CuCN·2LiCl. [c] The reaction is performed in the presence of 2 mol% of CuCN·2LiCl.

Products, such as **110f,** react again with *i*-PrMgCl·LiCl, providing the corresponding pyridylmagnesium specie **111** at -30 °C within 7 h. Addition of an electrophile such as 2-furylcarbonyl chloride or propionaldehyde furnishes the product **112a** (75%) and **112b** (80%) (Scheme 65).

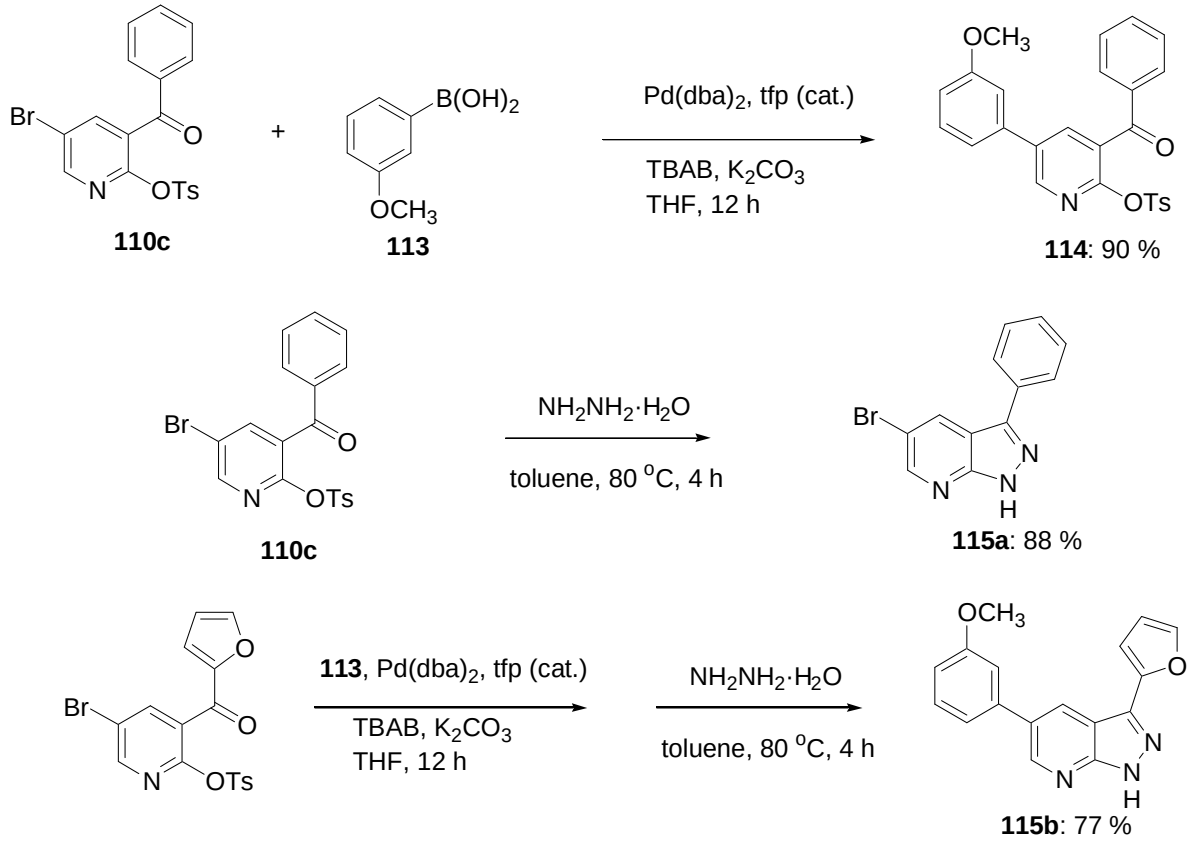


Scheme 65. Further Br/Mg exchange on compound **110f.**

Interestingly, the products of type **110** react well in Suzuki-Miyaura cross-coupling reactions.[95] The treatment of **110c** with 3-methoxyphenylboronic acid **113** in the presence of $Pd(dba)_2$ (5 mol%), tri-*o*-furylphosphine (tfp, 10 mol%), tetrabutylammonium bromide (10 mol%) and K_2CO_3 (2.0 equiv, 2.0 M in water) refluxed in THF for 12 h, leading to the arylated pyridine **114** in 90% yield (Scheme 66). Products of type **110** can be readily converted into pyrazolo [3, 4-b] pyridines by heating with $NH_2NH_2 \cdot H_2O$ in toluene (80 °C, 4 h). These heterocycles are potential anti-cancer therapeutic agents since members of this class

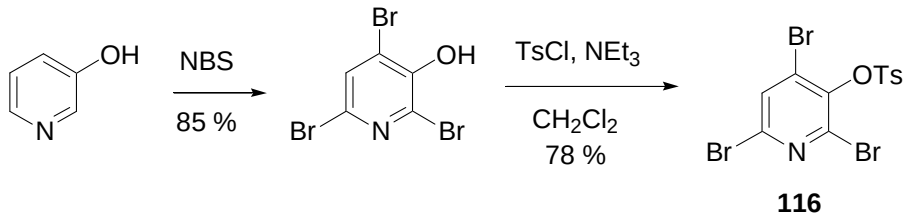
[95] (a) N. Miyaura, A. Suzuki, *Chem. Rev*., 1995, **95**, 2457; (b) G. A. Molander and B. Biolatto, *J. Org. Chem*., 2003, **68**, 4302; (c) W. Yang, Y. Wang and J. R. Corte, *Org. Lett*., 2003, **5**, 3131; (d) J. Witherington, V. Bordas, S. L. Garland, D. M. B. Hickey, R. J. Ife, J. Liddle, M. Saunders, D. G. Smith and R. W. Ward, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1577.

of heterocycles are kinase inhibitors.[96] Thus, the treatment of **110c** with $NH_2NH_2 \cdot H_2O$ in toluene at 80 °C for 4 h produces the heterocycle **115a** in 88% yield. The Suzuki-Miyaura cross-coupling and cyclization step can be combined in a one-pot procedure as shown, starting with the bromopyridine **110d,** which is then submitted to a Pd-catalyzed cross-coupling with the arylboronic acid **113** and subsequently to the reaction with $NH_2NH_2 \cdot H_2O$, leading to pyrazolo [3, 4-b] pyridine **115b** in 77% overall yield (Scheme 66).



Scheme 66. Preparation of [3,4-b]pyridine *via* one pot reaction.

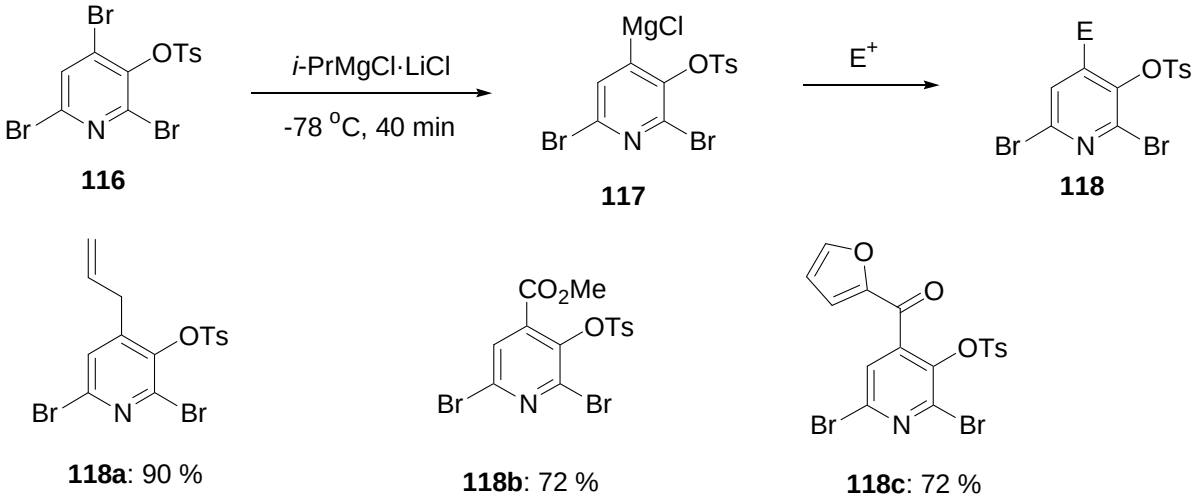
This type of successive exchange can be extended to tribromopyridine **116**, which was easily prepared from 3-hydroxy-pyridine *via* bromination with *N*-bromosuccinimide (Scheme 67).



Scheme 67. Preparation of tribromopyridine **116.**

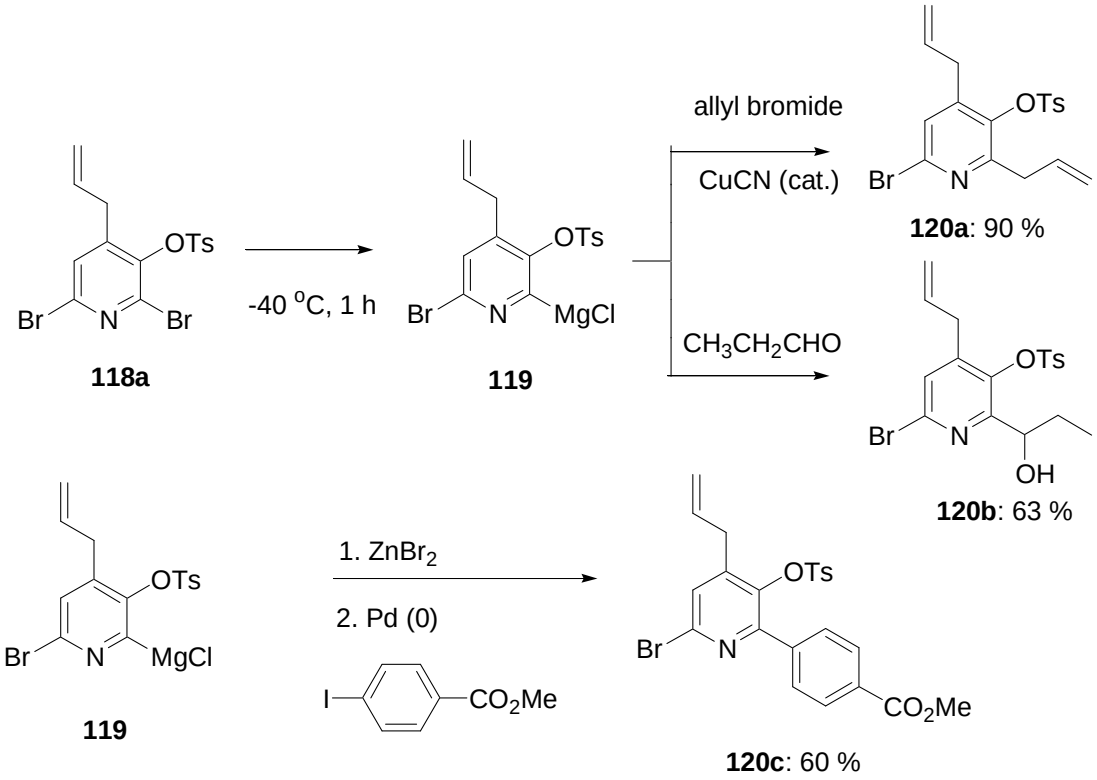
[96] R. N. Misra, H. Xiao, D. B. Rawlins, W. Shan, K. A. Kellar, J. G. Mulheron, J. S. Sack, J. S. Tokarski, S. D. Kimball and K. R. Webster, *Bioorg. Med. Chem. Lett.*, 2003, **13,** 2405.

When treating 2,4,6-tribromo-3-tosyloxypyridine **116** with *i*-PrMgCl·LiCl at -78 °C, a very fast and regioselective exchange was found. In the presence of catalytic amounts of CuCN·2LiCl (2 mol %), the allylation of the Grignard **117** proceeds smoothly, affording the allylated product **118a** in 93% yield. Direct trapping of the Grignard **117** with methyl chloroformate provides the compound **118b** in 72% yield. After transmetalation with CuCN·2LiCl, the Grignard **117** reacted with furan-2-carbonyl chloride leading to the 4-substitued dibromopyridine **118c** in 72% yield (Scheme 68).



Scheme 68. Regioselectively functionalized polybromopyridine *via* Br/Mg exchange.

The product of mono-addition such as **118a** reacted again with *i*-PrMgCl·LiCl, providing the corresponding pyridylmagnesium species **119** at -40 °C within 1 h. Addition of an electrophile such as allyl bromide or propionaldehyde furnished the product **120a** (90%) and **120b** (63%) (Scheme 69). After transmetalation with $ZnBr_2$, a Negishi cross-coupling reaction with methyl 4-iodobenzoate took place in the presence of $Pd(dba)_2$ (5 mol%) and tri(2-furyl)phosphine (tfp, 10 mol %), providing the 2-aryl-substituted pyridine **120c** in 60% yield (Scheme 69).



Scheme 69. Further Br/Mg exchange on compound **118a**.

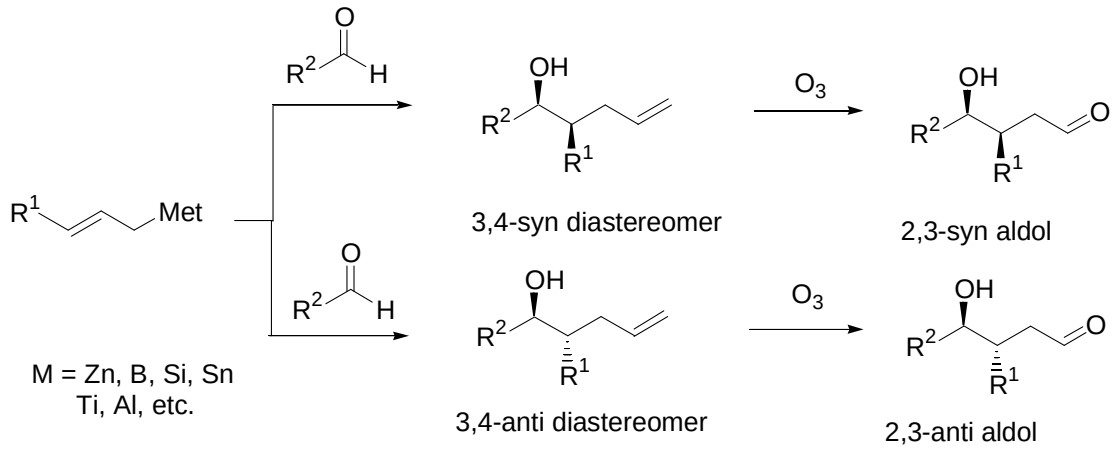
4.4 Conclusion

In summary, we have developed a stereoselective synthesis of polyfunctional alkenylmagnesium compounds bearing various functional groups using the new reagent *i*-PrMgCl·LiCl. We have also shown that the Br/Mg-exchange on a tosyloxy-substituted 3, 5-dibromopyridine is highly regioselective due to the inductive effect of the tosyloxy group. The resulting polyfunctional trisubstituted pyridines may be useful for the preparation of pharmacologically relevant heterocycles.

5. Preparation of Allylic Zinc Reagents and their Applications

5.1 Introduction

Methods that involve C-C bond formation with the establishment of two or more new stereogenic centers are of considerable interest in organic synthesis. The reaction of allyl metal reagents and carbonyl compounds has proven very useful in this regard.[97] Additional synthetic versatility is that the homoallylic alcohol products are easily manipulated to other useful synthetic intermediates by transformation of the double bond (Scheme 70).



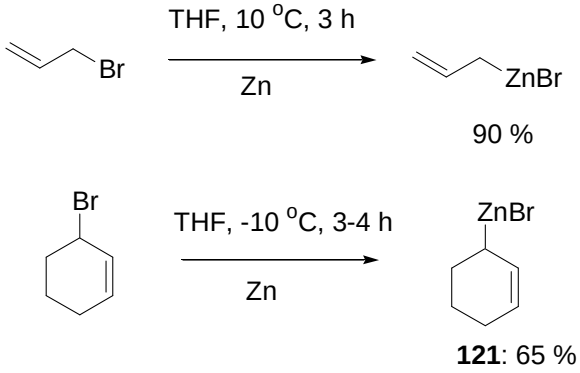
Scheme 70. The reaction of allyl metal reagents and carbonyl compounds.

5.2 Preparation of acyclic and cyclic zinc reagents

5.2.1 Direct insertion of zinc to allylic bromides

Normally, allylic zinc reagents are prepared by the insertion of the zinc dust into the corresponding allylic halides. Allyl bromide can be converted to allylzinc bromide in almost quantitative yield (zinc, THF, 10 ^{o}C, 3 h).[98] But when treating substituted allylic bromides such as 2-(bromomethyl)hexene with zinc dust under the same conditions, appreciate amounts of *Wurtz*-homocoupling products were formed. At lower temperature, the 2-cyclohexenylzinc bromide **121** can be obtained from 3-bromo-cyclohexene in 65 % yield.[99]

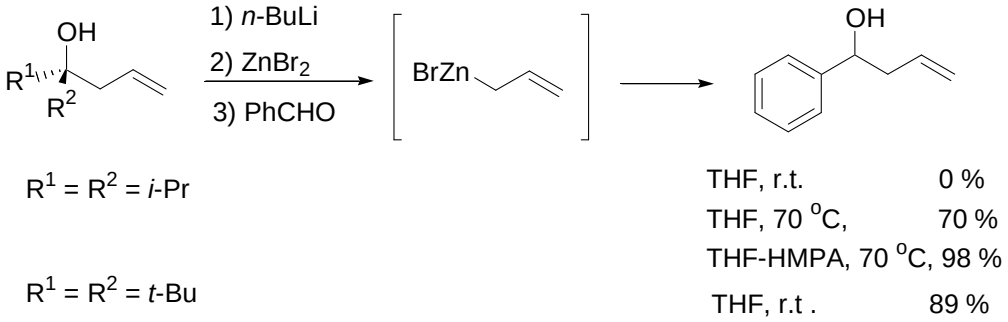
[97] a) W. R. Roush, in Comprehensive Organic Synthesis, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, Oxford, 1991, vol. 2, pp. 1-53; b) P. Knochel, in Comprehensive Organic Synthesis, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, Oxford, 1991, vol. 1, pp. 211.
[98] M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, 974.
[99] M. Bellassoued, Y. Frangin, M. Gaudemar, *Synthesis*, **1977**, 205.



Scheme 71. Preparation of allylic zinc reagents *via* direct insertion.

5.2.2 Masked allylic zinc reagents from a fragmentation reaction

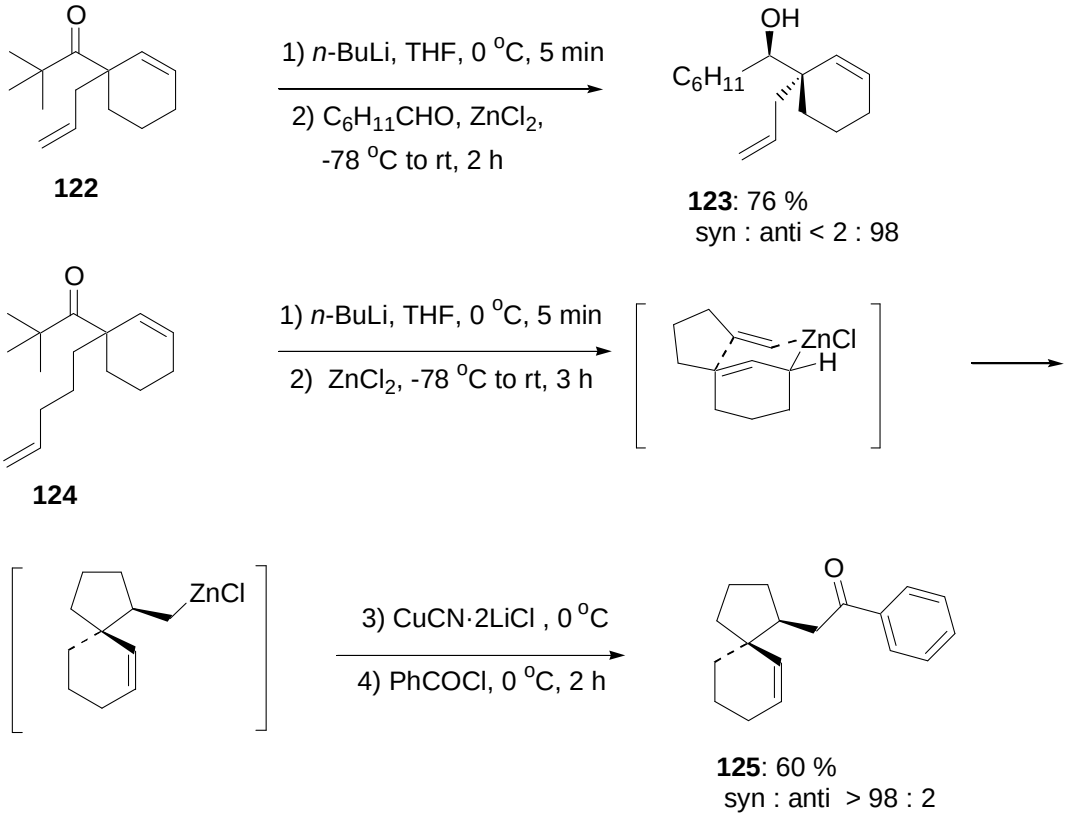
In order to avoid the formation of *Wurtz*-homocoupling products, P. Knochel developed a new fragmentation reaction of sterically hindered tertiary homoallylic alcohols to form allylic zinc reagents *in situ* (Scheme 72).[100] This methodology has also revealed an excellent stereocontrol in the subsequent reaction with an aldehyde.[101]



Scheme 72. Formation of masked allylic zinc reagents *in situ.*

This method has been applied in a stereoselective zinc-ene cyclization to prepare a new kind of spirobicyclic zinc reagents.[102] Thus, the ketone **122** is converted to an allylic zinc alcoholate by the addition of *n*-BuLi followed by zinc chloride in the presence of an aldehyde, leading to the homoallylic alcohol **123** in 76 % yield as one diastereoisomer (syn: anti < 2:98). The generation of highly substituted allylic zinc reagents has also been exploited in intramolecular ene reactions to form the spirobicyclic compound **125** in 60 % yield (Scheme 73).

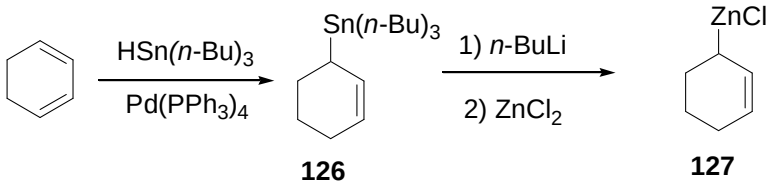
[100] P. Jones, N. Millot, P. Knochel, *Chem. Commum*. **1998**, 2405.
[101] P. Jones, P. Knochel, *Chem. Commum*. **1998**, 2407.
[102] N. Millot, P. Knochel, *Tetrahedron lett.* **1999**, *40*, 7779.



Scheme 73: Stereoselective zinc-ene cyclization.

5.2.3 Preparation of allylic zinc reagents from the corresponding Tin reagents

Recently, E. J. Corey and coworkers developed a Sn/Li exchange to prepare 2-cyclohexenylzinc chloride in their total synthesis of *Salinosporamide A*. 2-Cyclohexenyl-tri-*n*-butyltin **126**, which was obtained from Pd(0) catalyzed 1,4-addition of tributyltin hydride to 1,3-cyclohexadiene,[103] was sequentially transmetalated by treatment with 1 equiv of *n*-BuLi and 1 equiv of zinc chloride to form 2-cyclohexenylzinc chloride **127** in THF solution.

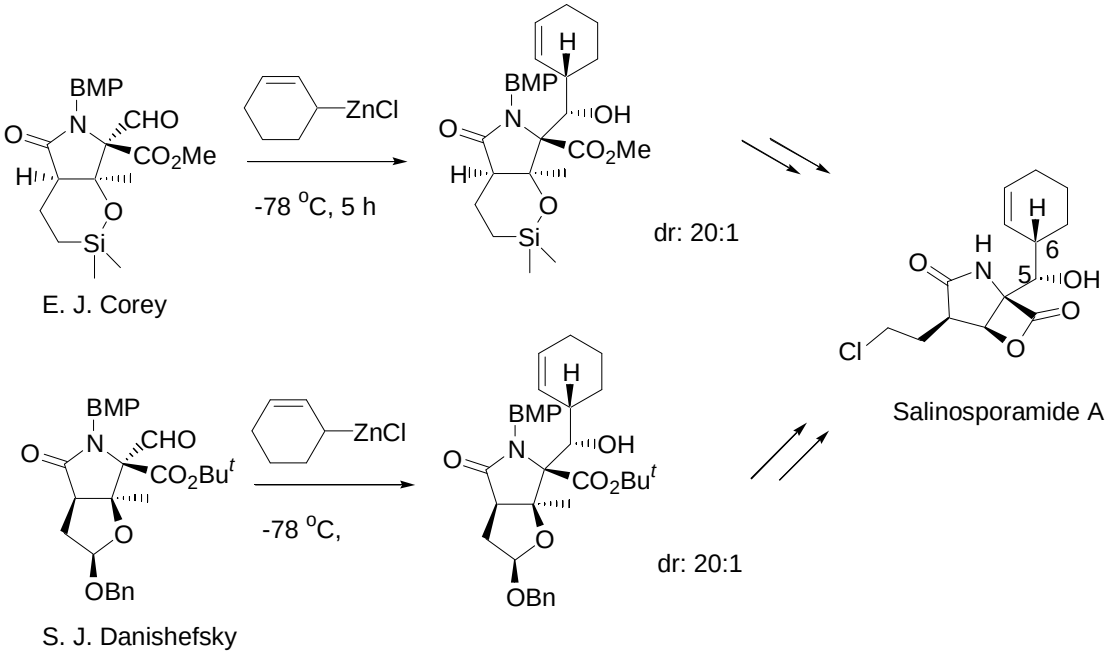


Scheme 74. Preparation of allylic zinc reagents *via* Sn/Li exchange.

5.3 Applications of 2-cyclohexenylzinc chloride

[103] H. Miyake, K. Yamamura, *Chem. Lett*. **1992**, 507.

Salinosporamide A which bears a cyclohexene ring was recently discovered by Fenical and his group as bioactive products of a marine microorganism that is wide distributed in ocean sediments.[104] The challenge in the synthesis of this molecule is not closing the *β*–lactone, but rather the stereocontrolled assembly of stereochemistry at carbon 5 and 6. E. J. Corey established a cyclohexenylzinc addition to control both of these stereogenic centers [105]and also worked well in S. J. Danishefsky's synthesis.[106]



Scheme 75. The key step to *Salinosporamide A* using cyclohexenylzinc addition.

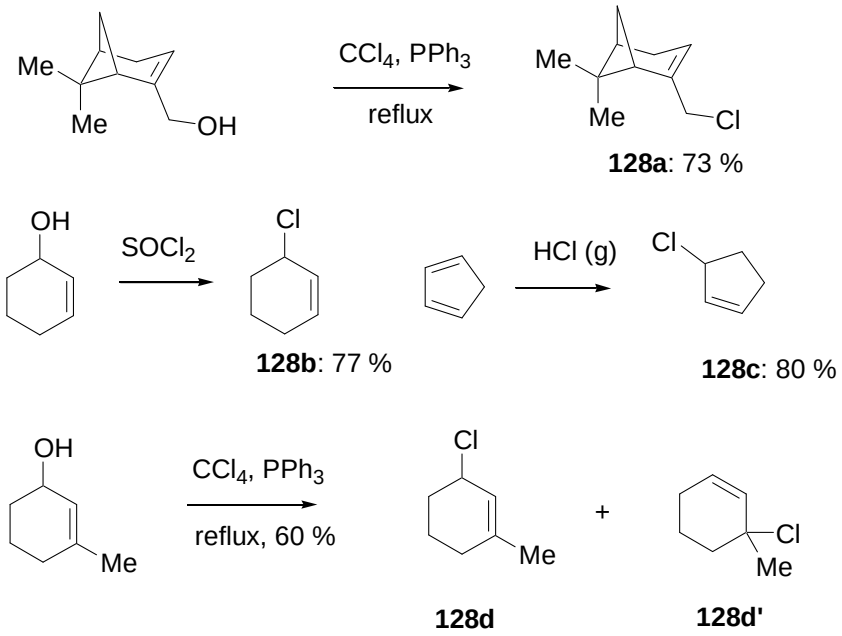
5.4 Preparation of the starting allylic chlorides

Allylic chloride can be easily prepared from the corresponding allylic alcohol using chlorination reagents, such as thionyl chloride and chlorophosphonium ions[107] which was generated *in situ* by reaction of triphenylphosphine and carbon tetrachloride.

Thus, the treatment of (-)-myrtenol with triphenylphosphine in carbon tetrachloride provided the corresponding allylic chloride **128a** in 73%. This method also suited for the preparation of 3-chloro-1-methyl-1-cyclohexene **128d** (the ratio of **128d** : **128d'** = 90 : 10) whereas the bad result was obtained using thionyl chloride (the ratio of **128d** : **128d'** = 70 : 30).[108] 3-Chloro-

[104] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem., Int. Ed.* **2003**, *42*, 355.
[105] L. R. Reddy, P. Saravanan, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 6230.
[106] A. Endo, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 8298.
[107] R. Appel, *Angew. Chem., Int. Ed.***1975**, *14*, 801.
[108] T. Carrillo-Marquez, L. Caggiano, R. F. W. Jackson, U. Grabowska, A. Rae, M. J. Tozer, *Org. Biomol. Chem.*, **2005**, *3*, 4117.

cyclohexene **128b** was prepared from cyclohex-2-enol using thionyl chloride in 77 % yield and 3-chloro-cyclopentene **128c** was obtained according to the literature from cyclopenta-1,3-diene in 80 % yield (Scheme 76).[109]

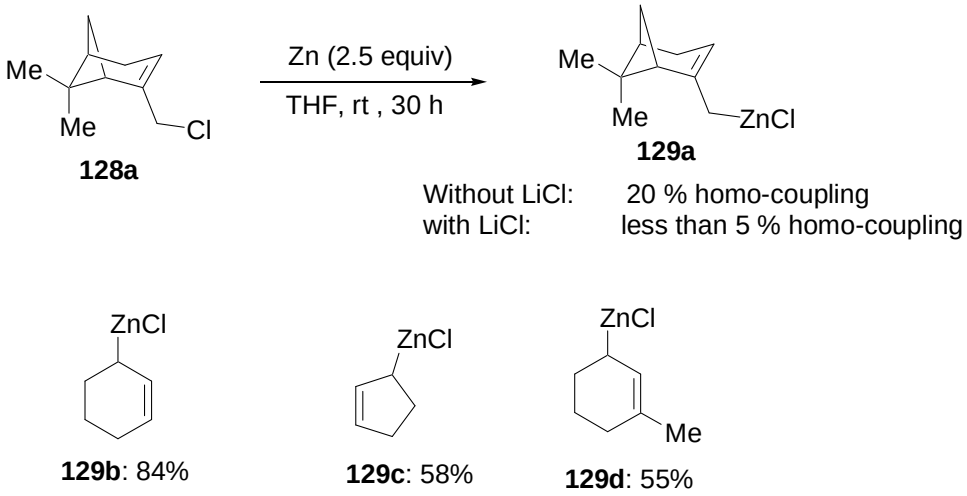


Scheme 76. Preparation of allylic chlorides.

5.5 Preparation of allylic zinc reagents using zinc·LiCl insertion

Initially, we treated the allylic chloride **128a** with zinc dust and it gave the corresponding allylic zinc reagent **129a** as well as the *Wurtz* homo-coupling products (20% from GC analysis). But when the reaction was carried out in the presence of LiCl (1.2 equiv), the *Wurtz* homo-coupling products were decreased to less than 5%. This result showed us that the LiCl can active the zinc dust which has been proved by the preliminary results in our group [110]and hindered the *Wurtz* homo-coupling reaction. This procedure can be successfully extended to previously cyclohexenylzinc chloride **129a** (84% yield) and unknown allylic zinc reagents such as cyclopentenylzinc chloride (**129c**: 58% yield), and the trisubstituted 3-methyl-cyclohexenylzinc chloride (**129d**: 55% yield) (Scheme 77).

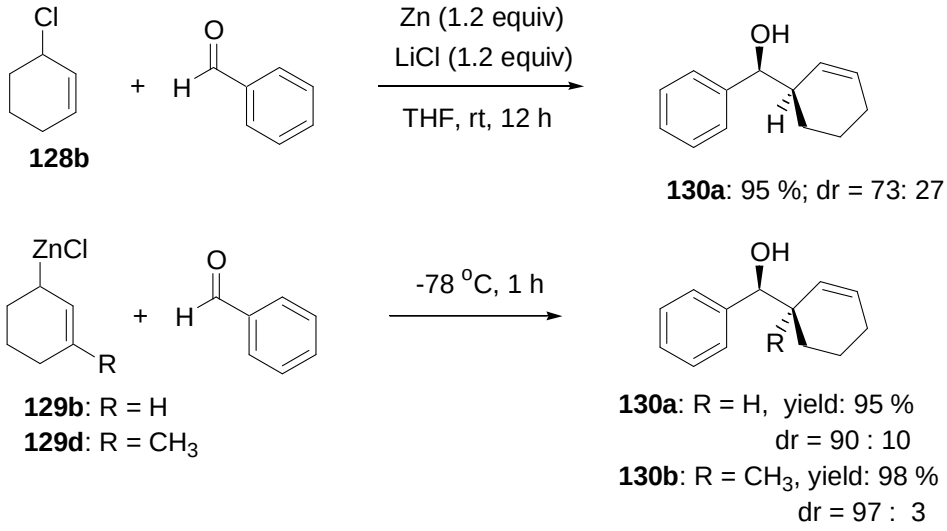
[109] J. J. Tufariello, A. C. Bayer, J. J. Spadaro Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3309.
[110] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.



Scheme 77. Preparation of organozinc reagents **129a-d**.

5.6 Highly diastereoselective synthesis of homoallylic alcohols bearing adjacent quaternary centers using trisubstituted allylic zinc reagents

The availability of these highly reactive allylic organometallics allows us to study their diastereoselective reaction with various aldehydes and ketones. Preliminary results showed that the reaction of 3-chloro-cyclohexene **128b** with benzaldehyde under Barbier reaction[111] conditions provided poor diastereoselectivity (dr = 73:27). To our delight, when the reaction was carried out using the allylic zinc reagent **129b,** a good diastereoselectivity (dr = 90 : 10) was observed (Scheme 78). When 1-methyl-1-cyclohexenyl zinc chloride **129d** was used, the diastereoselectivity was increased (dr = 97: 3).

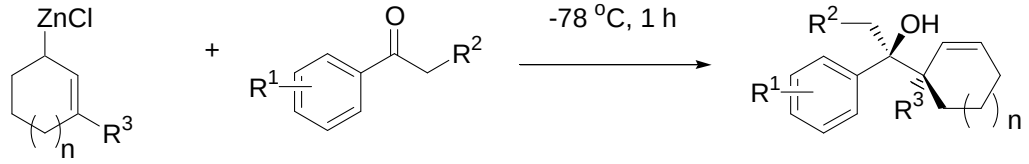


Scheme 78. Poor diastereoselectivity *vs* good diastereoselectivity.

[111] a) G. W. Breton, J. H. Shugart, C. A. Hughey, B. P. Conrad, S. M. Perala, *Molecules*, **2001**, *6*, 655.

As shown in table 9, the reaction proceeds under exceedingly mild conditions and high yields as well as excellent diastereoselectivities and complete regioselectivity. Treatment of allylic zinc reagent **129b** with paraformaldehyde provides cyclohex-2-enylmethanol **130c** in 94% yield (entry 1 of Table 9). An amino function is well tolerated and does not require a protection. Thus, 2-amino-5-chlorobenzaldehyde **131b** was directly converted to homoallylic alcohol **130d** without protecting the amino group in 94% yield with an excellent diastereoselectivity (dr > 99 : 1, entry 2). The poor diastereoselectivity observed with pivalaldehyde showed that an aromatic substituent is important in these addition reactions (entry 3). Remarkablely, acetophenone and related ketones always give excellent diastereoselectivities and high yields (entries 4-10). Regardless of the aryl substitution (entries 4, 5 and 7), the use of heterocyclic ketone (entry 6), of a ferrocenyl ketone (entry 7), of a cyclic aryl ketone such as 6-methoxyl-1-tetralone (entry 9) or a branched aryl ketone such as 2-methyl-1-phenylpropan-1-one (entry 10) high diastereoselectivities are obtained. With cyclic allylic zinc reagent **129c**, when reacted with ketones also give high diastereoselectivities (entries 11-13). Treatment of indole aldehyde with 3-methylcyclohexenylzinc chloride **129d,** the heterocyclic allylic alcohol **130p** was obtained in 87% yield (entry 14). Interestingly, when the zinc reagent **129d** reacts with ketones, two quaternary centers was generated in high diastereoselectivity. Thus, exposure of 2-acetonaphthone (**131k**) and *p*-bromo-acetophenone (**131e**) to **129d**, the allylic compounds **130q** and **130r** were obtained in 99 % yield as well as excellent diastereoselectivities (entries 15-16, dr > 98 :2).

Table 9: Diastereoselective preparation of homoallylic alcohol using allylic zinc reagents



129 **131** **130:** yield: 87-99%

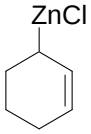
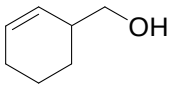
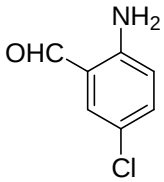
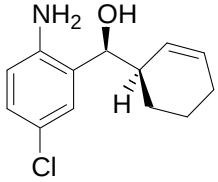
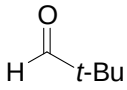
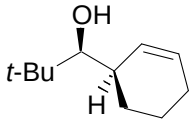
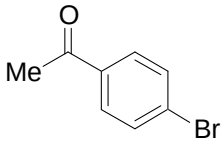
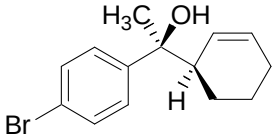
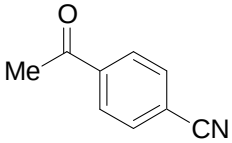
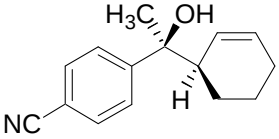
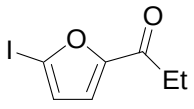
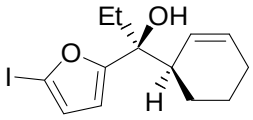
Entry	Allylic zinc reagent	Aldehyde or ketone **131**	Product of type **130**	dr[a]	Yield[b] (%)[a]
		**$(CH_2O)_n$**			
1	**129b**	**131a**	**130c**		94
					
2	**129b**	**131b**	**130d**	>99:1	94
					
3	**129b**	**131c**	**130e**	68:32	96
					
4	**129b**	**131d**	**130f**	>99:1	96
					
5	**129b**	**131e**	**130g**	>99:1	97
					
6	**129b**	**131f**	**130h**	97:3	95

Table 9 (continued)

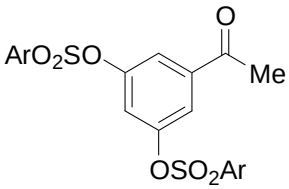
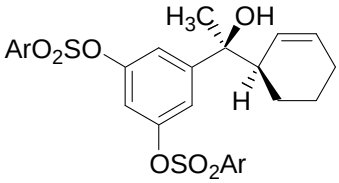
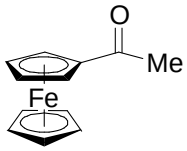
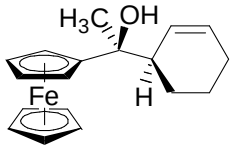
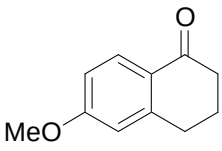
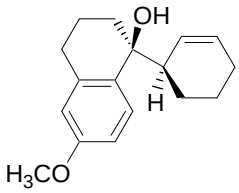
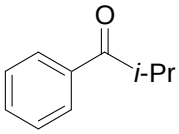
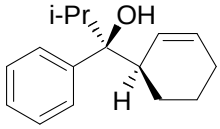
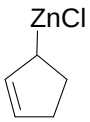
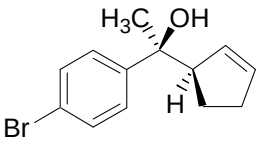
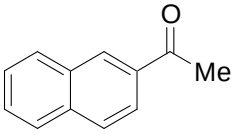
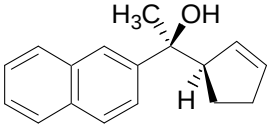
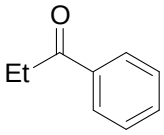
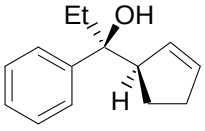
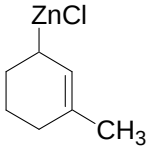
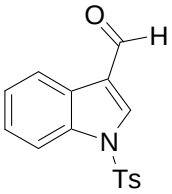
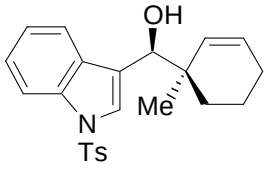
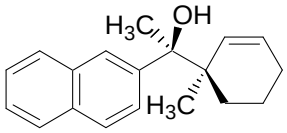
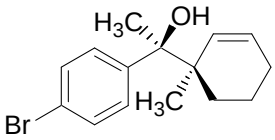
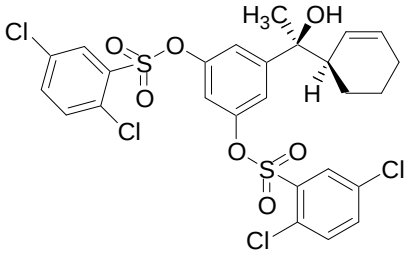
					
7	**129b**	**131g**: Ar = 2,5-$Cl_2C_6H_3$	**130i**: Ar = 2,5-$Cl_2C_6H_3$	99:1	95
					
8	**129b**	**131h**	**130j**	>98:2	95
					
9	**129b**	**131i**	**130k**	96:4	97
					
10	**129b**	**131j**	**130l**	>99:1	96
					
11	**129c**	**131e**	**130m**	>99:1	99
					
12	**129c**	**131k**	**130n**	>99:1	97

Table 9 (continued)

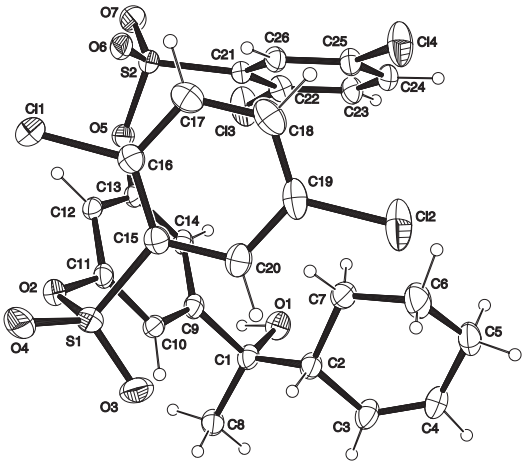
					
13	**129c**	**131l**	**130o**	>99:1	98
					
14	**129d**	**131m**	**130p**	95:5	87
					
15	**129d**	**131k**	**130q**	>98:2	99
					
16	**129d**	**131e**	**130r**	>98:2	99

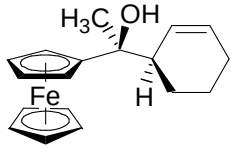
[a] dr was determined by NMR analysis. [b] Isolated yield of analytically pure products.

The structures of homoallylic alcohol **130i** and **130j** were determined by X-ray crystallography (Scheme 79).

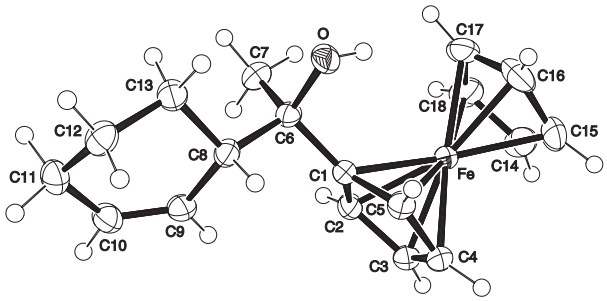


130i



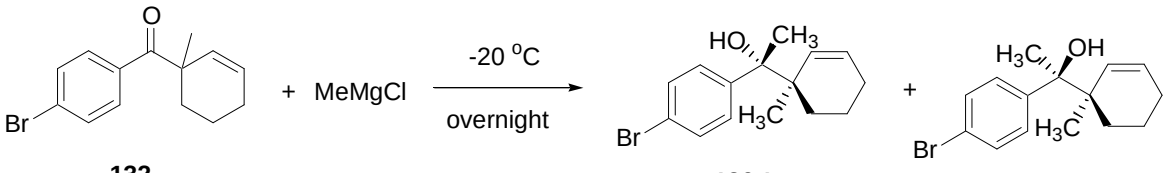


130j



Scheme 79. Homoallylic alcohols **130i** and **130j**with ORTEP plot.

In order to confirm the structure of **130r**, we prepared the other isomer **132r'** using the reaction of MeMgCl on the ketone **132** (Scheme 80). The structure of **130r** was proved by ^{1}H-NMR and NOESY NMR analysis.



132

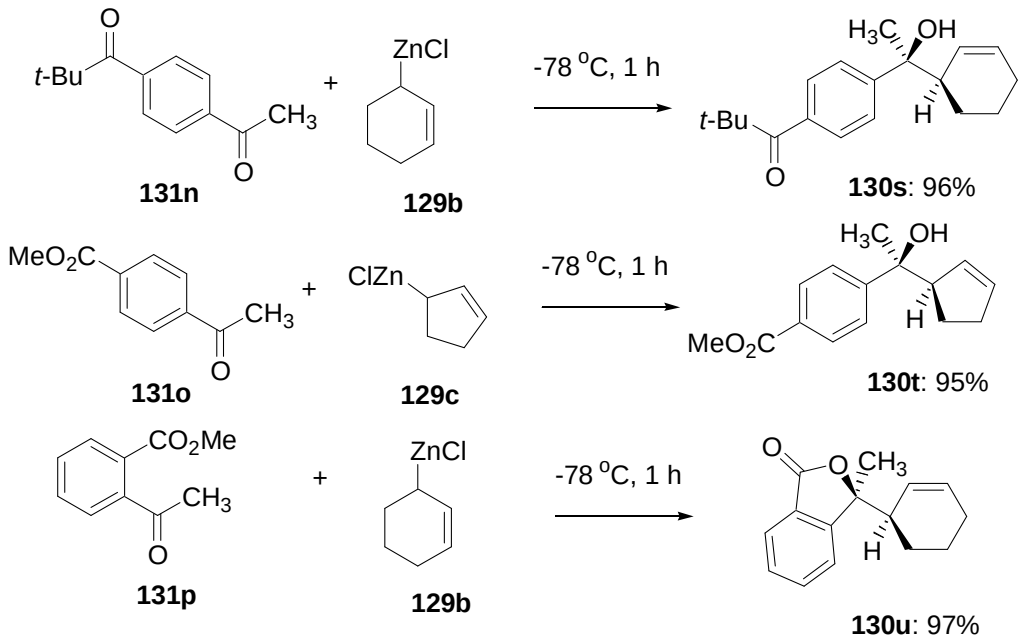
130r'
(major)

130r

Scheme 80: Preparation of another isomer **130r'**.

When two active groups were involved, this type of reaction also shows an excellent chemoselectivity. When the allylic zinc chloride (**129b** or **129c**) reacted with 1-(4-ccetyl-phenyl)-2,2-dimethyl-propan-1-one (**131n**) and 4-acetyl-benzoic acid methyl ester (**131o**), only single products **130s** and **130t** were obtained in 95-96% yields. Interestingly, by the

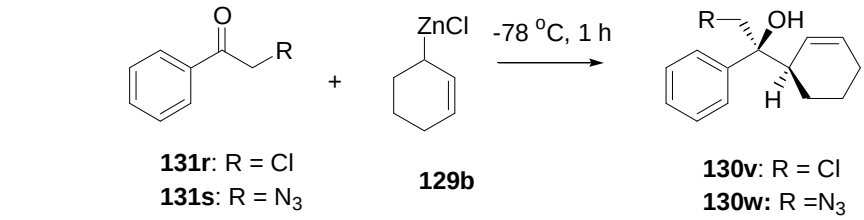
treatment of 2-acetyl-benzoic acid methyl ester with allylic zinc chloride (**129b**), the lactone **130u** was obtained in 97% yield as well as an excellent diastereoselectivity (Scheme 81).



Scheme 81: Chemo- and diastereoselective addition allylic zinc reagents to ketones.

Interestingly, α-substituted acetophenone also give excellent diastereoselectivities. Thus, exposure of 2-chloro-1-phenyl-ethanone **131r** to the allylic zinc reagent **129b** provided the chloride substituted homoallylic alcohol **130v** in 97% yield and excellent diastereoselectivities (dr > 98:2). Even 2-azido-1-phenyl-ethanone **131s** also gives azides **130w** in excellent result (93% yield and dr = 99:1). The compound of **130w** is a very interesting structure since organoazides were engaged in "click chemistry".[112] The 1,2,3-triazoles of **133a** and **133b** can be obtained in 85-90% yields with excellent regioselective and diastereoselectivities in the presence of CuCN·2LiCl (5 mol%) in one pot (Scheme 82). The structure of **133b** was determined by X-ray crystallography.

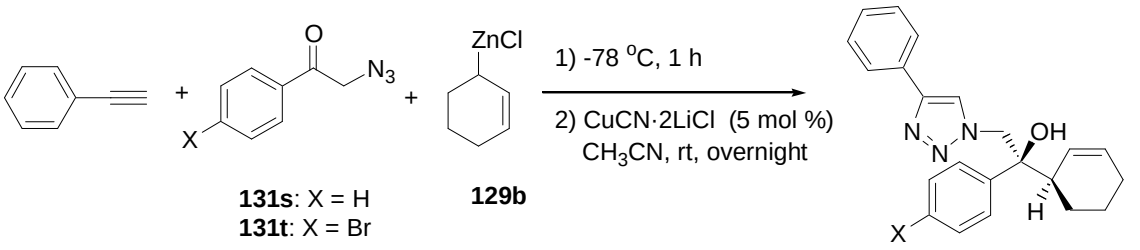
[112] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.



131r: R = Cl
131s: R = N_3

129b

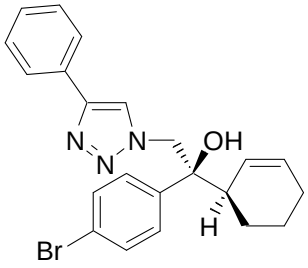
130v: R = Cl
130w: R =N_3



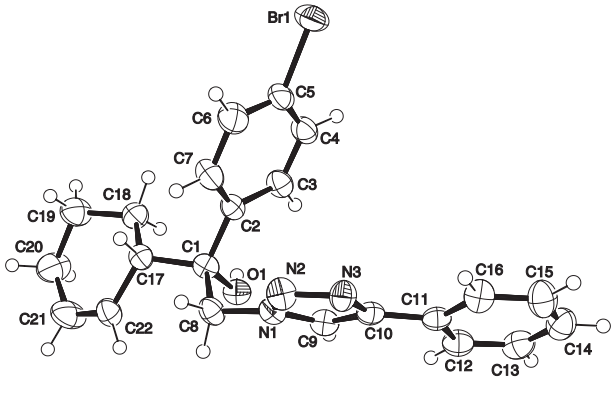
131s: X = H
131t: X = Br

129b

133a: X=H, Yield : 90%; dr > 99 : 1
133b: X=Br, Yield : 85%; dr > 95 : 5

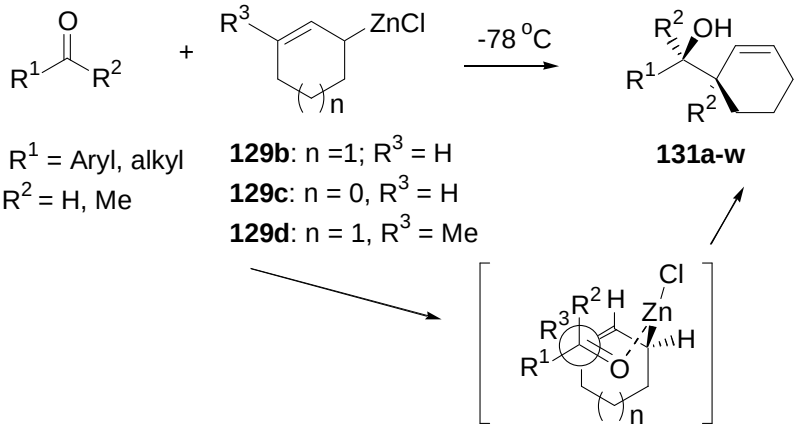


133b



Scheme 82. Preparation of 1,2,3-triazoles of **133a-b** from allylic zinc reagents and α-substituted acetophenones and X-ray crystallography of **133b**.

The excellent diastereoselectivity can be explained by the translation state of **134**.



131: R^1 = Aryl, alkyl
R^2 = H, Me

129b: n =1; R^3 = H
129c: n = 0, R^3 = H
129d: n = 1, R^3 = Me

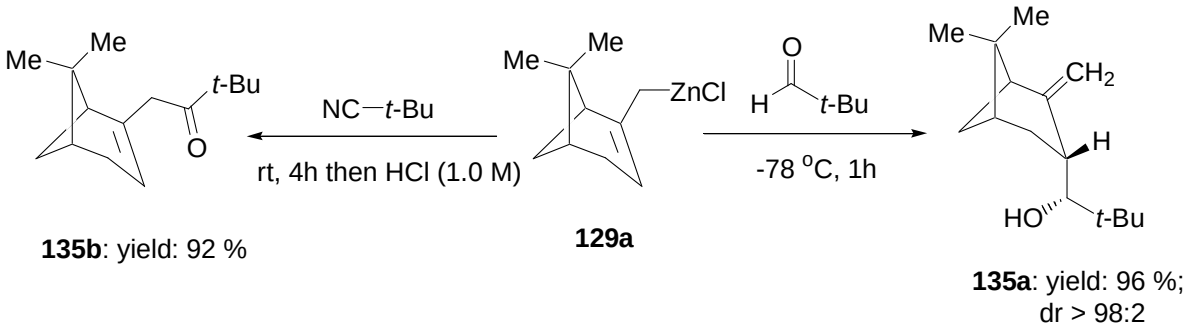
131a-w

134

Scheme 83. Diastereoselective and regioselective reaction of cycloalkenylzinc chloride with carbonyl compounds.

When treating the allylic zinc reagent **129a** with pivaldehyde, the allylic alcohol **135a** was obtained in 96% yield as well as excellent regioselectivity and diastereoselectivity (dr > 98:2).

To our surprise, when pivalonitrile was involved in this reaction, the regioselectivity was converted (Scheme 84), providing the ketone **135b** in 92% yield after hydrolysis with HCl (1.0M in water).



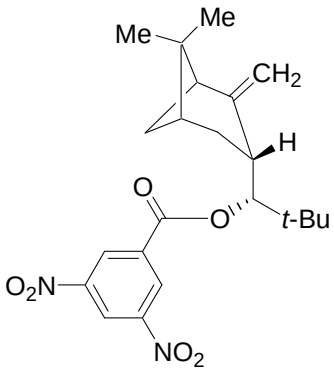
135b: yield: 92 %

129a

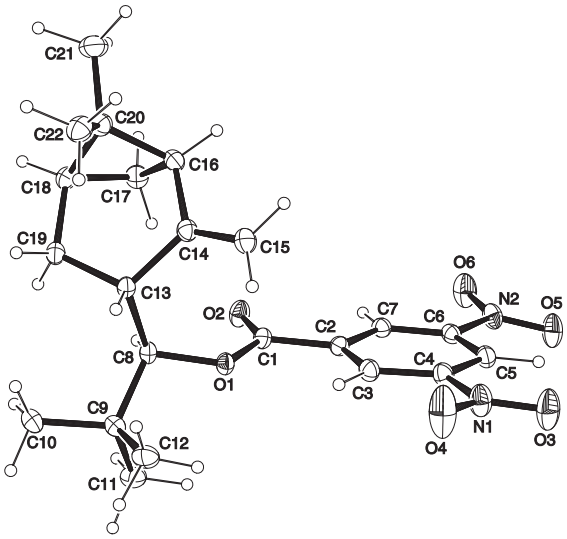
135a: yield: 96 %; dr > 98:2

Scheme 84. The reaction of **129a** with pivaldehyde and pivalonitrile.

The structure of **135a** was conformed by by X-ray crystallography of its derivative **136**.



136



Scheme 85. X-ray crystallography of **136.**

5.7 Conclusion

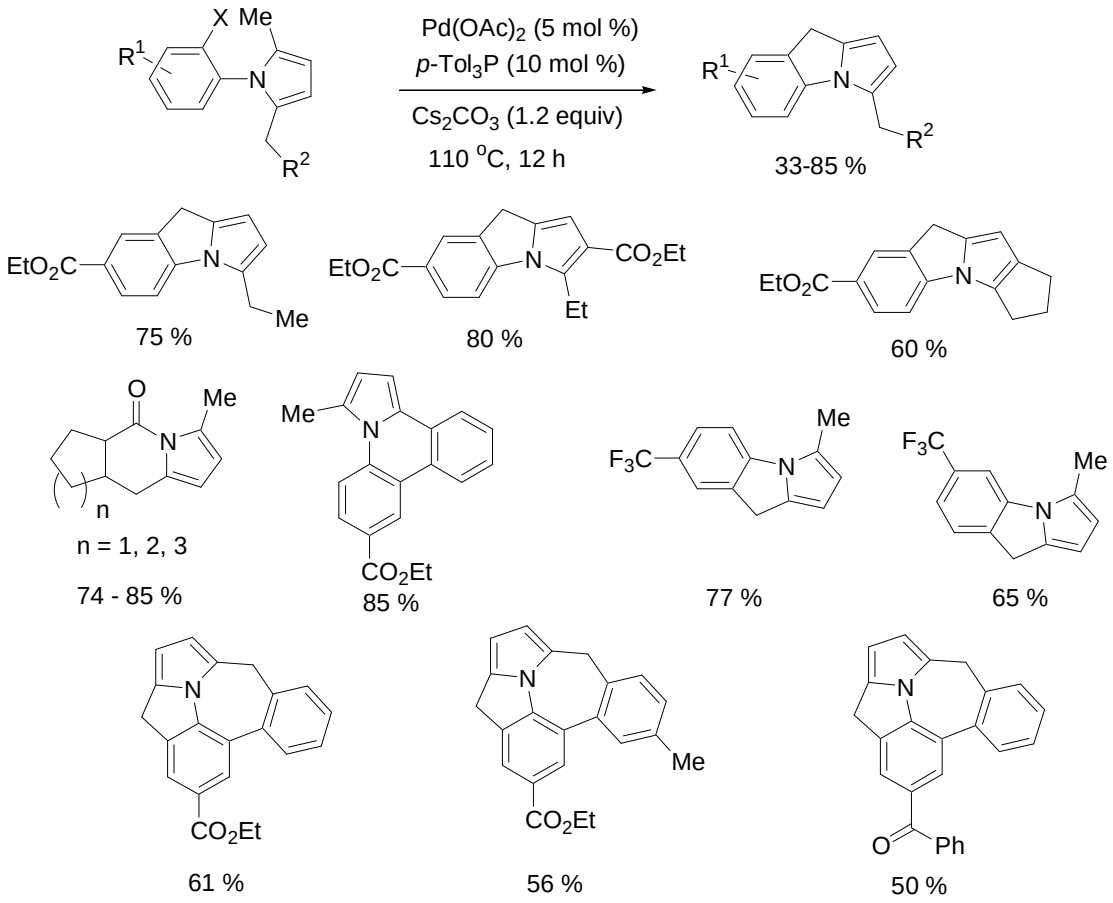
In conclusion, we have described a convenient method to prepare substituted allylic zinc chloride using LiCl-mediated zinc dust insertion to the corresponding allylic chloride. This approach avoids the formation of large amount of homocoupling products. These new allylic zinc reagents undergo highly diastereoselective addition to aldehydes or ketones leading to homoallylic alcohols bearing adjacent quaternary centers in high regioselectivity and diastereoselectivity. Extensions of this work are currently underway in our laboratories.

6. Summary and Outlook

This work has been focused on the formation of complex polycyclic heterocycles using sp^3 C-H bond activation reaction. Furthermore, novel methods for preparation of alkenylmagnesium and allylic zinc reagents were developed as well as their applications in organic synthesis.

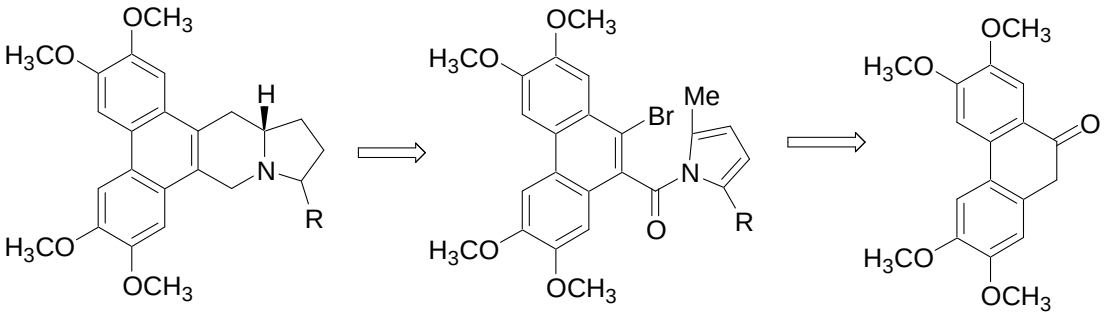
6.1 Chemoselective Benzylic C-H Activations for the Preparation of Condensed *N*-Heterocycles

In the first project, the preparation of condensed *N*-heterocycles using sp^3 C-H bond activation reaction was achieved in the presence of $Pd(OAc)_2$ (5 mol %), *p*-Tol_3P (10 mol %) and Cs_2CO_3 (1.2 equiv). Remarkably, the chemoselective sp^3 C-H bond activation was observed in the case of 2,5-unsymmetrically substituted monobromo derivatives. Furthermore, the formation of pentaheterocyclic compounds using domino reaction was also described.



Scheme 86. Preparation of condensed *N*-heterocycles *via* benzylic C-H activations.

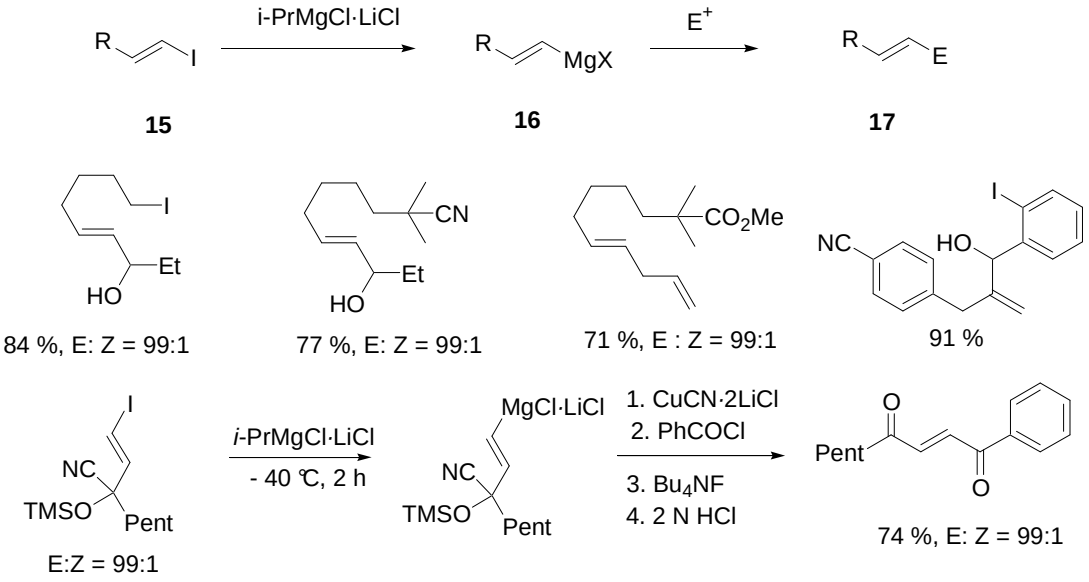
As an extension, the application to several interesting target molecules could be investigated such as (+)-(S)-tylophorine and its analogs.



Scheme 87: Retrosynthetic analysis of Tyloporine analogs.

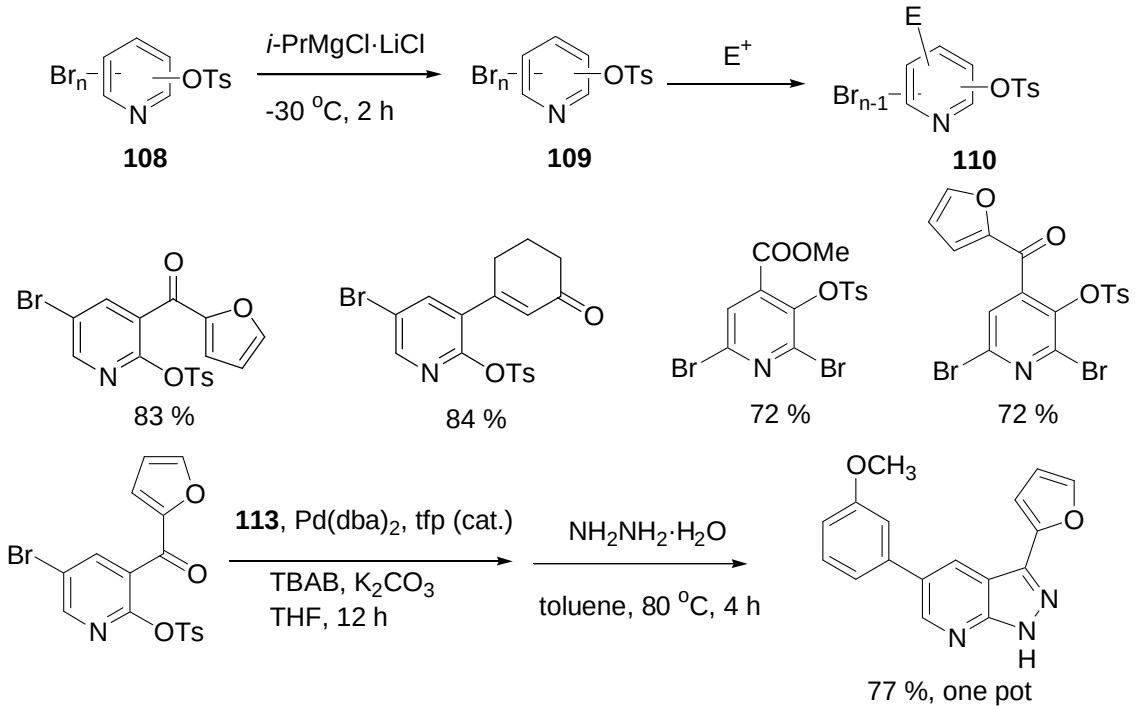
6.2 Preparation of Functionalized Alkenylmagnesium Reagents and Polysubstituted Pyridylmagnesium Reagents Using *i*-PrMgCl•LiCl

With the reagent *i*-PrMgCl·LiCl (**11a**), the I/Mg-exchange of alkenyliodides proceeded at lower temperature. A variety of functionalized alkenyl iodides can be converted to the corresponding Grignard species with retention of the double bond configuration. The reaction with various electrophiles provides polyfunctional alkenes with good yields and excellent stereoselectivity.



Scheme 88. Preparation of functionalized alkenyl organomagnesium reagents.

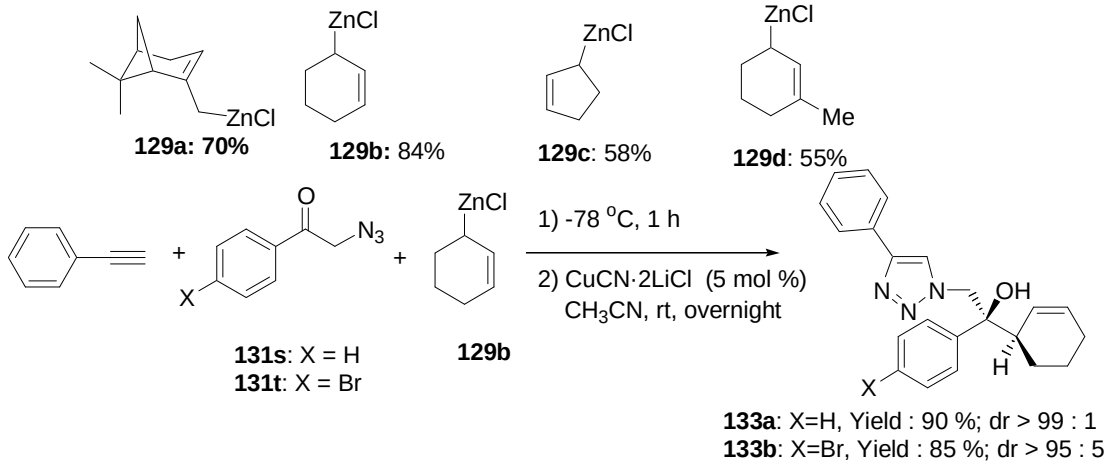
Furthermore, the functionalized polysubstituted pyridylmagnesium reagents also can be obtained from Br/Mg exchange using *i*-PrMgCl•LiCl. And a new method to prepare pyrazolo [3, 4-b] pyridine was developed.



Scheme 89. Preparation of the functionalized polysubstituted pyridylmagnesium reagents using Br/Mg exchange.

6.3 Preparation of Polysubstituted Allylic Zinc Reagents and their Applications.

A variety of allylic zinc reagents were prepared using direct Zn•LiCl insertion. And excellent regioselective and diastereoselectivities were obtained when the allylic zinc reagents reacted with aldehyde and ketones



Scheme 90. Preparation of polysubstituted allylic zinc reagents and their applications.

EXPERIMENTAL PART

7. General Conditions

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under nitrogen. Syringes were used to transfer reagents, and solvents were purged with nitrogen prior to use.

Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under nitrogen.

CH_2Cl_2, **toluene** and **Dimethylformamide (DMF)** were predried over $CaCl_{2(s)}$ and distilled from $CaH_{2(s)}$.

Diethyl ether, 1, 2-dimethoxyethane (DME) and **THF** were continueously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Ethanol and **Methanol** were treated with Phthalic anhydride (25g/L) and sodium, heated to reflux for 6 h and distilled.

Pyridine and **triethylamine** were dried over $KOH_{(s)}$ and distilled from $KOH_{(s)}$.

Reagents

Reagents of >98% purity were used as obtained from Aldrich, Acros and Lancaster.

***n*-Butyllithium** was used as a 1.5 M solution in hexane purchased by Chemetall.

CuCN·2LiCl solution (1.0 M/THF) was prepared by drying CuCN (869 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in a Schlenk flask under vacuum for 5 h at 140 °C. After cooling to room temperature, dry THF (10 mL) was added and stirred continuously until the salts were dissolved.

***i*-PrMgCl:** A dry three-necked flask equipped with a nitrogen inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50

mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at room temperature. The grey solution of *i*-PrMgCl was cannulated to another flask under nitrogen and removed in this way from excess of magnesium. A yield of ca. 85-90% of *i*-PrMgCl was obtained and the *i*-PrMgCl solution was titrated prior to use according to reported literature.[113]

***i*-PrMgCl·LiCl:** A dry three-necked flask equipped with an nitrogen inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at room temperature. The grey solution of *i*-PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 85-90% of *i*-PrMgCl·LiCl was obtained and the *i*-PrMgCl·LiCl solution was titrated prior to use according to reported literature.

$ZnBr_2$ solution (1.0 M/THF) was prepared by drying $ZnBr_2$ (33.78 g, 150 mmol) under vacuum for 5 h at 120 °C. After cooling to room temperature, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV light and/or by staining of the TLC plate with the solution bellow followed by heating with a heat gun:

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL)

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh ASTM) from Merck. The diameters of the columns and the amount of silicagel were calculated according to the recommendation of W. C. Still.[114]

[113] (a) H. S. Lin, L. Paquette, *Synth. Commun.* **1994**, *24*, 2503; (b) A. Krasoskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[114] W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

Analysis

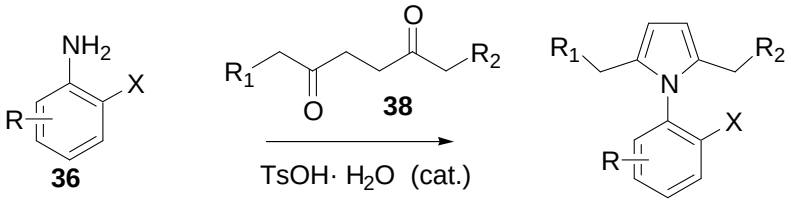
Analytical data collection was done as follows:

- **Melting points** were uncorrected and measured on a Büchi B-540 apparatus.
- **NMR** spectra were recorded on a Bruker ARX 200, AC 300, WH 400, or AMX 600 instruments. Chemical shifts were given relative to $CDCl_3$ (7.24 ppm for ^1H NMR, 77.0 ppm for ^{13}C NMR), DMSO-d_6 (2.50 ppm for ^1H NMR, 39.4 ppm for ^{13}C NMR), acetone-d_6 (2.04 ppm for ^1H NMR, 29.3 ppm for ^{13}C NMR). For the characterization of the observed signal multiplicities the following abbreviations were applied: s (single), d (doublet), dd (double doublet), dt (double triplet), t (triplet), td (triple doublet), q (quartet), quint (quintet), m (multiplet) as well as br (broad).
- **IR** spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR, a Perkin-Elmer 281 IR spectrometer, or a Perkin Elmer Spectrometer BX FT-IR-System with a Smith Dura sampl IR II ATR-unit. Samples were measured either as neat materials (neat) or as a film between potassium bromide plates (film) or as potassium bromide tablets (KBr). The absorption bands are reported in wave numbers (cm^{-1}). For the band characterization the following abbreviations were applied: br (broad), s (strong), m (medium), vs (very strong), w (weak).
- **Gas chromatography (GC)** was perfomed using a Hewlett-Packard 5890 Series II (Column A: 2.5% phenylmethylpolysiloxane (HP Ultra 2) 12 m × 0.2 mm × 0.33 μm). The compounds were detected with a flame ionization detector.
- **Mass spectroscopy:** Mass spectra were recorded on a Varian MAT CH 7A for electron impact ionization (EI) and high resolution mass spectra (HRMS) on a Varian MAT 711 spectrometers. Fast atom bombardment (FAB) samples were recorded in either a 2-nitrobenzyl alcohol- or glycerine-matrix. Additionally, for the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used (Column B: 5% phenylmethylpolysiloxane (HP 5) 30 m × 0.25 mm × 0.25 μm; Column C: 5% phenylmethylpolysiloxane (HP 5) 15 m × 0.25 mm × 0.25 μm).
- **Elemental analysis** was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of the Department Chemie und Biochemie, Ludwig-Maximilians Universität, Munich.

8. Typical Procedure (TP)

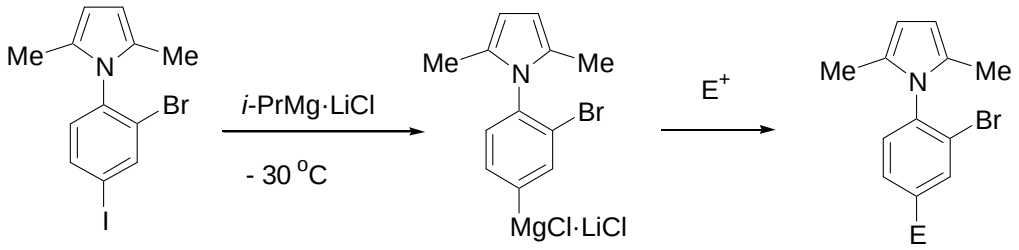
8.1 Typical procedure for preparation of bromo or iodo-*N*-arylpyrrole derivatives

Typical Procedure 1 (TP1): *via* Paal-Knorr reaction



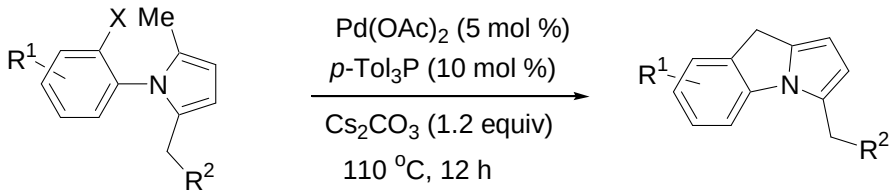
The mixture of bromoaniline **36**, 1, 4-dione **38** and catalytic amounts of TsOH·H_2O (1.0 or 2.0 mol %) in toluene was heated in a flask equipped with a Dean-Stark apparatus for 2-5 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo.* Purification by flash chromatography provided the desired products **39**.

Typical Procedure 2 (TP2): *via* I/Mg exchange



To a solution of 1-(2-bromo-4-iodo-phenyl)-2, 5-dimethyl-*1H*-pyrrole (1.880 g, 5.0 mmol) in THF (10.0 mL) was slowly added *i*-PrMgCl·LiCl (5.50 mmol, 3.5 mL, 1.55 M in THF) at –30 °C. After 2 h, THF (5.0 mL) and CuCN·2LiCl (5.0 mmol, 5.0 mL, 1.0 M in THF) was added at this temperature and stirred for 15 min. Acid chloride (7.5 mmol) was added and the reaction mixture was stirred at –30 °C for 1 h, then warmed to rt and stirred for 1 h. Aq. NH_3 (5 ml) and water (10 mL) were added and the aqueous phase was extracted with diethyl ether (3×25 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography provided the desired products **39**.

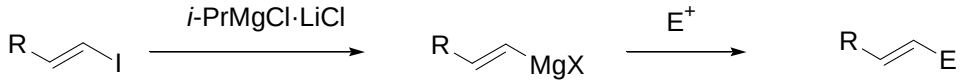
8.2 Typical procedure for preparation of polycyclic heterocycles *via* C-H activation reaction



39 **41**

Typical Procedure 3 (TP3): The reaction was performed in a sealed tuber with a mixture of bromo or iodo-*N*-arylpyrrole derivatives **39** (1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(*p*-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) at 110 °C using toluene (5.0 mL) as solvent for 12 h. After cooling to room temperature, water (10 mL) was added in. The mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography provided the desired products **41**.

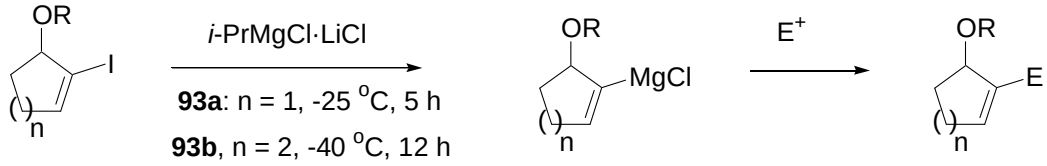
8.3 Typical procedure for preparation of functionalized acyclic alkenyl compounds



79 **82** **83**

Typical Procedure 4 (TP4): To a solution of alkenyl iodides **79** (0.5 mmol) in THF (0.2 mL) was slowly added *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) at –40 °C. After 7 h, a complete conversion to the Grignard reagent **82** was observed by GC-analysis of hydrolyzed reaction aliquots. The solution of electrophile (0.55 mmol in 0.5 mL of THF) was added in directly or added after the Grignard reagent was transmetalated to copper reagent with CuCN·2LiCl. The reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography afforded the pure product**.**

8.4 Typical procedure for preparation of functionalized cyclic alkenyl compounds



93a : n = 1
93b : n = 2

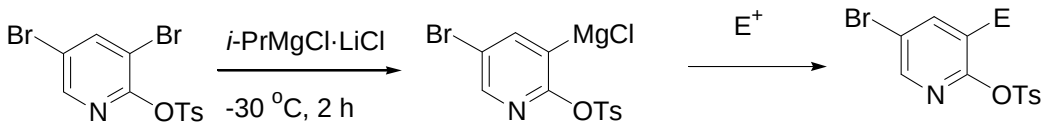
R = $EtOCH_2$ (EOM)

94a : n = 1
94b : n = 2

95

Typical Procedure 5 (TP5): To a solution of 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (1.0 mmol) or 6-ethoxymethoxy-1-iodo-cyclohexene **93b** (1.0 mmol) in THF (0.3 mL) was slowly added *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) at low temperature (**93a**: -25 °C and **93b**: -40 °C). A complete conversion to the Grignard reagent **94a** or **94b** was observed by GC-analysis of hydrolyzed reaction aliquots after 5 h (the exchange for **93a**) or 12 h (the exchange for **93b**). The solution of electrophile (0.55 mmol in 0.5 mL of THF) was added in directly or added after the Grignard reagent was transmetalated to copper reagent with CuCN·2LiCl. The reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography afforded the pure product.

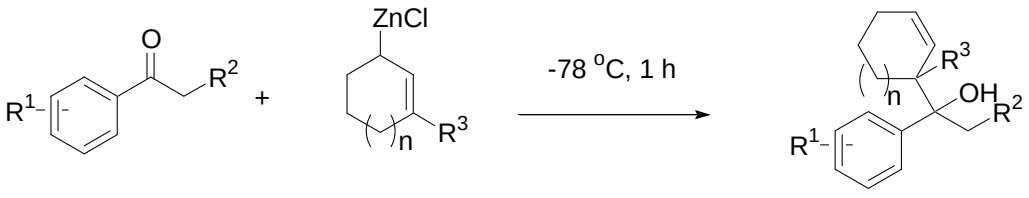
8.5 Typical procedure for the performance of punctionalized pyridines:



108 **109** **110**

Typical Procedure 6 (TP6): The solution of *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was slowly added to a solution of 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol) in dry THF (1.5 mL) and the resulting mixture was stirred at this temperature for 2 h to form the Grignard **109** completely. The solution of electrophile (0.55 mmol in 0.5 mL of THF) was added in directly or added after the Grignard reagent was transmetalated to copper reagent with CuCN·2LiCl. The reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography afforded the pure product **110.**

8.6 Typical procedure for the preparation of homoallylic alcohol:

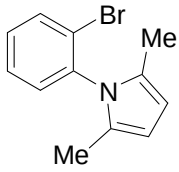


129 **130**

Typical Procedure 7 (TP7): The allyliczinc chloride (1.2 mmol) was added to the solution of aldehyde or ketone (1.0 mmol) in THF (2.0 mL) at -78 ^{o}C and the resulting mixture was stirred at this temperature for 1 h. After quenching with water (10 mL), the reaction mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (The silica gel was buffered with 1% Et_3N in pentane) provided the pure compound.

9. Preparation of Condensed *N*-Heterocycles by sp^3 C-H Bond Activation Reactions

Synthesis of 1-(2-bromo-phenyl)-2,5-dimethyl-*1H*-pyrrole (**39a**)



RHJ165F

It was prepared from 2-bromoaniline (3.440 g, 20.0 mmol), 2, 5-hexanedione (2.740 g, 24.0 mmol) and $TsOH \cdot H_2O$ (38 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided **39a** (4.251 g, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.72 (d, J = 8.0 Hz, 1 H), 7.40-7.46 (m, 1 H), 7.28-7.34 (m, 2 H), 5.94 (s, 2 H), 1.97 (s, 6 H);

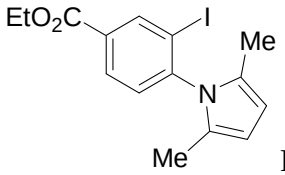
^{13}C NMR ($CDCl_3$, 75 MHz): 138.5, 133.3, 130.5, 129.8, 128.4, 128.1, 124.1, 105.6, 12.5;

IR (neat): 2918 (s), 1588 (m), 1524 (s), 1485 (vs), 1436 (vs) cm^{-1};

MS (EI, 70 ev): 251 (M^+ (^{81}Br), 91%), 250 (M^+ (^{81}Br)-H, 100%), 249 (M^+ (^{79}Br), 91%), 248 (M^+ (^{79}Br)-H, 100%), 168 (25%), 154 (69%), 83 (26%);

HRMS (EI): calcd. for $C_{12}H_{12}BrN$ (M^+, ^{79}Br): 249.0153, **found**: 249.0134 (M^+, ^{79}Br).

Synthesis of 4-(2,5-dimethyl-pyrrol-1-yl)-3-iodo-benzoic acid ethyl ester (**39b**)



RHJ054G

It was prepared from 4-amino-3-iodo-benzoic acid ethyl ester[115] (2.911 g, 10.0 mmol), 2, 5-hexanedione (1.372 g, 12.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 4 h. Purification by flash chromatography (eluent: pentane: ether = 15: 1) provided **39b** (1.480 g, 40%) as a brown solid, mp.: 80.2-80.6 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.59 (d, J = 1.8 Hz, 1 H), 8.13 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 5.93 (s, 2 H), 4.41 (q, J = 7.1 Hz, 2 H), 1.93 (s, 6 H), 1.41 (t, J = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 164.4, 146.2, 140.6, 131.9, 130.3, 129.5, 127.8, 106.3, 100.3, 61.6, 14.3, 12.8;

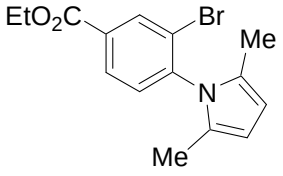
[115] Y: Tobe, N. Utsumi, K. Kawabata, A. Nagano, K. Adachi, S. Araki, M. Sonoda, K. Hirose, K. Naemura, *J. Am. Chem. Soc.* **2002,** *124*, 5350.

IR (neat): 2915 (w), 1723 (s), 1590 (w), 1483 (s), 1395 (s) cm^{-1};

MS (EI, 70 ev): 369 (100%), 340 (15%), 324 (5%), 296 (5%), 168 (19%), 154 (11%);

HRMS (EI): calcd. for $C_{15}H_{16}INO_2$: 369.0226 (M^+), **found**: 369.0219 (M^+).

Synthesis of 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-benzoic acid ethyl ester (**39c**)



RHJ092G

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (2.44 g, 10.0 mmol), 2, 5-hexanedione (1.37 g, 12.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39c** (2.810 g, 87%) as a brown solid, mp.: 56.1-56.9 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.37 (d, J = 1.8 Hz, 1 H), 8.80 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 5.93 (s, 2 H), 4.41 (q, J = 7.1 Hz, 2 H), 1.94 (s, 6 H), 1.41 (t, J = 7.1 Hz, 3 H);

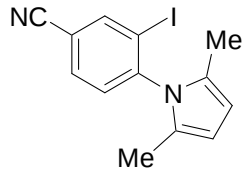
^{13}C NMR ($CDCl_3$, 75 MHz): 164.6, 142.6, 134.4, 132.1, 130.5, 129.3, 128.3, 124.5, 106.2, 61.6, 14.3, 12.5;

IR (neat): 2979 (w), 1724 (vs), 1402 (s), 1283 (vs) cm^{-1};

MS (EI, 70 ev): 323 (M^+ (^{81}Br), 100%), 321(M^+ (^{79}Br), 100%), 294 (M^+ (^{81}Br), 70%), 292 (M^+ (^{79}Br), 70%), 198 (25%), 168 (62%), 154 (49%);

HRMS (EI): calcd. for $C_{15}H_{16}BrNO_2$ (M^+, ^{79}Br): 321.0364, found: 321.0369 (M^+, ^{79}Br).

Synthesis of 4-(2,5-dimethyl-pyrrol-1-yl)-3-iodo-benzonitrile (**39d**)



RHJ059G

It was prepared from 4-amino-3-iodo-benzonitrile[116] (2.440 g, 10.0 mmol), 2, 5-hexanedione (1.370 g, 20.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 5 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39d** (1.541 g, 48%) as a brown solid, mp.: 102.3-102.8 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.23 (d, J = 1.8 Hz, 1 H), 7.76 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1 H), 7.37 (d, J = 8.1 Hz, 1 H), 5.94 (s, 2 H), 1.93 (s, 6 H);

[116] C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid; P. Knochel, *Tetrahedron*, **2003**, *59*, 1571.

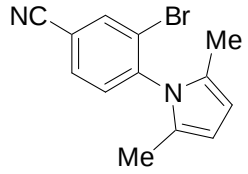
^{13}C NMR ($CDCl_3$, 75 MHz): 146.7, 142.7, 132.7, 130.2, 127.7, 116.3, 113.9, 106.8, 101.0, 12.7;

IR (neat): 2915 (w), 2231 (w), 1481 (s), 1397 (s) cm^{-1};

MS (EI, 70 ev): 322 (100%), 321 (81%), 307 (3%), 193 (8%), 179 (12%), 127 (11%);

HRMS (EI): calcd. for $C_{13}H_{11}IN_2$ (M^+): 321.9967, **found**: 321.9977 (M^+).

Synthesis of 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-benzonitrile (**39e**)



RHJ098G

It was prepared from 4-amino-3-bromo-benzonitrile [117] (1.970 g, 10.0 mmol), 2, 5-hexanedione (1.370 g, 12.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39e** (2.598 g, 94%) as a brown solid, mp.: 94.7-95.2 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.00 (d, J = 1.8 Hz, 1 H), 7.72 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 5.94 (s, 2 H), 1.94 (s, 6 H);

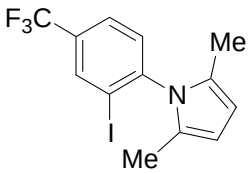
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 136.7, 131.9, 131.4, 128.2, 125.5, 116.6, 114.0, 106.7, 12.5;

IR (Neat): 2915 (w), 2232 (m), 1487 (vs), 1400 (vs), 1380 (s) cm^{-1};

MS (EI, 70 ev): 276 (M^+ (^{81}Br), 72%), 275(M^+ (^{81}Br)-H, 100%), 274 (M^+ (^{79}Br), 75%), 273(M^+ (^{79}Br)-H, 100%), 261 (5%), 193 (11%), 179 (55%);

HRMS (EI): calcd. for $C_{13}H_{11}BrN_2$ (M^+, ^{79}Br): 274.0106, **found**: 274.0080 (M^+, ^{79}Br).

Synthesis of 1-(2-iodo-4-trifluoromethyl-phenyl)-2,5-dimethyl-*1H*-pyrrole (**39f**)



RHJ087G

It was prepared from 2-iodo-4-trifluoromethyl-phenylamine (2.870 g, 10.0 mmol), 2,5-hexanedione (1.370 g, 12.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 5 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided **39f** (1.825 g, 50%) as a brown solid, mp.: 80.6-81.2 ^oC.

[117] Y. Tobe, N. Utsumi, K. Kawabata, A. Nagano, K. Adachi, S. Araki, M. Sonoda, K. Hirose, K. Naemura, *J. Am. Chem. Soc*. **2002**, *124*, 5350.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.20 (s, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 1 H), 5.94 (s, 2 H), 1.94 (s, 6 H);

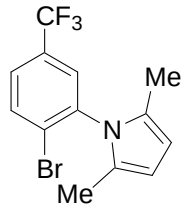
^{13}C NMR ($CDCl_3$, 75 MHz): 145.7, 136.5 (q, $J_{C\text{-}F}$ = 3.5 Hz), 131.9 (q, $J_{C\text{-}F}$ = 33.5 Hz), 130.0, 127.9, 126.2 (q, $J_{C\text{-}F}$ = 3.5 Hz), 122.6 (q, $J_{C\text{-}F}$ = 273.0 Hz), 106.5, 100.7, 12.8;

IR (neat): 2921 (m), 1599 (m), 1523 (w), 1491 (m), 1322 (s), 1312 (s) cm^{-1};

MS (EI, 70 ev): 365 (M^+, 100%), 236 (14%), 222 (16%), 168 (6%);

HRMS (EI): calcd. for $C_{13}H_{11}BrF_3NI$ (M^+): 364.9888, **found**: 364.9887 (M^+).

Synthesis of 1-(2-bromo-5-trifluoromethyl-phenyl)-2,5-dimethyl-*1H*-pyrrole (39g)



RHJ149G

It was prepared from 2-bromo-4-trifluoromethyl-phenylamine (1.501 g, 6.3 mmol), 2,5-hexanedione (0.860 g, 7.5 mmol) and $TsOH{\cdot}H_2O$ (12 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided **39g** (1.631 g, 82%) as a brown solid, mp.: 74.5-75.3 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.86 (d, J = 8.8 Hz, 1 H), 7.50-7.60 (m, 2 H), 5.94 (s, 2 H), 1.95 (s, 6 H);

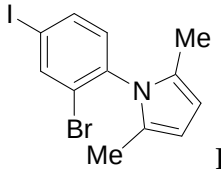
^{13}C NMR ($CDCl_3$, 75 MHz): 139.5, 134.1, 131.0 (q, $J_{C\text{-}F}$ = 33.3 Hz), 128.8, 128.4, 127.5 (q, $J_{C\text{-}F}$ = 3.5 Hz), 126.5 (q, $J_{C\text{-}F}$ = 3.5 Hz), 123.2 (q, $J_{C\text{-}F}$ = 273.2 Hz), 106.4, 12.5;

IR (neat): 2920 (w), 1483 (s), 1433 (vs), 1338 (vs), 1174 (vs) cm^{-1};

MS (EI, 70 ev): 319 (M^+ (^{81}Br), 82%), 318 (M^+ (^{81}Br)-H, 100%), 317 (M^+ (^{79}Br), 80%), 316 (M^+ (^{79}Br)-H, 95%), 236 (9%), 222 (23%), 168 (15%);

HRMS (EI): calcd. for $C_{13}H_{11}BrF_3N$ (M^+, ^{79}Br): 317.0027, **found**: 317.0005 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-iodo-phenyl)-2,5-dimethyl-*1H*-pyrrole (39aa)



RHJ039K

It was prepared from 2-bromo-4-iodo-phenylamine (1.790 g, 6.0 mmol), 2,5-hexanedione (0.820 g, 7.2 mmol) and $TsOH{\cdot}H_2O$ (12 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided **39aa** (1.831 g, 81%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.06 (d, J = 1.8 Hz, 1 H), 7.74 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.01 (d, J = 7.9 Hz, 1 H), 5.92 (s, 2 H), 1.95 (s, 6 H);

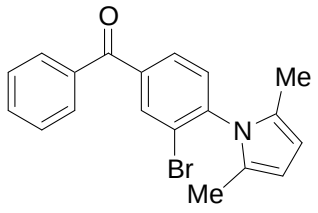
^{13}C NMR ($CDCl_3$, 75 MHz): 141.4, 138.4, 137.5, 131.9, 128.3, 125.5, 106.0, 94.0, 12.6;

IR (neat): 2915 (w), 1483 (vs), 1499 (s), 1399(m), 993 (m) cm^{-1};

MS (EI, 70 ev): 377 (M^+ (^{81}Br), 100%), 375(M^+ (^{79}Br), 100%), 249 (20%), 167 (45%), 154 (39%), 83 (23%);

HRMS (EI): calcd. for $C_{12}H_{11}BrIN$ (M^+, ^{79}Br): 374.9120, **found**: 374.9075 (M^+, ^{79}Br).

Synthesis of [3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-phenyl]-phenyl-methanone (39h)



RHJ052I

It was prepared from 1-(2-bromo-4-iodo-phenyl)-2, 5-dimethyl-*1H*-pyrrole **39aa** (1.880 g, 5.0 mmol), *i*-PrMgCl·LiCl (3.8 mL, 1.55 M in THF) and benzoyl chloride (7.5 mmol) according to **TP2**. Purification by flash chromatography (eluent: pentane: ether =10: 1) provided the pure product **39h** (1.451 g, 82%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.17 (d, J = 1.9 Hz, 1 H), 7.81-7.88 (m, 3 H), 7.61-7.68 (m, 1 H), 7.51-7.56 (m, 2 H), 7.41 (d, J = 1.9 Hz, 1 H), 5.96 (s, 2 H), 2.01 (s, 6 H);

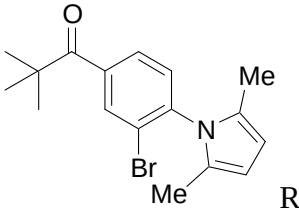
^{13}C NMR ($CDCl_3$, 75.0 MHz): 194.1, 142.0, 138.8, 136.4, 134.5, 132.9, 130.3, 129.8, 129.6, 128.4, 128.2, 124.6, 106.1, 12.5;

IR (neat): 2918 (w), 1698 (m), 1661 (s), 1594 (m), 1489 (m), 1401 (m), 1282 (vs) cm^{-1};

MS (EI, 70 ev): 355 (M^+ (^{81}Br), 100%), 353 (M^+ (^{79}Br), 98%), 258 (10%), 168 (25%), 105 (51%);

HRMS (EI): calcd. for $C_{19}H_{16}BrNO$ (M^+, ^{79}Br): 353.0415, **found**: 353.0403 (M^+, ^{79}Br).

Synthesis of 6-(1-tert-butyl-vinyl)-3-methyl-*8H*-3a-aza-cyclopenta[a]indene (39i).



RHJ060J

It was prepared from 1-(2-bromo-4-iodo-phenyl)-2, 5-dimethyl-*1H*-pyrrole **39aa** (1.880 g, 5.0 mmol), *i*-PrMgCl·LiCl (3.8 mL, 1.55 M in THF) and 2, 2-dimethyl-propionyl chloride (7.5

mmol) according to **TP2**. Purification by flash chromatography (eluent: pentane: ether=10: 1) provided the pure product **39i** (1.336 g, 82%) as a white solid, mp.: 125.1-126.2 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.99 (d, J = 1.8 Hz, 1 H), 7.72 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H), 5.92 (s, 2 H), 1.95 (s, 6 H), 1.37 (s, 9 H);

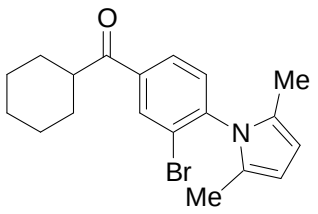
^{13}C NMR ($CDCl_3$, 75 MHz): 207.0, 140.7, 139.8, 132.8, 130.1, 128.4, 127.5, 124.5, 106.1, 44.4, 27.9, 12.6;

IR (neat): 2963 (w), 1669 (s), 1592 (vs), 1494 (m), 1473 (vs), 1396 (s), 1179 (s) cm^{-1};

MS (EI, 70 ev): 335 (M^+ (^{81}Br), 75%), 333 (M^+ (^{79}Br), 74%), 276 (24%), 248 (100%), 167 (47%), 154 (35%);

HRMS (EI): calcd. for $C_{17}H_{20}BrNO$ (M^+,^{79}Br): 333.0728, **found**: 333.0715 (M^+, ^{79}Br).

Synthesis of cyclohexyl-(3-methyl-*8H*-3a-aza-cyclopenta[a]inden-6-yl)-methanone (39j)



RHJ062J

It was prepared from 1-(2-bromo-4-iodo-phenyl)-2, 5-dimethyl-*1H*-pyrrole **39aa** (1.880 g, 5.0 mmol), *i*-PrMgCl·LiCl (3.8 mL, 1.55 M in THF) and cyclohexanecarbonyl chloride (7.5 mmol) according to **TP2**. Purification by flash chromatography (eluent: pentane: ether = 10:1) provided the pure product **39j** (1.458 g, 81%) as a white solid, mp.: 133.6-134.7 °C.

^{1}H NMR ($CDCl_3$, 300 MHz):8.24 (d, J = 1.8 Hz, 1 H), 7.95 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 5.93 (s, 2 H), 3.10-3.30 (m, 1 H), 1.95 (s, 6 H), 1.20-1.93 (m, 10 H);

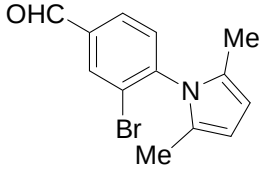
^{13}C NMR ($CDCl_3$, 75 MHz): 201.6, 142.4, 137.6, 133.2, 130.7, 128.3, 127.9, 125.1, 106.2, 45.8, 29.3, 25.8, 25.7, 12.6;

IR (neat): 2932 (m), 1676 (s), 1592 (m), 1492 (m), 1394 (s), 1200 (m) cm^{-1};

MS (EI, 70 ev): 361 (M^+ (^{81}Br), 100%), 359 (M^+ (^{79}Br), 100%), 248 (34%), 167 (20%), 154 (10%);

HRMS (EI): calcd. for $C_{19}H_{22}BrNO$ (M^+, ^{79}Br): 359.0885, **found**: 359.0853 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-benzaldehyde (39k)



RHJ053I

It was prepared from 1-(2-bromo-4-iodo-phenyl)-2, 5-dimethyl-*1H*-pyrrole **39aa** (1.880 g, 5.0 mmol), *i*-PrMgCl·LiCl (3.8 mL, 1.55 M in THF) and DMF (1.0 mL) according to **TP2.** Purification by flash chromatography (eluent: pentane: ether =10: 1) yielded the pure product **39k** (1.084 g, 78%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz):10.03 (s, 1 H), 8.22 (d, J = 1.9 Hz, 1 H), 7.94 (d, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 5.94 (s, 2 H), 1.96 (s, 6 H);

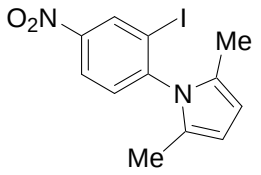
^{13}C NMR ($CDCl_3$, 75.0 MHz): 189.6, 143.8, 137.2, 134.1, 131.3, 129.1, 128.1, 125.5, 106.4, 12.5;

IR (neat): 2918 (w), 1697 (vs), 1594 (m), 1492 (s), 1397 (s), 1187 (s) cm^{-1};

MS (EI, 70 ev): 279 (M^+ (^{81}Br), 100%), 277 (M^+ (^{79}Br), 98%), 182 (10%), 168 (40%), 154 (25%), 128 (8%);

HRMS (EI): calcd. for $C_{13}H_{12}BrNO$ (M^+, ^{79}Br): 277.0102, **found**: 277.0082 (M^+, ^{79}Br).

Synthesis of 1-(2-iodo-4-nitro-phenyl)-2,5-dimethyl-*1H*-pyrrole (**39l**)



RHJ058G

It was prepared from 2-iodo-4-nitro-phenylamine (5.280 g, 20.0 mmol), 2, 5-hexanedione (2.740 g, 24.0 mmol) and $TsOH·H_2O$ (38 mg, 1.0 mol %) according to **TP1**. Reaction time: 5 h. Purification by flash chromatography (eluent: pentane: ether =10: 1) provided **39l** (3.080 g, 45.0%) as a brown solid, mp.: 114.8-115.2 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.78 (d, J = 2.5 Hz, 1 H), 8.32 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 7.43 (d, J = 8.5 Hz, 1 H), 5.95 (s, 2 H), 1.95 (s, 6 H);

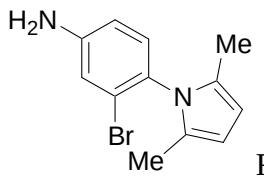
^{13}C NMR ($CDCl_3$, 75 MHz): 148.3, 147.5, 134.5, 130.1, 127.7, 124.1, 106.9, 100.6, 12.8;

IR (neat): 2913 (w), 1594 (m), 1574 (w), 1518 (vs), 1476 (s), 1341 (vs) cm^{-1};

MS (EI, 70 ev): 342 (100%), 341 (46%), 296 (17%), 168 (29%), 154 (19%);

HRMS (EI): calcd. for $C_{12}H_{11}IN_2O_2$ (M^+): 341.9865, **found**: 341.9877 (M^+).

Synthesis of 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-phenylamine (39m)



RHJ030K

A mixture of 1-(2-bromo-4-nitro-phenyl)-2, 5-dimethyl-*1H*-pyrrole (1.520 g, 5 mmol), activated carbon (0.240 g, 20 mmol) and $FeCl_3 \cdot 7H_2O$ (144mg, 0. 5 mmol) in MeOH (20 mL) was heated to reflux under nitrogen for 10 min. Hydrazine monohydrate (0.6 mL, 20 mmol) was slowly added and the mixture heated to reflux for 6 h. The cooled solution was diluted with DCM (50 mL) and water (10 mL), and then filtered through celite. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give **39m** (1.056 g, 80%) as a white solid, mp.: 109.5-110.9 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.02 (d, J = 8.8 Hz, 1 H), 6.98 (d, J = 2.6 Hz, 1 H), 6.64 (dd, J_1 = 7.9 Hz, J_2 = 2.6 Hz, 1 H), 5.89 (s, 2 H), 3.84 (bs, 2 H), 1.96 (s, 6 H);

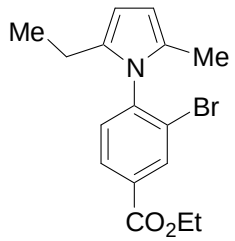
^{13}C NMR ($CDCl_3$, 75 MHz): 147.4, 130.6, 128.9, 128.5, 124.7, 118.5, 114.2, 105.0, 12.6;

IR (neat): 3480 (w), 3429 (w), 3382 (w), 3357 (w), 3342 (w), 2916(w), 1617 (m), 1601 (m), 1503 (s), 1404 (m), 1243 (m) cm^{-1};

MS (EI, 70 ev): 266 (M^+(^{81}Br), 100%), 264 (M^+(^{79}Br), 100%), 249 (17%), 183 (29%), 169 (39%), 144 (34%), 91 (34%);

HRMS (EI): calcd. for $C_{12}H_{13}BrN_2$ (M^+, ^{79}Br): 264.0262, **found**: 264.0271 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2-ethyl-5-methyl-pyrrol-1-yl)-benzoic acid ethyl ester (39n)



RHJ153H

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (1.220 g, 5.0 mmol), heptane-2, 5-dione (768 mg, 6.0 mmol) and $TsOH \cdot H_2O$ (5 mg, 1.0 mol %) according to **TP1**. Reaction time: 4 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39n** (1.341 g, 80.0%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.37 (d, J = 1.8 Hz, 1 H), 8.08 (d, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 6.00 (s, 2 H), 4.42 (t, J = 7.1 Hz, 2 H), 2.13-2.40 (m, 2 H), 1.94 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H), 1.09 (t, J = 7.6 Hz, 3 H);

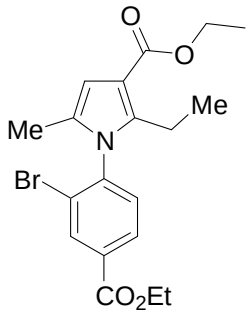
^{13}C NMR ($CDCl_3$, 75 MHz): 164.6, 142.6, 134.8, 134.4, 132.0, 130.6, 129.3, 128.2, 124.6, 106.1, 104.4, 61.6, 20.1, 14.2, 13.0, 12.4;

IR (neat): 2971 (m), 1721 (vs), 1598 (m), 1495 (m), 1408 (m), 1210 (vs) cm^{-1};

MS (EI, 70 ev): 337 (M^+ (^{81}Br), 56%), 335 (M^+ (^{79}Br), 56%), 322 (100%), 292 (43%), 226 (8%), 198 (11%), 168 (54%);

HRMS (EI): calcd. for $C_{16}H_{18}BrNO_2$ (M^+, ^{79}Br): 335.0521, **found**: 335.0511 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2-ethyl-5-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (39o)



RHJ180H

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (0.976 g, 4.0 mmol), 3-oxo-2-(2-oxo-propyl)-pentanoic acid ethyl ester (0.960 g, 4.8 mmol) and $TsOH \cdot H_2O$ (5 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 6: 1) provided **39o** (1.355 g, 83%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.38 (d, J = 1.9 Hz, 1 H), 8.10 (dd, J_1 = 8.1 Hz, J_2= 1.9 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 6.39 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 2.72-2.78 (m, 1 H), 2.44-2.50 (m, 1 H), 1.87 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.6 Hz, 3 H);

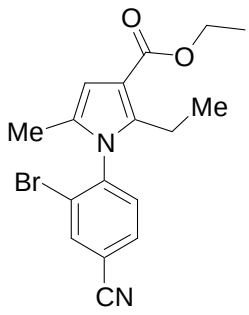
^{13}C NMR ($CDCl_3$, 150 MHz): 165.1, 164.4, 141.6, 141.1, 134.6, 132.7, 130.5, 129.4, 128.1, 124.2, 111.6, 108.2, 61.8, 59.3, 19.4, 14.4, 14.24, 14.22, 12.1;

IR (neat): 2978 (w), 1723 (s), 1698 (vs), 1532 (m), 1494 (m), 1273 (vs) cm^{-1};

MS (EI, 70 ev): 409 (M^+ (^{81}Br), 73%), 407 (M^+ (^{79}Br), 72%), 394 (60%), 392 (58%), 380 (100%), 378 (100%), 212 (36%), 167 (33%);

HRMS (EI): calcd. for $C_{19}H_{22}BrNO_4$ (M^+, ^{79}Br): 407.0732, **found**: 407.0721 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-cyano-phenyl)-2-ethyl-5-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (39p)



RHJ182H

It was prepared from 4-amino-3-bromo-benzonitrile (0.788 g, 4.0 mmol), 3-oxo-2-(2-oxo-propyl)-pentanoic acid ethyl ester (0.960 g, 4.8 mmol) and $TsOH \cdot H_2O$ (5 mg, 1.0 mol %)

according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided **39p** (1.155 g, 80%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.03 (d, *J* = 1.9 Hz, 1 H), 7.75 (dd, J_1 = 8.1 Hz, J_2= 1.9 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 6.39 (s, 1 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 2.70-2.77 (m, 1 H), 2.41-2.48 (m, 1 H), 1.87 (s, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 0.95 (t, *J* = 7.2 Hz, 3 H);

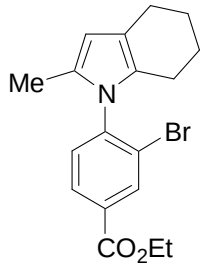
^{13}C NMR ($CDCl_3$, 150 MHz): 164.9, 141.7, 141.4, 136.9, 131.9, 131.4, 127.9, 125.2, 116.3, 114.7, 112.0, 108.6, 59.4, 19.3, 14.4, 14.2, 12.1;

IR (neat): 2977 (w), 2235 (m), 1694 (vs), 1532 (m), 1490 (m), 1192 (vs) cm^{-1};

MS (EI, 70 ev): 362 (M^+ (^{81}Br), 62%), 360 (M^+ (^{79}Br), 61%), 347 (40%), 345 (41%), 333 (99%), 331 (100%), 207 (36%), 193 (71%);

HRMS (EI): calcd. for $C_{17}H_{17}BrN_2O_2$ (M^+, ^{79}Br): 360.0473, **found**: 360.0470 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2-methyl-4,5,6,7-tetrahydro-indol-1-yl)-benzoic acid ethyl ester (39q)



RHJ004I

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (0.976 g, 4.0 mmol), 2-(2-oxo-propyl)-cyclohexanone (0.739 g, 4.8 mmol) and $TsOH \cdot H_2O$ (15 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39q** (1.042 g, 72%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.35 (d, *J* = 1.9 Hz, 1 H), 8.06 (dd, J_1 = 8.1 Hz, J_2= 1.9 Hz, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 5.83 (s, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 2.44-2.58 (m, 2 H), 2.08-2.23 (m, 2 H), 1.96 (s, 3 H), 1.66-1.79 (m, 4 H), 1.41 (t, *J* = 7.2 Hz, 3 H);

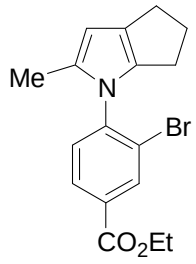
^{13}C NMR ($CDCl_3$, 150 MHz):164.6, 142.5, 134.3, 131.8, 130.5, 129.2, 127.8, 127.5, 124.3, 117.2, 106.0, 61.6, 23.7, 23.3, 22.9, 22.3, 14.3, 12.1;

IR (neat): 2925 (m), 1721 (vs), 1598 (m), 1495 (m), 1244 (vs) cm^{-1};

MS (EI, 70 ev): 363 (M^+ (^{81}Br), 97%), 361 (M^+ (^{79}Br), 100%), 335 (60%), 333 (62%), 254 (12%), 208 (11%), 181 (41%);

HRMS (EI): calcd. for $C_{18}H_{20}BrNO_2$ (M^+, ^{79}Br): 361.0677, **found**: 361.0675 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2-methyl-5,6-dihydro-*4H*-cyclopenta[b]pyrrol-1-yl)-benzoic acid ethyl ester (39r)



RHJ014I

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (0.976 g, 4.0 mmol), 2-(2-oxo-propyl)-cyclopentanone (0.672 g, 4.8 mmol), and $TsOH \cdot H_2O$ (15 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39r** (0.970 g, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz):8.36 (d, J = 1.9 Hz, 1 H), 8.05 (dd, J_1 = 8.1 Hz, J_2= 1.9 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 5.86 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.30-2.71 (m, 6 H), 2.01 (s, 3 H), 1.41 (t, J = 7.2 Hz, 3 H);

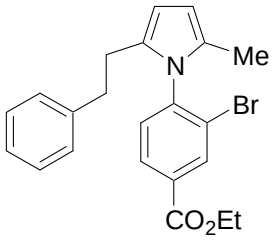
^{13}C NMR ($CDCl_3$, 75.0 MHz):164.6, 143.0, 137.7, 134.4, 132.1, 131.5, 129.7, 129.1, 125.8, 123.1, 102.9, 61.5, 28.5, 25.7, 25.1, 14.2, 12.8;

IR (neat): 2854 (w), 1718 (vs), 1597 (m), 1498 (m), 1227 (vs) cm^{-1};

MS (EI, 70 ev): 349 (M^+ (^{81}Br), 100%), 347 (M^+ (^{79}Br), 98%), 321 (10%), 319 (10%), 268 (25%), 240 (23%), 194 (16%);

HRMS (EI): calcd. for $C_{17}H_{18}BrNO_2$ (M^+, ^{79}Br): 347.0521, **found**: 347.0522 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2-methyl-5-phenethyl-pyrrol-1-yl)-benzoic acid ethyl ester (39s)



RHJ041I

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (0.976 g, 4.0 mmol) 7-phenyl-heptane-2,5-dione (0.979 g, 4.8 mmol) and $TsOH \cdot H_2O$ (15 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether =10: 1) provided **39s** (1.236 g, 75%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.38 (d, J = 1.9 Hz, 1 H), 8.06 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1 H), 7.11-7.30 (m, 4 H), 7.00-7.08 (m, 2 H), 5.98-6.05 (m, 2 H), 4.43 (q, J = 7.2 Hz, 2 H), 2.77-2.88 (m, 2 H), 2.41-2.65 (m, 2 H), 1.96 (s, 3 H), 1.42 (t, J = 7.2 Hz, 3 H);

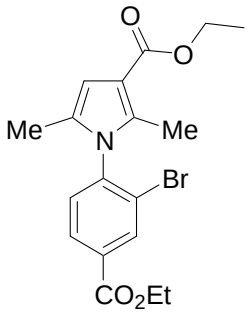
^{13}C NMR ($CDCl_3$, 75 MHz): 164.5, 142.4, 141.5, 134.4, 132.5, 132.1, 130.7, 129.3, 128.4, 128.3, 125.9, 124.6, 106.3, 105.5, 61.7, 35.4, 29.0, 14.3, 12.4;

IR (neat): 2898 (w), 1698 (vs), 1619 (s), 1284 (vs) cm^{-1};

MS (EI, 70 ev): 413 (M^+ (^{81}Br), 10%), 411 (M^+ (^{79}Br), 10%), 322 (100%), 320 (100%), 292 (8%), 168 (11%);

HRMS (EI): calcd. for $C_{22}H_{22}BrNO_2$ (M^+, ^{79}Br): 411.0834, **found**: 411.0848 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2,5-dimethyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (39t)



RHJ164H

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (1.220 g, 5.0 mmol), 2-acetyl-4-oxo-pentanoic acid ethyl ester (1.120 g, 6.0 mmol) and $TsOH \cdot H_2O$ (15 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether =3: 1) provided **39t** (1.596 g, 81%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz):8.37 (d, J = 1.9 Hz, 1 H), 8.09 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 6.38 (s, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 4.24 (q, J = 7.2 Hz, 2 H), 2.19 (s, 3 H), 1.88 (s, 3 H), 1.39 (t, J = 7.2 Hz, 3 H), 1.31 (t, J = 7.2 Hz, 3 H);

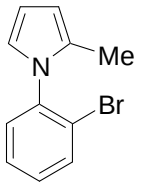
^{13}C NMR ($CDCl_3$, 75 MHz):165.4, 164.3, 141.1, 135.6, 134.6, 132.7, 130.3, 129.5, 128.0, 124.0, 112.2, 107.9, 61.8, 59.3, 14.5, 14.2, 12.2, 11.9;

IR (KBr): 2979 (m), 1722 (s), 1697 (vs), 1538 (m), 1495 (m), 1410 (m), 1254 (vs) cm^{-1};

MS (EI, 70 ev): 395 (M^+ (^{81}Br), 92%), 393 (M^+ (^{79}Br), 92%), 366 (100%), 364 (100%), 350 (31%), 348 (31%), 240 (29%), 168 (25%);

HRMS (EI): calcd. for $C_{18}H_{20}BrNO_4$ (M^+, ^{79}Br): 393.0576, **found**: 393.0552 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-phenyl)-2-methyl-*1H*-pyrrole (39u)



RHJ023G

It was prepared from 2-bromoaniline (3.44 g, 20.0 mmol), 4-oxo-pentanal[118] (2.400 g, 24.0 mmol) and $TsOH \cdot H_2O$ (38 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane) provided **39u** (4.012 g, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz):7.69 (dd, J_1= 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.20-7.44 (m, 3 H), 6.60-6.64 (m, 1 H), 6.22 (t, J = 3.5 Hz, 1 H), 6.00-6.07 (m, 1 H), 2.04 (s, 3 H);

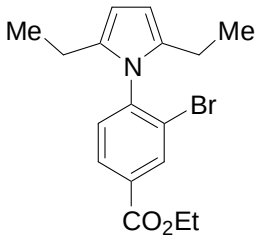
^{13}C NMR ($CDCl_3$, 75 MHz):139.6, 133.3, 129.8, 129.6, 128.0, 123.1, 121.1, 108.0, 106.9, 12.1;

IR (neat): 2914 (w), 1653 (w), 1540 (w), 1489 (s), 1437 (m), 1330 (m) cm^{-1};

MS (EI, 70 ev): 237 (M^+ (^{81}Br), 95%), 235 (M^+ (^{79}Br), 100%), 154 (65%), 128 (10%), 115 (29%), 77(41%);

HRMS (EI): calcd. for $C_{11}H_{10}BrN$ (M^+, ^{79}Br): 234.9997, **found**: 235.0001 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2,5-diethyl-pyrrol-1-yl)-benzoic acid ethyl ester (39v)



RHJ137H

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (1.220 g, 5.0 mmol), octane-3, 6-dione (0.852 g, 6.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 2.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 15: 1) provided **39v** (1.575 g, 90%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.37 (d, J = 1.8 Hz, 1 H), 8.08 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 5.98 (s, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.12-2.32 (m, 4 H), 1.41 (t, J = 7.2 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 6 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 164.5, 142.6, 134.7, 134.4, 132.0, 130.7, 129.2, 124.7, 104.4, 61.6, 19.9, 14.2, 13.0;

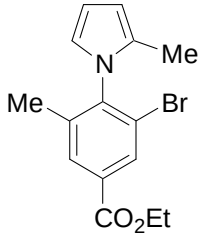
IR (neat): 2968 (m), 1721 (vs), 1598 (m), 1495 (m), 1416 (m), 1220 (vs) cm^{-1};

MS (EI, 70 ev): 351 (M^+ (^{81}Br), 30%), 349 (M^+ (^{79}Br), 30%), 334 (100%), 306 (16%), 167 (12%);

HRMS (EI): calcd. for $C_{17}H_{20}BrNO_2$ (M^+, ^{79}Br): 349.0677, **found**: 349.0656 (M^+, ^{79}Br).

[118] T. K. Hutton, K. W. Muir, D. J. Procter, *Org. Lett*. **2003**, *5*, 4811.

Synthesis of 3-bromo-5-methyl-4-(2-methyl-pyrrol-1-yl)-benzoic acid ethyl ester (39w)



RHJ050J

It was prepared from 4-amino-3-bromo-5-methyl-benzoic acid ethyl ester (893 mg, 3.5 mmol), 4-oxo-pentanal (525 mg, 5.25 mmol), and $TsOH \cdot H_2O$ (8 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39w** (789 mg, 70%) as white solid, mp.: 56.9-57.7 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.17 (s, 1 H), 7.92 (s, 1 H), 6.47 (s, 1 H), 6.26 (s, 1 H), 6.06 (s, 1 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 2.06 (s, 3 H), 1.94 (s, 3 H), 1.41 (t, *J* = 7.0 Hz, 3 H);

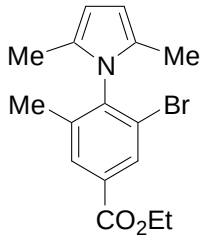
^{13}C NMR ($CDCl_3$, 75 MHz): 164.8, 142.4, 139.6, 131.58, 131.55, 130.6, 128.6, 124.2, 119.2, 108.9, 107.3, 61.6, 18.0, 14.3, 11.8;

IR (neat): 2903 (w), 1718 (vs), 1653 (m), 1559 (m), 1280 (s) cm^{-1};

MS (EI, 70 ev): 323 (M^+ (^{81}Br), 100%), 321 (M^+ (^{79}Br), 100%), 308 (86%), 306 (76%), 199 (39%), 168 (75%), 154 (97%);

HRMS (EI): calcd. for $C_{15}H_{16}BrNO_2$ (M^+, ^{79}Br): 321.0364, **found**: 321.0346 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-5-methyl-benzoic acid ethyl ester (39x)



RHJ010I

It was prepared from 4-amino-3-bromo-5-methyl-benzoic acid ethyl ester (1.032 g, 4.0 mmol), 2, 5-hexanedione (0.547 g, 6.0 mmol) and $TsOH \cdot H_2O$ (8 mg, 1.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **39x** (1.280 g, 95%) as a brown solid, mp.: 80.0-80.8 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.20 (d, *J* = 1.7 Hz, 1 H), 7.94 (s, 1 H), 5.95 (s, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.02 (s, 3 H), 1.88 (s, 6 H), 1.41 (t, *J* = 7.2 Hz, 3 H);

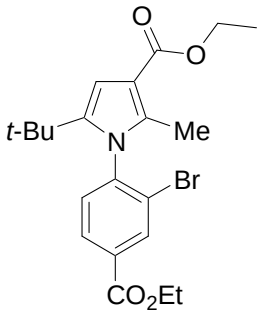
^{13}C NMR ($CDCl_3$, 75 MHz): 164.9, 141.4, 140.0, 131.7, 130.6, 126.9, 125.0, 106.3, 61,6, 18.1, 14.3, 12.2;

IR (neat): 2918 (w), 1716 (vs), 1473 (m), 1392 (s), 1284 (vs) cm^{-1};

MS (EI, 70 ev): 337 (M^+ (^{81}Br), 100%), 335 (M^+ (^{79}Br), 100%), 320 (16%), 306 (36%), 212 (19%), 168 (45%);

HRMS (EI): calcd. for $C_{16}H_{18}BrNO_2$ (M^+, ^{79}Br): 335.0521, **found**: 335.0513 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-ethoxycarbonyl-phenyl)-5-tert-butyl-2-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (39y)



RHJ172H

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (1.220 g, 5.0 mmol), 2-acetyl-5, 5-dimethyl-4-oxo-hexanoic acid ethyl ester (1.370 g, 6.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane: ether = 8: 1) provided **39y** (1.918 g, 88%) as a white solid, mp.: 105.0-106.5 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.34 (d, J = 1.9 Hz, 1 H), 8.08 (dd, J_1 = 8.1 Hz, J_2= 1.9 Hz, 1 H), 7.45 ((d, J = 8.1 Hz, 1 H), 6.46 (s, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 2.08 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 1.09 (s, 9 H);

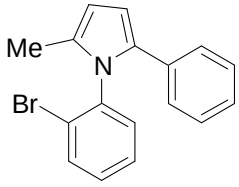
^{13}C NMR ($CDCl_3$, 150 MHz): 165.5, 164.3, 143.2, 141.6, 137.3, 134.5, 132.6, 131.7, 128.9, 125.8, 111.5, 106.9, 61.8, 59.4, 32.5, 30.7, 14.5, 14.2, 11.6;

IR (neat): 2979 (w), 1720 (s), 1699 (vs), 1574 (m), 1240 (vs) cm^{-1};

MS (EI, 70 ev): 437 (M^+ (^{81}Br), 14%), 435 (M^+ (^{79}Br), 14%), 422 (100%), 392 (14%), 225 (4%);

HRMS (EI): calcd. for $C_{21}H_{26}BrNO_4$ (M^+, ^{79}Br): 435.1045, **found**: 435.1029 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole (44a).



RHJ011K

It was prepared from 2-bromo-phenylamine (344 mg, 2.0 mmol), 1-phenyl-pentane-1, 4-dione (394 mg, 2.2 mmol) and $TsOH \cdot H_2O$ (8 mg, 2.0 mol %) according to **TP1**. Reaction time: 2 h. Purification by flash chromatography (eluent: pentane) provided **44a** (445 mg, 71%) as a white solid, mp.: 96.9-98.5 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.67 (d, *J* = 7.9 Hz, 1 H), 7.23-7.38 (m, 3 H), 7.07-7.20 (m, 5 H), 6.41 (d, *J* = 3.5 Hz, 1 H), 6.15 (d, *J* = 3.5 Hz, 1 H), 2.08 (s, 3 H);

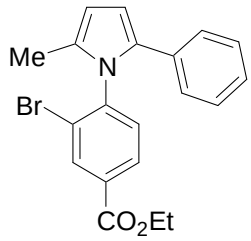
^{13}C NMR ($CDCl_3$, 75 MHz): 139.0, 134.3, 133.31, 133.28, 131.6, 131.1, 129.6, 128.1, 128.0, 127.4, 125.9, 124.4, 108.4, 107.4, 12.7;

IR (neat): 2913 (w), 1646 (w), 1602 (w), 1516 (m), 1482 (s), 1395 (m), 1022 (m) cm^{-1};

MS (EI, 70 ev): 313 (M^+ (^{81}Br), 100%), 311 (M^+ (^{79}Br), 100%), 230 (82%), 217 (85%), 154 (12%), 115 (29%);

HRMS (EI): calcd. for $C_{17}H_{14}BrN$ (M^+, ^{79}Br): 311.0310, **found**: 311.0319 (M^+, ^{79}Br).

Synthesis of 3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-benzoic acid ethyl ester (**44b**)



RHJ190G

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (1.220 g, 5.0 mmol), 1-phenyl-pentane-1, 4-dione (0.968 g, 5.5 mmol) and $TsOH \cdot H_2O$ (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 4 h. Purification by flash chromatography (eluent: pentane: ether = 20: 1) provided **44b** (1.709 g, 89%) as a brown solid, mp.: 92.3-93.6 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.32 (d, *J* = 1.8 Hz, 1 H), 7.98 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 7.05-7.17 (m, 5 H), 6.38 (d, *J* = 3.4 Hz, 1 H), 6.13 (dd, J_1 = 3.4 Hz, J_2 = 0.8 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.05 (d, *J* = 0.8 Hz, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H);

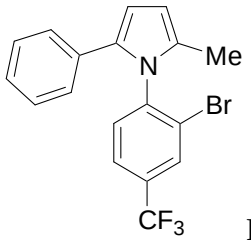
^{13}C NMR ($CDCl_3$, 75 MHz): 164.6, 143.1, 134.5, 134.4, 133.0, 131.8, 131.4, 131.0, 129.2, 128.1, 127.5, 126.1, 124.4, 108.9, 108.0, 61.6, 14.2, 12.7;

IR (neat): 2903 (w), 1716 (vs), 1598 (m), 1496 (m), 1395 (s), 1240 (vs) cm^{-1};

MS (EI, 70 ev):385 (M^+ (^{81}Br), 100%), 383 (M^+ (^{79}Br), 100%), 276 (40%), 261 (36%), 230 (63%), 115 (21%);

HRMS (EI): calcd. for $C_{20}H_{18}BrNO_2$ (M^+, ^{79}Br): 383.0521, **found**: 383.0499 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-trifluoromethyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole (44c).



RHJ024K

It was prepared from 2-bromo-4-trifluoromethyl-phenylamine (720 mg, 3.0 mmol), 1-phenyl-pentane-1, 4-dione (630 mg, 3.6 mmol) and $TsOH \cdot H_2O$ (6 mg, 1.0 mol %) according to **TP1**. Reaction time: 4 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **44c** (920 mg, 81%) as a white solid, mp.: 90.6-91.9 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.93 (s, 1 H), 7.58 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 7.03-7.20 (m, 5 H), 6.39 (d, J = 3.5 Hz, 1 H), 6.15 (d, J = 3.5 Hz, 1 H), 2.06 (s, 3 H);

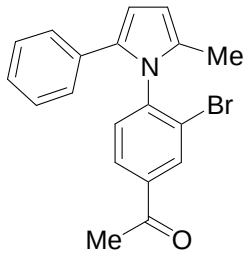
^{13}C NMR ($CDCl_3$, 75.0 MHz): 142.5, 134.5, 132.9, 131.7 (q, J_{C-F} = 33.2 Hz), 131.5, 131.4, 130.5 (q, J_{C-F} = 3.3 Hz), 128.2, 127.5, 126.3, 125.1 (q, J_{C-F} = 3.3 Hz), 124.9, 122.8, 109.1, 108.2, 12.7;

IR (neat): 2914 (w), 1605 (w), 1519 (w), 1500 (m), 1389 (m), 1325 (s), 1316 (s), 1128 (vs) cm^{-1};

MS (EI, 70 ev): 381 (M^+ (^{81}Br), 100%), 379 (M^+ (^{79}Br), 100%), 298 (54%), 285 (63%), 230 (10%), 115 (10%);

HRMS (EI): calcd. for $C_{18}H_{13}BrF_3N$ (M^+, ^{79}Br): 379.0183, **found**: 379.0193 (M^+, ^{79}Br).

Synthesis of 1-[3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-phenyl]-ethanone (44d)



RHJ071J

It was prepared from 1-(4-amino-3-bromo-phenyl)-ethanone (1.070 g, 5.0 mmol), 1-phenyl-pentane-1, 4-dione (1.056g, 6.0 mmol) and $TsOH \cdot H_2O$ (19 mg, 2.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 5: 1) provided **44d** (1.327 g, 75%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.22 (d, *J* = 1.8 Hz, 1 H), 7.88 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.05-7.20 (m, 5 H), 6.38 (d, *J* = 3.5 Hz, 1 H), 6.14 (d, *J* = 3.5 Hz, 1 H), 2.60 (s, 3 H), 2.05 (s, 3 H);

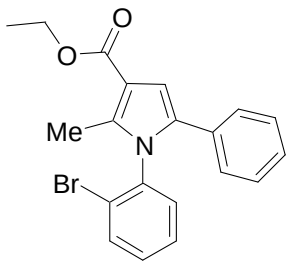
^{13}C NMR ($CDCl_3$, 75.0 MHz): 195.7, 143.2, 137.8, 134.4, 133.3, 132.9, 131.4, 131.2, 128.1, 127.8, 127.4, 126.1, 124.9, 109.0, 108.0, 26.6, 12.7;

IR (neat): 2917 (w), 1687 (vs), 1593 (m), 1490 (m), 1388 (s), 1231 (s) cm^{-1};

MS (EI, 70 ev): 355 (M^+ (^{81}Br), 100%), 353 (M^+ (^{79}Br), 100%), 274(34%), 259 (43%), 230 (95%), 115 (30%);

HRMS (ESI): calcd. for $C_{19}H_{17}BrNO$ (M^++H, ^{79}Br): 354.0494, **found**: 354.0483 (M^++H, ^{79}Br).

Synthesis of 1-(2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44e).



RHJ015K

It was prepared from 2-bromo-phenylamine (0.860 g, 5.0 mml), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (1.490 g, 6.0 mmol) and $TsOH \cdot H_2O$ (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided **44e** (1.721 g, 89%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz):7.68 (d, *J* = 7.9 Hz, 1 H), 7.07-7.40 (m, 8 H), 6.84 (s, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 2.35 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H);

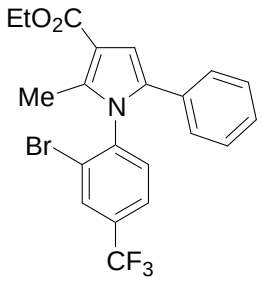
^{13}C NMR ($CDCl_3$, 75.0 MHz):165.4, 138.0, 137.7, 133.8, 133.5, 132.1, 130.8, 130.3, 128.3, 128.0, 127.9, 126.7, 124.0, 113.0, 109.8, 59.5, 14.5, 12.0;

IR (neat): 2978 (w), 1717 (vs), 1700 (m), 1559 (m), 1493 (s), 1250 (vs) cm^{-1};

MS (EI, 70 ev): 385 (M^+ (^{81}Br), 51%), 383 (M^+ (^{79}Br), 51%), 354 (49%), 274 (9%), 230 (100%), 216 (11%), 128 (11%);

HRMS (EI): calcd. for $C_{20}H_{18}BrNO_2$ (M^+, ^{79}Br): 383.0521, **found**: 383.0485 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-trifluoromethyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44f)



RHJ021K

It was prepared from 2-bromo-4-trifluoromethyl-phenylamine (1.200 g, 5.0 mmol), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (1.490 g, 6.0 mmol) and $TsOH \cdot H_2O$ (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 8: 1) provided **44f** (1.853 g, 82%) as a white solid, mp.: 81.3-82.7 °C.

^{1}H NMR ($CDCl_3$, 300 MHz):7.92 (d, J = 1.8 Hz, 1 H), 7.59 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 1 H), 7.11-7.20 (m, 3 H), 7.01-7.10 (m, 2 H), 6.81 (s, 1 H), .4.32 (q, J = 7.1 Hz, 2 H), 2.32 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H);

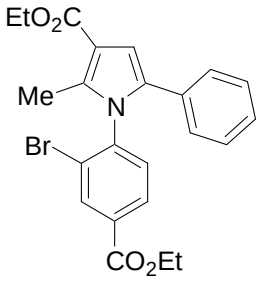
^{13}C NMR ($CDCl_3$, 75.0 MHz): 165.3, 141.1, 137.7, 133.9, 132.4 (J_{C-F} = 33.2 Hz), 131.7, 131.4, 130.7 (J_{C-F} = 3.3 Hz), 128.3, 128.0, 127.1, 125.3 (J_{C-F} = 3.3 Hz), 124.7, 122.6 (J_{C-F} = 273.1 Hz), 113.7, 110.4, 59.7, 14.5, 12.1;

IR (neat): 2986 (w), 1694 (vs), 1606 (m), 1379 (m), 1318 (s), 1223 (s), 1318 (s), 1072 (vs) cm^{-1};

MS (EI, 70 ev): 453 (M^+ (^{81}Br), 36%), 451 (M^+ (^{79}Br), 36%), 424 (40%), 342 (13%), 298 (100%), 228 (35%), 128 (37%);

HRMS (EI): calcd. for $C_{21}H_{17}BrF_3NO_2$ (M^+, ^{79}Br): 451.0395, **found**: 451.0357 (M^+, ^{79}Br).

Synthesis of 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44g)



RHJ017K

It was prepared from 4-amino-3-bromo-benzoic acid ethyl ester (452 mg, 1.8 mmol), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (546 mg, 2.2 mmol) and $TsOH \cdot H_2O$ (7 mg, 2.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 2: 1) provided **44g** (591 mg, 72%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz):8.36 (s, 1 H), 8.03 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H), 7.00-7.25 (m, 5 H), 6.85 (s, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 2.36 (s, 3 H), 1.36-1.46 (m, 6 H);

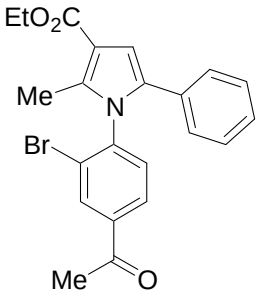
^{13}C NMR ($CDCl_3$, 75.0 MHz): 165.2, 164.2, 141.5, 137.6, 134.5, 133.8, 132.3, 131.8, 130.8, 129.2, 128.1, 127.9, 126.9, 124.1, 113.4, 110.1, 61.7, 59.5, 14.4, 14.2, 12.0;

IR (neat): 2933 (w), 1721 (s), 1700 (s), 1492 (m), 1449 (m), 1388 (m), 1274 (s), 1230 (vs) cm^{-1};

MS (EI, 70 ev): 457 (M^+ (^{81}Br), 100%), 455 (M^+ (^{79}Br), 100%), 428 (84%), 302 (43%), 274 (97%), 228 (95%), 128 (33%);

HRMS (EI): calcd. for $C_{23}H_{22}BrNO_4$ (M^+, ^{79}Br): 455.0732, **found**: 455.0741 (M^+, ^{79}Br).

Synthesis of 1-(4-acetyl-2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44h)



RHJ070J

It was prepared from 1-(4-amino-3-bromo-phenyl)-ethanone (642 mg, 3.0 mmol), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (893 mg, 3.6 mmol) and $TsOH \cdot H_2O$ (11 mg, 2.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 2: 1) provided **44h** (891 mg, 69%) as a yellow solid, mp.: 163.5-164.7 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):8.21 (d, J = 1.8 Hz, 1 H), 7.87 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 1 H), 7.03-7.20 (m, 5 H), 6.80(s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 2.59 (s, 3 H), 2.31 (s, 3 H), 1.36 (m, 3 H);

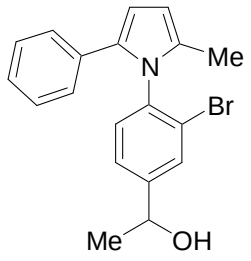
^{13}C NMR ($CDCl_3$, 75.0 MHz): 195.5, 165.3, 141.8, 138.4, 137.7, 133.8, 133.4, 131.8, 131.2, 128.2, 127.99, 127.96, 127.0, 124.7, 113.6, 110.3, 59.6, 26.6, 14.5, 12.1;

IR (neat): 2982 (w), 1682 (vs), 1558 (m), 1411 (m), 1250 (vs) cm^{-1};

MS (EI, 70 ev): 427 (M^+ (^{81}Br), 100%), 425 (M^+ (^{79}Br), 100%), 396 (84%), 382 (33%), 272 (60%), 230 (75%);

HRMS (EI): calcd. for $C_{22}H_{20}BrNO_3$ (M^+, ^{79}Br): 425.0627, **found**: 425.0598 (M^+, ^{79}Br).

Synthesis of 1-[3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-phenyl]-ethanol (44i)



RHJ042K

The $NaBH_4$ (98 mg, 2.6 mmol) was added to the solution of 1-[3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-phenyl]-ethanone **44d** (789 mg, 2.2 mmol) in CH_3OH (25 mL) at 0 ^oC. After the mixture was stirred for 2 h at this temperature, water (1.0 mL) was added and the CH_3OH was removed *in vacuo*. Purification by flash chromatography (eluent: pentane: ether =3: 1) provided **44i** (705 mg, 90%) as a yellow solid, mp.: 93.7-94.8 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):7.72 (dd, J_1 = 11.5 Hz, J_2 = 1.8 Hz, 1 H), 7.21-7.40 (m, 2 H), 7.07-7.21 (m, 5 H), 6.43 (d, J = 3.5 Hz, 1 H), 6.17 (d, J = 3.5 Hz, 1 H), 4.92 (q, J = 7.1 Hz, 1 H), 2.16 (bs, 1 H), 2.10 (s, 3 H), 1.54 (d, J = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 147.7, 137.8, 134.3, 133.3, 131.7, (130.9, 130.8), (130.15, 130.10), 128.0, 127.4, 125.9, (125.1, 125.0), (124.4, 124.3), 108.4, 107.4, 69.1, 25.2, 12.7;

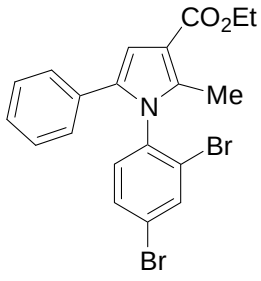
All the carbons of (130.9, 130.8), (130.15, 130.10), (125.1, 125.0), (124.4, 124.3) bearing double pearks indicate that two diastereoisomers were involved.

IR (neat): 3266 (m), 2919 (w), 1600 (w), 1515 (m), 1494 (m), 1393 (m) cm^{-1};

MS (EI, 70 ev): 357 (M^+ (^{81}Br), 100%), 355 (M^+ (^{79}Br), 100%), 276 (24%), 260 (23%), 232 (60%), 217 (65%), 115 (22%);

HRMS (EI): calcd. for $C_{19}H_{18}BrNO$ (M^+, ^{79}Br): 355.0572, **found**: 355.0572 (M^+, ^{79}Br).

Synthesis of 1-(2,4-dibromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44j)



RHJ019K

It was prepared from 2, 4-dibromo-phenylamine (1.250 g, 5.0 mmol), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (1.490 g, 6.0 mmol) and $TsOH \cdot H_2O$ (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 4: 1) provided **44j** (1.921 g, 83%) as a white solid, mp.: 103.5-105.2 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.80 (d, *J* = 2.6 Hz, 1 H), 7.45 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.13-7.20 (m, 3 H), 7.02-7.11 (m, 3 H), 6.79 (s, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.31 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H);

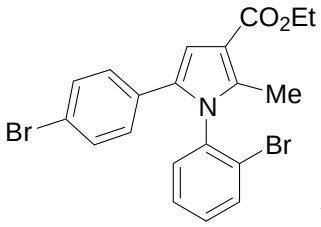
^{13}C NMR ($CDCl_3$, 75 MHz): 165.3, 137.8, 136.9, 135.9, 133.8, 131.85, 131.80, 131.5, 128.2, 128.0, 127.0, 124.9, 123.2, 113.3, 110.1, 59.6, 14.5, 12.0;

IR (neat): 2974 (w), 1694 (s), 1474 (s), 1420 (s), 1217 (s), 1072 (vs) cm^{-1};

MS (EI, 70 ev): 465 (M^+ ($^{81}Br^{81}Br$), 45%), 463 (M^+ ($^{79}Br^{81}Br$), 90%), 461 (M^+ ($^{79}Br^{79}Br$), 45%), 434 (85%), 418 (33%), 310 (65%), 274 (33%), 228 (100%), 129 (34%);

HRMS (EI): calcd. for $C_{20}H_{17}Br_2NO_2$ (M^+, $^{79}Br^{79}Br$): 460.9626; **found**: 460.9620 (M^+, $^{79}Br^{79}Br$).

Synthesis of 5-(4-bromo-phenyl)-1-(2-bromo-phenyl)-2-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester (44k)



RHJ031K

It was prepared from 2-bromo-phenylamine (0.860 g, 5.0 mmol), 3-oxo-2-(2-oxo-2-phenyl-ethyl)-butyric acid ethyl ester (1.490 g, 6.0 mmol) and $TsOH \cdot H_2O$ (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 5: 1) provided **44k** (1.995 g, 86%) as a white solid, mp.: 95.8-96.7 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.66 (d, *J* = 7.9 Hz, 1 H), 7.17-7.39 (m, 5 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.82 (s, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 2.32 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H);

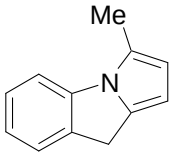
^{13}C NMR ($CDCl_3$, 75.0 MHz): 165.2, 138.4, 137.4, 133.6, 132.6, 131.2, 131.0, 130.7, 130.5, 129.3, 128.4, 123.9, 120.8, 113.2, 110.2, 59.6, 14.5, 12.0;

IR (neat): 2974 (w), 1692 (s), 1566 (m), 1558 (m), 1479 (m), 1417 (m), 1226 (s) cm^{-1};

MS (EI, 70 ev): 465 (M^+ ($^{81}Br^{81}Br$), 50%), 463 (M^+ ($^{79}Br^{81}Br$), 99%), 461 (M^+ ($^{79}Br^{79}Br$), 50%), 434 (85%), 418 (33%), 308 (99%), 274 (33%), 228 (100%), 129 (34%);

HRMS (EI): calcd. for $C_{20}H_{18}Br_2NO_2$ (M^++H, $^{79}Br^{79}Br$): 461.9704; **found**: 461.9697 (M^++H, $^{79}Br^{79}Br$).

Synthesis of 3-methyl-*8H*-3a-aza-cyclopenta[a]indene (**41a**)



RHJ167F

It was prepared from 1-(2-bromo-phenyl)-2,5-dimethyl-*1H*-pyrrole **39a** according to **TP3**. Purification by flash chromatography (eluent: hexane) provided **41a** (144 mg, 85%) as a white solid, mp.: 61.0-61.5 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.34-7.44 (m, 2 H), 7.27 (t, *J* = 7.7 Hz, 1 H), 7.06 (t, *J* = 7.7 Hz, 1 H), 6.00-6.05 (m, 1 H), 5.94-5.99 (m, 1 H), 3.80 (s, 2 H), 2.58 (s, 3 H);

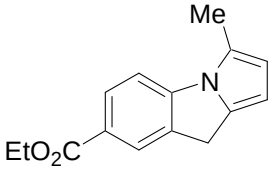
^{13}C NMR ($CDCl_3$, 75 MHz): 142.0, 135.3, 134.5, 127.2, 125.9, 122.5 (2 C), 111.2, 110.4, 100.5, 28.8, 13.2;

IR (KBr): 2918 (w), 1614 (m), 1597 (m), 1489 (s), 1455 (vs) cm^{-1};

MS (EI, 70 ev): 169 (M^+, 86%), 154 (100%), 139 (5%), 83 (27%);

HRMS (EI): calcd. for $C_{12}H_{11}N$ (M^+): 169.0891, **found**: 169.0884 (M^+).

Synthesis of 3-methyl-*8H*-3a-aza-cyclopenta[a]indene-6-carboxylic acid ethyl ester (**41b**)



RHJ057G

It was prepared from 4-(2,5-dimethyl-pyrrol-1-yl)-3-iodo-benzoic acid ethyl ester **39b** according to **TP3**. Purification by flash chromatography (eluent: hexane: ether = 20: 1) afforded **41b** (195 mg, 81%) as a white solid, mp.: 77.9-78.9 °C. The yield is 83% from **39c.**

^{1}H NMR ($CDCl_3$, 300 MHz): 7.96-8.05 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 6.03-6.05 (m, 1 H), 5.95-5.99 (m, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.79 (s, 2 H), 2.56 (d, *J* = 0.9 Hz, 3 H), 1.40 (t, *J* =7.1 Hz, 3 H);

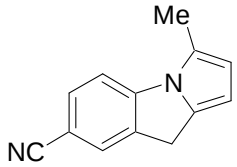
^{13}C NMR ($CDCl_3$, 75 MHz): 166.4, 145.4, 135.3, 135.2, 130.0, 127.0, 124.6, 122.8, 112.5, 109.6, 101.4, 60.8, 28.4, 14.3, 13.1;

IR (neat): 2984 (w), 1704 (s), 1612 (m), 1600 (m), 1408 (s), 1271 (s) cm^{-1};

MS (EI, 70 ev): 241 (M^+, 86%), 226 (33%), 212 (31%), 198 (32%), 168 (100%), 90 (6%);

HRMS (EI): calcd. for $C_{15}H_{15}NO_2$ (M^+): 241.1103, found: 241.1113 (M^+).

Synthesis of 3-methyl-*8H*-3a-aza-cyclopenta[a]indene-6-carbonitrile (**41c**)



RHJ062G

It was prepared from 4-(2,5-dimethyl-pyrrol-1-yl)-3-iodo-benzonitrile **39d** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41c** (136 mg, 70%) as a white solid, mp.: 171.3-171.9 °C. The yield is 60% from **39e**.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.60 (s, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 6.03-6.07 (m, 1 H), 5.97-6.00 (m, 1 H), 3.77 (s, 2 H), 2.53 (s, 3 H);

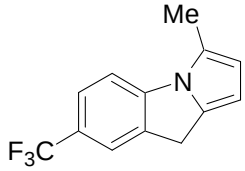
^{13}C NMR ($CDCl_3$, 75 MHz): 145.0, 136.2, 134.6, 132.6, 129.0, 122.9, 119.2, 113.2, 110.4, 105.4, 101.9, 28.3, 13.0;

IR (KBr): 2898 (m), 2220 (m), 1614 (s), 1565 (m), 1492 (s), 1411 (s) cm^{-1};

MS (EI, 70 ev): 194 (M^+, 76%), 179 (100%), 164 (6%), 140 (5%);

HRMS (EI): calcd. for $C_{13}H_{10}N_2$ (M^+): 194.0844, **found**: 194.0837 (M^+).

Synthesis of 3-methyl-6-trifluoromethyl-*8H*-3a-aza-cyclopenta[a]indene (**41d**)



RHJ089G

It was prepared from 1-(2-iodo-4-trifluoromethyl-phenyl)-2,5-dimethyl-*1H*-pyrrole **39f** according to **PT3**. Purification by flash chromatography (eluent: pentane) afforded **41d** (182 mg, 77%) as a white solid, mp.: 63.0-63.8 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.60 (s, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 6.04-6.06 (m, 1 H), 5.98-6.01 (m, 1 H), 3.81 (s, 2 H), 2.56 (s, 3 H);

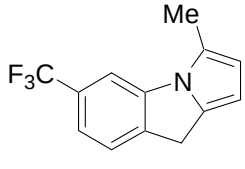
^{13}C NMR ($CDCl_3$, 75 MHz): 144.5, 136.0, 134.8, 125.2 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.5 (q, $J_{C\text{-}F}$ = 271.2 Hz), 124.6 (q, $J_{C\text{-}F}$ = 32.3 Hz), 122.9 (2 x C), 112.5, 109.9, 101.5, 28.6, 13.1;

IR (KBr): 2918 (w), 1623 (m), 1573 (w), 1497 (s), 1410 (s), 1320 (vs), 1282 (vs) cm^{-1};

MS (EI, 70 ev): 237 (M^+, 67%), 222 (100%), 168 (26%);

HRMS (EI): calcd. for $C_{13}H_{10}F_3N$ (M^+): 237.0765, **found**: 237.0773 (M^+).

Synthesis of 3-methyl-5-trifluoromethyl-*8H*-3a-aza-cyclopenta[a]indene (**41e**)



RHJ150G

It was prepared from 1-(2-bromo-5-trifluoromethyl-phenyl)-2,5-dimethyl-*1H*-pyrrole **39g** according to **TP3**. Purification by flash chromatography (eluent: pentane) afforded **41e** (153 mg, 65%) as a white solid, mp.: 51.7-52.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.54 (s, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 6.01-6.08 (m, 1 H), 5.95-6.00 (m, 1 H), 3.83 (s, 2 H), 2.58 (s, 3 H);

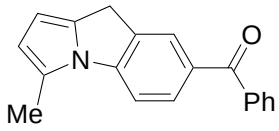
^{13}C NMR ($CDCl_3$, 75 MHz): 142.3, 139.4, 134.4, 130.0 (q, $J_{C\text{-}F}$ = 32.3 Hz), 125.9, 122.8, 124.2 (q, $J_{C\text{-}F}$ = 272.2 Hz), 119.5 (q, $J_{C\text{-}F}$ = 3.9 Hz), 112.2, 106.9 (q, $J_{C\text{-}F}$ = 3.8 Hz), 101.3, 28.7, 13.1;

IR (KBr): 2976 (w), 1629 (m), 1599 (m), 1500 (s), 1474 (vs), 1338 (vs) cm^{-1};

MS (EI, 70 ev): 237 (M^+, 77%), 235 (72%), 222 (100%), 168 (26%);

HRMS (EI): calcd. for $C_{13}H_{10}F_3N$ (M^+): 237.0765, **found**: 237.0772 (M^+).

Synthesis of (3-methyl-*8H*-3a-aza-cyclopenta[a]inden-6-yl)-phenyl-methanone (41f)



RHJ055I

It was prepared from [3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-phenyl]-phenyl-methanone **39h** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 4: 1) afforded **41f** (167 mg, 61%) as a white solid, mp.: 105.4-106.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz):7.89 (s, 1 H), 7.73-7.82 (m, 3 H), 7.54-7.60 (m, 1 H), 7.44-7.51 (m, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 6.03-6.09 (m, 1 H), 5.97-6.02 (m, 1 H), 3.84 (s, 2 H), 2.57 (d, J = 1.0 Hz, 3 H);

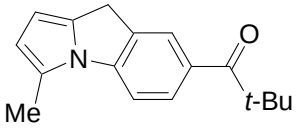
^{13}C NMR ($CDCl_3$, 75.0 MHz):195.7, 145.4, 138.2, 135.6, 135.3, 132.0, 131.8, 131.4, 129.7, 128.2, 127.8, 123.0, 112.7, 109.5, 101.7, 28.6, 13.2;

IR (KBr): 3066 (w), 1645 (m), 1607 (s), 1595 (s), 1489 (m), 1444 (m), 1408 (s) cm^{-1};

MS (EI, 70 ev): 273 (M^+, 100%), 258 (50%), 196 (10%), 168 (86%), 105 (23%);

HRMS (EI): calcd. for $C_{19}H_{15}NO$ (M^+): 273.1154, **found**: 273.1163 (M^+).

Synthesis of 6-(1-tert-butyl-vinyl)-3-methyl-*8H*-3a-aza-cyclopenta[a]indene (41g).



RHJ061J

It was prepared from 6-(1-tert-butyl-vinyl)-3-methyl-*8H*-3a-aza-cyclopenta[a]indene **39i** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 15: 1) afforded **41g** (167 mg, 66%) as a white solid, mp.: 142.4-143.8 ^{o}C.

^{1}H NMR (C_6D_6, 400 MHz): 7.74 (s, 1 H), 7.71 (d, *J* = 8.2 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.07-6.13 (m, 1 H), 5.97-6.03 (m, 1 H), 3.31 (s, 2 H), 2.23 (s, 3 H), 1.31 (s, 9 H);

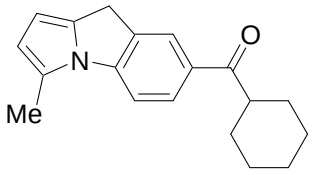
^{13}C NMR (C_6D_6, 100.0 MHz): 205.0, 144.3, 135.4, 135.1, 132.2, 129.2, 126.9, 122.5, 113.0, 109.3, 102.0, 43.9, 28.51, 28.49, 13.0;

IR (neat): 2952 (w), 1649 (s), 1609 (vs), 1569 (m), 1409 (vs), 1194 (vs) cm^{-1};

MS (EI, 70 ev): 253 (M^+, 32%), 196 (100%), 167 (30%), 153 (8%);

HRMS (EI): calcd. for $C_{17}H_{19}NO$ (M^+): 253.1467, **found**: 253.1459 (M^+).

Synthesis of cyclohexyl-(3-methyl-*8H*-3a-aza-cyclopenta[a]inden-6-yl)-methanone (41h).



RHJ063J

It was prepared from cyclohexyl-(3-methyl-*8H*-3a-aza-cyclopenta[a]inden-6-yl)-methanone **39j** according to **TP3.** Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41h** (192 mg, 69%) as a white solid, mp.: 134.0-134.6 ^oC.

^{1}H NMR (C_6D_6, 400 MHz): 7.87 (s, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 6.07-6.13 (m, 1 H), 5.97-6.03 (m, 1 H), 3.33 (s, 2 H), 3.00-3.10 (m, 1 H), 2.22 (s, 3 H), 1.82-1.96 (m, 2 H), 1.50-1.80 (m, 5 H), 1.10-1.32 (m, 3 H);

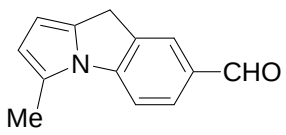
^{13}C NMR (C_6D_6, 100.0 MHz): 201.0, 145.4, 136.0, 135.3, 131.3, 129.2, 126.3, 122.7, 113.3, 109.8, 102.2, 45.6, 30.0, 28.5, 26.4, 26.2, 13.1;

IR (neat): 2917 (w), 1668 (s), 1610 (w), 1593 (m), 1495 (m), 1180 (m) cm^{-1};

MS (EI, 70 ev): 279 (M^+, 26%), 264 (1%), 224 (4%), 211 (3%), 196 (100%), 168 (25%);

HRMS (EI): calcd. for $C_{19}H_{21}NO$ (M^+): 279.1623, **found**: 279.1609 (M^+).

Synthesis of 3-methyl-*8H*-3a-aza-cyclopenta[a]indene-6-carbaldehyde (41i)



RHJ056I

It was prepared from 3-bromo-4-(2,5-dimethyl-pyrrol-1-yl)-benzaldehyde **39k** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41i** (108 mg, 55%) as a white solid, mp.: 111.1-111.8.0 ^oC

^{1}H NMR ($CDCl_3$, 300 MHz): 9.92 (s, 1 H), 7.88 (s, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 6.04-6.10 (m, 1 H), 5.95-6.03 (m, 1 H), 3.83 (s, 2 H), 2.57 (s, 3 H);

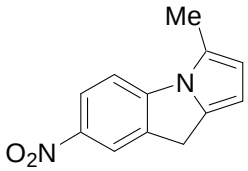
^{13}C NMR ($CDCl_3$, 75.0 MHz): 190.9, 146.7, 136.3, 135.4, 131.9, 131.4, 126.2, 123.1, 113.2, 110.1, 101.9, 28.4, 13.2;

IR (neat): 2892 (w), 1683 (s), 1607 (s), 1567 (m), 1493 (s), 1207 (s) cm^{-1};

MS (EI, 70 ev): 197 (M^+, 100%), 182 (90%), 168 (91%), 154 (16%), 139 (8%);

HRMS (EI): calcd. for $C_{13}H_{11}NO$ (M^+): 197.0841, **found**: 197.0841 (M^+).

Synthesis of 3-methyl-6-nitro-*8H*-3a-aza-cyclopenta[a]indene (41j)



RHJ063G

It was prepared from 1-(2-iodo-4-nitro-phenyl)-2,5-dimethyl-*1H*-pyrrole **39l** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 6: 1) afforded **41j** (70 mg, 33%) as golden crystals, mp.: 142.0-142.5 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.19-8.25 (m, 2 H), 7.37 (d, *J* = 7.1 Hz, 1 H), 6.06-6.09 (m, 1 H), 6.00-6.02 (m, 1 H), 3.83 (s, 2 H), 2.55 (s, 3 H);

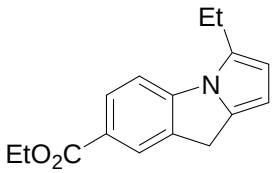
^{13}C NMR ($CDCl_3$, 75 MHz): 146.6, 143.0, 136.4, 135.3, 124.8, 123.2, 121.5, 113.7, 109.4, 102.5, 28.5, 13.0;

IR (KBr): 2906 (w), 1620 (m), 1601 (m), 1574 (m), 1508 (s), 1486 (s) cm^{-1};

MS (EI, 70 ev): 214 (M^+, 100%), 199 (76%), 167 (89%), 153 (35%);

HRMS (EI): calcd. for $C_{12}H_{10}N_2O_2$ (M^+): 214.0742, **found**: 214.0753 (M^+).

Synthesis of 3-ethyl-*8H*-3a-aza-cyclopenta[a]indene-6-carboxylic acid ethyl ester (41k)



RHJ154H

It was prepared from 3-bromo-4-(2-ethyl-5-methyl-pyrrol-1-yl)-benzoic acid ethyl ester **39n** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 15:1) afforded **41k** (179 mg, 70%) as a white solid, mp.: 66.5-67.5 ^oC

^{1}H NMR ($CDCl_3$, 300 MHz): 8.03 (s, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 6.05-6.10 (m, 1 H), 5.98-6.03 (m, 1 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 3.82 (s, 2 H), 2.95 (q, *J* = 7.6 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H), 1.35 (t, *J* = 7.6 Hz, 3 H);

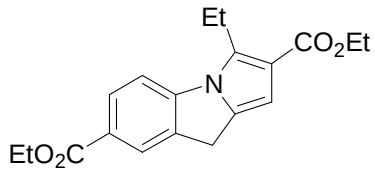
^{13}C NMR ($CDCl_3$, 75 MHz): 166.4, 145.3, 135.4, 135.3, 130.1, 129.6, 127.0, 124.6, 110.5, 110.0, 101.4, 60.8, 28.5, 20.6, 14.4, 13.0;

IR (KBr): 2982 (m), 1710 (vs), 1602 (m), 1614 (m), 1489 (s) cm^{-1};

MS (EI, 70 ev): 255 (M^+, 100%), 240 (44%), 226 (100%), 198 (23%), 167 (60%);

HRMS (EI): calcd. for $C_{16}H_{17}NO_2$ (M^+): 255.1259; **found**: 255.1252 (M^+).

Synthesis of 3-ethyl-*8H*-3a-aza-cyclopenta[a]indene-2,6-dicarboxylic acid diethyl ester (41l)



RHJ181H

It was prepared from 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2-ethyl-5-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **39o** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 3: 1) afforded **41l** (262 mg, 80%) as a white solid, mp.: 115.0-116.0 ^oC

^{1}H NMR ($CDCl_3$, 600 MHz): 8.04-8.08 (m, 2 H), 7.45 (d, *J* = 9.0 Hz, 1 H), 6.46 (t, *J* = 1.6 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 2 H), 3.34 (q, *J* = 7.6 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.6 Hz, 3 H);

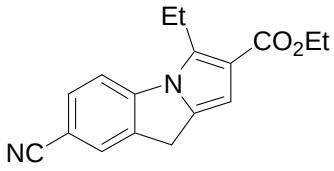
^{13}C NMR ($CDCl_3$, 150 MHz): 166.1, 165.3, 144.3, 135.9, 135.8, 134.1, 130.3, 127.2, 126.2, 116.6, 111.3, 103.4, 61.0, 59.5, 28.3, 19.0, 14.4, 14.3, 13.8;

IR (neat): 2971 (m), 1712 (vs), 1701 (vs), 1616 (m), 1490 (s), 1263 (s) cm^{-1};

MS (EI, 70 ev): 327 (M^+, 74%), 312 (34%), 298 (53%), 282 (28%), 254 (100%), 211 (20%), 180 (30%);

HRMS (EI): calcd. for $C_{19}H_{21}NO_4$ (M^+): 327.1471; **found**: 327.1477 (M^+).

Synthesis of 6-cyano-3-ethyl-*8H*-3a-aza-cyclopenta[a]indene-2-carboxylic acid ethyl ester (41m)



RHJ183H

It was prepared from 1-(2-bromo-4-cyano-phenyl)-2-ethyl-5-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **39p** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 3: 1) afforded **41m** (227 mg, 81%) as a white solid, mp.: 174.1-175.4 ^oC

^{1}H NMR ($CDCl_3$, 600 MHz): 7.66 (s, 1 H), 7.65 (d, *J* = 8.6 Hz, 1 H), 7.49 (d, *J* = 8.6 Hz, 1 H), 6.48 (t, *J* = 1.6 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 3.85 (s, 2 H), 3.32 (q, *J* = 7.6 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.6 Hz, 3 H);

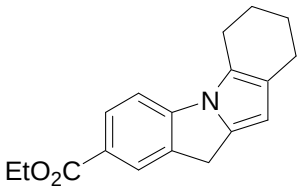
^{13}C NMR ($CDCl_3$, 150 MHz): 165.0, 144.1, 136.8, 136.0, 133.5, 132.9, 129.4, 118.8, 117.3, 112.2, 107.3, 103.8, 59.7, 28.3, 18.9, 14.4, 13.7;

IR (neat): 2979 (m), 2218 (s), 1694 (vs), 1612 (m), 1485 (s) cm^{-1};

MS (EI, 70 ev): 280 (M^+, 84%), 265 (34%), 251 (73%), 235 (48%), 207 (100%), 192(55%);

HRMS (EI): calcd. for $C_{17}H_{16}N_2O_2$ (M^+): 280.1212, **found**: 280.1226 (M^+).

Synthesis of 6, 8, 9, 11-tetrahydro-*7H*-indolo[1,2-a]indole-2-carboxylic acid ethyl ester (41n)



RHJ005I

It was prepared from 3-bromo-4-(2-methyl-4,5,6,7-tetrahydro-indol-1-yl)-benzoic acid ethyl ester **39q** according to **TP3.** Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41n** (180 mg, 64%) as a white solid, mp.: 127.0-127.5 ^oC

^{1}H NMR ($CDCl_3$, 300 MHz):8.05 (s, 1 H), 8.04 (d, *J* = 8.1 Hz, 1 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 5.94 (s, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 3.84 (s, 2 H), 2.98 (t, *J* = 5.6 Hz, 2 H), 2.62 (t, *J* = 5.6 Hz, 2 H), 1.89-2.04 (m, 2 H), 1.77-1.89 (m, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H);

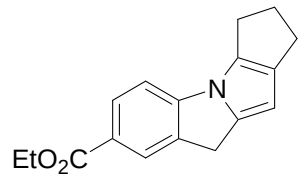
^{13}C NMR ($CDCl_3$, 75 MHz): 166.5, 145.3, 134.8, 134.3, 130.2, 126.9, 124.1, 123.9, 121.8, 109.2, 101.5, 60.7, 28.5, 23.7, 23.3, 23.2, 22.7, 14.4;

IR (neat): 2920 (w), 1706 (s), 1617 (m), 1498 (m), 1444 (m), 1278 (s) cm^{-1};

MS (EI, 70 ev): 281 (M, 100%), 253 (M^+, 62%), 236 (10%), 208 (58%), 180 (53%);

HRMS (EI): calcd. for $C_{18}H_{19}NO_2$ (M^+): 281.1416, **found**: 281.1396 (M^+).

Synthesis of tetracyclic heterocycle 41o



RHJ016I

It was prepared from 3-bromo-4-(2-methyl-5,6-dihydro-*4H*-cyclopenta[b]pyrrol-1-yl)-benzoic acid ethyl ester **39r** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41o** (159 mg, 60%) as a white solid, mp.:108.3-109.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.97-8.02 (m, 2 H), 7.12 (d, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1 H), 5.92 (t, J = 1.7 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 3.81 (s, 2 H), 2.91-3.00 (m, 2 H), 2.62-2.74 (m, 2 H), 2.43-2.54 (m, 2 H), 1.39 (t, J = 7.2 Hz, 3 H);

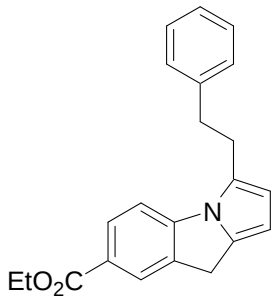
^{13}C NMR ($CDCl_3$, 75 MHz): 166.5, 144.4, 139.1, 134.3, 133.2, 130.2, 128.9, 127.0, 124.3, 108.6, 98.6, 60.7, 29.1, 29.0, 25.6, 24.6, 14.4;

IR (neat): 2852 (m), 1712 (s), 1614 (m), 1503 (s), 1269 (vs), 1254 (s) cm^{-1};

MS (EI, 70 ev): 267 (M^+, 70%), 239 (100%), 222 (10%), 211 (18%), 194 (63%);

HRMS (EI): calcd. for $C_{17}H_{17}NO_2$ (M^+): 267.1259, **found**: 267.1245 (M^+).

Synthesis of 3-phenethyl-*8H*-3a-aza-cyclopenta[a]indene-6-carboxylic acid ethyl ester (41p)



RHJ044I

It was prepared from 3-bromo-4-(2-methyl-5-phenethyl-pyrrol-1-yl)-benzoic acid ethyl ester **39s** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **41p** (188 mg, 57%) as a yellow solid, mp.:69.0-70.1^{o}C

^{1}H NMR ($CDCl_3$, 600 MHz):8.08 (s, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 7.34-7.40 (m, 3 H), 7.25-7.33 (m, 3 H), 6.16 (d, J = 2.9 Hz, 1 H), 6.05-6.09 (m, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 3.86 (s, 2 H), 3.26 (t, J = 8.1 Hz, 2 H), 3.08 (t, J = 8.1 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H);

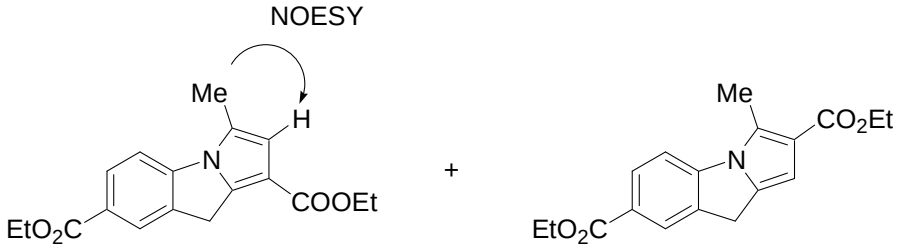
^{13}C NMR ($CDCl_3$, 150 MHz): 166.3, 145.2, 141.2, 135.4, 130.1, 128.5, 128.3, 127.2, 127.0, 126.1, 124.7, 111.6, 109.9, 101.5, 60.8, 35.2, 29.3, 28.4, 14.3;

IR (KBr): 2986 (w), 1698 (vs), 1619 (s), 1492 (vs), 1285 (vs) cm^{-1};

MS (EI, 70 ev): 331 (M^+, 11%), 286 (4%), 240 (100%), 167 (63%);

HRMS (EI): calcd. for $C_{22}H_{21}NO_2$ (M^+): 331.1572, **found**: 331.1569 (M^+).

Synthesis of 3-methyl-*8H*-3a-aza-cyclopenta[a]indene-1,6-dicarboxylic acid diethyl ester (41q) and 3-methyl-*8H*-3a-aza-cyclopenta[a]indene-2,6-dicarboxylic acid diethyl ester (41r)



41q **41r** RHJ265H

It was prepared from 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2,5-dimethyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **39t** according to **TP3**. Short flash chromatography (eluent: pentane: ether = 1: 1) afforded the mixture of **41q** and **41r** (251 mg, 80%, **41q**: **41r** = 2: 1) as a white solid. Repeated purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the more polar pure compound **41q** as a white solid, mp.: 132.5-133.0 ^{o}C

The data for more polar compound **41q** (The structureof **41q** was determined by H-H NOESY):

^{1}H NMR ($CDCl_3$, 300 MHz): 8.10 (s, 1 H), 8.05 (d, *J* = 8.3 Hz, 1 H), 7.42 (d, *J* = 8.3 Hz, 1 H), 6.43 (q, *J* = 1.0 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 4.00 (s, 2 H), 2.54 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H);

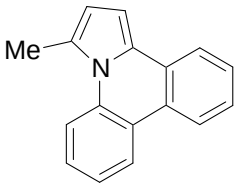
^{13}C NMR ($CDCl_3$, 75 MHz): 166.1, 164.6, 144.7, 141.6, 135.2, 130.1, 127.2, 125.9, 124.0, 112.6, 110.6, 109.2, 61.0, 59.7, 30.4, 14.5, 14.3, 13.1;

IR (neat): 2975 (w), 1712 (vs), 1677 (vs), 1607 (m), 1580 (s), 1083 (vs) cm^{-1};

MS (EI, 70 ev): 313 (M^+, 52%), 284 (100%), 268 (21%), 240 (88%), 212 (24%), 167 (32%);

HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ (M^+): 313.1314, **found**: 313.1291 (M^+).

Synthesis of 3-methyl-pyrrolo[1,2-f]phenanthridine (45a).



RHJ014K

It was prepared from 1-(2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole **44a** according to **TP3**. Purification by flash chromatography (eluent: pentane) afforded **45a** (215 mg, 93%) as a white solid, mp.: 97.8-99.6 ºC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.35 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 8.27 (d, *J* = 8.8 Hz, 1 H), 8.20 (, *J* = 7.9 Hz, 1 H), 7.97 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.40-7.50 (m, 2 H), 7.30-7.39 (m, 2 H), 6.91 (d, *J* = 3.5 Hz, 1 H), 6.45 (d, *J* = 3.5 Hz, 1 H), 2.93 (s, 3 H);

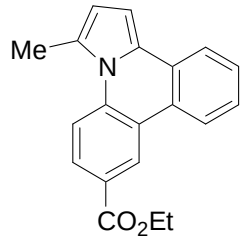
^{13}C NMR ($CDCl_3$, 75 MHz):135.6, 130.1, 128.0, 127.6, 127.2, 126.8, 125.4, 124.4, 123.8, 123.3, 122.9, 122.24, 122.21, 116.7, 113.7, 100.8, 18.9;

IR (neat): 1517 (m), 1438 (m), 1337 (m), 733 (vs) cm^{-1};

MS (EI, 70 ev): 231 (M^+, 96%), 230 (100%), 215 (2%), 202 (8%), 114 (15%);

HRMS (EI): calcd. for $C_{17}H_{13}N$ (M^+): 231.1048, **found**: 231.1058 (M^+).

Synthesis of 3-methyl-pyrrolo[1,2-f]phenanthridine-7-carboxylic acid ethyl ester (**45b)**



RHJ003H

It was prepared from 3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-benzoic acid ethyl ester **44b** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 15: 1) afforded **45b** (258 mg, 85%) as a white solid, mp.: 118.0-119.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.99 (d, J = 2.0 Hz, 1 H), 8.18-8.29 (m, 2 H), 8.06 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 7.90-7.95 (m, 1 H), 7.33-7.47 (m, 2 H), 6.88 (d, J = 3.8 Hz, 1 H), 6.45 (dd, J_1 = 3.8 Hz, J_2 = 0.8 Hz, 1 H), 4.44 (q, J = 7.1 Hz, 2 H), 2.89 (s, 3 H), 1.45 (t, J = 7.1 Hz, 3 H);

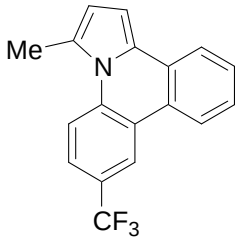
^{13}C NMR ($CDCl_3$, 75 MHz): 166.2, 138.4, 130.4, 128.53, 128.46, 127.6, 126.7, 125.7 (2 C), 125.0, 123.9, 122.7, 122.5, 122.2, 116.3, 114.6, 101.5, 61.1, 18.9, 14.4;

IR (KBr): 2976 (w), 1709 (vs), 1616 (m), 1519 (m), 1451 (m), 1287 (s), 1261 (s) cm^{-1};

MS (EI, 70 ev): 303 (M^+, 100%), 274 (74%), 228 (51%), 129 (10%), 114 (13%);

HRMS (EI): calcd. for $C_{20}H_{17}NO_2$ (M^+): 303.1259, **found**: 303.1234 (M^+).

Synthesis of 3-methyl-7-trifluoromethyl-pyrrolo[1,2-f]phenanthridine (45c).

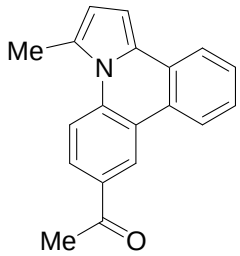


RHJ025K

It was prepared from 1-(2-bromo-4-trifluoromethyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole **44c** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 15:1) afforded **45c** (258 mg, 85%) as a white solid: mp.: 152.7-153.6 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.46 (s, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.08 (d, *J* = 7.9 Hz, 1 H), 7.87 (d, *J* = 7.9 Hz, 1 H), 7.60 (dd, J_1 = 8.0 Hz, J_2 = 2.6 Hz, 1 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.32 (t, *J* = 8.8 Hz, 1 H), 6.84 (d, *J* = 3.5 Hz, 1 H), 6.42 (d, *J* = 3.5 Hz, 1 H), 2.84 (s, 3 H);
^{13}C NMR ($CDCl_3$, 75 MHz): 137.3, 130.1, 128.8, 127.5, 126.8, 125.6, 125.0 (q, J_{C-F} = 33.0 Hz), 124.3 (q, J_{C-F} = 272.0 Hz), 123.9 (q, J_{C-F} = 3.3 Hz), 123.3, 123.0, 122.22, 122.18, 120.9 (q, J_{C-F} = 3.3 Hz), 116.8, 114.5, 101.5, 18.8;
IR (neat): 1611 (w), 1599 (w), 1518 (m), 1450 (m), 1344 (s), 1311 (s), 1108 (vs) cm^{-1};
MS (EI, 70 ev): 299 (M^+, 100%), 298 (100%), 280 (5%), 228 (33%), 139 (10%), 114 (10%);
HRMS (EI): calcd. for $C_{18}H_{12}F_3N$ (M^+): 299.0922, **found**: 299.0900 (M^+).

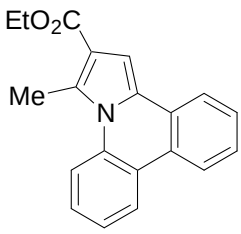
Synthesis of 1-(3-methyl-pyrrolo[1,2-f]phenanthridin-7-yl)-ethanone (45d)



RHJ037K

It was prepared from 1-[3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-phenyl]-ethanone **44d** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 2: 1 afforded **45d** (167 mg, 61%) as a brown solid, mp.: 180.0-181.0 ^oC.
^{1}H NMR ($CDCl_3$, 300 MHz): 8.81 (d, *J* = 2.6 Hz, 1 H), 8.15 (t, *J* = 8.8 Hz, 2 H), 7.89 (d, *J* = 8.8 Hz, 2 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.33 (t, *J* = 7.9 Hz, 1 H), 6.85 (d, *J* = 3.5 Hz, 1 H), 6.42 (d, *J* = 3.5 Hz, 1 H), 2.84 (s, 3 H), 2.64 (s, 3 H);
^{13}C NMR ($CDCl_3$, 75.0 MHz): 196.8, 138.4, 131.6, 130.4, 128.6, 127.6, 127.4, 126.7, 125.7, 124.2, 123.8, 122.6, 122.3, 122.2, 116.3, 114.7, 101.6, 26.4, 18.9;
IR (neat): 2961 (w), 1681 (s), 1605 (s), 1517 (m), 1380 (m), 1356 (m) cm^{-1};
MS (EI, 70 ev): 273 (M^+, 100%), 228 (50%), 215 (5%), 129 (10%), 114 (11%);
HRMS (EI): calcd. for $C_{19}H_{15}NO$ (M^+): 273.1154, **found**: 273.1131 (M^+).

Synthesis of 3-methyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (45e).



RHJ016K

It was prepared from 1-(2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44e** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 15: 1) afforded **45e** (251 mg, 83%) as a white solid, mp.: 148.8-150.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.32 (t, *J* = 8.8 Hz, 2 H), 8.18 (d, *J* = 7.9 Hz, 1 H), 7.98 (d, *J* = 7.1 Hz, 1 H), 7.38-7.51 (m, 4 H), 7.35 (s, 1 H), 4.36 (q, *J* = 7.5 Hz, 2 H), 3.22 (s, 3 H), 1.41 (t, *J* = 7.5 Hz, 3 H);

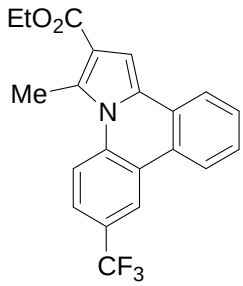
^{13}C NMR ($CDCl_3$, 75 MHz): 165.6, 134.6, 133.3, 133.0, 128.9, 128.2, 127.5, 126.13, 126.09, 124.7, 124.4, 123.8, 122.4, 122.1, 117.8, 116.2, 103.0, 59.8, 16.5, 14.5;

IR (neat): 2954 (w), 1689 (s), 1528 (m), 1412 (m), 1214 (vs) cm^{-1};

MS (EI, 70 ev): 303 (M^+, 91%), 274 (100%), 258 (10%), 228 (78%), 114 (12%);

HRMS (EI): calcd. for $C_{20}H_{17}NO_2$ (M^+): 303.1259, **found**: 303.1271 (M^+).

Synthesis of 3-methyl-7-trifluoromethyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (45f).



RHJ023K

It was prepared from 1-(2-bromo-4-trifluoromethyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44f** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 3:1 afforded **45f** (319 mg, 86%) as a white solid, mp.: 154.2-156.1 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.11 (s, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.72 (d, *J* = 7.9 Hz, 1 H), 7.51 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.39 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.10-7.23 (m, 2 H), 6.90 (s, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 2.84 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H);

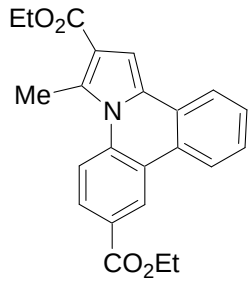
^{13}C NMR ($CDCl_3$, 75 MHz): 165.1, 136.1, 132.9, 128.8, 128.4, 126.2, 125.9 (q, J_{C-F} = 33.2 Hz), 125.8, 123.9 (q, J_{C-F} = 272.0 Hz), 123.6 (q, J_{C-F} = 3.3 Hz), 123.55, 123.2, 122.1, 121.8, 120.6 (q, J_{C-F} = 3.3 Hz), 117.6, 116.7, 103.3, 59.9, 16.2, 14.4;

IR (neat): 1605 (w), 1519 (w), 1389 (m), 1325 (s), 1316 (s), 1128 (vs) cm^{-1};

MS (EI, 70 ev): 371 (76%), 342 (100%), 326 (11%), 298 (33%), 228 (49%);

HRMS (EI): calcd. for $C_{21}H_{16}F_3NO_2$ (M^+): 371.1133, **found**: 371.1141 (M^+).

Synthesis of 3-methyl-pyrrolo[1,2-f]phenanthridine-2, 7-dicarboxylic acid diethyl ester (45g).



RHJ018K

It was prepared from 1-(2-bromo-4-ethoxycarbonyl-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44g** according to **TP3.** Purification by flash chromatography (eluent: pentane: ether = 3:1) afforded **45g** (315 mg, 84%) as a white solid, mp.: 187.3-189.1 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz):8.78 (d, *J* = 1.8 Hz, 1 H), 8.02-8.12 (m, 2 H), 7.94 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.79 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.26-7.41 (m, 2 H), 7.17 (s, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 3.06 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H);

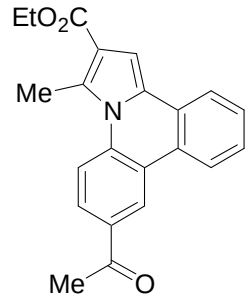
^{13}C NMR ($CDCl_3$, 75.0 MHz): 165.8, 165.3, 137.3, 133.3, 132.2, 130.4, 129.1, 128.7, 128.2, 126.4, 126.0, 125.4, 124.1, 123.5, 122.3, 117.4, 116.9, 103.4, 61.1, 60.0, 16.5, 14.45, 14.37;

IR (neat): 2928 (w), 1716 (vs), 1703 (vs), 1526 (m), 1246 (m), 1210 (vs) cm^{-1};

MS (EI, 70 ev): 375 (100%), 346 (83%), 330 (11%), 318 (13%), 273 (12%), 228 (80%);

HRMS (EI): calcd. for $C_{23}H_{21}NO_4$ (M^+): 375.1471, **found**: 375.1453 (M^+).

Synthesis of 7-acetyl-3-methyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (45h)



RHJ044K

It was prepared from 1-(4-acetyl-2-bromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44h** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 2:1) afforded **45h** (159 mg, 46%) as a white solid, mp.: 187.7-189.9 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz):8.65 (d, *J* = 2.6 Hz, 1 H), 7.98-8.06 (m, 2 H), 7.74-7.82 (m, 2 H), 7.25-7.40 (m, 2 H), 7.16 (s, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 3.01 (s, 3 H), 2.61 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H);

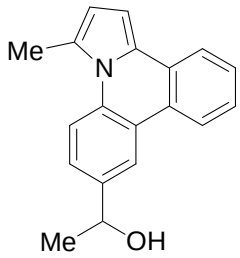
^{13}C NMR ($CDCl_3$, 75.0 MHz): 196.5, 165.2, 137.4, 133.3, 132.4, 129.0, 128.8, 127.2, 126.5, 126.0, 124.1, 124.0, 123.6, 122.4, 122.2, 117.4, 117.0, 103.5, 60.0, 26.4, 16.5, 14.5;

IR (neat): 2984 (w), 1700 (vs), 1678 (vs), 1604 (m), 1531 (m), 1217 (vs) cm^{-1};

MS (EI, 70 ev): 345 (100%), 316 (99%), 300 (10%), 273 (16%), 228 (80%);

HRMS (EI): calcd. for $C_{22}H_{19}NO_3$ (M^+): 345.1365, **found**: 345.1378 (M^+).

Synthesis of 1-(3-methyl-pyrrolo[1,2-f]phenanthridin-7-yl)-ethanol (45i)



RHJ045K

It was prepared from 1-[3-bromo-4-(2-methyl-5-phenyl-pyrrol-1-yl)-phenyl]-ethanol **44i** according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 2: 1) afforded **45i** (146 mg, 53%) as a white solid, mp.: 144.8-145.9 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):8.25 (d, *J* = 2.2 Hz, 1 H), 8.16 (d, *J* = 7.9 Hz, 1 H), 8.14 (d, *J* = 8.8 Hz, 1 H), 7.94 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1 H), 7.25-7.45 (m, 3 H), 6.88 (d, *J* = 4.4 Hz, 1 H), 6.42 (d, *J* = 4.4 Hz, 1 H), 4.98 (q, *J* = 6.2 Hz, 1 H), 2.87 (s, 3 H), 2.00 (bs, 1 H), 1.55 (d, *J* = 6.2 Hz, 3 H);

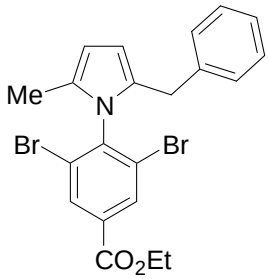
^{13}C NMR ($CDCl_3$, 75 MHz): 140.6, 134.7, 130.1, 128.1, 127.1, 126.8, 125.3, 124.7, 124.3, 122.8, 122.26, 122.21, 120.4, 116.7, 113.6, 100.7, 70.1, 25.3, 18.8;

IR (neat): 3308 (m), 2967 (w), 1518 (m), 1449 (m), 1526 (m), 774 (s) cm^{-1};

MS (EI, 70 ev): 257 (M^+-H_2O, 100%), 241 (6%), 228 (10%), 127 (13%);

HRMS (EI): calcd. for $C_{19}H_{17}NO$ (M^+): 275.1310, **found**: 275.1287 (M^+).

Synthesis of 4-(2-benzyl-5-methyl-pyrrol-1-yl)-3,5-dibromo-benzoic acid ethyl ester (**46a**)



RHJ012H

It was prepared according to **TP1**. 4-Amino-3,5-dibromo-benzoic acid ethyl ester (1.615 g, 5.0 mmol), 1-phenyl-hexane-2,5-dione (1.14 g, 6.0 mmol) and TsOH·H_2O (20 mg, 2.0 mol %) were dissolved in toluene (20 mL) and heated in a flask equipped with a Dean-Stark apparatus for 3 h. After cooling, another part of 1-phenyl-hexane-2, 5-dione (1.140 g, 6.0 mmol) was added to the mixture and refluxed for 3 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo.* Purification by flash chromatography (eluent: pentane: ether = 30: 1) provided **46a** (1.322g, 55%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.30 (s, 2 H), 7.15-7.21 (m, 3 H), 7.01-7.06 (m, 2 H), 6.01-6.05 (m, 1 H), 5.93 (d, *J* = 3.1 Hz, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 3.61 (s, 2 H), 1.97 (s, 3 H), 1.46 (t, *J* = 7.1 Hz, 3 H);

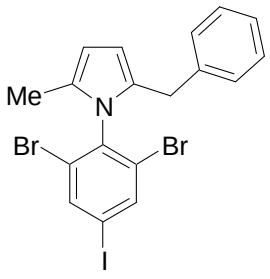
^{13}C NMR ($CDCl_3$, 75 MHz): 163.3, 141.3, 138.5, 133.0, 132.8, 131.0, 128.9, 128.0, 127.8, 126.1, 126.0, 107.6, 106.7, 61.9, 33.6, 14.1, 12.0;

IR (KBr): 2981 (m), 1726 (vs), 1543 (m), 1399 (s), 1265 (vs) cm^{-1};

MS (EI, 70 ev): 479 (M^+ ($^{81}Br^{81}Br$), 57%), 477 (M^+ ($^{81}Br^{79}Br$), 100%), 475 (M^+ ($^{79}Br^{79}Br$), 57%), 400 (71%), 372 (31%), 167 (30%);

HRMS (EI): calcd. for $C_{21}H_{19}Br_2NO_2$ (M^+,$^{79}Br^{79}Br$): 474.9783, **found**: 474.9766 (M^+, $^{79}Br^{79}Br$).

Synthesis of 2-benzyl-1-(2,6-dibromo-4-iodo-phenyl)-5-methyl-*1H*-pyrrole (46b)



RHJ058I

It was prepared according to **TP1**. 2, 6-Dibromo-4-iodo-phenylamine[119] (1.885 g, 5.0 mmol), 1-phenyl-hexane-2,5-dione (1.141 g, 6.0 mmol) and TsOH·H_2O (10 mg, 1.0 mol %) were dissolved in toluene (20 mL) and heated in a flask equipped with a Dean-Stark apparatus for 3

[119] J. Chae, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 3336.

h. After cooling, another part of 1-phenyl-hexane-2, 5-dione (1.140 g, 6.0 mmol) was added to the mixture and refluxed for 3 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 30: 1) provided **46b** (1.460 g, 55%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.94 (s, 2 H), 7.12-7.21 (m, 3 H), 6.98-7.05 (m, 2 H), 5.97 (d, *J* = 3.5 Hz, 1 H), 5.87 (d, *J* = 3.5 Hz, 1 H), 3.57 (s, 2 H), 1.94 (s, 3 H);

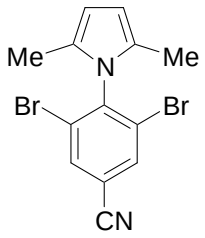
^{13}C NMR ($CDCl_3$, 75 MHz): 140.5, 140.4, 138.7, 137.5, 131.2, 129.1, 128.1, 126.8, 126.1, 107.5, 106.6, 94.1, 33.7, 12.1;

IR (neat): 2907 (w), 1528 (m), 1450 (vs) cm^{-1};

MS (EI, 70 ev): 531 (M^+ ($^{81}Br^{79}Br$), 100%), 454 (78%), 404 (10%), 327 (12%), 241 (11%);

HRMS (EI): calcd. for $C_{18}H_{13}Br_2IN$ (M^+-H, $^{79}Br^{79}Br$): 527.8459, **found**: 527.8437 (M^+-H, $^{79}Br^{79}Br$).

Synthesis of 3,5-dibromo-4-(2,5-dimethyl-pyrrol-1-yl)-benzonitrile (46c)



RHJ110G

It was prepared from 4-amino-3,5-dibromo-benzonitrile (5.520 g, 20.0 mmol), hexane-2,5-dione (4.790 g, 42.0 mmol) and $TsOH{\cdot}H_2O$ (38 mg, 2.0 mol %) according to **TP1**. Reaction time: 10 h. Purification by flash chromatography (eluent: pentane: ether = 5: 1) provided **46c** (3.186 g, 45%) as a white solid, mp.: 132.0 ^{o}C decompose.

^{1}H NMR ($CDCl_3$, 300 MHz):7.96 (s, 2 H), 5.97 (s, 2 H), 1.93 (s, 6 H);

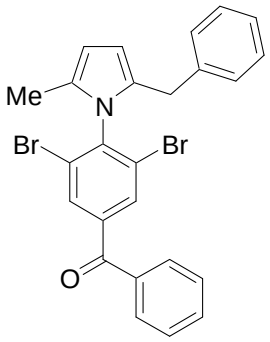
^{13}C NMR ($CDCl_3$, 75 MHz):142.7, 135.4, 127.1, 126.9, 115.3, 115.1, 107.1, 12.2;

IR (KBr): 2911 (w), 2238 (m), 1532 (s), 1471 (vs) cm^{-1};

MS (EI, 70 ev): 354 (M^+ ($^{81}Br^{79}Br$), 100%), 259 (7%), 192 (16%), 179 (22%);

HRMS (EI): calcd. for $C_{13}H_{10}Br_2N_2$ (M^+, $^{79}Br^{79}Br$): 351.9211, **found**: 351.9191 (M^+, $^{79}Br^{79}Br$).

Synthesis of [4-(2-benzyl-5-methyl-pyrrol-1-yl)-3,5-dibromo-phenyl]-phenyl-methanone (46d)



RHJ062I

It was prepared from 2-benzyl-1-(2,6-dibromo-4-iodo-phenyl)-5-methyl-*1H*-pyrrole (1.062 g, 2.0 mmol), *i*-PrMgCl·LiCl (1.5 mL, 1.5 M in THF) and benzoyl chloride (3.5 mmol) according to **TP2**. Purification by flash chromatography (eluent: pentane: ether = 10:1) provided the pure product **46d** (0.825 g, 81%) as a white solid, mp.: 155.0-155.9 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.99 (s, 2 H), 7.83 (d, *J* = 7.4 Hz, 2 H), 7.68 (t, *J* = 7.4 Hz, 1 H), 7.56 (t, *J* = 7.4 Hz, 2 H), 7.13-7.22 (m, 3 H), 7.00-7.09 (m, 2 H), 6.00-6.05 (m, 1 H), 5.94 (d, *J* = 3.3 Hz, 1 H), 3.65 (s, 2 H), 2.00 (s, 3 H);

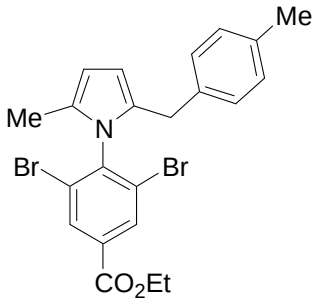
^{13}C NMR ($CDCl_3$, 75 MHz): 192.8, 140.9, 139.7, 138.6, 135.9, 133.4, 133.2, 131.1, 130.0, 129.0, 128.7, 128.1, 128.0, 126.2, 126.1, 107.8, 106.7, 33.8, 12.2;

IR (neat): 2912 (w), 1663 (s), 1597 (m), 1261 (s) cm^{-1};

MS (EI, 70 ev): 509 (M^+ ($^{81}Br^{79}Br$), 100%), 432 (38%), 430 (18%), 105 (32%);

HRMS (EI): calcd. for $C_{25}H_{19}Br_2NO$ (M^+, $^{79}Br^{79}Br$): 506.9833, **found**: 506.9844 (M^+, $^{79}Br^{79}Br$).

Synthesis of 3, 5-dibromo-4-[2-methyl-5-(4-methyl-benzyl)-pyrrol-1-yl]-benzoic acid ethyl ester (46e)



RHJ070H

It was prepared from 4-amino-3,5-dibromo-benzoic acid ethyl ester (1.615 g, 5.0 mmol), 1-p-tolyl-hexane-2,5-dione (3.061 g, 15.0 mmol) and TsOH·H_2O (10 mg, 1.0 mol %) according to **TP1**. Reaction time: 6 h. Purification by flash chromatography (eluent: pentane: ether = 20: 1) provided **46e** (1.490 g, 61%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.27 (s, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 5.97-6.03 (m, 1 H), 5.87 (d, *J* = 3.3 Hz, 1 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 3.53 (s, 2 H), 2.29 (s, 3 H), 1.94 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H);

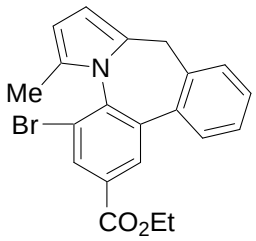
^{13}C NMR ($CDCl_3$, 75 MHz): 163.5, 141.5, 135.52, 135.49, 133.1, 132.8, 131.4, 128.9, 128.7, 127.8, 126.2, 107.5, 106.7, 62.1, 33.2, 21.0, 14.2, 12.1;

IR (neat): 2915 (w), 1723 (s), 1542 (m), 1514 (m), 1240 (vs) cm^{-1};

MS (EI, 70 ev): 493 (M^+ ($^{81}Br^{81}Br$), 51%), 491 (M^+ ($^{81}Br^{79}Br$), 100%), 489 (M^+ ($^{79}Br^{79}Br$), 52%), 400 (36%), 372 (31%), 167 (30%);

HRMS (EI): calcd. for $C_{22}H_{21}Br_2NO_2$ (M^+, $^{79}Br^{79}Br$): 488.9939, **found**: 488.9925 (M^+, $^{79}Br^{79}Br$).

Synthesis of 4-bromo-5-methyl-*8H*-4b-aza-dibenzo[e,g]azulene-2-carboxylic acid ethyl ester (**47**)



RHJ018H

It was prepared from 4-(2-benzyl-5-methyl-pyrrol-1-yl)-3,5-dibromo-benzoic acid ethyl ester **46a** according to **TP3**. Reaction time: 12 h. Purification by flash chromatography (eluent: hexane: ether = 20: 1) provided **47** (245 mg, 62%) as a white solid, mp.: 112.0-113.1 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.33 (d, *J* = 1.9 Hz, 1 H), 8.20 (d, *J* = 1.9 Hz, 1 H), 7.55-7.60 (m, 1 H), 7.28-7.34 (m, 2 H), 7.19-7.23 (m, 1 H), 5.89-5.95 (m, 2 H), 4.43 (qd, J_1 = 7.1 Hz, J_2 = 1.7 Hz, 2 H), 3.71 (d, *J* = 14.4 Hz, 1 H), 3.51 (d, *J* = 14.4 Hz, 1 H), 2.15 (s, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H);

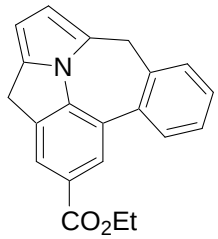
^{13}C NMR ($CDCl_3$, 75 MHz): 165.2, 142.0, 140.1, 139.2, 137.2, 136.0, 133.9, 131.5, 131.2, 130.4, 129.8, 129.2, 127.5, 127.3, 121.8, 109.3, 104.1, 62.0, 33.5, 14.8, 14.2;

IR (KBr): 2978 (w), 1721 (vs), 1469 (m), 1229 (s) cm^{-1};

MS (EI, 70 ev): 397 (M^+(^{81}Br), 99%), 395 (M^+(^{79}Br), 100%), 380 (17%), 286 (11%), 241 (89%), 228 (29%), 120 (47%);

HRMS (EI): calcd. for $C_{21}H_{18}BrNO_2$ (M^+,^{79}Br): 395.0521, **found**: 395.0514 (M^+, ^{79}Br).

Synthesis of pentacyclic heterocycle (48a)



RHJ020H

It was prepared from 4-(2-benzyl-5-methyl-pyrrol-1-yl)-3,5-dibromo-benzoic acid ethyl ester **46a** (477 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(*p*-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (717 mg, 2.2 mmol) according to **TP3**. Reaction time: 24 h. Purification by flash chromatography (eluent: hexane: ether = 30:1) afforded **48a** (193 mg, 61%) as a white solid, mp.: 114.8-115.7 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.51 (s, 1 H), 8.00 (s, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.26-7.40 (m, 3 H), 6.06-6.12 (m, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 4.12 (s, 2 H), 3.90 (s, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H);

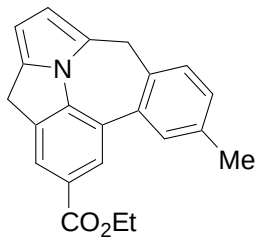
^{13}C NMR ($CDCl_3$, 75 MHz): 166.6, 141.3, 136.2, 135.8, 134.9, 133.9, 131.2, 130.3, 128.4 (2 x C), 127.4, 125.7, 125.6, 125.3, 123.0, 109.7, 103.4, 61.0, 34.5, 29.4, 14.3;

IR (KBr): 2977 (w), 1709 (vs), 1606 (m), 1500 (vs), 1269 (s) cm^{-1};

MS (EI, 70 ev): 315 (M^+, 100%), 286 (21%), 242 (77%), 135(10%), 120 (33%);

HRMS (EI): calcd. for $C_{21}H_{17}NO_2$ (M^+): 315.1259, **found**: 315.1272 (M^+).

Synthesis of pentacyclic heterocycle (48b)



RHJ072H

It was prepared from 3, 5-dibromo-4-[2-methyl-5-(4-methyl-benzyl)-pyrrol-1-yl]-benzoic acid ethyl ester **46e** (295 mg, 0.6 mmol), Pd $(OAc)_2$ (7 mg, 5 mol%), tri(*p*-tolyl)phosphine (18 mg, 10 mol%) and Cs_2CO_3 (411 mg, 2.2 mmol) according to **TP3**. Reaction time: 24 h. Purification by flash chromatography (eluent: pentane: ether = 20: 1) afforded **48b** (110 mg, 56%) as a white solid, mp.: 155.0-157.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.44 (s, 1 H), 7.92 (d, *J* = 1.1 Hz, 1 H), 7.42 (s, 1 H), 7.15 (d, *J* = 8.1 Hz, 1 H), 7.03 (d, *J* = 8.1 Hz, 1 H), 5.97-6.04 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 2 H), 3.81 (s, 2 H), 2.31 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H)

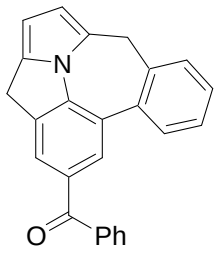
^{13}C NMR ($CDCl_3$, 75 MHz): 166.7, 141.4, 136.9, 135.8, 134.6, 133.8, 133.3, 131.1, 130.9, 129.1, 128.4, 125.66, 125.60, 125.4, 123.2, 109.5, 103.3, 61.0, 34.0, 29.4, 21.0, 14.4;

IR (neat): 2979 (w), 1716 (vs), 1608 (m), 1499 (s), 1287 (vs) cm^{-1};

MS (EI, 70 ev): 329 (M^+, 100%), 314 (15%), 300 (15%), 256 (46%), 241 (13%);

HRMS (EI): calcd. for $C_{22}H_{19}NO_2$ (M^+): 329.1416, **found**: 329.1430 (M^+).

Synthesis of pentacyclic heterocycle (48c)



RHJ059I

It was prepared from [4-(2-benzyl-5-methyl-pyrrol-1-yl)-3,5-dibromo-phenyl]-phenyl-methanone **46d** (509 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(*p*-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (717 mg, 2.2 mmol) according to **TP3**. Reaction time: 24 h. Purification by flash chromatography (eluent: hexane: ether = 15: 1) afforded **48c** (174 mg, 50%) as a white solid, mp.: 162.0-163.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.24 (s, 1 H), 7.80-7.89 (m, 3 H), 7.45-7.65 (m, 4 H), 7.26-7.40 (m, 3 H), 6.12-6.16 (m, 1 H), 6.06-6.12 (m, 1 H), 4.15 (s, 2 H), 3.93 (s, 2 H);

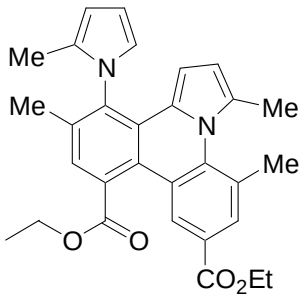
^{13}C NMR ($CDCl_3$, 75 MHz): 195.9, 141.2, 138.3, 136.3, 135.9, 134.8, 133.9, 133.0, 132.1, 131.2, 130.3, 129.8, 129.6, 128.5, 128.3, 127.4, 126.4, 125.3, 122.8, 109.9, 103.5, 34.5, 29.5;

IR (neat): 2924 (m), 1697 (s), 1657 (vs), 1593 (s), 1577 (m), 1302 (vs) cm^{-1};

MS (EI, 70 ev): 345 (M^+-H_2, 100%), 315 (9%), 268 (9%), 240 (66%), 119 (8%);

HRMS (EI): calcd. for $C_{25}H_{17}NO$ (M^+): 347.1310, **found**: 347.1286 (M^+).

Synthesis of 3, 5, 11-trimethyl-12-(2-methyl-pyrrol-1-yl)-pyrrolo[1,2-f]phenanthridine-7,9-dicarboxylic acid diethyl ester (50)



RHJ051J

The reaction was performed in a sealed tuber with a mixture of 3-bromo-5-methyl-4-(2-methyl-pyrrol-1-yl)-benzoic acid ethyl ester **39w** (322 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(*p*-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) at 110 °C using toluene (5.0 mL) as solvent for 12 h. After cooling to room temperature, water (10 mL)

was added in. The mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided **50** (206 mg, 85%) as a yellow solid, mp.: 73.0-75.0 ^oC.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.32 (s, 1 H), 7.96 (s, 1 H), 7.52 (s, 1 H), 6.49-6.52 (m, 1 H), 6.33 (t, J = 3.1 Hz, 1 H), 6.25 (dd, J_1 = 4.0 Hz, J_2 = 0.9 Hz, 1 H), 6.15-6.19 (m, 1 H), 5.08 (d, J = 4.0 Hz, 1 H), 4.49 (q, J = 7.1 Hz, 2 H), 4.40 (q, J = 7.1 Hz, 2 H), 2.43 (s, 3 H), 2.42 (s, 3 H), 2.12 (s, 3 H), 1.89 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H), 1.37 (t, J = 7.1 Hz, 3 H);

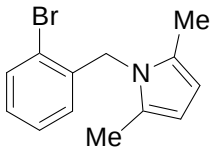
^{13}C NMR ($CDCl_3$, 150 MHz): 170.3, 160.0, 137.2, 135.6, 133.6, 132.6, 131.7, 129.7, 129.2, 128.3, 128.2, 127.7, 127.4, 127.0, 126.0, 125.7, 124.4, 118.8, 114.3, 109.4, 108.1, 107.2, 62.1, 61.1, 20.2, 17.4, 15.2, 14.4, 14.0, 11.9;

IR (neat): 2978 (w), 1717 (vs), 1700 (vs), 1558 (s), 1216 (vs) cm^{-1};

MS (EI, 70 ev): 482 (M^+, 100%), 467 (19%), 453 (2%), 411 (8%), 241 (12%), 204 (9%);

HRMS (EI): calcd. for $C_{30}H_{31}N_2O_4$ (M^++ H): 483.2284, **found**: 483.2270 (M^++ H).

Synthesis of 1-(2-bromo-benzyl)-2,5-dimethyl-*1H*-pyrrole (54a)



RHJ176F

It was prepared from 2-bromo-benzylamine (2.790 g, 15.0 mmol), 2,5-hexanedione (1.881 g, 16.5 mmol) and $TsOH{\cdot}H_2O$ (28 mg, 1.0 mol %) according to **TP1**. Reaction time: 3 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided **54a** (3.500 g, 90%) as a white solid, mp.: 85.4-86.2 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):7.56 (d, J = 7.9 Hz, 1 H), 7.06-7.21 (m, 2 H), 6.22 (d, J = 7.9 Hz, 1 H), 5.89 (s, 2 H), 4.99 (s, 2 H), 2.11 (s, 6 H);

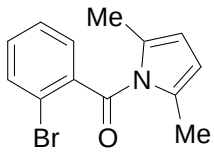
^{13}C NMR ($CDCl_3$, 75MHz):137.6, 132.3, 128.6, 128.0, 127.9, 126.9, 121.4, 105.7, 47.2, 12.2;

IR (neat): 2928 (w), 1462 (w), 1436 (m), 1408 (s), 1027 (w) cm^{-1};

MS (EI, 70 ev): 265 (M^+ (^{81}Br), 48%), 263 (M^+ (^{79}Br), 48%), 184 (100%), 169 (56%), 90 (34%);

HRMS (EI): calcd. for $C_{13}H_{14}BrN$ (M^+, ^{79}Br): 263.0310, found: 263.0327 (M^+, ^{79}Br).

Synthesis of (2-bromo-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (40a)



RHJ121G

It was prepared from 2-bromo-benzamide (2.000 g, 10.0 mmol), 2,5-hexanedione (1.370 g, 12.0 mmol) and TsOH·H_2O (19 mg, 1.0 mol %) according to **TP1**. Reaction time: 5 h. Purification by flash chromatography (eluent: pentane: ether = 4: 1) provided **40a** (1.200 g, 43%) as a brown solid, mp.: 58.0-59.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.61 (dd, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 1 H), 7.31-7.43 (m, 3 H), 5.84 (s, 2 H), 2.03 (s, 6 H);

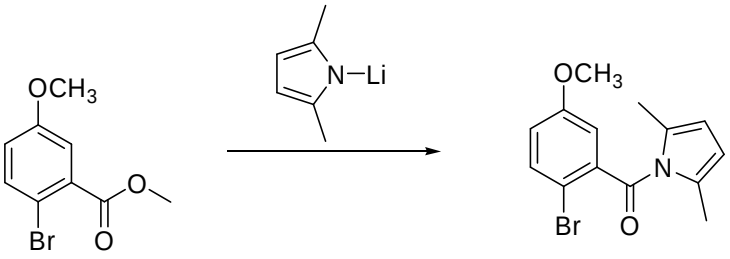
^{13}C NMR ($CDCl_3$, 75 MHz): 168.7, 138.3, 133.5, 132.1, 130.9, 129.9, 127.5, 120.6, 111.7, 15.4;

IR (KBr): 2919 (w), 1690 (vs), 1588 (m), 1542 (m), 1355 (vs), 1226 (vs) cm^{-1};

MS (EI, 70 ev): 279 (M^+ (^{81}Br), 17%), 277(M^+ (^{79}Br), 19%), 198 (9%), 185 (M^+ (^{81}Br), 100%), 183 (M^+ (^{79}Br), 100%);

HRMS (EI): calcd. for $C_{13}H_{12}BrNO$ (M^+, ^{79}Br): 277.0102, **found**: 277.0106 (M^+, ^{79}Br).

Synthesis of (2-bromo-5-methoxy-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**40b**)



RHJ025H

To the solution of 2,5-dimethyl-*1H*-pyrrole (0.57 g, 6.0 mmol) in THF (10.0 mL) was dropwise added *n*-BuLi (2.0 M, 3.0 mL) at -78 ^oC under nitrogen. The resulting mixture was allowed to stir at -78^oC for 30 min. The solution of 2-bromo-5-methoxy-benzoic acid methyl ester (1.225 g, 5.0 mmol) in THF (5.0 mL) was added in and the resulting mixture was stirred at -78 ^oC for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before it was quenched with aq NH_3. The reaction mixture was diluted with water and extracted with ether (3 x 30 mL). The combined organic phase were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (eluent: pentane: ether = 8: 1) afforded **40b** (1.301 g, 84%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.47 (d, J = 8.4 Hz, 1 H), 6.93 (d, J = 3.1 Hz, 1 H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 3.1 Hz, 1 H), 5.84 (s, 2 H), 3.78 (s, 3 H), 2.06 (s, 6 H);

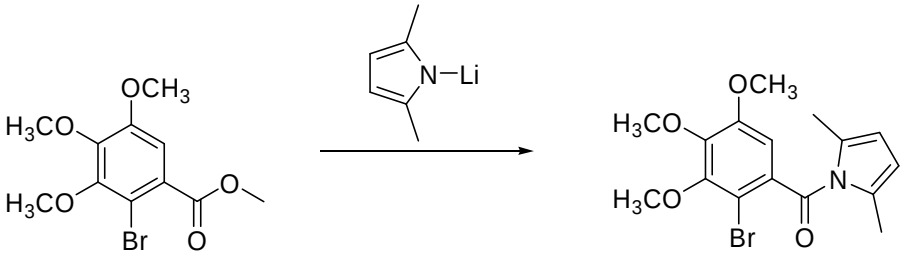
^{13}C NMR ($CDCl_3$, 75 MHz): 168.5, 159.0, 138.9, 134.2, 131.0, 118.3, 115.0, 111.8, 110.9, 55.7, 15.4;

IR (KBr): 2960 (m), 2924 (m), 1695 (vs), 1593 (m), 1570 (m), 1471 (vs) cm^{-1};

MS (EI, 70 ev): 309 (M^+ (^{81}Br), 7%), 307(M^+ (^{79}Br), 7%), 228 (44%), 215 (M^+ (^{81}Br), 99%), 213 (M^+ (^{79}Br), 100%), 185 (10%);

HRMS (EI): calcd. for $C_{14}H_{14}BrNO_2$ (M^+, ^{79}Br): 307.0208, **found**: 307.0218 (M^+, ^{79}Br).

Synthesis of (2-bromo-3,4,5-trimethoxy-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (40c)



RHJ044H

To the solution of 2,5-dimethyl-*1H*-pyrrole (0.57 g, 6.0 mmol) in THF (10.0 mL) was dropwise added *n*-BuLi (2.0 M, 3.0 mL) at -78 ^{o}C under nitrogen. The resulting mixture was allowed to stir at -78^{o}C for 30 min. The solution of 2-bromo-3, 4, 5-trimethoxy-benzoic acid methyl ester (1.525 g, 5.0 mmol) in THF (5.0 mL) was added in and the resulting mixture was stirred at -78 ^{o}C for 1h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h before it was quenched with aq. NH_3. The reaction mixture was diluted with water and extracted with ether (3 x 30 mL). The combined organic phase were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (eluent: pentane: ether = 3: 1) afforded **40c** (1.331 g, 72%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.76 (s, 1 H), 5.83 (s, 2 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 2.05 (s, 6 H);

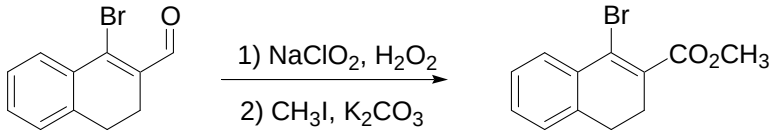
^{13}C NMR ($CDCl_3$, 75 MHz): 168.4, 153.2, 151.4, 145.4, 133.4, 130.9, 111.7, 108.6, 108.1, 61.3, 61.1, 56.4, 15.3;

IR (KBr): 2938 (m), 1694 (vs), 1564 (m), 1349 (vs), 1289 (vs) cm^{-1};

MS (EI, 70 ev): 369 (M^+ (^{81}Br), 5%), 367 (M^+ (^{79}Br), 5%), 275 (^{81}Br, 100%), 273 (^{79}Br, 100%), 230 (10%), 93 (5%);

HRMS (EI): calcd. for $C_{16}H_{18}BrNO_4$ (M^+, ^{79}Br): 367.0419, **found**: 367.0421 (M^+, ^{79}Br).

Synthesis of 1-bromo-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (56c)



56c RHJ128H

Bromo-3, 4-dihydro-naphthalene-2-carboxylic acid

A solution of $NaClO_2$ (80% purity, 3.2 g, 28 mmol) in water (30 mL) was added dropwise to a stirred mixture of 1-bromo-3, 4-dihydro-naphthalene-2-carbaldehyde[120] (4.740 g, 20 mmol) in CH_3CN (20 mL), NaH_2PO_4 (0.64 g) in water (10 mL) and 30% aqueous H_2O_2 (2.4 mL) in 2 h at 0 ^oC. The resulting mixture was stirred for 2 h at 10 ^oC. The mixture was poured into saturated Na_2CO_3 aqueous solution (50 mL), and washed with ether (30 mL). The ether phase was discarded. The aqueous phase was poured into 1 N HCl solution (200 mL), and extracted with ether (50 mL x 3).The extract was dried over Na_2SO_4. The combined organic phase was concentrated *in vacuo* to afford 2-bromo-1-cyclopentenecarboxylic acid (3.542 g, 70%) as a white solid; mp.: 122.7-123.8 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz):10.81-11.82 (bs, 1 H), 7.82-7.88 (m, 1 H), 7.25-7.32 (m, 2 H), 7.12-7.17 (m, 1 H), 2.80-2.91 (m, 2 H), 2.68-2.78 (m, 2 H);

^{13}C NMR ($CDCl_3$, 100 MHz):172.7, 137.3, 133.3, 130.1, 129.4, 129.3, 128.5, 127.1, 127.0, 27.5, 27.3;

IR (neat): 2829 (vs), 1654 (s), 1554 (s), 1283 (s) cm^{-1};

MS (EI, 70 ev): 254 (M^+ (^{81}Br), 25%), 252 (M^+ (^{79}Br), 25%), 155 (25%), 128 (100%);

HRMS (EI): calcd. for $C_{11}H_9BrO_2$ (M^+, ^{79}Br): 251.9786, **found**: 251.9765 (M^+, ^{79}Br).

Bromo-3, 4-dihydro-naphthalene-2-carboxylic acid methyl ester (56c)

The mixture of bromo-3,4-dihydro-naphthalene-2-carboxylic acid (1.265 g, 5.0 mmol), CH_3I (1.420 g, 10.0 mmol) and K_2CO_3 (828 mg, 6.0 mmol) in DMF (15 mL) was stirred overnight. The reaction mixture was diluted with ether (50 mL) and washed with water (20 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (eluent: pentane: ether = 6: 1) afforded **56c** (1.135 g, 85%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz):7.60-7.79 (m, 1 H), 7.14-7.26 (m, 2 H), 7.00-7.08 (m, 1 H), 3.77 (s, 3 H), 2.74-2.81 (m, 2 H), 2.54-2.61 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz):167.9, 136.8, 133.1, 130.8, 129.6, 128.7, 127.1, 126.9, 125.2, 52.0, 27.5, 27.4;

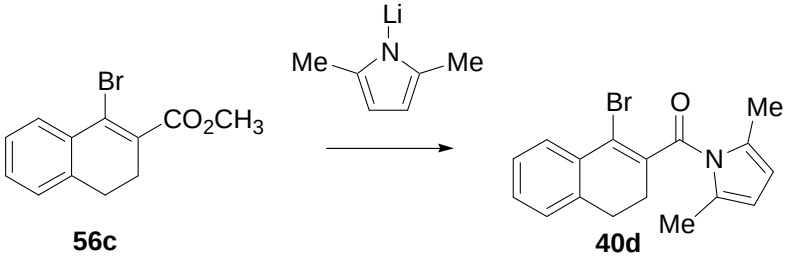
IR (KBr): 2949 (w), 1719 (s), 1694 (s), 1596 (s), 1444 (m), 1433 (m) cm^{-1};

[120] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc*. **1989**, *111*, 314.

MS (EI, 70 ev): 268 (M^+ (^{81}Br), 35%), 266 (M^+ (^{79}Br), 35%), 235 (25%), 187 (20%), 155 (21%), 128 (100%);

HRMS (EI): calcd. for $C_{12}H_{11}BrO_2$ (M^+, ^{79}Br): 265.9942, **found**: 265.9939 (M^+, ^{79}Br).

Synthesis of (1-bromo-3,4-dihydro-naphthalen-2-yl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (40d)



56c **40d** RHJ131H

To the solution of 2,5-dimethyl-*1H*-pyrrole (0.57 g, 6.0 mmol) in THF (10.0 mL) was dropwise added *n*-BuLi (2.0 M, 3.0 mL) at -78 ^oC under nitrogen. The resulting mixture was allowed to stir at -78^oC for 30 min. The solution of bromo-3, 4-dihydro-naphthalene-2-carboxylic acid methyl ester **56c** (1.335 g, 5.0 mmol) in THF (5.0 mL) was added in and the resulting mixture was stirred at -78 ^oC for 1h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h before it was quenched with aq. NH_3. The reaction mixture was diluted with water and extracted with ether (3 x 30 mL). The combined organic phase were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (eluent: pentane: ether = 10: 1) afforded **40d** (1.039 g, 63%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.65-7.72 (m, 1 H), 7.23-7.31 (m, 2 H), 7.11-7.17 (m, 1 H), 5.86 (s, 2 H), 2.98 (t, *J* = 8.3 Hz, 2 H), 2.73 (t, *J* = 8.3 Hz, 2 H), 2.34 (s, 6 H);

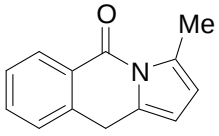
^{13}C NMR ($CDCl_3$, 75 MHz): 170.1, 136.1, 134.9, 132.3, 130.3, 129.8, 128.0, 127.3, 127.1, 123.5, 111.6, 28.1, 27.4, 15.4;

IR (neat): 2921 (w), 1680 (s), 1543 (m), 1450 (w), 1361 (vs) cm^{-1};

MS (EI, 70 ev): 331 (M^+ (^{81}Br), 5%), 329 (M^+ (^{79}Br), 5%), 235 (100%), 128 (80%);

HRMS (EI): calcd. for $C_{17}H_{16}BrNO$ (M^+, ^{79}Br): 329.0415, **found**: 329.0382 (M^+, ^{79}Br).

Synthesis of 3-methyl-10H-pyrrolo[1,2-b]isoquinolin-5-one (**42a**)



RHJ120G

It was prepared from (2-bromo-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**40a**, 278 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Purification by flash chromatography (eluent: hexane: ether = 20:1) afforded **42a** (148 mg, 75%) as a white solid, mp.: 83.8-84.3 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.79 (d, *J* = 7.5 Hz, 1 H), 7.51-7.57 (m, 1 H), 7.38-7.44 (m, 2 H), 6.30-6.35 (m, 1 H), 6.07 (d, *J* = 5.6 Hz, 1 H), 5.30-5.35 (m, 1 H), 4.76 (s, 1 H), 1.57 (s, 3 H);

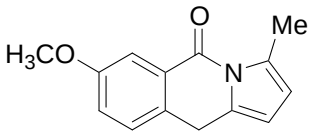
^{13}C NMR ($CDCl_3$, 75 MHz): 171.2, 150.9, 146.0, 136.1, 133.0, 131.9, 129.6, 128.6, 125.1, 121.6, 96.3, 77.1, 28.3;

IR (KBr): 2976 (w), 1703 (vs), 1633 (s), 1610 (m), 1467 (m), 1317 (vs) cm^{-1};

MS (EI, 70 ev): 197 (M^+, 10%), 182 (100%), 153 (4 5), 127 (12%);

HRMS (EI): calcd. for $C_{13}H_{11}NO$ (M^+): 197.0841, **found**: 197.0821 (M^+).

Synthesis of 7-methoxy-3-methyl-*10H*-pyrrolo[1,2-b]isoquinolin-5-one (**42b)**



RHJ026H

It was prepared from (2-bromo-5-methoxy-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**40b**, 308 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Purification by flash chromatography (eluent: hexane: ether = 3: 1) afforded **42b** (181 mg, 80%) as a white solid, mp.: 147.7-149.9 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.23 (d, *J* = 8.6 Hz, 1 H), 7.20 (d, *J* = 2.2 Hz, 1 H), 7.04 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1 H), 6.24-6.27 (m, 1 H), 5.99 (d, *J* = 5.8 Hz, 1 H), 5.25-5.27 (m, 1 H), 4.69 (s, 1 H), 3.75 (s, 3 H), 1.49 (s, 3 H);

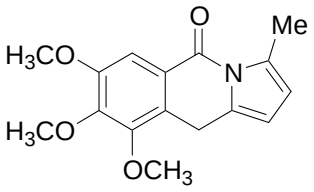
^{13}C NMR ($CDCl_3$, 75 MHz): 171.2, 160.3, 146.0, 143.3, 136.5, 133.2, 129.3, 122.4, 121.3, 107.4, 96.1, 76.7, 55.6, 28.2;

IR (KBr): 2972 (m), 1709 (vs), 1637 (m), 1615 (m), 1495 (s), 1334 (vs), 1319 (vs) cm^{-1};

MS (EI, 70 ev): 227 (M^+, 13%), 212 (100%), 197 (12%), 169 (6%);

HRMS (EI): calcd. for $C_{14}H_{13}NO_2$ (M^+): 227.0946, **found**: 227.0960 (M^+).

Synthesis of 7,8,9-trimethoxy-3-methyl-*10H*-pyrrolo[1,2-b]isoquinolin-5-one (**42c**)



RHJ045H

It was prepared from (2-bromo-3,4,5-trimethoxy-phenyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**40c**, 368 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Purification by flash chromatography (eluent: pentane: ether = 3: 1) afforded **42c** (232 mg, 81%) as a white solid, mp.: 75.5-78.6 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.06 (s, 1 H), 6.34-6.45 (m, 1 H), 6.04 (d, *J* = 5.9 Hz, 1 H), 5.21-5.31 (m, 1 H), 4.70 (s, 1 H), 3.99 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 1.59 (s, 3 H);

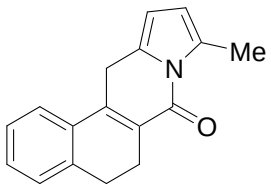
^{13}C NMR ($CDCl_3$, 75 MHz): 171.0, 155.3, 147.9, 146.1, 145.9, 136.39, 136.36, 129.1, 127.3, 102.6, 95.5, 76.2, 60.97, 60.92, 56.3, 26.9;

IR (KBr): 2939 (w), 1715 (vs), 1634 (m), 1609 (m), 1479 (s), 1346 (vs) cm^{-1};

MS (EI, 70 ev): 287 (M^+, 19%), 272 (100%), 256 (6%), 242 (15%);

HRMS (EI): calcd. for $C_{16}H_{17}NO_4$ (M^+): 287.1158, **found**: 287.1142 (M^+).

Synthesis of 9-methyl-6,12-dihydro-*5H*-benzo[f]pyrrolo[1,2-b]isoquinolin-7-one (42d)



RHJ133H

It was prepared from (1-bromo-3,4-dihydro-naphthalen-2-yl)-(2,5-dimethyl-pyrrol-1-yl)-methanone **40d** (330 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Reaction temperature: 80 ^oC. Purification by flash chromatography (eluent: pentane: ether =1: 1) afforded **42d** (184 mg, 74%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.07-7.36 (m, 4 H), 6.36-6.44 (m, 1 H), 6.05 (d, *J* = 5.8 Hz, 1 H), 5.14-5.22 (m, 1 H), 4.64 (s, 1 H), 2.78-3.00 (m, 2 H), 2.50-2.62 (m, 1 H), 2.30-2.47 (m, 1 H), 1.57 (s, 3 H);

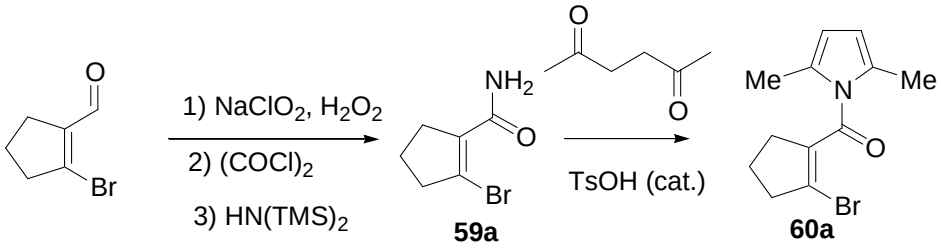
^{13}C NMR ($CDCl_3$, 75 MHz): 173.9, 157.5, 145.5, 138.4, 135.4, 130.9, 130.4, 130.0, 128.83, 128.82, 126.8, 124.4, 95.2, 77.8, 28.1, 27.2, 18.1;

IR (neat): 2927 (w), 1698 (vs), 1633 (m), 1566 (m), 1449 (m, 1386 (s), 1320 (vs) cm^{-1};

MS (EI, 70 ev): 249 (M^+, 59%), 234 (100%), 220 (6%), 206 (25%), 102 (5%);

HRMS (EI): calcd. for $C_{17}H_{15}NO$ (M^+): 249.1154, **found**: 249.1158 (M^+).

Synthesis of (2-bromo-cyclopent-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (60a)



RHJ092H

2-Bromo-1-cyclopentenecarboxylic acid: A solution of $NaClO_2$ (80% purity, 3.2 g, 28 mmol) in water (30 mL) was added dropwise to a stirred mixture of 2-bromocyclopent-1-enecarbaldehyde[121] (3.50 g, 20 mmol) in CH_3CN (20 mL), NaH_2PO_4 (0.64 g) in water (10 mL) and 30% aqueous H_2O_2 (2.4 mL) in 2 h at 0 ^oC. The resulting mixture was stirred for 2 h at 10 ^oC. The mixture was poured into saturated Na_2CO_3 aqueous solution (50 mL), and washed with ether (30 mL). The ether phase was discarded. The aqueous phase was poured into 1 N HCl solution (200 mL), and extracted with ether (50 mL x 3).The extract was dried over Na_2SO_4. The combined organic phase was concentrated *in vacuo* to afford 2-bromo-1-cyclopentenecarboxylic acid (3.418 g, 89%) as a white solid; mp.: 122.7-123.8 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):11.44 (bs, 1 H, COOH), 2.83 (tt, J_1 = 7.7 Hz, J_2 = 2.5 Hz, 2 H), 2.65 (tt, J_1 = 7.7 Hz, J_2 = 2.5 Hz, 2 H), 1.96 (pent, J = 7.7 Hz, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz):169.5, 135.7, 131.4, 43.5, 32.8, 21.5;

IR (neat): 2488-3045 (bs), 1665 (vs), 1613 (vs), 1281 (vs) cm^{-1};

MS (EI, 70 ev): 192 (M^+ (^{81}Br), 89%), 190 (M^+ (^{79}Br), 89%), 145 (34%), 11 (100%), 83 (40%).

Spectral datas match with those reported in the literature[122]

2-Bromo-1-cyclopentenecarboxylic amide (59a): Oxalyl dichloride (9.810 g, 30.0 mmol) was added to the solution of 2-bromo-1-cyclopentenecarboxylic acid (1.910 g, 10.0 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC , 2-3 drops of dry DMF was added and the resulting mixture was stirred for 4 h at this temperature. 1,1,1,3,3,3-Hexamethyl-disilazane (12.1 g, 75 mmol) was dropwise added at 0 ^oC and the mixture was stirred at room temperature overnight. Cooled to 0 ^oC, methanol (15.0 mL) was added to the mixture and it was stirred for 3 h at room temperature. Usual workup and purification by flash chromatography (eluent: ether) afforded **61b** (1.337 g, 70%) as a white solid, mp.: 146.0-147.0 ^oC.

[121] T. Bekele, S. R. Brunette, M. A. Lipton, *J. Org. Chem.* **2003**, *68*, 8471.
[122] K. Ohe, K. Miki, T. Yokoi, F. Nishino, S. Uemura, *Organometallics* **2000**, *19*, 5525.

^{1}H NMR ($CDCl_3$, 300 MHz):6.06-6.74 (m, 2 H, NH_2), 2.82 (tt, J_1 = 7.7 Hz, J_2 = 2.5 Hz, 2 H), 2.67 (tt, J_1 = 7.7 Hz, J_2 = 2.5 Hz, 2 H), 1.92 (pent, J = 7.7 Hz, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz):166.0, 135.2, 125.1, 43.1, 33.5, 21.1;

IR (neat): 3330 (s), 3156 (s), 1657 (s), 1613 (vs), 1398 (vs) cm^{-1};

MS (EI, 70 ev): 191 (M^+ (^{81}Br), 52%), 189 (M^+ (^{79}Br), 51%), 175 (23%), 147 (9%), 110 (100%), 67 (88%);

HRMS (EI): calcd. for C_6H_8BrNO (M^+, ^{79}Br): 188.9789, **found**: 188.9767 (M^+, ^{79}Br).

(2-Bromo-cyclopent-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**60a**) 2-Bromo-1-cyclopentenecarboxylic amide **59a** (570 mg, 3.0 mmol), 2,5-hexanedione (684 mg, 6.0 mmol), and $TsOH \cdot H_2O$ (6 mg, 1.0 mol%) were dissolved in toluene (20 mL) and heated in a flask equipped with a Dean-Stark apparatus for 6 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo.* Purification by flash chromatography (eluent: pentane = 10: 1) to provide **60a** (322 mg, 40%) as crystals: mp.: 54.4-55.4 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):5.82 (s, 2 H), 2.70-2.85 (m, 4 H), 2.24 (s, 6 H), 2.01-2.12 (m, 2 H);

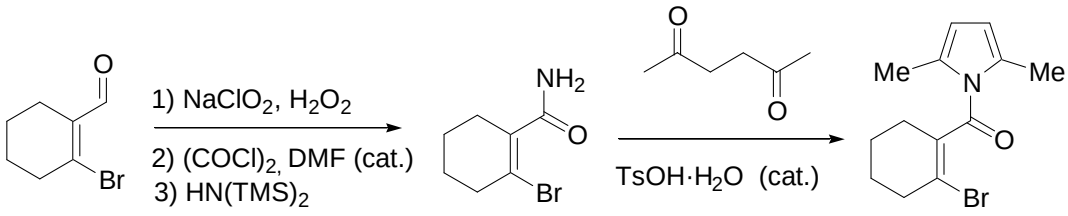
^{13}C NMR ($CDCl_3$, 75 MHz):167.6, 137.6, 129.7, 128.1, 111.0, 42.0, 34.0, 22.2, 14.7;

IR (neat): 2914 (w), 1677 (vs), 1615 (m), 1542 (m), 1361 (vs) cm^{-1};

MS (EI, 70 ev): 269 (M^+ (^{81}Br), 18%), 267 (M^+ (^{79}Br), 18%), 188 (6%), 175 ((^{81}Br), 99%), 173 ((^{79}Br), 100%), 95 (28%);

HRMS (EI): calcd. for $C_{12}H_{14}BrNO$ (M^+, ^{79}Br): 267.0259, **found**: 267.0252 (M^+, ^{79}Br).

Synthesis of (2-bromo-cyclohex-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**60b**):



59b **60b** RHJ083H

2-Bromo-1-cyclohexenecarboxylic acid: A solution of $NaClO_2$ (80% purity, 3.2 g, 28 mmol) in water (30 mL) was added dropwise to a stirred mixture of 2-bromocyclohex-1-enecarbaldehyde[123] (3.78 g, 20 mmol) in CH_3CN (20 mL), NaH_2PO_4 (0.64 g) in water (10 mL) and 30% aqueous H_2O_2 (2.4 mL) in 2 h at 0 ^oC. The resulting mixture was stirred for 2 h at 10 ^oC. The mixture was poured into saturated Na_2CO_3 aqueous solution (50 mL), and washed with ether (30 mL). The ether phase was discarded. The aqueous phase was poured

[123] J.-J. Lian, A. Odedra, C.-J. Wu, R.-S. Liu, *J. Am. Chem. Soc*. **2005**, *127*, 4186.

into 1 N HCl solution (200 mL), and extracted with ether (3 x 50 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford 2-bromo-1-cyclohexenecarboxylic acid (3.501 g, 85%) as a white solid; mp 102.0-103.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):11.14 (bs, 1 H, COOH), 2.56-2.67 (m, 2 H), 2.36-2.46 (m, 2 H), 1.62-1.75 (m, 4 H);

^{13}C NMR ($CDCl_3$, 75 MHz):172.9, 129.6, 129.4, 38.0, 28.6, 23.9, 21.3;

IR (KBr): 2488-3055 (bs), 1687 (vs), 1672 (vs), 1248 (vs) cm^{-1};

MS (EI, 70 ev): 206 (M^+ (^{81}Br), 33%), 204 (M^+, 33%), 125 (34%), 97 (35%), 79 (100%).

Spectral datas match with those reported in the literature[124]

2-Bromo-1-cyclohexenecarboxylic amide (59b): Oxalyl dichloride (1.91 g, 15.0 mmol) was added to the solution of 2-bromo-1-cyclohexenecarboxylic acid (1.025 g, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC , 2-3 drops of dry DMF was added and the resulting mixture was stirred for 4 h at this temperature. 1,1,1,3,3,3-Hexamethyl-disilazane (4.83 g, 30 mmol) was dropwise added at 0 ^oC and the mixture was stirred at room temperature overnight. Cooled to 0 ^oC, methanol (10.0 mL) was added to the mixture and it was stirred for 3 h at room temperature. Usual workup and purification by flash chromatography (eluent: ether) afforded **59b** (0.816 g, 80%) as a white solid, mp.: 163.0-164.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):5.67-6.39 (m, 2 H, NH_2), 2.48-2.61 (m, 2 H), 2.27-2.41 (m, 2 H), 1.59-1.78 (m, 4 H);

^{13}C NMR ($CDCl_3$, 75 MHz):171.1, 134.3, 121.3, 36.4, 29.2, 24.1, 21.4;

IR (KBr): 3362 (m), 3171 (m), 2929 (m), 1638 (vs), 1620 (vs), 1392 (s) cm^{-1};

MS (EI, 70 ev): 205 (M^+ (^{81}Br), 44%), 203 (M^+ (^{79}Br), 43%), 124 (86%), 81 (100%);

HRMS (EI): calcd. for $C_7H_{10}BrNO$ (M^+, ^{79}Br): 202.9946, **found**: 202.9926 (M^+, ^{79}Br).

(2-Bromo-cyclohex-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**60b**): 2-Bromo-1-cyclohexenecarboxylic amide **59b** (612 mg, 3.0 mmol), 2,5-hexanedione (684 mg, 6.0 mmol), and $TsOH \cdot H_2O$ (6 mg, 1.0 mol%) were dissolved in toluene (20 mL) and heated in a flask equipped with a Dean-Stark apparatus for 4 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo.* Purification by flash chromatography (eluent: pentane = 10: 1) provided **60b** (668 mg, 79%) as crystals: mp.: 38.7-39.6 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):5.82 (s, 2 H), 2.50-2.58 (m, 2 H), 2.38-2.44 (m, 2 H), 2.31 (s, 6 H), 1.72-1.79 (m, 4 H);

^{13}C NMR ($CDCl_3$, 75 MHz):170.1, 134.9, 130.5, 124.5, 111.6, 36.2, 29.3, 23.8, 21.3, 15.4;

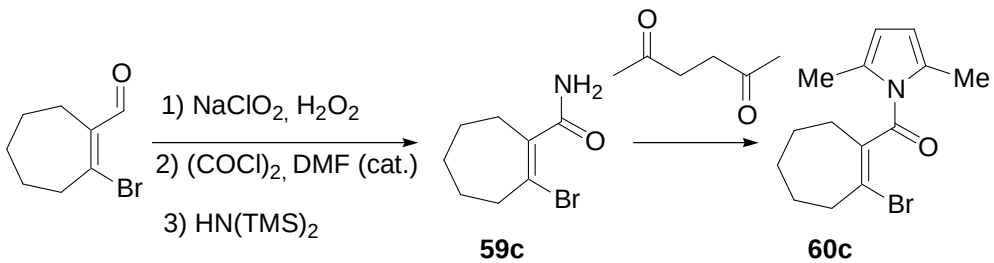
[124] W. R. Baker, R. M. Coates, J. Org. Chem. **1979**, *44*, 1022.

IR (neat): 2927 (m), 1684 (vs), 1543 (m), 1362 (vs) cm^{-1};

MS (EI, 70 ev): 283 (M^+ (^{81}Br), 15%), 281 (M^+ (^{79}Br), 16%), 189 ((^{81}Br), 99%), 187 ((^{79}Br), 100%), 95 (34%), 79 (35%);

HRMS (EI): calcd. for $C_{13}H_{16}BrNO$ (M^+, ^{79}Br): 281.0415, **found**: 281.0419 (M^+, ^{79}Br).

Synthesis of (2-bromo-cyclohept-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**60c**)



59c **60c** RHJ094H

2-Bromo-cyclohept-1-enecarboxylic acid: A solution of $NaClO_2$ (80% purity, 3.2 g, 28 mmol) in water (32 mL) was added dropwise to a stirred mixture of 2-bromo-cyclohept-1-enecarbaldehyde (3.78 g, 20 mmol) in CH_3CN (20 mL), NaH_2PO_4 (0.64 g) in water (10 mL) and 30% aqueous H_2O_2 (2.4 mL) in 2 h at 0 ^oC. The resulting mixture was stirred for 2h at 10 ^oC. The mixture was poured into saturated Na_2CO_3 aqueous solution (50 mL), and washed with ether (30 mL). The ether phase was discarded. The aqueous phase was poured into 1 N HCl solution (200 mL), and extracted with ether (50 mL x 3). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford 2-bromo-cyclohept-1-enecarboxylic acid (3.635 g, 83%) as a white solid; mp.: 104.4-105.5 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz):11.40 (bs, 1 H, COOH), 2.80-2.93 (m, 2 H), 2.40-2.56 (m, 2 H), 1.70-1.81 (m, 2 H), 1.53-1.68 (m, 4 H);

^{13}C NMR ($CDCl_3$, 75 MHz):174.0, 135.2, 132.1, 42.9, 31.1, 31.0, 25.5, 24.6;

IR (KBr): 2678-3055 (bs, s), 1687 (vs), 1626 (s), 1289 (vs) cm^{-1};

MS (EI, 70 ev): 220 (M^+ (^{81}Br), 25%), 218 (M^+ (^{79}Br), 25%), 139 (34%), 11 (30%), 93 (100%);

HRMS (EI): calcd. for $C_8H_{11}BrO_2$ (M^+, ^{79}Br): 217.9942, **found**: 217.9926 (M^+, ^{79}Br).

2-Bromo-cyclohept-1-enecarboxylic acid amide (59c): Oxalyl dichloride (1.91 g, 15.0 mmol) was added to the solution of 2-bromo-cyclohept-1-enecarboxylic acid (1.095 g, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC , 2-3 drops of dry DMF was added and the resulting mixture was stirred for 4 h at this temperature. 1,1,1,3,3,3-Hexamethyl-disilazane (4.83 g, 30 mmol) was dropwise added at 0 ^oC and the mixture was stirred at room temperature overnight. Cooled to 0 ^oC, methanol (10.0 mL) was added to the mixture and it was stirred for 3 h at

room temperature. Usual workup and purification by flash chromatography (eluent: ether) afforded **59c** (0.926 g, 85%) as a white solid, mp.: 144.3-145.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz):6.03 (bs, 1 H), 5.70 (bs, 1 H), 2.69-2.86 (m, 2 H), 2.32-2.49 (m, 2 H), 1.68-1.81 (m, 2 H), 1.53-1.67 (m, 4 H);

^{13}C NMR ($CDCl_3$, 75 MHz):172.3, 139.4, 124.7, 41.8, 31.9, 31.0, 26.1, 25.0;

IR (KBr): 3378 (m), 3160 (m), 1638 (vs), 1613 (vs), 1409 (s) cm^{-1};

MS (EI, 70 ev): 219 (M^+ (^{81}Br), 25%), 217 (M^+ (^{79}Br), 25%), 138 (100%), 110 (95%), 95 (74%);

HRMS (EI): calcd. for $C_8H_{12}BrNO$ (M^+, ^{79}Br): 217.0102, **found**: 217.0079 (M^+, ^{79}Br).

(2-Bromo-cyclohept-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone (**60c**): 2-Bromo-cyclohept-1-enecarboxylic acid amide (1.090 g, 5.0 mmol), 2, 5-hexanedione (1.140 g, 10.0 mmol), and $TsOH\cdot H_2O$ (10 mg, 1.0 mol%) were dissolved in toluene (20 mL) and heated in a flask equipped with a Dean-Stark apparatus for 4 h. After cooling, the dark brown reaction mixture was concentrated *in vacuo.* Purification by flash chromatography (eluent: pentane = 10: 1) provided **60c** (1.201 g, 81%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz):5.81 (s, 2 H), 2.76-2.87 (m, 2 H), 2.39-2.51 (m, 2 H), 2.30 (s, 6 H), 1.60-1.85 (m, 6 H);

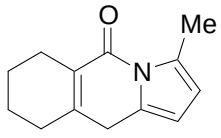
^{13}C NMR ($CDCl_3$, 75 MHz):171.5, 139.8, 130.9, 128.5, 111.9, 42.5, 32.8, 31.3, 26.5, 25.1, 16.0;

IR (KBr): 2923 (m), 1684 (vs), 1627 (m), 1541 (m), 1364 (vs) cm^{-1};

MS (EI, 70 ev): 297 (M^+ (^{81}Br), 11%), 295 (M^+ (^{79}Br), 11%), 216 (45%), 200 (100%), 122 (40%), 93 (51%);

HRMS (EI): calcd. for $C_{14}H_{18}BrNO$ (M^+, ^{79}Br): 295.0572, **found**: 295.0570 (M^+, ^{79}Br).

Synthesis of 5,6,7,8,9,10-hexahydro-pyrrolo[1,2-b]isoquinoline (**61a**)



RHJ086H

It was prepared from (2-bromo-cyclohex-1-enyl)-(2, 5-dimethyl-pyrrol-1-yl)-methanone **60a** (282 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TPIII**. Purification by flash chromatography (eluent: hexane: ether = 3: 1) afforded **61a** (171 mg, 85%) as a white solid, mp.: 108.2-109.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.08-6.12 (m, 1 H), 6.00 (d, J = 5.8 Hz, 1 H), 5.13 (s, 1 H), 4.62 (s, 1 H), 2.11-2.29 (m, 4 H), 1.58-1.77 (m, 4 H), 1.37 (s, 3 H);

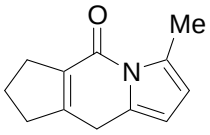
^{13}C NMR ($CDCl_3$, 75 MHz): 175.5, 162.6, 146.4, 135.1, 131.0, 129.8, 95.0, 79.1, 25.2, 22.8, 21.9, 21.6, 20.1;

IR (KBr): 2926 (w), 1690 (vs), 1658 (m), 1632 (m), 1310 (vs) cm^{-1};

MS (EI, 70 ev): 201 (M^+, 25%), 186 (100%), 158 (13%), 130 (9%);

HRMS (EI): calcd. for $C_{13}H_{15}NO$ (M^+): 201.1154, **found**: 201.1151 (M^+).

Synthesis of 3-methyl-5,6,7,8-tetrahydro-3a-aza-s-indacen-4-one (**61b**)



RHJ095H

It was prepared from (2-bromo-cyclopent-1-enyl)-(2, 5-dimethyl-pyrrol-1-yl)-methanone **60b** (268 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Purification by flash chromatography (eluent: hexane: ether = 3:1) afforded **61b** (149 mg, 80%) as a white solid, mp.: 90.0-91.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.07 (d, *J* = 5.8 Hz, 1 H), 6.01 (d, *J* = 5.8 Hz, 1 H), 5.08 (s, 1 H), 4.58 (s, 1 H), 2.23-2.57 (m, 6 H), 1.40 (s, 3 H);

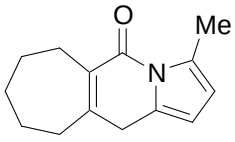
^{13}C NMR ($CDCl_3$, 75 MHz): 174.6, 171.5, 146.4, 141.4, 134.6, 130.2, 94.5, 76.4, 27.9, 27.6, 25.4, 25.1;

IR (KBr): 2926 (w), 1692 (vs), 1632 (s), 1316 (vs), 1295 (vs) cm^{-1};

MS (EI, 70 ev): 187 (M^+, 35%), 172 (100%), 158 (13%), 144 (42%);

HRMS (EI): calcd. for $C_{12}H_{13}NO$ (M^+): 187.0997, **found**: 187.0973 (M^+).

Synthesis of 3-methyl-5,6,7,8,9,10-hexahydro-3a-aza-cyclohepta[f]inden-4-one (**61c**)



RHJ096H

It was prepared from (2-bromo-cyclohept-1-enyl)-(2,5-dimethyl-pyrrol-1-yl)-methanone **60c** (296 mg, 1.0 mmol), Pd $(OAc)_2$ (11 mg, 5 mol%), tri(p-tolyl)phosphine (30 mg, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol) according to **TP3**. Purification by flash chromatography (eluent: hexane: ether = 3:1) afforded **61c** (160 mg, 74%) as a white solid, mp.: 99.0-100.0 ^oC.

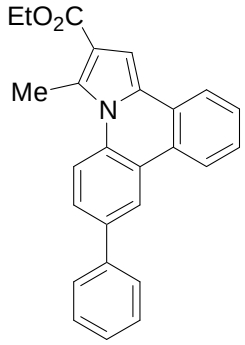
^{1}H NMR ($CDCl_3$, 300 MHz): 6.09-6.13 (m, 1 H), 5.99 (d, *J* = 5.8 Hz, 1 H), 5.10-5.14 (m, 1 H), 4.58-4.64 (m, 1 H), 2.22-2.46 (m, 4 H), 1.42-1.90 (m, 6 H), 1.38 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 175.8, 164.8, 146.7, 135.3, 134.3, 129.8, 94.9, 79.1, 30.9, 28.4, 26.9, 26.7, 25.0, 24.4;

IR (KBr): 2918 (w), 1686 (s), 1656 (m), 1631 (m), 1309 (s) cm^{-1};

MS (EI, 70 ev): 215 (M^+, 21%), 200 (100%), 186 (2%), 172 (5%), 158 (2%), 130 (4%);
HRMS (EI): calcd. for $C_{14}H_{17}NO$ (M^+): 215.1310, **found**: 215.1306 (M^+).

Synthesis of 3-methyl-7-phenyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (63a)

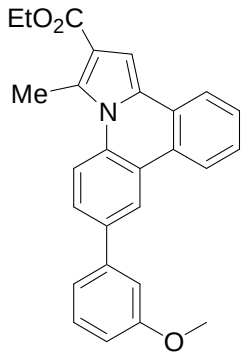


RHJ073J

The reaction was performed in a sealed tuber with a mixture of 1-(2,4-dibromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44j** (463 mg, 1.0 mmol), benzeneboronic acid (146 mg, 1.2 mmol), Pd $(OAc)_2$ (22 mg, 10 mol%), tri(*p*-tolyl)phosphine (60 mg, 20 mol%) and Cs_2CO_3 (717 mg, 2.2 mmol) at 110 °C using toluene (10.0 mL) as solvent for 12 h. After cooling to room temperature, water (10 mL) was added in. The mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the mixture of desired product **63a** and double Suzuki coupling compound. The pure compound **63a** was obtained (246 mg, 65%) after recrystallization using ether and pentane as a white solid, mp.: 155.0-156.2 ^oC.

^{1}H NMR ($CDCl_3$, 600 MHz): 8.32 (s, 1 H), 8.10 (d, *J* = 8.8 Hz, 1 H), 8.06 (d, *J* = 7.9 Hz, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.62 (d, *J* = 7.1 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.48 (t, *J* = 7.1 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.35 (t, *J* = 7.1 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.21 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 3.08 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H);
^{13}C NMR ($CDCl_3$, 150 MHz): 165.5, 139.9, 136.8, 133.7, 132.9, 128.8, 128.7, 128.2, 127.4, 126.9, 126.12, 126.06, 126.0, 124.6, 123.9, 122.4, 122.0, 121.9, 118.0, 116.1, 103.0, 59.8, 16.4, 14.5;
IR (neat): 2983 (w), 1687 (s), 1526 (m), 1442 (m), 1218 (s), 1063 (m) cm^{-1};
MS (EI, 70 ev): 379 (100%), 350 (95%), 334 (8%), 304 (53%), 228 (20%), 152 (15%);
HRMS (ESI): calcd. for $C_{26}H_{22}NO_2$ (M^++ H): 380.1651, **found**: 380.1655 (M^++ H).

Synthesis of 7-(3-methoxy-phenyl)-3-methyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (63b)



RHJ082J

The reaction was performed according to the procedure for preparation of **63a** from 1-(2,4-dibromo-phenyl)-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44j** (232 mg, 0.5 mmol), 3-methoxylbenzeneboronic acid (91 mg, 0.6 mmol), Pd $(OAc)_2$ (11 mg, 10 mol%), tri(*p*-tolyl)phosphine (30 mg, 20 mol%) and Cs_2CO_3 (359 mg, 1.1 mmol). Reaction conditions: 110 °C, 20 h. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the desired product **63b** (182 mg, 89%) as a white solid, mp.: 132.1-133.2 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.43 (s, 1 H), 8.24 (d, *J* = 7.9 Hz, 1 H), 8.17 (d, *J* = 7.9 Hz, 1 H), 7.92 (d, *J* = 7.9 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.17-7.50 (m, 6 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.18 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H);

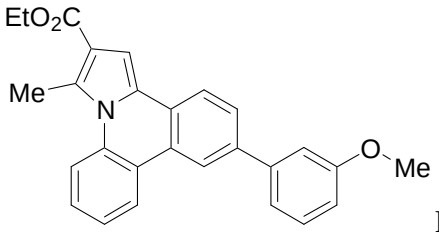
^{13}C NMR ($CDCl_3$, 75 MHz): 165.6, 160.1, 141.6, 136.98, 136.95, 134.0, 133.1, 129.9, 128.9, 128.4, 126.33, 126.26, 124.8, 124.2, 122.5, 122.3, 122.2, 119.5, 118.2, 116.3, 113.0, 112.7, 103.2, 59.9, 55.4, 16.5, 14.5;

IR (neat): 2976 (w), 1691 (s), 1606 (m), 1580 (m), 1439 (m), 1120 (s) cm^{-1};

MS (EI, 70 ev): 409 (M^+, 100%), 380 (86%), 337 (19%), 292 (23%), 190 (10%);

HRMS (EI): calcd. for $C_{27}H_{23}NO_3$ (M^+): 409.1678, **found**: 409.1661 (M^+).

Synthesis of 10-(3-methoxy-phenyl)-3-methyl-pyrrolo[1,2-f]phenanthridine-2-carboxylic acid ethyl ester (63c)



RHJ048K

The reaction was performed according to the procedure for preparation of **63a** from 5-(4-bromo-phenyl)-1-(2-bromo-phenyl)-2-methyl-*1H*-pyrrole-3-carboxylic acid ethyl ester **44k** (232 mg, 0.5 mmol), 3-methoxylbenzeneboronic acid (91 mg, 0.6 mmol), Pd $(OAc)_2$ (11 mg,

10 mol%), tri(*p*-tolyl)phosphine (30 mg, 20 mol%) and Cs_2CO_3 (359 mg, 1.1 mmol). Reaction conditions: 110 °C, 12 h. Purification by flash chromatography (eluent: pentane: ether =4: 1) provided the desired product **63c** (121 mg, 59%) as a white solid, mp.: 157.9-158.5 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.40 (d, *J* = 7.1 Hz, 1 H), 8.35 (s, 1 H), 8.30 (d, *J* = 7.9 Hz, 1 H), 8.01 (dd, J_1 = 7.9 Hz, J_2 = 3.5 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.19-7.58 (m, 6 H), 6.97 (dd, J_1 = 7.9 Hz, J_2 = 2.6 Hz, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 3.94 (s, 3 H), 3.24 (s, 3 H), 1.47 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 165.6, 160.1, 142.4, 138.8, 134.9, 133.3, 129.9, 128.8, 127.8, 127.5, 125.4, 125.1, 124.6, 124.0, 123.9, 123.0, 120.8, 119.6, 118.0, 116.5, 113.0, 112.6, 103.2, 59.9, 55.4, 16.6, 14.5;

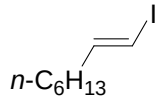
IR (neat): 2972 (w), 1696 (s), 1604 (w), 1580 (m), 1559 (m), 1414 (s), 1214 (vs) cm^{-1};

MS (EI, 70 ev): 409 (100%), 380 (85%), 337 (14%), 292 (13%), 207 (30%), 145 (15%);

HRMS (EI): calcd. for $C_{27}H_{23}NO_3$ (M^+): 409.1678, **found**: 409.1697 (M^+).

10. Preparation of Functionalized Alkenyl Organomagnesium Reagents and Polysubstituted Pyridylmagnesium Reagents Using *i*-PrMgCl•LiCl

Synthesis of (*E*)-1-iodo-1-octene (79a)



RHJ139B

To a solution of 1-octyne (2.75 g, 25 mmol, in 50 mL of dry hexane) was slowly added neat DIBAL (2.85 g, 25 mmol) and the temperature was kept below 40 ^{o}C. The reaction was heated at 50 ^{o}C for 4 h, then cooled to rt and hexane was removed under vacuum. THF (20 mL) was added and the solution was cooled to –50 ^{o}C, and iodine (6.35 g, 25 mmol) in THF (20 mL) was slowly added. The mixture was then warmed to rt change colour from brownish-red to almost colorless. The reaction mixture was then quenched by dropwise addition of 20% sulfuric acid and was poured in a mixture of ice and 20% sulfuric acid. The mixture was then extracted with pentane, and the organic extracts were washed with sodium thiosulfate, sodium bicarbonate solutions, dried (MgSO4), and the solvents were removed *in vacuo*. Purification by flash chromatography (pentane) afforded the pure product **79a** (5.68 g, 95%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.49 (dt, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1 H), 5.95 (dt, J_1 = 14.4 Hz, J_2 = 1.5 Hz, 1 H), 2.03 (dq, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 2 H), 1.18-1.44 (m, 8 H), 0.86 (t, *J* = 6.9 Hz, 3 H);

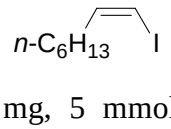
^{13}C NMR ($CDCl_3$, 75 MHz): 146.8, 74.2, 36.0, 31.5, 28.6, 28.3, 22.5, 14.0;

IR (film): 2926 (vs), 1606 (w), 1465 (m), 943 (m) cm^{-1};

MS (EI, 70 ev), m/z (%): 238 (M^+, 50%), 167 (35%), 154 (34%), 69 (100%).

Spectral data match those reported in the literature.[125]

Synthesis of (*Z*)-1-iodo-1-octene (79b)



RHJ155B

To a solution of 1-octyne (550 mg, 5 mmol) in anhydrous CH_2Cl_2 was slowly added $HBBr_2{\cdot}SMe_2$ (5 mL, 1.0 M in CH_2Cl_2) and the mixture was stirred for 10 h. Water (0.9 mL) and ether (2.5 mL) was added to the reaction mixture at 0 ^{o}C. The reaction mixture was stirred for about 20 min after the addition and more ether (25 mL) was added. The organic layer was washed with cold water, brine and dried ($MgSO_4$). After evaporation of the solvent under

[125] J. K. Stille, J. H. Simpson, *J. Am. Chem . Soc.* **1987**, *109*, 2138.

reduced pressure, the boronic acid was obtained in satisfactory purity. The boronic acid was then dissolved in the mixture solvent of ether and tetrahydrofuran (5 mL, 1:1) in a 25-mL flask and cooled to 0 ^{o}C. Elemental iodine (13 mmol) was added and the mixture was stirred for 8 h at 0 ^{o}C. Aqueous sodium thiosulfate was added until iodine colour disappeared; the mixture was extracted with pentane, washed with brine and dried over $MgSO_4$. Purification by flash chromatography (pentane) afforded the pure product **79b** (800 mg, 67%) as a colorless oil. GC and ^{1}H NMR analysis indicated 98% isomeric purity (*E*: *Z* = 2:98).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.11-6.19 (m, 2 H), 2.07-2.16 (m, 2 H), 1.18-1.50 (m, 8 H), 0.87 (t, *J* = 6.9 Hz, 3 H);

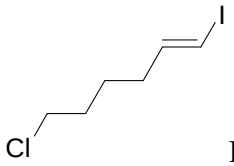
^{13}C NMR ($CDCl_3$, 75 MHz): 141.5, 82.1, 34.7, 31.6, 28.8, 27.9, 22.6, 14.0;

IR (film): 2926 (vs), 1610 (w), 1465 (w), 1285 (w) cm^{-1};

MS (EI, 70 ev), m/z (%): 238 (M^+, 52%), 167 (25%), 154 (30%), 69 (100%).

Spectral data match those reported in the literature.[126]

Synthesis of (*E*)-6-chloro-1-iodo-hex-1-ene (79c)



RHJ148B

The reaction was carried out according to the procedure for preparation of (*E*)-1-iodo-1-octene **79a**. 6-Chloro-1-hexyne (2.33 g, 20 mmol), neat DIBAL (2.28 g, 20 mmol) and I_2 (5.08 g, 20 mmol) afforded the product (*E*)-6-chloro-1-iodo-hex-1-ene **79c** (3.98 g, 81%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.48 (dt, J_1 = 14.7 Hz, J_2 = 7.2 Hz, 1 H), 6.01 (dt, J_1 = 14.7 Hz, J_2 = 1.8 Hz, 1 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 2.07 (qd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H, 2 H), 1.75 (m, 2 H), 1.54 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 145.7, 75.1, 44.6, 35.2, 31.7, 25.5;

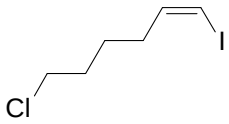
IR (film): 2937 (vs), 1606 (m), 1454 (m), 1230 (m), 947 (vs) cm^{-1};

MS (EI, 70 ev): 246 (M^+,^{37}Cl, 33%), 244 (M^+, ^{35} Cl, 100%), 180 (9%), 167 (59%), 154 (32%), 127 (14%), 81 (52%);

HRMS (EI): calcd. for $C_6H_{10}ClI$ (M^+, ^{35}Cl): 243.9516, **found**: 243.9512 (M^+, ^{35}Cl).

[126] H. C. Brown, C. Subrahmanyam, T. Hamaoka,; N. Ravindran, D. H. Bowman,; S. Misumi, M. K. Unni, V. Somayaji, N. G. Bhat, *J. Org. Chem.* **1989**, *54*, 6068.

Synthesis of (*Z*)-6-chloro-1-iodo-hex-1-ene (79d)



RHJ163B

The reaction was carried out according to the procedure for preparation of (*Z*)-1-iodo-1-octene. 6-chloro-1-hexyne **79b** (291 mg, 2.5 mmol), $HBBr_2 \cdot SMe_2$ (2.5 mL, 1.0 M in CH_2Cl_2) and I_2 (1.7 g, 6.75 mmol) afforded the product (*Z*)-6-chloro-1-iodo-hex-1-ene **79d** (469 mg, 77%) as a colorless oil. GC and ^{1}H NMR analysis indicated 97% isomeric purity (*E*: *Z* = 3: 97).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.11- 6.23 (m, 2 H), 3.53 (t, *J* = 6.3 Hz, 2 H), 2.16 (q, *J* = 7.2 Hz, 2 H), 1.80 (m, 2 H), 1.57 (m, 2 H);

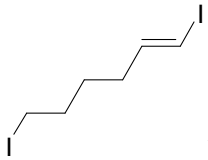
^{13}C NMR ($CDCl_3$, 75 MHz): 140.5, 83.0, 44.7, 33.8, 31.8, 25.1;

IR (film): 2939 (vs), 1610 (m), 1454 (m), 1297 (s), 1284 (s), 690 (s) cm^{-1};

MS (EI, 70 ev): 246 (M^+, ^{37}Cl, 16%), 244 (M^+, ^{35}Cl, 49%), 167 (35%), 154 (28%), 117 (13%), 81 (100%);

HRMS (EI): calcd. for $C_6H_{10}ClI$ (M^+, ^{35}Cl): 243.9516, **found**: 243.9521 (M^+, ^{35}Cl).

Synthesis of (*E*)-1,6-diiodo-hex-1-ene (79e)



RHJ153B

A mixture of (*E*)-6-chloro-1-iodo-hex-1-ene **79c** (732 mg, 3.0 mmol), NaI (900 mg, 6.0 mmol) and acetone (5 mL) was stirred at 70 °C overnight. After cooling to room temperature, water (10 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 100:1) yielded the product **79e** (912 mg, 90%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*:*Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.47 (dt, J_1 = 14.6 Hz, J_2 = 6.6 Hz, 1 H), 6.00 (d, *J* = 14.6 Hz, 1 H), 3.15 (t, *J* = 6.3 Hz, 2 H), 2.01-2.10 (m, 2 H), 1.70-1.85 (m, 2 H), 1.49 (m, 2 H);

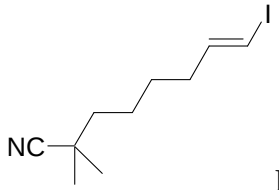
^{13}C NMR ($CDCl_3$, 75 MHz): 145.6, 75.3, 34.8, 32.5, 29.1, 6.3;

IR (film): 2928 (s), 1605 (m), 1450 (m), 1219 (m), 1187 (m), 943 (m) cm^{-1};

MS (EI, 70 ev): 336 (20%), 209 (79%), 167 (94%), 81 (100%);

HRMS (EI): calcd. for $C_6H_{10}I_2$ (M^+): 335.8872, **found**: 335.8894 (M^+).

Synthesis of (*E*)-8-iodo-2,2-dimethyl-oct-7-enenitrile (79f)



RHJ190B

To a solution of isobutyronitrile (104 mg, 1.5 mmol) in THF (3 mL) was added LDA (1.5 mmol in 3 mL THF, It was prepared from *n*-BuLi and HN(*i*-Pr)$_2$) at –78 ^{o}C and the mixture was stirred for 1 h. Then, the solution of **79f** (336 mg, 1.0 mmol, in 1 mL THF) was added and stirred at this temperature for 2 h. The reaction mixture was warmed to room temperature and stirred for 1 h, then quenched with NH_4Cl (aq). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 50:1) yielded the pure product **79f** (191 mg, 69%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.47 (dt, J_1 = 14.1 Hz, J_2 = 7.2 Hz, 1 H), 5.98 (dt, J_1 = 14.1 Hz, J_2 = 1.2 Hz, 1 H), 2.02-2.10 (m, 2 H), 1.36-1.51 (m, 6 H), 1.30 (s, 6 H);

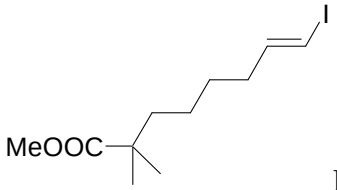
^{13}C NMR ($CDCl_3$, 75 MHz): 145.9, 125.0, 74.8, 40.7, 35.7, 32.2, 28.2, 26.6, 24.5;

IR (film): 2938 (vs), 2234 (m), 1606 (w), 1462 (m), 1207 (m), 949 (s) cm^{-1};

MS (EI, 70 ev): 277 (11%), 180 (26%), 167 (58%), 150 (100%), 123 (17%);

HRMS (EI): calcd. for $C_{10}H_{16}IN$ (M^+): 277.0327, **found**: 277.0359 (M^+).

Synthesis of (*E*)-8-iodo-2,2-dimethyl-oct-7-enoic acid methyl ester (79g)



RHJ185B

To a solution of methyl isobutyrate (174 mg, 1.5 mmol) in THF (3 mL) was added LDA (1.5 mmol, in 3 mL THF, It was prepared from *n*-BuLi and HN(*i*-Pr)$_2$) at –78 ^{o}C and the mixture was stirred for 1 h. Then, the solution of **79e** (336 mg, 1.0 mmol in 1 mL THF) was added and the mixture was stirred for 2 h at this temperature. The reaction mixture was warmed to room temperature and stirred for 1 h, then quenched with NH_4Cl (aq). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography

(pentane:ether = 25:1) yielded the pure product **15g** (224 mg, 81%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.46 (dt, J_1 = 14.1 Hz, J_2 = 6.9 Hz, 1 H), 5.95 (dt, J_1 = 14.1 Hz, J_2 = 1.5 Hz, 1 H), 3.63 (s, 3 H), 1.98-2.06 (m, 2 H), 1.40-1.50 (m, 2 H), 1.26-1.40 (m, 2 H), 1.13-1.23 (m, 2 H), 1.13 (s, 6 H);

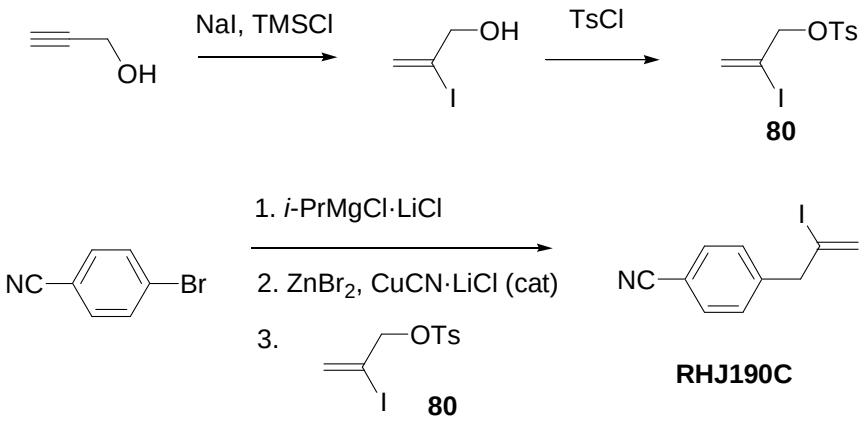
^{13}C NMR ($CDCl_3$, 75 MHz): 178.4, 146.4, 74.5, 51.7, 42.2, 40.4, 35.8, 28.7, 25.1, 24.2;

IR (film): 2938 (s), 1732 (vs), 1606 (w), 1473 (m), 1193 (s), 1156 (s), 948 (s) cm^{-1};

MS (EI, 70 ev): 311 (M^++1, 0.7%), 251 (0.8%), 195 (3.3%), 183 (33.9%), 123 (100%), 102 (77%);

HRMS (EI): calcd. for $C_{11}H_{20}IO_2$ (M^++H): 311.0508, **found**: 311.0488 (M^++H).

Synthesis of 4-(2-iodo-allyl)-benzonitrile (79h)



2-Iodo-prop-2-en-1-ol was obtained according to a literature procedure.[127] The mixture of 2-iodo-prop-2-en-1-ol (2.13 g, 11.6 mmol), TsCl (2.43 g, 12.8 mmol) and Et_3N (1.74 g, 17.4 mmol) in CH_2Cl_2 (25 mL) were stirred at 0 ^{o}C for 7 h. Then, the mixture was washed with brine and dried ($MgSO_4$). The crude product was purified on silica gel, yielding the 2-iodoallyl tosylate (3.33 g, 85%) as a colorless oil.

To a solution of 4-bromobenzonitrile (1.82 g, 10 mmol) in THF (10 mL) was added the *i*-PrMgCl·LiCl (5.5 mL, 2.0 M in THF, 11.0 mmol) at –10 ^{o}C and stirred for 4 h. $ZnBr_2$ (11.0 mL, 1.0 M in THF) was added and the reaction mixture was stirred at this temperature for 30 min. Then the solution of 2-iodoallyl tosylate (3.38 g, 10 mmol) in THF (5 mL), CuCN·2LiCl (2.0 mL, 1.0 M in THF) and NMP (4 mL) were added subsequently to the reaction mixture. The reaction mixture was stirred at room temperature overnight then quenched with NH_4Cl (aq) (5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*.

[127] S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis* **1988**, 367.

Purification by flash chromatography (pentane: ether = 15: 1) yielded the pure product **79h** (1.690 g, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.60 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 6.09-6.10 (m, 1 H), 5.84 (s, 1 H), 3.81 (s, 2 H);

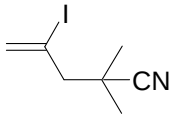
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 132.3, 129.7, 128.1, 118.7, 110.9, 107.2, 51.4;

IR (film): 2976 (w), 2228 (s), 1607 (m), 1504 (w), 1188 (m) cm^{-1};

MS (EI, 70 ev): 269 (M^+, 78%), 142 (100%), 115 (81%);

HRMS (EI): calcd. for $C_{10}H_8IN$ (M^+): 268.9701, **found**: 268.9726 (M^+).

Synthesis of 4-iodo-2,2-dimethyl-pent-4-enenitrile (79i)



RHJ077C

To a solution of isobutyronitrile (104 mg, 1.5 mmol) in THF (3 mL) was added LDA (1.5 mmol in 3 mL THF, prepared from *n*-BuLi and HN(*i*-Pr)$_2$) at –78 ^{o}C and stirred for 1 h. Then, the solution of 2-iodoallyl tosylate (338 mg, 1.0 mmol) in THF (1 mL) was added and the mixture was stirred for 2 h at this temperature then quenched with NH_4Cl (aq). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 25:1) yielded the pure product **79i** (134 mg, 57%) as a solid; mp.: 36.9-37.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.25-6.28 (m, 1 H), 6.03 (d, *J* = 1.8 Hz, 1 H), 2.73 (d, *J* = 1.3 Hz, 2 H), 1.44 (s, 6 H);

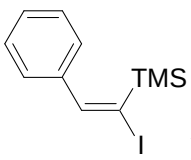
^{13}C NMR ($CDCl_3$, 75 MHz): 131.7, 124.1, 99.5, 53.9, 33.1, 26.8;

IR (KBr): 2977 (m), 2234 (m), 1611 (s), 1184 (s), 909 (vs) cm^{-1};

MS (EI, 70 ev): 235 (M^+, 100%), 167 (21%), 127 (10%), 108 (11%), 81 (32%);

HRMS (EI): calcd. for $C_7H_{10}IN$ (M^+): 234.9858, **found**: 234.9844 (M^+).

Synthesis of (1-iodo-2-phenyl-vinyl)-trimethyl-silane (79j)



RHJ006D

To a solution of trimethyl-phenylethynyl-silane (1.540 g, 8.9 mmol) in dry hexane (20 mL) was slowly added neat DIBAL (1.001 g, 8.9 mmol) and the temperature was kept below 40

^{o}C. The reaction was then heated at 50 ^{o}C for 4 hr, and then cooled to rt and hexane was removed under vacuum. THF (20 mL) was added and the solution was cooled to –50 ^{o}C, and iodine (6.35 g, 25 mmol) in THF (20 mL) was slowly added. The mixture was then warmed to rt change color from brownish-red to almost colorless. The reaction mixture was then quenched by dropwise addition of 20% sulfuric acid and poured into a mixture of ice and 20% sulfuric acid. The mixture was then extracted with pentane, and the organic extracts were washed with sodium thiosulfate, sodium bicarbonate solutions, and dried (MgSO4), and the solvents were removed *in vacuo*. Purification by flash chromatography (pentane) afforded the pure product **79j** (2.192 g, 82%) as a colorless oil. GC and ^{1}H NMR analysis indicated 95% isomeric purity (*E*: *Z* = 95: 5).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.19-7.52 (m, 6 H), 0.22 (s, 9 H);

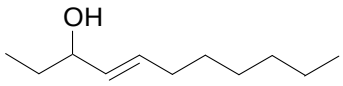
^{13}C NMR ($CDCl_3$, 75 MHz): 144.2, 139.1, 128.4, 128.2, 127.9, 111.8, -1.3;

IR (KBr): 2957 (m), 1592 (m), 1488 (m), 1444 (m), 1247 (vs) cm^{-1};

MS (EI, 70 ev): 302 (M^+, 100%), 287 (9%), 185 (90%), 175 (21%), 73 (89%);

Spectral data match those reported in the literature. [128]

Synthesis of (*E*)-undec-4-en-3-ol (83a)



RHJ147B

According to **TP4**, the reaction was carried out with (*E*)-1-iodo-1-octene **79a** (119 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 7 h. Purification by flash chromatography (pentane: ether = 3:1) afforded the pure product **83a** (70 mg, 82% yield) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99: 1).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.61 (ddt, J_1 = 15.5 Hz, J_2 = 6.6 Hz, J_3 = 0.9 Hz, 1 H), 5.41 (ddt, J_1 = 15.5 Hz, J_2 = 6.6 Hz, J_3 = 1.3 Hz, 1 H), 3.94 (q, *J* = 6.6 Hz, 1 H), 1.97-2.03 (m, 2 H), 1.17-1.60 (m, 7 H), 0.81-0.90 (m, 6 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 132.7, 132.4, 74.5, 32.2, 31.7, 30.1, 29.2, 28.8, 22.6, 14.0, 9.7;

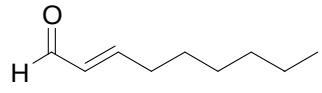
IR (film): 3350 (vs), 2960 (vs), 1670 (w), 1464 (m), 966 (s) cm^{-1};

MS (EI, 70 ev): 170 (M^+, 0.4%), 152 (11%), 141 (54%), 123 (26%), 85 (83%), 57 (100%).

Spectral data match those reported in the literature. [129]

[128] E. Negishi, T. Takahashi, , *J. Am. Chem . Soc.* **1986**, *108*, 3402.
[129] W. Oppolzer, , R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170-3.

Synthesis of (*E*)-non-2-enal (83b)



RHJ197B

According to **TP4**, the reaction was carried out with (*E*)-1-iodo-1-octene **79a** (119 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and DMF (0.75 mmol in 0.5 ml THF). Exchange conditions: -40 ^{o}C, 7 h. Purification by flash chromatography (pentane: ether = 30:1) afforded the pure product **83b** (50 mg, 71% yield) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 9.46 (d, J = 7.9 Hz, 1 H), 6.81 (dt, J_1 = 15.5 Hz, J_2 = 6.6 Hz, 1 H), 6.08 (ddt, J_1 = 15.9 Hz, J_2 = 7.9 Hz, J_3 = 1.3 Hz, 1 H), 2.25-2.34 (m, 2 H), 1.20-1.52 (m, 8 H), 0.85 (t, J = 6.6 Hz, 3 H);

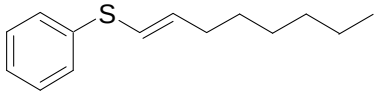
^{13}C NMR ($CDCl_3$, 75 MHz): 194.1, 159.0, 132.9, 32.7, 31.5, 28.7, 27.7, 22.5, 14.0;

IR (film): 2928 (vs), 1697 (vs), 1421 (vs), 1308 (vs), 977 (s) cm^{-1};

MS (EI, 70 ev): 139 (M^+-H, 0.6%), 122 (6%), 111 (13%), 96 (35%), 70 (100%).

Spectral data match those reported in the literature**.** [130]

Synthesis of (*E*)-oct-1-enylsulfanyl-benzene (83f)



RHJ145B

According to **TP4**, the reaction was carried out with (*E*)-1-iodo-1-octene **79a** (119 mg, 0.5 mmol), *i*-PrMgCl·LiCl and diphenyl disulfide (120 mg, 0.55 mmol, 1.1 equiv.). Exchange conditions: -40 ^{o}C, 7 h. Quenched as usual and extracted with ether (3 x 30 ml). The organic fractions were washed with 2 N NaOH (10 ml) thoroughly and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane) afforded the pure product **83f** (86 mg, 78%) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.16-7.36 (m, 5 H), 6.16 (dt, J_1 = 14.8 Hz, J_2 = 0.9 Hz, 1 H), 6.03 (dt, J_1 = 14.8 Hz, J_2 = 6.6 Hz, 1 H), 2.19 (m, 2 H), 1.24-1.50 (m, 8 H), 0.93 (t, J = 6.6 Hz, 3 H);

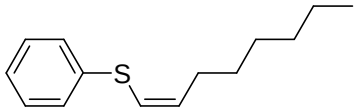
^{13}C NMR ($CDCl_3$, 75 MHz): 137.8, 136.7, 128.9, 128.4, 126.0, 120.6, 33.1, 31.6, 29.0, 28.8, 22.6, 14.1;

IR (film): 2926 (vs), 1738 (w), 1584 (m), 1439 (m), 738 (s);

[130] D. Ma, X. Lu, *Chem. Comm.* **1989**, *14*, 890-1.

MS (EI, 70 ev): 220 (M^+, 83%), 149 (100%), 134 (31%), 116 (84%).
Spectral data match those reported in the literature. [131]

Synthesis of (*Z*)-oct-1-enylsulfanyl-benzene (83d)



RHJ160B

According **TP4**, the reaction was carried out with (*Z*)-1-iodo-1-octene **79b** (119 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and diphenyl disulfide (120 mg, 0.55 mmol, 1.1 equiv.). Exchange conditions: -40 ^oC, 20 h. Quenched as usual and extracted with ether (3 x 30 ml). The organic fractions were washed with 2 N NaOH (10 ml) thoroughly and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane) afforded the pure product **83d** (76 mg, 69% yield) as a colorless oil. ^1H NMR analysis indicated 98% isomeric purity (*E*: *Z* = 2:98).

^1H NMR ($CDCl_3$, 300 MHz): 7.08-7.29 (m, 5 H), 6.11 (dt, J_1 = 8.8 Hz, J_2 = 1.3 Hz, 1 H), 5.75 (dt, J_1 = 8.8 Hz, J_2 = 7.5 Hz, 1 H), 2.13-2.22 (m, 2 H), 1.17-1.14 (m, 8 H), 0.82 (t, *J* = 6.6 Hz, 3 H);

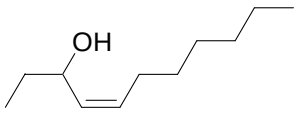
^{13}C NMR ($CDCl_3$, 75 MHz): 136.6, 133.8, 128.9, 128.7, 126.1, 122.5, 31.7, 29.1, 29.0, 28.9, 22.6, 14.1;

IR (film): 2926 (vs), 1609 (w), 1585 (m), 1479 (s), 736 (s) cm^{-1};

MS (EI, 70 ev): 220 (M^+, 60%), 149 (100%), 134 (25%), 116 (67%), 110 (51%), 91 (12%), 69 (56%);

HRMS (EI): calcd. for $C_{14}H_{20}S$ (M^+): 220.1286; **found**: 220.1302 (M^+).

Synthesis of (*Z*)-undec-4-en-3-ol (83e)



According to **TP4**, the reaction was carried out with (*Z*)-1-iodo-1-octene **79b** (119 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^oC, 20 h. Purification by flash chromatography (pentane: ether = 3:1) afforded the pure product **83e** (59 mg, 70%) as a colorless oil. ^1H NMR analysis indicated 98% isomeric purity (*E*: *Z* = 2:98).

[131] X. Huang, X. Xu, W. Zheng, *Synth. Commun*. **1999**, *29*, 2399.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.48 (ddt, J_1 = 11.1 Hz, J_2 = 7.5 Hz, J_3 = 0.9 Hz, 1 H), 5.33 (m, 1 H), 4.33 (m, 1 H), 1.97-2.13 (m, 2 H), 1.12-1.67 (m, 10 H), 0.87 (m, 6 H);

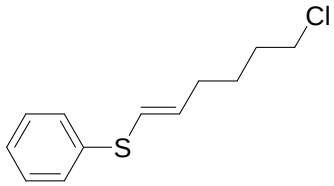
^{13}C NMR ($CDCl_3$, 75 MHz): 132.7, 132.2, 69.1, 31.7, 30.4, 29.7, 28.9, 27.7, 22.6, 14.1, 9.7;

IR (film): 3339 (vs), 2959 (w), 1658 (w), 1464 (m), 1007 (m) cm^{-1};

MS (EI, 70 ev): 170 (M^+, 0.4%), 152 (13%), 141 (51%), 123 (36%), 85 (87%), 81 (95%), 57 (100%);

HRMS (EI): calcd. for $C_{11}H_{22}O$ (M^+), 170.1671; **found**: 170.1621 (M^+).

Synthesis of (*E*)-(6-chloro-hex-1-enylsulfanyl)-benzene (83f)



RHJ152B

According to **TP4**, the reaction was carried out with (*E*)-6-chloro-1-iodo-hex-1-ene **79c** (122 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF), diphenyl disulfide (120 mg, 0.55 mmol, 1.1 equiv.). Exchange conditions: -40 ^{o}C, 7 h. Quenched as usual and extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with 2 M NaOH (10 mL) thoroughly and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 100: 1) afforded the pure product **83f** (85 mg, 75%) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.08-7.27 (m, 5 H), 6.09 (dt, J_1 = 15.0 Hz, J_2 = 1.3 Hz, 1 H), 5.86 (dt, J_1 = 15.0 Hz, J_2 = 6.6 Hz, 1 H), 3.47 (t, J = 6.6 Hz, 2 H), 2.08-2.16 (m, 2 H), 1.68-1.79 (m, 2 H), 1.44-1.56 (m, 2 H);

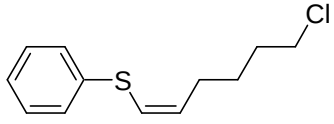
^{13}C NMR ($CDCl_3$, 75 MHz): 136.2, 135.8, 128.9, 128.7, 126.2, 121.9, 44.7, 32.2, 31.9, 26.2;

IR (film): 2936 (m), 1731 (w), 1583 (m), 1479 (s), 1439 (s), 951 (m), 739 (vs) cm^{-1};

MS (EI, 70 ev): 228 (M^+, ^{37}Cl, 10%), 226 (M^+, ^{35}Cl, 39%), 149 (100%), 134 (19%), 116 (58%), 59 (88%);

HRMS (EI): calcd. for $C_{12}H_{15}ClS$ (M^+, ^{35}Cl), 226.0583; **found**: 226.0582 (M^+, ^{35}Cl).

Synthesis of (*Z*)-(6-chloro-hex-1-enylsulfanyl)-benzene (83g)



RHJ148B

According to **TP4**, the reaction was carried out with (*Z*)-6-chloro-1-iodo-hex-1-ene **79d** (122 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and diphenyl disulfide (120 mg, 0.55 mmol, 1.1 equiv.). Exchange conditions: -40 °C, 20 h. Quenched as usual and extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with 2 M NaOH (10 mL) thoroughly and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane:ether = 100:1) afforded the pure product **83g** (92 mg, 81%) as a colorless oil. ^{1}H NMR analysis indicated 97% isomeric purity (*E*:*Z* = 3:97).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.10-7.28 (m, 5 H), 6.16 (dt, J_1 = 9.0 Hz, J_2 = 1.3 Hz, 1 H), 5.72 (dt, J_1 = 9.3 Hz, J_2 = 7.5 Hz, 1 H), 3.49 (t, J = 6.6 Hz, 2 H), 2.17-2.26 (m, 2 H), 1.70-1.81 (m, 2 H), 1.48-1.58 (m, 2 H);

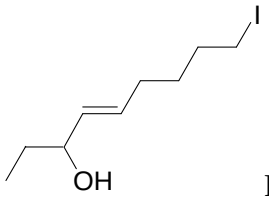
^{13}C NMR ($CDCl_3$, 75 MHz): 136.2, 132.3, 129.0, 128.8, 126.3, 123.7, 44.8, 32.0, 28.2, 26.2;

IR (film): 2934 (m), 1731 (w), 1584 (m), 1479 (s), 1439 (s) cm^{-1};

MS (EI, 70 ev): 228 (M^+, ^{37}Cl, 15%), 226 (M^+, ^{35}Cl, 44%), 149 (100%), 116 (45%), 110 (63%), 91 (37%);

HRMS (EI): calcd. for $C_{12}H_{15}ClS$ (M^+, ^{35}Cl), 226.0583; **found**: 226.0585 (M^+, ^{35}Cl).

Synthesis of (*E*)-9-iodo-non-4-en-3-ol (83h)



RHJ161B

According to **TP4**, the reaction was carried out with (*E*)-1, 6-diiodo-hex-1-ene **79e** (168 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 °C, 7 h. Purification by flash chromatography (pentane: ether = 4:1) afforded the pure product **83h** (112 mg, 84%) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*:*Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.59 (dt, J_1 = 15.0 Hz, J_2 = 6.6 Hz, 1 H), 5.44 (ddt, J_1 = 15.0 Hz, J_2 = 6.6 Hz, J_3 = 1.3 Hz, 1 H), 3.95 (m, 1 H), 3.16 (t, J = 7.2 Hz, 2 H), 2.04 (q, J = 7.2 Hz, 2 H), 1.74-1.86 (m, 2 H), 1.40-1.58 (m, 4 H), 0.87 (t, J = 7.5 Hz, 3 H);

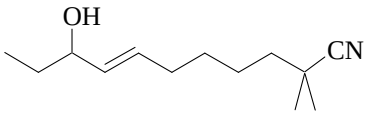
^{13}C NMR ($CDCl_3$, 75 MHz): 133.5, 131.1, 74.3, 32.9, 31.0, 30.1, 29.9, 9.7, 6.7;

IR (film): 3368 (vs), 2930 (vs), 1669 (w), 1455 (m), 966 (s) cm^{-1};

MS (EI, 70 ev): 267 (M^+-H, 0.4%), 250 (30%), 239 (50%), 155 (14%), 81 (54%), 57 (100%);

HRMS (EI): calcd. for $C_9H_{16}IO$: 267.0246 (M^+-H); **found**: 267.0242 (M^+-H).

Synthesis of (*E*)-9-hydroxy-2, 2-dimethyl-undec-7-enenitrile (83i)



RHJ193B

According to **TP4**, the reaction was carried out with (*E*)-8-iodo-2, 2-dimethyl-oct-7-enenitrile **79f** (139 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 7 h. Purification by flash chromatography (pentane: ether = 2:1) afforded the pure product **83i** (80 mg, 77%) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.59 (dt, J_1 = 15.6 Hz, J_2 = 6.6 Hz, 1 H), 5.43 (ddt, J_1 = 15.6 Hz, J_2 = 6.6 Hz, J_3 = 1.3 Hz, 1H), 3.92-3.96 (m, 1 H), 2.04 (q, *J* = 6.6 Hz, 2 H), 1.35-1.66 (m, 8 H), 1.30 (s, 6 H), 0.87 (t, J = 7.5 Hz, 3 H);

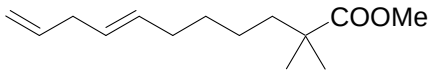
^{13}C NMR ($CDCl_3$, 75 MHz): 133.3, 131.4, 125.1, 74.3, 40.8, 32.3, 31.8, 30.1, 28.9, 26.63, 26.58, 24.6, 9.7;

IR (film): 3436 (vs), 2974 (vs), 2235 (m), 1730 (w), 1669 (w), 1463 (m), 968 (m) cm^{-1};

MS (EI, 70 ev): 208 (M^+-H, 0.1%), 192 (2%), 180 (100%), 162 (29%), 135 (32%), 85 (96%);

HRMS (EI): calcd. for $C_{13}H_{22}NO$: 208.1701 (M^+-H); **found**: 208.1681 (M^+-H).

Synthesis of (*E*)-2,2-dimethyl-undeca-7,10-dienoic acid methyl ester (83j)



RHJ188B

According to **TP4**, the reaction was carried out with (*E*)-8-iodo-2, 2-dimethyl-oct-7-enoic acid methyl ester **79g** (155 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and allyl bromide (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 12 h. Purification by flash chromatography (pentane: ether = 25:1) afforded the pure product **83j** (80 mg, 71%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*:*Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.73-5.86 (m, 1 H), 5.34-5.43 (m, 2 H), 4.90-5.04 (m, 2 H), 3.63 (s, 3 H), 2.64-2.79 (m, 2 H), 1.90-2.01 (m, 2 H), 1.16-1.51 (m, 6 H), 1.13 (s, 6 H);

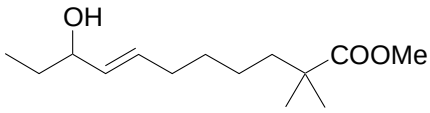
^{13}C NMR ($CDCl_3$, 75 MHz): 178.5, 137.4, 131.4, 127.7, 114.7, 51.6, 42.3, 40.6, 36.7, 32.3, 29.8, 25.1, 24.4;

IR (film): 2935 (s), 1734 (vs), 1639 (w), 1154 (m), 969 (m), 912 (m) cm^{-1}

MS (EI, 70 ev): 224 (M^+, 0.1%), 192 (10%), 123 (11%), 102 (100%), 81 (48%);

HRMS (EI): calcd. for $C_{14}H_{24}O_2$ (M^+): 224.1776; **found**: 224.1775 (M^+).

Synthesis of (*E*)-9-hydroxy-2,2-dimethyl-undec-7-enoic acid methyl ester (83k)



RHJ017D

According to **TP4**, the reaction was carried out with (*E*)-8-iodo-2, 2-dimethyl-oct-7-enoic acid methyl ester **79g** (155 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 12 h. Purification by flash chromatography (pentane: ether = 2:1) afforded the pure product **83k** (99 mg, 82%) as a colorless oil. ^{1}H NMR analysis indicated 99% isomeric purity (*E*:*Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.58 (dt, J_1 = 15.6 Hz, J_2 = 6.6 Hz, 1 H), 5.40 (ddt, J_1 = 15.6 Hz, J_2= 6.6 Hz, J_3 = 1.3 Hz, 1 H), 3.93 (q, J = 6.6 Hz, 1 H), 3.62 (s, 3 H), 1.99 (q, J = 7.2 Hz, 2 H), 1.12-1.59 (m, 6 H), 1.12 (s, 8 H), 0.86 (t, J = 7.2 Hz, 3 H);

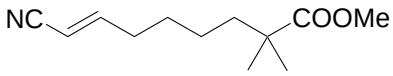
^{13}C NMR ($CDCl_3$, 75 MHz): 178.5, 132.9, 131.9, 74.4, 51.6, 42.2, 40.5, 31.9, 30.1, 29.5, 25.2, 25.1, 24.3, 9.7;

IR (film): 3498 (vs), 2970 (s), 1733 (s), 1194 (m), 1148 (s) cm^{-1}

MS (EI, 70 ev): 224 (M^+-H_2O, 1%), 213 (15%), 192 (64%), 153 (76%), 102 (100%);

HRMS (EI): calcd. for $C_{14}H_{24}O_2$ (M^+-H_2O): 224.1776; **found**: 224.1728 (M^+-H_2O).

Synthesis of 8-cyano-2,2-dimethyl-oct-7-enoic acid methyl ester (83l)



RHJ016D

According to **TP4**, the reaction was carried out with (*E*)-8-iodo-2, 2-dimethyl-oct-7-enoic acid methyl ester **79g** (155 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and TsCN (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 12 h. Purification by flash chromatography (pentane: ether = 4:1) afforded the pure product **83l** (78 mg, 75%) as a colorless oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.67 (dt, J_1 = 16.3 Hz, J_2 = 6.9 Hz, 1 H), 5.29 (dt, J_1 = 16.3 Hz, J_2 = 1.8 Hz, 1 H), 3.63 (s, 3 H), 2.15-2.22 (m, 2 H), 1.16-1.51 (m, 6 H), 1.13 (s, 6 H);

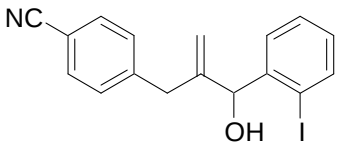
^{13}C NMR ($CDCl_3$, 75 MHz): 178.2, 155.7, 117.4, 99.8, 51.7, 42.1, 40.2, 33.0, 27.9, 25.1, 24.3;

IR (film): 2975 (m), 2223 (m), 1729 (s), 1633 (m), 1474 (m), 971 (m) cm^{-1};

MS (EI, 70 ev): 210 (M^++H, 1%), 194 (1%), 150 (52%), 134 (23%), 102 (100%);

HRMS (EI): calcd. for $C_{12}H_{20}NO_2$ (M^+ +H): 210.1494; **found**: 210.1464 (M^++H).

Synthesis of 4-{2-[hydroxy-(2-iodo-phenyl)-methyl]-allyl}-benzonitrile (83m)



RHJ003D

According to **TP4**, the reaction was carried out with 4-(2-iodo-allyl)-benzonitrile **79h** (135 mg, 0.5 mmol, *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and 2-iodobenzaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 5 h. Purification by flash chromatography (pentane: ether = 1:1) afforded the pure product **83m** (170 mg, 91%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.72 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 5.22 (s, 1 H), 5.28 (s, 1 H), 4.88 (s, 1 H), 3.40 (d, *J* = 15.6 Hz, 1 H), 3.24 (d, *J* = 15.6 Hz, 1 H), 2.16 (bs, 1 H);

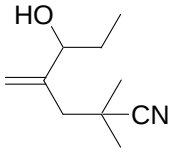
^{13}C NMR ($CDCl_3$, 75 MHz): 147.7, 144.6, 143.3, 139.5, 132.0, 130.0, 129.7, 128.6, 128.2, 119.0, 115.1, 110.0, 99.4, 79.1, 39.6;

IR (film): 3430 (vs), 2228 (s), 1647 (m), 1607 (m), 1434 (m), 1009 (s) cm^{-1};

MS (EI, 70 ev): 375 (M^+, 10%), 357 (10%), 259 (67%), 231 (34%), 132 (100%);

HRMS (EI): calcd. for $C_{17}H_{14}INO$ (M^+): 375.0120; **found**: 375.0144 (M^+).

Synthesis of 4-(1-hydroxy-propyl)-2,2-dimethyl-pent-4-enenitrile (83n)



RHJ084C

According to **TP4**, the reaction was carried out with 4-iodo-2, 2-dimethyl-pent-4-enenitrile **79i** (118 mg, 0.5 mmol, *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and propionaldehyde (0.55 mmol in 0.5 mL THF). Exchange conditions: -40 ^{o}C, 7 h. Purification by flash chromatography (pentane: ether = 2:1) afforded the pure product **83n** (59 mg, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.29 (t, *J* = 1.2 Hz, 1 H), 5.15 (s, 1 H), 4.10 (m, 1 H), 2.34 (d, *J* = 14.6 Hz, 1 H), 2.18 (d, *J* = 14.6 Hz, 1 H), 1.83 (bs, 1 H), 1.43-1.70 (m, 2 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 0.91 (t, *J* = 7.5 Hz, 3 H);

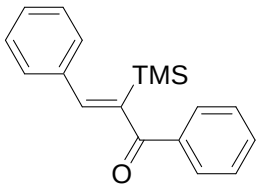
^{13}C NMR ($CDCl_3$, 75 MHz): 146.5, 125.3, 114.6, 75.7, 42.5, 31.8, 28.6, 27.4, 26.9, 9.8;

IR (film): 3436 (vs), 2975 (vs), 2235 (m), 1646 (w), 1456 (s), 982 (w), 913 (s) cm^{-1};

MS (EI, 70 ev): 167 (M^+, 1%), 152 (12%), 138 (62%), 111 (100%), 93 (65%);

HRMS (EI): calcd. for $C_{10}H_{17}NO$ (M^+): 167.1310; **found**: 167.1324 (M^+).

Synthesis of 1,3-diphenyl-2-trimethylsilanyl-propenone (83o)



RHJ011D

According to **TP4**, the reaction was carried out with (1-iodo-2-phenyl-vinyl)-trimethyl-silane **79j** (151 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) at –40°C for 4 h. After transmetalation with CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF), benzoyl chloride (0.7 mmol in 0.5 mL of THF) was added. The reaction mixture was stirred at –40 °C for 1 h then warmed to rt and stirred for 1 h before quenching with water. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 6:1) afforded the pure product **83o** (113 mg, 81%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.66-7.71 (m, 2 H), 6.78-7.25 (m, 9 H), 0.01 (s, 9 H)

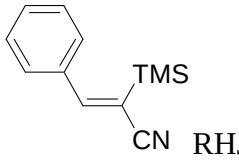
^{13}C NMR ($CDCl_3$, 75 MHz): 202.3, 147.3, 139.4, 136.5, 136.3, 133.0, 129.1, 128.7, 128.4, 128.2, -1.4;

IR (film): 2958 (m), 1646 (vs), 1597 (m), 1446 (m), 1225 (vs) cm^{-1};

MS (EI, 70 ev): 280 (M^+, 100%), 265(92%), 203(32%), 191 (90%);

HRMS (EI): calcd. for $C_{18}H_{20}OSi$ (M^+): 280.1283; **found**: 280.1280 (M^+).

Synthesis of 3-phenyl-2-trimethylsilanyl-acrylonitrile (83p)



RHJ010D

According to **TP4**, the reaction was carried out with (1-iodo-2-phenyl-vinyl)-trimethyl-silane **79j** (151 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and TsCN (100 mg, 0.55 mmol). Exchange conditions: -40 °C, 4 h. Purification by flash chromatography (pentane: ether = 6:1) afforded the pure product **83p** (77 mg, 77%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.83-7.87 (m, 2 H), 7.41-7.63 (m, 3 H), 7.17 (s, 1 H), 0.32 (s, 9 H);

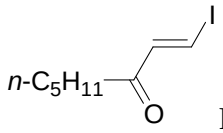
^{13}C NMR ($CDCl_3$, 75 MHz): 154.2, 135.3, 130.7, 128.9, 128.7, 119.3, 111.5, -2.1;

IR (film): 2958 (w), 2188 (m), 1590 (m), 1568 (m), 1251 (s) cm^{-1};

MS (EI, 70 ev): 201 (M^+, 55%), 186(100%), 170(42%), 73 (43%);

HRMS (EI): calcd. for $C_{12}H_{15}NSi$ (M^+): 201.0974; **found**: 201.0973 (M^+).

Synthesis of 1-iodo-oct-1-en-3-one (84)



RHJ033D

A mixture of oct-1-yn-3-one (496 mg, 4.0 mmol), LiI (643 mg, 4.8 mmol) and HOAc (4 mL) was stirred at room temperature for 3 h. Water (10 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with saturated aqueous $NaHCO_3$, brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 15:1) afforded the product **84** (927 mg, 92%) as a white solid; mp.: 37.7-38.4 ^oC (lit. 36-37 ^oC). GC and ^1H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^1H NMR ($CDCl_3$, 300 MHz): 7.78 (d, *J* = 15.0 Hz, 1 H), 7.13 (d, *J* = 15.0 Hz, 1 H), 2.47 (t, *J* = 7.3 Hz, 2 H), 1.50-1.65 (m, 2 H), 1.18-1.35 (m, 4 H), 0.86 (t, *J* = 6.9 Hz, 3 H)

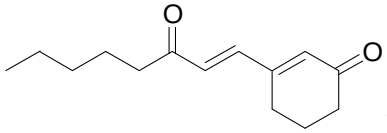
^{13}C NMR ($CDCl_3$, 75 MHz): 197.5, 144.6, 98.6, 40.4, 31.3, 23.4, 22.4, 13.9;

IR (KBr): 2955 (m), 1695 (m), 1675 (m), 1572 (m), 1466 (m), 955 (m) cm^{-1};

MS (EI, 70 ev): 253 (M^+ + 1, 0.4%), 196 (95%), 181 (100%), 153 (19%), 125 (46%).

Spectral data match those reported in the literature. [132]

Synthesis of 3-(3-oxo-oct-1-enyl)-cyclohex-2-enone (87a)



RHJ036D

TMSCN (75 mg, 0.75 mmol) was added dropwise to a solution of 1-iodo-oct-1-en-3-one **84** (126 mg, 0.5 mmol) and CsF (11 mg, 0.07 mmol) in dry CH_3CN (0.5 mL). The resulting mixture was stirred continuously and the reaction conversion was monitored by TLC. Water (5 mL) was added after 1 h and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. GC and ^1H NMR analysis indicated a high purity of the product.

i-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) was slowly added to a solution of the corresponding silylated cyanhydrine derivative **85** in THF (0.2 mL) at –40 °C. After 2 h, a complete conversion to the Grignard reagent **86** was observed by GC-analysis of hydrolyzed reaction aliquots. THF (1.0 mL) and CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) was added at this temperature and stirred for 15 min. 3-Iodo-cyclohex-2-enone (0.55 mmol in 0.5

[132] S. Ma, X. Lu, *J. Org. Chem.* **1992**, *57*, 709.

mL of THF) was added and the reaction mixture was stirred continuously 4 h at –30 °C. The reaction minxture was warmed to 25 °C, TBAF (0.5 mL, 0.5 mmol, 1.0 M in THF) and HCl (1.0 mL, 2 M in H_2O) were added. The mixture was stirred for another 2 h before the addition of aq. NH_3 (2 ml). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 2:1) afforded the pure product **87a** (85 mg, 77%) as a pale yellow solid; mp.: 52.9-53.4 °C. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99: 1).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.17 (d, *J* = 16.2 Hz, 1 H), 6.47 (d, *J* = 16.2 Hz, 1 H), 6.16 (s, 1 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 2.41-2.50 (m, 4 H), 2.01-2.10 (m, 2 H), 1.56-1.67 (m, 2 H), 1.22-1.36 (m, 4 H), 0.87 (t, *J* = 6.9 Hz, 3 H);

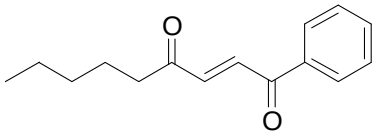
^{13}C NMR ($CDCl_3$, 75 MHz): 200.0, 199.5, 154.2, 141.7, 132.9, 131.1, 41.0, 37.6, 31.3, 24.8, 23.7, 22.4, 22.0, 13.9;

IR (KBr): 2954 (m), 1691 (s), 1661 (s), 1605 (m), 1581 (m), 1467 (m) cm^{-1};

MS (EI, 70 ev): 220 (M^+, 11%), 191 (9%), 164 (95%), 149 (100%), 136 (43%), 121 (51%);

HRMS (EI): calcd. for $C_{14}H_{20}O_2$ (M^+): 220.1463; **found**: 260.1451 (M^+).

Synthesis of 1-phenyl-non-2-ene-1,4-dione (87b)



RHJ035D

According to the procedure for preparation of **87a**, the reaction was carried out with silylated cyanhydrine derivative **85** (0.5 mmol) in THF (0.2 ml), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) and benzoyl chloride (0.7 mmol in 0.5 mL of THF). Purification by flash chromatography (pentane: ether = 3:1) afforded the pure product **87b** (85 mg, 74%) as a pale yellow oil. GC and ^{1}H NMR analysis indicated 99% isomeric purity (*E*: *Z* = 99:1).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.90-8.00 (m, 2 H), 7.71 (d, *J* = 15.9 Hz, 1 H), 7.55-7.63 (m, 1 H), 7.44-7.52 (m, 2 H), 7.10 (d, *J* = 15.9 Hz, 1 H), 2.66 (t, *J* = 7.5 Hz, 2 H), 1.61-1.71 (m, 2 H), 1.22-1.39 (m, 4 H), 0.88 (t, *J* = 6.9 Hz, 3 H);

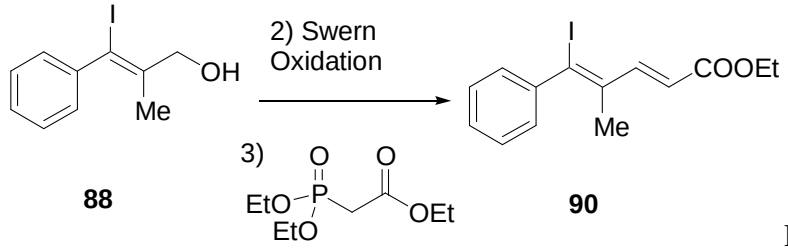
^{13}C NMR ($CDCl_3$, 75 MHz): 200.2, 190.3, 137.8, 136.8, 133.8, 133.1, 128.83, 127.78, 42.4, 31.3, 23.4, 22.4, 13.8;

IR (film): 2957 (m), 1701 (m), 1666 (s), 1597 (m), 1580 (m), 1287 (m) cm^{-1};

MS (EI, 70 ev): 230 (M^+, 9%), 201 (14%), 174 (20%), 159 (51%), 131 (100%), 105 (89%);

HRMS (EI): calcd. for $C_{15}H_{18}O_2$ (M^+): 230.1307; **found**: 230.1339 (M^+).

Synthesis of (*E*,*E*)-5-iodo-4-methyl-5-phenyl-penta-2,4-dienoic acid ethyl ester (**90**)



88 **90**

RHJ083F

To a solution of oxalyl chloride (1.78 g, 14 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC under nitrogen was added dry DMSO (2.0 mL) and the resulting mixture was stirred for 5 min. The solution of alcohol **88** (2.74 g, 10 mmol) in CH_2Cl_2 (5.0 mL) was added and the mixture was stirred for 20 min at -78 ^oC. Triethylamine (20 mmol) was added and the thick white mixture was warmed to 0 ^oC and poured into water. The organic layer was washed with water and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, the pale yellow oil (2.791 g, 100%) was left. It was used without further purification.

NaH (60% in oil, 560 mg) was added to the solution of diethoxy-phosphoryl-acetic acid ethyl ester (3.36 g, 15 mmol) in THF (20 mL) at 0 ^oC and the resulting mixture was stirred for 30 min. The solution of the crude aldehyde in THF (20 mL) was added to the mixture and the resulting mixture was stirred overnight at room temperature. Quenched with NH_4Cl (aq.) (10 mL) and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 10:1) afforded the pure product **90** (2.531 g, 74%) as a yellow solid, mp.: 37.9-38.6 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.82 (d, *J* = 15.5 Hz, 1 H), 7.22-7.31 (m, 2 H), 7.10-7.22 (m, 3 H), 5.98 (d, *J* = 15.5 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.74 (s, 3 H), 1.26 (t, *J* = 7.1, 3 H);

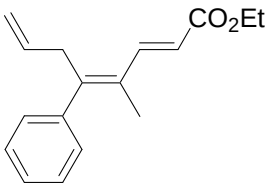
^{13}C NMR ($CDCl_3$, 75 MHz): 166.6, 150.0, 144.5, 137.1, 128.23, 128.19, 122.51, 122.50, 109.0, 60.5, 16.4, 14.3;

IR (film): 2980 (w), 1711 (vs), 1621 (s), 1442 (m), 1366 (m), 1291 (vs), 1180 (vs) cm^{-1};

MS (EI, 70 ev): 342 (M^+, 13%), 297 (11%), 268 (14%), 215 (100%), 187 (97%), 141 (67%), 115 (70%);

HRMS (EI): calcd. for $C_{14}H_{15}IO_2$ (M^+): 342.0117, **found**: 342.0116 (M^+).

Synthesis of (*E*, *E*)-4-methyl-5-phenyl-octa-2,4,7-trienoic acid ethyl ester (92a)



RHJ086F

To a solution of (*E*,*E*)-5-iodo-4-methyl-5-phenyl-penta-2, 4-dienoic acid ethyl ester **90** (171 mg, 0.5 mmol) in THF (1.5 mL) was slowly added *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) at –78°C. After 10 min, a complete conversion to the Grignard reagent **91** was observed by GC-analysis of hydrolyzed reaction aliquots. Allyl bromide (0.55 mmol in 0.5 mL of THF) and CuCN·2LiCl (1 drop) was added and the reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 25: 1) afforded the pure product **92a** (117 mg, 92%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.88 (d, *J* = 15.5 Hz, 1 H), 7.14-7.32 (m, 2 H), 7.00-7.06 (m, 3 H), 5.91 (d, *J* = 15.5 Hz, 1 H), 5.59-5.73 (m, 1 H), 4.82-4.97 (m, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.31 (d, *J* = 6.2 Hz, 2 H), 1.65 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H);

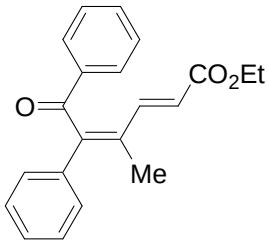
^{13}C NMR ($CDCl_3$, 75 MHz): 167.5, 146.0, 142.8, 142.7, 135.0, 128.8, 128.2, 128.0, 127.0, 118.6, 116.2, 60.2, 38.9, 16.1, 14.3;

IR (film): 2980 (m), 1711 (vs), 1617 (vs), 1443 (m), 1366 (m), 1297 (vs), 1176 (vs) cm^{-1};

MS (EI, 70 ev): 256 (M^+, 27%), 228 (11%), 215 (84%), 183 (100%), 167 (97%), 141 (67%), 115 (70%), 91 (65%);

HRMS (EI): calcd. for $C_{17}H_{20}O_2$ (M^+): 256.1463, **found**: 256.1488 (M^+).

Synthesis of 4-methyl-6-oxo-5,6-diphenyl-hexa-2,4-dienoic acid ethyl ester (**92b**)



RHJ087F

According to the procedure for preparation of **92a**, the reaction was carried out with (*E*,*E*)-5-iodo-4-methyl-5-phenyl-penta-2,4-dienoic acid ethyl ester **90** (171 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.28 mL, 0.55 mmol, 2.00 M in THF) at –78 °C for 10 min. THF (1.0 mL) and CuCN·2LiCl (0.55 mmol, 0.55 mL,1.0 M in THF) was added at this temperature and stirred for 15 min. Benzoyl chloride (0.7 mmol in 0.5 mL of THF) was added and the reaction mixture was stirred at –40 ^{o}C for 1 h, then warmed to rt and stirred for 1 h. Aq. NH_3 (2 ml)

and water (5 mL) were added and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 4:1) afforded the pure product **92b** (140 mg, 88%) as a yellow solid, mp.: 104.0-105.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.82-7.90 (m, 2 H), 7.40-7.48 (m, 1 H), 7.17-7.37 (m, 8 H), 6.00 (d, *J* = 15.5 Hz, 1 H), 4.05 (d, *J* = 7.1 Hz, 2 H), 1.97 (s, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H);

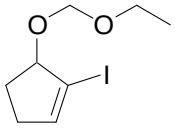
^{13}C NMR ($CDCl_3$, 75 MHz): 197.2, 166.5, 147.0, 142.9, 136.3, 135.6, 133.7, 132.6, 129.9, 129.0, 128.7, 128.6, 128.3, 120.9, 60.4, 15.1, 14.1;

IR (film): 2956 (w), 1712 (vs), 1664 (vs), 1627 (vs), 1450 (m), 1443 (m), 1380 (m), 1366 (m), 1305 (vs), 1208 (m), 1188 (vs) cm^{-1};

MS (EI, 70 ev): 320 (M^+, 7%), 291 (11%), 215 (84%), 183 (100%), 167 (97%), 141 (67%), 115 (70%), 91 (65%);

HRMS (EI): calcd. for $C_{21}H_{20}O_3$ (M^+): 320.1412, **found**: 320.1416 (M^+).

Synthesis of 5-ethoxymethoxy-1-iodo-cyclopentene (**93a**)



RHJ079B

Chloromethoxy-ethane (228 mg, 2.41 mmol) was slowly added to a solution of 2-iodo-cyclopent-2-enol (390 mg, 1.86 mmol) and (*i*-Pr)$_2$NEt (311 mg, 2.41 mmol) in CH_2Cl_2 (4.0 mL) at - 20 °C and the reaction mixture was stirred for 1 h at this temperature and then warmed to rt for 2 h. CH_2Cl_2 (10 mL) was added and the organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography afforded the pure product **93a** (430 mg, 86%) as a colorless oil.

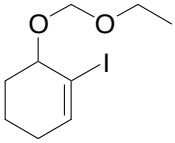
^{1}H NMR ($CDCl_3$, 300 MHz): 6.30-6.35 (m, 1 H), 4.76 (s, 2 H), 4.58-4.64 (m, 1 H), 3.55-3.81 (m, 2 H), 2.40-2.55 (m, 1 H), 2.18-2.34 (m, 2 H), 1.84-1.95 (m, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 143.6, 96.4, 94.2, 86.6, 63.4, 32.8, 29.9, 15.0;

IR (film): 2931 (m), 1606 (w), 1391 (w), 1098 (s), 1036 (vs), 1012 (vs);

MS (IE, 70 ev): 268 (M^+, 0.3%), 238 (9%), 222 (35%), 192 (100%), 111 (47%).

Synthesis of 6-ethoxymethoxy-1-iodo-cyclohexene (**93b**)



RHJ092B

According to the procedure for preparation of **93a**, the reaction was carried out with 2-iodo-cyclohex-2-enol (1.630 g, 7.3 mmol) and (*i*-Pr)$_2$NEt (1.410 g, 11 mmol). Purification by flash chromatography afforded the pure product **93b** (1.910 g, 93%) as a colorless oil.

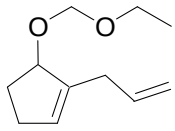
^{1}H NMR ($CDCl_3$, 300 MHz): 6.52 (t, *J* = 4.0 Hz, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.73 (d, *J* = 7.1 Hz, 1 H), 4.09 (t, *J* = 4.2 Hz, 1 H), 3.74-3.84 (m, 1 H), 3.58-3.68 (m, 1 H), 1.55-2.17 (m, 6 H), 1.20 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 142.0, 99.0, 94.2, 77.1, 63.7, 30.0, 29.3, 17.0, 14.9;

IR (film): 2936 (s), 1629 (w), 1440 (w), 1391 (m), 1028 (vs) cm^{-1};

MS (EI, 70 ev): 282 (M^+, 0.5%), 252 (4%), 236 (33%), 206 (99%), 125 (100%), 79 (98%).

Synthesis of 1-allyl-5-ethoxymethoxy-cyclopentene (**95a**)



RHJ100B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and allyl bromide (1.5 mmol in 1.0 mL THF). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography afforded the pure product **95a** (166 mg, 91%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.79-5.90 (m, 1 H), 5.57-5.60 (m, 1 H), 4.99-5.07 (m, 2 H), 4.74 (d, *J* = 6.9 Hz, 1 H), 4.68 (d, *J* = 6.9 Hz, 1 H), 4.56-4.59 (m, 1 H), 3.54-3.67 (m, 2 H), 2.75-2.96 (m, 2 H), 2.34-2.47 (m, 1 H), 2.11-2.28 (m, 2 H), 1.75-1.85 (m, 1 H), 1.20 (t, *J* = 7.1 Hz, 3 H);

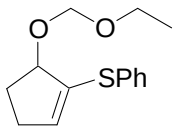
^{13}C NMR ($CDCl_3$, 75 MHz): 142.8, 135.9, 128.9, 115.7, 94.2, 83.6, 63.2, 32.9, 30.9, 30.0, 15.1;

IR (film): 2976 (m), 1738 (w), 1640 (m), 1391 (m), 1364 (m), 1099 (m), 1039 (vs) cm^{-1};

MS (EI, 70 ev): 181 (M^+-H, 0.2%), 141 (21%), 106 (95%), 91 (53%), 79 (62%);

HRMS (EI): calcd. for $C_{11}H_{17}O_2$ (M^+-H): 181.1229, **found**: 181.1243 (M^+-H).

Synthesis of (5-ethoxymethoxy-cyclopent-1-enylsulfanyl)-benzene (**95b**)



RHJ106B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and diphenyl

disulfide (240 mg, 1.10 mmol, 1.1 equiv.). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography afforded the pure product **95b** (205 mg, 82%) as a colorless oil.

^{1}H NMR (CDCl3, 300 MHz): 7.32-7.40 (m, 2 H), 7.14-7.26 (m, 3 H), 5.69-5.75 (m, 1 H), 4.63 (d, *J* = 7.0 Hz, 1 H), 4.56-4.61 (m, 1 H), 4.55 (d, *J* = 7.0 Hz, 1 H), 3.43-3.57 (m, 2 H), 2.36-2.51 (m, 1 H), 2.13-2.31 (m, 2 H), 1.83-1.95 (m, 1 H), 1.07 (t, *J* = 7.1 Hz, 3 H);

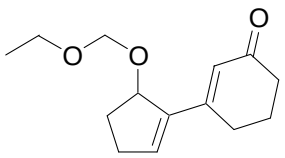
^{13}C NMR ($CDCl_3$, 75 MHz): 137.8, 134.1, 133.7, 131.7, 129.0, 127.2, 94.1, 82.0, 63.1, 31.2, 30.6, 14.9;

IR (film): 2974 (m), 1738 (w), 1584 (m), 1477 (m), 1440 (m), 1098 (s), 1042 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 250 (M^+, 13%), 174 (100%), 147 (15%), 110 (14%);

HRMS (EI): calcd. for $C_{14}H_{18}O_2S$ (M^+): 250.1028, **found**: 250.1031 (M^+).

Synthesis of 3-(5-ethoxymethoxy-cyclopent-1-enyl)-cyclohex-2-enone (**95c**)



RHJ103B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF), CuCN·2LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF) and 3-iodo-cyclohex-2-enone (244 mg, 1.1 mmol). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography afforded the pure product **95c** (144 mg, 61%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.47 (t, *J* = 2.7 Hz, 1 H), 6.08 (s, 1 H), 4.90 (dt, J_1 = 6.6 Hz, J_2 = 2.2 Hz, 1 H), 4.75 (d, *J* = 7.1 Hz, 1 H), 4.68 (d, *J* = 7.1 Hz, 1 H), 3.49-3.67 (m, 2 H), 2.32-2.70 (m, 6 H), 1.95-2.18 (m, 4 H), 1.20 (t, *J* = 7.1 Hz, 3 H);

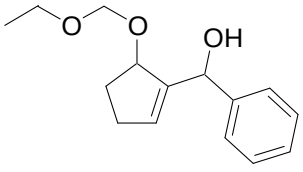
^{13}C NMR (CDCl3, 75 MHz): 200.3, 152.9, 143.1, 140.1, 124.9, 94.4, 81.0, 64.0, 37.4, 31.3, 30.7, 26.6, 22.4, 14.9;

IR (film): 2972 (s), 1659 (vs), 1613 (vs), 1584 (m), 1448 (m), 1101 (s), 1030 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 236 (M^+, 0.1%), 206 (2%), 192 (2%), 160 (100%), 147 (11%), 133 (19%), 91 (51%);

HRMS (EI): calcd. for $C_{14}H_{20}O_3$ (M^+): 236.1413, **found**: 236.1435 (M^+).

Synthesis of (5-ethoxymethoxy-cyclopent-1-enyl)-phenyl-methanol (**95d**)



RHJ102B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and benzaldehyde (117 mg, 1.10 mmol, 1.1 equiv.). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography afforded the pure product **95b** (221 mg, 89%) as a colorless oil. dr = 66:34 (determined by HPLC).

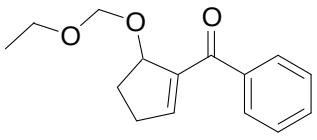
^{1}H NMR ($CDCl_3$, 300 MHz): 7.08-7.32 (m, 5 H), 5.62 (s, 1 H), 5.34 (s, 1 H), 4.58 (d, *J* = 7.0 Hz, 1 H), 4.49 (d, *J* = 7.0 Hz, 1 H), 3.42 (q, *J* = 7.1 Hz, 2 H), 2.25-2.40 (m, 1 H), 2.03-2.16 (m, 2 H), 1.67-1.79 (m, 1 H), 1.03 (t, *J* = 7.1 Hz, 3 H). The following signals are discernible for the minor isomer: 5.58 (s, 1 H), 5.23 (s, 1 H), 4.60-4.62 (m, 1 H), 4.51-4.52 (m, 1 H), 3.45 (q, *J* = 7.1 Hz, 2 H);

^{13}C NMR (CDCl3, 75 MHz): 145.1, 142.7, 132.8, 128.0, 126.9, 125.8, 94.2, 82.7, 71.9, 63.6, 31.2, 29.9, 14.8.

IR (film): 3437 (s), 2932 (s), 1603 (w), 1493 (m), 1452 (m), 1106 (s), 1029 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 247 (M^+-H, 0.1%), 230 (0.2%), 172 (100%), 143 (10%), 105 (79%).

Synthesis of (5-ethoxymethoxy-cyclopent-1-enyl)-phenyl-methanone (**95e**)



RHJ119B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF), CuCN·2LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF) and benzoyl chloride (211 mg, 1.5 mmol). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography afforded the pure product **95e** (144 mg, 61%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.75-7.80 (m, 2 H), 7.47-7.54 (m, 1 H), 7.37-7.44 (m, 2 H), 6.61 (t, *J* = 2.2 Hz, 1 H), 5.20-5.26 (m, 1 H), 4.83 (d, *J* = 7.1 Hz, 1 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 3.58 (q, *J* = 7.1 Hz, 2 H), 2.70-2.84 (m, 1 H), 2.39-2.52 (m, 1 H), 2.23-2.36 (m, 1 H), 1.93-2.05 (m, 1 H), 1.16 (t, *J* = 7.1 Hz, 3 H);

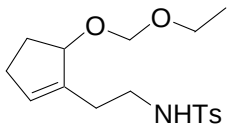
^{13}C NMR (CDCl3, 75 MHz): 193.0, 148.0, 144.6, 138.6, 132.1, 129.0, 128.2, 94.7, 81.0, 63.2, 31.9, 30.7, 15.0;

IR (film): 2974 (m), 1738 (w), 1651 (vs), 1447 (m), 1107 (m), 1037 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 201 (M^+- OC_2H_5, 1%), 187 (8%), 172 (100%), 157 (7%), 144 (9%), 105 (89%);

HRMS (EI): calcd. for $C_{13}H_{13}O_2$ (M^+-OC_2H_5): 201.0916, **found**: 201.0907 (M^+-OC_2H_5).

Synthesis of *N*-[2-(5-ethoxymethoxy-cyclopent-1-enyl)-ethyl]-4-methyl-benzenesulfonamide (95f)



RHJ131B

According to **TP5**, the reaction was carried out with 5-ethoxymethoxy-1-iodo-cyclopentene **93a** (268 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and 1-(toluene-4-sulfonyl)-aziridine (217 mg, 1.1 mmol). Exchange conditions: -25 °C, 5 h. Purification by flash chromatography (pentane: ether = 1:2) afforded the pure product **95f** (214 mg, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.70, (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 5.50-5.54 (m, 1 H), 5.00-5.10 (m, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 4.60 (d, *J* = 7.1 Hz, 1 H), 4.40-4.48 (m, 1 H), 3.48-3.58 (m, 2 H), 2.93-3.17 (m, 2 H), 2.39 (s, 3 H), 2.05-2.39 (m, 5 H), 1.65-1.81 (m, 1 H), 1.16 (t, *J* = 7.1 Hz, 3 H);

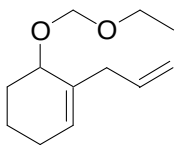
^{13}C NMR ($CDCl_3$, 75 MHz): 143.1, 140.3, 137.0, 131.9, 129.5, 127.1, 94.1, 83.8, 63.5, 41.9, 30.7, 30.1, 28.4, 21.4, 15.0;

IR (film): 3279 (s), 2930(s), 1598 (m), 1495 (m), 1435 (m), 1328 (s), 1160 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 280 (M^+-$CH_2OCH_2CH_3$, 8%), 263 (9%), 184 (60%), 155 (100%), 138 (12%), 108 (12%).

HRMS (EI): calcd. for $C_{13}H_{13}O_2$ (M^+-C_2H_6): 309.1035, **found**: 309.0982 (M^+-C_2H_6).

Synthesis of 1-allyl-6-ethoxymethoxy-cyclohexene (95g)



According to **TP5**, the reaction was carried out with 6-ethoxymethoxy-1-iodo-cyclohexene **93b** (282 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and allyl bromide (1.10 mmol, 1.1 equiv.). Exchange conditions: -40 °C, 12 h. Purification by flash chromatography afforded the pure product **95g** (159 mg, 81%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.70-5.86 (m,1 H), 5.56-5.65 (m, 1 H), 4.96-5.05 (m, 1 H), 4.98 (t, *J* = 1.3 Hz, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 3.94 (s, 1 H), 3.54-3.73 (m, 2 H), 2.77-2.82 (m, 2 H), 1.82-2.09 (m, 3 H), 1.47-1.73 (m, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H);

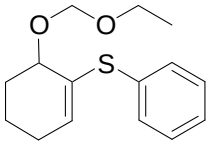
^{13}C NMR ($CDCl_3$, 75 MHz): 136.7, 136.1, 127.0, 115.8, 94.0, 72.0, 63.3, 38.6, 28.5, 25.3, 17.8, 15.0;

IR (film): 2975 (m), 1738 (w), 1639 (w), 1440 (m), 1391 (m), 1099 (m), 1033 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 195 (M^+-H, 0.1%), 166 (1%), 155 (10%), 120 (100%), 105 (21%), 79 (80%);

HRMS (EI): calcd. for $C_{12}H_{19}O_2$ (M^+-H): 195.1385, **found**: 195.1390 (M^+-H).

Synthesis of (6-ethoxymethoxy-cyclohex-1-enylsulfanyl)-benzene (**95h**)



RHJ109B

According to **TP5**, the reaction was carried out with 6-ethoxymethoxy-1-iodo-cyclohexene **93b** (282 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and diphenyl disulfide (240 mg, 1.10 mmol, 1.1 equiv.). Exchange conditions: -40 °C, 12 h. Purification by flash chromatography afforded the pure product **95h** (214 mg, 81%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.08-7.30 (m, 5 H), 6.07 (t, *J* = 4.0 Hz, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 4.58 (d, J = 7.1 Hz, 1 H), 3.98 (s, 1 H), 3.46-3.68 (m, 2 H), 1.50-2.19 (m, 6 H), 1.07 (t, *J* = 7.1 Hz, 3 H);

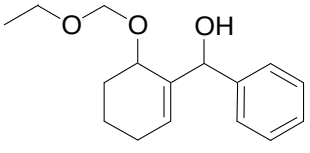
^{13}C NMR ($CDCl_3$, 75 MHz): 136.9, 135.3, 132.8, 130.3, 128.9, 126.4, 94.2, 71.4, 63.2, 29.3, 27.0, 16.9, 14.9;

IR (film): 2933 (m), 1582 (m), 1478 (m), 1440 (m), 1106 (m), 1032 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 264 (M^+, 11%), 188 (100%), 173 (8%), 147 (12%), 110 (14%);

HRMS (EI): calcd. for $C_{12}H_{20}O_2S$ (M^+): 264.1184, **found**: 264.1190 (M^+).

Synthesis of (6-ethoxymethoxy-cyclohex-1-enyl)-phenyl-methanol (**95i**)



RHJ111B

According to **TP5**, the reaction was carried out with 6-ethoxymethoxy-1-iodo-cyclohexene **93b** (282 mg, 1.0 mmol), *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) and and

benzaldehyde (117 mg, 1.10 mmol, 1.1 equiv.). Exchange conditions: -40 °C, 12 h. Purification by flash chromatography afforded the pure product **95i** (212 mg, 81%) as a colorless oil. dr = 80:20 (determined by GC). The two isomers can be separated by repeated flash chromatography on silica gel.

Less polar isomer:

^{1}H NMR ($CDCl_3$, 300 MHz): 7.18-7.38 (m, 5 H), 5.87 (t, *J* = 3.5 Hz, 1 H), 5.23 (d, *J* = 6.6 Hz, 1 H), 4.68 (d, *J* = 6.6 Hz, 1 H), 4.49 (d, *J* = 6.6 Hz, 1 H), 4.06-4.09 (m, 1 H), 3.67 (d, *J* = 7.1 Hz, 1 H), 3.43-3.58 (m, 2 H), 1.49-2.24 (m, 6 H), 1.13 (t, *J* = 7.1 Hz, 3 H);

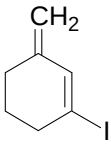
^{13}C NMR ($CDCl_3$, 75 MHz): 143.0, 138.8, 131.3, 128.0, 126.7, 125.8, 94.2, 77.8, 72.0, 63.8, 28.6, 25.2, 18.2, 14.9;

IR (film): 3450 (s), 2932 (m), 1602 (w), 1492 (m), 1450 (m), 1104 (m), 1031 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 262 (M^+, 0.1%), 203 (3%), 186 (100%), 168 (11%), 157 (22%), 129 (21%), 105 (48%).

HRMS (EI): calcd. for $C_{13}H_{15}O(M^+-C_3H_7O_2)$: 187.1123, **found**: 187.1100 ($M^+-C_3H_7O_2$).

Synthesis of 1-iodo-3-methylene-cyclohexene (**96**)



RHJ099C

To a solution of methyltriphenylphosphonium bromide (1.181 g, 3.3 mmol) in THF (15 mL) was slowly added *n*-BuLi (2.2 mL, 3.3 mmol, 1.50 M in Hexane) at -78°C, then warmed to 0 ^{o}C and stirred for 1 h. The reaction mixture was cooled to - 78°C and slowly transfered to a solution of 3-iodo-cyclohex-2-enone (666 mg, 3.0 mmol) in THF (20 mL) and stirred overnight at room temperature. Quenched with NH_4Cl (aq) and the aqueous phase were extracted with diethyl ether (3 × 200 mL). The organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane) afforded the pure product **96** (554 mg, 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.79 (s, 1 H), 4.72 (s, 1 H), 4.65 (s, 1 H), 2.60 (t, *J* = 6.2 Hz, 2 H), 2.29-2.35 (m, 2 H), 1.70-1.79 (m, 2 H);

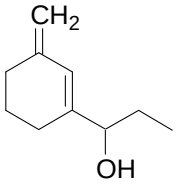
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 139.9, 111.6, 100.8, 39.6, 29.0, 24.9;

IR (film): 2937 (vs), 1676 (w), 1624 (s), 1589 (m), 1426 (m), 1335 (s), 892 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 220 (M^+, 100%), 192 (0.2%), 127 (1%), 91 (15%), 77 (16%);

HRMS (EI): calcd. for C_7H_9I (M^+): 219.9747, **found**: 219.9771 (M^+).

Synthesis of 1-(3-methylene-cyclohex-1-enyl)-propan-1-ol (**98a**)



RHJ103C

To a solution of 1-iodo-3-methylene-cyclohexene **96** (110 mg, 0.5 mmol) in THF (0.2 mL) was slowly added *i*-PrMgCl·LiCl (0.26 mL, 0.55 mmol, 2.16 M in THF) at - 40 °C. After 4 h, a complete conversion to the Grignard reagent **97** was observed by GC-analysis of hydrolyzed reaction aliquots. The solution of propionaldehyde (32 mg, 0.55 mmol) in THF (0.5 mL) was added and the reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 1: 3) afforded the pure product **98a** (69 mg, 91%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.09 (s, 1 H), 4.76(s, 1 H), 4.75 (s, 1 H), 3.96 (t, *J* = 6.6 Hz, 1 H), 2.25-2.35 (m, 2 H), 2.06-2.19 (m, 1 H), 1.92-2.03 (m, 1 H), 1.50-1.76 (m, 4 H), 0.87 (t, *J* = 7.5 Hz, 3 H);

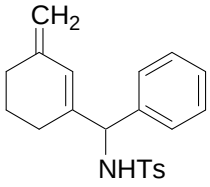
^{13}C NMR ($CDCl_3$, 75 MHz): 143.6, 143.2, 125.2, 110.6, 77.3, 30.8, 27.8, 24.1, 23.0, 9.9;

IR (film): 3391 (vs), 2960 (vs), 1662 (s), 1607 (m), 1455 (m) cm^{-1};

MS (EI, 70 ev), m/z (%): 152 (M^+, 11%), 134 (4%), 123 (100%), 95 (55%), 77 (20%);

HRMS (EI): calcd. for $C_{10}H_{16}O$ (M^+): 152.1201, **found**: 152.1203 (M^+).

Synthesis of 4-methyl-*N*-[(3-methylene-cyclohex-1-enyl)-phenyl-methyl]-benzenesulfonamide (**98b**)



RHJ107C

The solution of *N*-benzylidene-4-methyl-benzenesulfonamide (142 mg, 0.55 mmol) in THF (0.5 mL) was added to the Grignard **97**. The reaction mixture was warmed to 25 °C and quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 1:2) afforded the pure product **98b** (150 mg, 85%) as a white solid, mp: 127.1-127.7 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.61 (d, *J* = 8.4 Hz, 2 H), 7.03-7.22 (m, 7 H), 5.99 (s, 1 H), 5.02 (d, *J* = 7.7 Hz, 1 H), 4.90 (d, *J* = 7.7 Hz, 1 H), 4.73 (s, 1 H), 4.68 (s, 1 H), 2.36 (s, 3 H), 1.40-2.30 (m, 6 H);

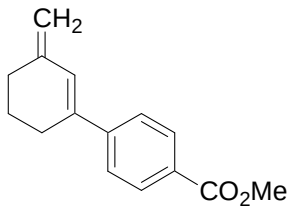
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 142.5, 138.9, 138.8, 137.5, 129.3, 128.5, 127.7, 127.6, 127.3, 126.9, 111.7, 62.8, 30.2, 25.6, 22.5, 21.4;

IR (KBr): 3436 (s), 3290 (m), 1643 (w), 1599 (w), 1494 (m), 1455 (m), 1435 (m), 1320 (m), 1160 (vs) cm^{-1};

MS (EI, 70 ev), m/z (%): 353 (M^+, 2%), 260 (3%), 198 (100%), 182 (19%), 167 (22%), 91 (43%);

HRMS (EI): calcd. for $C_{21}H_{23}NO_2S$ (M^+): 353.1449, **found**: 353.1463 (M^+).

Synthesis of 4-(3-methylene-cyclohex-1-enyl)-benzoic acid methyl ester (**98c**)



RHJ109C

The solution of $ZnBr_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF) was added to the Grignard **97** at -40 °C and warmed to 0 ^oC and stirred for 20 min. The solution of methyl 4-iodobenzoate (144 mg, 0.55 mmol) in THF (0.5 mL), $Pd(dba)_2$ (14.4 mg, 5 mol %) and tri(2-furyl)phosphine (12 mg, 10 mol%) were added in. The reaction mixture was stirred overnight at room temperature then quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 1:2) afforded the pure product **97c** (107 mg, 94%) as a white solid, mp: 59.3 - 60.7 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.97 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 6.67 (s, 1 H), 4.97 (s, 1 H), 4.92 (s, 1 H), 3.89 (s, 3 H), 2.51 (t, *J* = 5.7 Hz, 2 H), 2.36-2.42 (m, 2 H), 1.81-1.89 (m, 2 H);

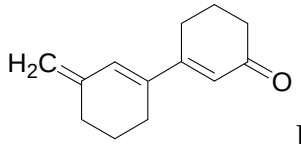
^{13}C NMR ($CDCl_3$, 75 MHz): 166.9, 145.8, 143.5, 138.1, 129.6, 128.6, 128.4, 125.0, 113.0, 52.0, 30.1, 27.3, 23.0;

IR (KBr): 2948 (s), 1718 (vs), 1601 (m), 1434 (m), 1289 (m), 1111 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 228 (M^+, 100%), 213 (7%), 197 (19%), 169 (22%), 154 (18%), 141 (23%);

HRMS (EI): calcd. for $C_{15}H_{16}O_2$ (M^+): 228.1150, **found**: 228.1132 (M^+).

Synthesis of 3-(3-methylene-cyclohex-1-enyl)-but-2-enal (**98d**)



RHJ131C

The solution of $ZnBr_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF) was added to the Grignard **97** at -40 °C and warmed to 0 °C and stirred for 20 min. The solution 3-bromo-cyclohex-2-enone (88 mg, 0.5 mmol) in THF (0.5 mL), $Pd(dba)_2$ (14.4 mg, 5 mol %) and tri(2-furyl)phosphine (12 mg, 10 mol%) were added in. The reaction mixture was stirred overnight at room temperature then quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 2:1) afforded the pure product **98d** (66 mg, 70%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.63 (s, 1 H), 6.10 (s, 1 H), 5.00-5.04 (m, 2 H), 2.54 (t, *J* = 6.0 Hz, 2 H), 2.23-2.41 (m, 6 H), 1.97-2.06 (m, 2 H), 1.71-1.79 (m, 2 H);

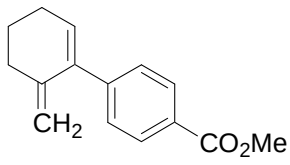
^{13}C NMR ($CDCl_3$, 75 MHz): 200.4, 158.5, 143.4, 137.8, 131.9, 123.9, 115.8, 37.5, 29.9, 25.7, 25.3, 22.54, 22.51;

IR (film): 2927 (m), 1706 (m), 1662 (s), 1187 (m) cm^{-1};

MS (EI, 70 ev), m/z (%): 188 (M^+, 100%), 173 (11%), 160 (32%), 145 (31%), 117 (53%);

HRMS (EI): calcd. for $C_{13}H_{16}O$ (M^+): 188.1201, **found**: 188.1189 (M^+).

Synthesis of 4-(6-methylene-cyclohex-1-enyl)-benzoic acid methyl ester (**101**)



RHJ113C

1-Iodo-6-methylene-cyclohexene **99** was prepared according to the procedure for preparation of 1-iodo-3-methylene-cyclohexene **96** from methyltriphenylphosphonium bromide (1.18 g, 3.3 mmol) and 2-iodo-cyclohex-2-enone (666 mg, 3.0 mmol). The product of 1-iodo-6-methylene-cyclohexene **99** was obtained in 10% yield as a colorless oil. Due to its unstable, the dienic iodide **99** was used for the next exchange reaction immediately.

To a solution of 1-iodo-6-methylene-cyclohexene **99** (60 mg, 0.27 mmol) in THF (0.1 mL) was slowly added *i*-PrMgCl·LiCl (0.15 mL, 0.30 mmol, 2.0 M in THF) at - 40 ℃. After 4 h, a complete conversion to the Grignard reagent **100** was observed by GC-analysis of hydrolyzed reaction aliquots. The solution of $ZnBr_2$ (0.3 mL, 0.3 mmol, 1.0 M in THF) was added at -40

°C and warmed to 0 °C and stirred for 20 min. The solution of methyl 4-iodobenzoate (78 mg, 0.3 mmol) in THF (0.3 mL), $Pd(dba)_2$ (8 mg, 5 mol%) and tri (2-furyl) phosphine (6 mg, 10 mol%) were added and the reaction mixture was stirred overnight at room temperature then quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 1:5) afforded the pure product **101** (55 mg, 90%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.96 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 5.78-5.82 (m, 1 H), 4.88 (s, 1 H), 4.64 (s, 1 H), 3.89 (s, 3 H), 2.47 (t, *J* = 6.2 Hz, 2 H), 2.26-2.33 (m, 2 H), 1.75-1.84 (m, 2 H);

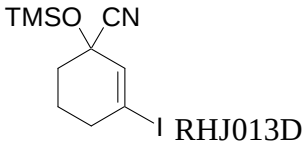
^{13}C NMR ($CDCl_3$, 75 MHz): 167.1, 146.6, 143.3, 139.8, 131.0, 129.2, 129.0, 128.5, 111.9, 52.0, 32.6, 26.6, 23.1;

IR (film): 2936 (m), 1724 (vs), 1608 (m), 1435 (m), 1277 (s), 1112 (s) cm^{-1};

MS (EI, 70 ev), m/z (%): 228 (M^+, 82%), 213 (11%), 197 (12%), 169 (100%), 153 (13%), 141 (63%);

HRMS (EI): calcd. for $C_{15}H_{16}O_2$ (M^+): 228.1150, **found**: 228.1133 (M^+).

Synthesis of 3-iodo-1-trimethylsilanyloxy-cyclohex-2-enecarbonitrile (**102**)



RHJ013D

To a stirred solution of 3-iodo-cyclohex-2-enone (222 mg, 1.0 mmol) and CsF (23 mg, 0.15 mmol) in dry CH_3CN (1 ml) was added dropwise TMSCN (149 mg, 1.5 mmol). The resulting solution was stirred continuously and progress of the reaction was followed by TLC. After purification by flash chromatography (pentane) the pure product **102** (282 mg, 88%) was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.39 (t, *J* = 2.0 Hz, 1 H), 2.54 (dt, J_1 = 6.2 Hz, J_2 = 2.0, 2 H), 2.11-2.19 (m, 1 H), 1.75-1.98 (m, 3 H), 0.22 (s, 9 H);

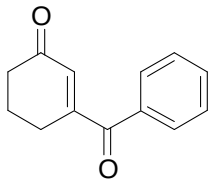
^{13}C NMR ($CDCl_3$, 75 MHz): 136.3, 120.5, 104.4, 68.3, 38.6, 35.7, 20.8, 1.3;

IR (film): 2958 (m), 2231 (w), 1629 (m), 1254 (m) cm^{-1};

MS (EI, 70 ev): 321 (M^+, 21%), 306 (30%), 279 (100%), 231 (19%), 194 (86%);

HRMS (EI): calcd. for $C_{10}H_{16}INOSi$ (M^+): 321.0046; **found**: 321.0021 (M^+).

Synthesis of 3-benzoyl-cyclohex-2-enone (104a)



RHJ019D

To a solution of 3-iodo-1-trimethylsilanyloxy-cyclohex-2-enecarbonitrile **102** (161 mg, 0.5 mmol) in THF (0.2 ml) was slowly added *i*-PrMgCl·LiCl (0.55 mmol, 2.00 M in THF) at –40°C. After 2 h, a complete conversion to the Grignard reagent **103** was observed by GC-analysis of hydrolyzed reaction aliquots. THF (1.0 ml) and CuCN·2LiCl (0.55 ml, 1.0 M in THF) was added at this temperature and the mixture was stirred for 15 min. Benzoyl chloride (0.7 mmol in 0.5 ml of THF) was added and the reaction mixture was stirred at –40^{o}C for 1 h, Then it was warmed to rt and stirred for another 1 h. TBAF (0.5 ml, 1.0 M in THF) was added and the mixture was stirred for 30 min, then HCl (1.0 ml, 2 M in H_2O) was added and the stirring continued for another 2 h before the addition of aq. NH_3 (2 ml). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (ether) afforded the pure product **104a** (71 mg, 74%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.70-7.77 (m, 2 H), 7.53-7.60 (m, 1 H), 7.40-7.47 (m, 2 H), 6.22 (t, J = 1.8 Hz, 1 H), 2.66 (dt, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 2 H), 2.51 (t, J = 6.6 Hz, 2 H), 2.07-2.18 (m, 2 H);

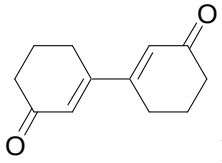
^{13}C NMR ($CDCl_3$, 75 MHz): 200.0, 197.0, 155.8, 135.5, 133.4, 132.3, 129.5, 128.6, 37.8, 25.5, 22.2;

IR (film): 2951 (m), 1680 (vs), 1658 (vs), 1448 (m), 1255 (m) cm^{-1};

MS (EI, 70 ev): 200 (M^+, 40%), 183 (15%), 171 (8%), 144 (10%), 105 (100%).

Spectral data match those reported in the literature.[133]

Synthesis of bicyclohexyl-1,1'-diene-3,3'-dione (**104b**)



RHJ021D

The solution of CuCN·2LiCl (0.55 ml, 1.0 M in THF) was added to the Grignard **103** at -40 ^{o}C and stirred for 15 min. 3-Iodo-cyclohex-2-enone (0.55 mmol in 0.5 ml of THF) was added and the reaction mixture was stirred at –30 ^{o}C for 4 h at this temperature. The reaction

[133] Z. Jin, P. L. Fuchs, *J. Am. Chem. Soc*. **1994**, *116*, 5995.

mixture was warmed to 25 °C and TBAF (0.5 ml, 1.0 M in THF) was added. After 30 min, HCl (0.5 ml, 2 M in H_2O) was added and the mixture was stirred for another 2 h before the addition of aq. NH_3 (2 ml). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (ether) afforded the pure product **104b** (71 mg, 74%) as a white solid, mp: 100.5-101.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 6.27 (s, 1 H), 2.50 (dt, J_1 = 6.2 Hz, J_2 = 1.3 Hz, 2 H), 2.42 (t, J = 6.2 Hz, 2 H), 2.01-2.10 (m, 2 H);

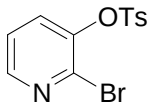
^{13}C NMR ($CDCl_3$, 75 MHz): 199.6, 156.5, 128.0, 37.4, 25.8, 22.2;

IR (KBr): 2951 (w), 1663 (s), 1576 (w), 1263 (m) cm^{-1};

MS (EI, 70 ev): 190 (M^+, 95%), 162 (45%), 134 (100%), 119 (45%), 106 (49%).

Spectral data match those reported in the literature.[134]

Synthesis of toluene-4-sulfonic acid 2-bromo-pyridin-3-yl ester (**105**)



A solution of 2-bromo-3-hydroxypyridine (3.480 g, 20 mmol), TsCl (4.19 g, 22 mmol), NEt_3 (2.420 g, 24 mmol) and DMAP (10 mol %) in CH_2Cl_2 (60 mL) was stirred at room temperature for 5 h. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane: ether = 3: 1), providing **105** (5.58 g, 85%) as a white solid; mp.: 64.5-65.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.19 (dd, J_1 = 4.9 Hz, J_2 = 1.8 Hz, 1 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.65 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.19-7.24 (m, 1 H), 2.37 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 147.7, 146.3, 144.3, 136.5, 132.0, 131.8, 129.9, 128.6, 123.5, 21.7;

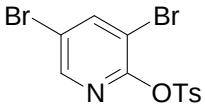
IR (KBr): 3072 (m), 1597 (s), 1570 (m), 1556 (vs), 1496 (vs), 1373 (vs), 1411 (vs), 1203 (vs), 859 (vs) cm^{-1};

MS (EI, 70 ev): 329 (^{81}Br, 6%), 327 (^{79}Br, 6%), 155 (94%), 91 (100%);

HRMS (EI): calcd. for $C_{12}H_{10}BrNO_3S$ (M^+, ^{79}Br): 326.9525, **found**: 326.9574 (M^+, ^{79}Br).

[134] C. J. Rao, P. Knochel, *J. Org. Chem*. **1991,** *56*, 4593.

Synthesis of 3,5-dibromo-2-pyridyl-4-methylbenzenesulfonate (**108**)



RHJ128D

A solution of 3, 5-dibromo-2-hydroxypyridine (5.060 g, 20 mmol), TsCl (4.190 g, 22 mmol), NEt_3 (2.420 g, 24 mmol) and DMAP (10 mol%) in CH_2Cl_2 (60 mL) was stirred at 0 ^oC overnight. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane: ether = 3: 1), providing **108** (6.51 g, 80%) as a white solid; m. p.: 97.4-97.9 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.22 (d, *J* = 2.2 Hz, 1 H), 8.06 (d, *J* = 2.2 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 2.44 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 153.2, 147.2, 145.7, 145.2, 133.7, 129.7, 128.8, 117.9, 112.0, 21.7;

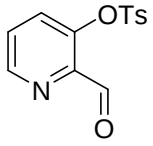
IR (KBr): 3064 (w), 1598 (m), 1557 (m), 1418 (vs), 1375 (vs), 770 (vs) cm^{-1};

MS (EI, 70 ev): 343 (M^+- C_5H_4 ($^{81}Br^{79}Br$), 40%), , 155 (50%), 91 (100%);

Anal. Calcd for $C_{12}H_9Br_2NO_3S$: C, 35.41; H, 2.23; N, 3.44;

Found: C, 35.28; H, 2.01; N, 3.39.

Synthesis of toluene-4-sulfonic acid 2-formyl-pyridin-3-yl ester (**107a**)



RHJ132D

i-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was slowly added to the solution of toluene-4-sulfonic acid 2-bromo-pyridin-3-yl ester **105** (164 mg, 0.5 mmol) in dry THF (1.5 mL) at -30 ^oC and the resulting mixture was stirred at this temperature for 7 h to form the Grignard **106** completely. DMF (1.0 mmol in 0.5 mL of THF) was added and the reaction mixture was warmed to 25 °C. After 1 h, saturated aqueous NH_4Cl was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **107a** (122 mg, 88%) as a white solid; mp.: 104.5-105.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 9.89 (s, 1 H), 8.67 (dd, J_1 = 4.4 Hz, J_2 = 1.3 Hz, 1 H), 7.68-7.75 (m, 1 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.52 (dd, J_1 = 8.4 Hz, J_2 = 4.4 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 2.41 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 187.9, 148.5, 146.8, 146.5, 144.8, 132.5, 131.2, 130.0, 128.5, 128.4, 21.7;

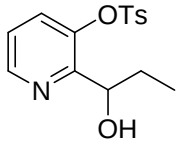
IR (KBr): 2847 (m), 1718 (vs), 1596 (m), 1578 (m), 1352 (vs), 1164 (vs), 889 (vs) cm^{-1};

MS (EI, 70 ev): 248 (M^+-CHO, 0.04%), 155 (51%), 139 (13%), 122 (57%), 91 (100%);

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05;

Found: C, 56.34; H, 4.06; N, 5.03.

Synthesis of toluene-4-sulfonic acid 2-(1-hydroxy-propyl)-pyridin-3-yl ester (**107b**)



RHJ127D

The solution of propionaldehyde (0.60 mmol) in THF (0.5 mL) was added to the Grignard **106** at -30 ^oC and the reaction mixture was warmed to 25 °C. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 1:2) afforded the product **107b** (130 mg, 85%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.38 (d, J = 4.9 Hz, 1 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.15-7.20 (m, 1 H), 4.46-4.50 (m, 1 H), 3.86 (bs, 1 H), 2.39 (s, 3 H), 1.41-1.68 (m, 2 H), 0.75 (t, J = 7.5 Hz, 3 H);

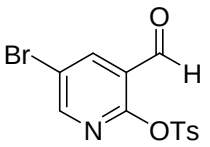
^{13}C NMR ($CDCl_3$, 75 MHz): 155.1, 146.3, 146.2, 143.3, 132.4, 130.2, 130.1, 128.1, 123.2, 69.3, 29.9, 21.7, 9.4;

IR (film): 3345 (vs), 2927 (s), 1598 (s), 1418 (vs), 1377 (vs) cm^{-1};

MS (EI, 70 ev): 306 (M^+- H, 0.08%), 290 (7%), 278 (100%), 263 (9%), 155 (92%), 124 (53%), 91 (99%);

HRMS (EI): calcd. for $C_{15}H_{16}NO_4S$ (M^+-H): 306.0800, **found**: 306.0807 (M^+-H).

Synthesis of toluene-4-sulfonic acid 5-bromo-3-formyl-pyridin-2-yl ester (**110a**)



RHJ133D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) and DMF (1.0 mmol in 0.5 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 3:1) afforded the product **110a** (158 mg, 88%) as a white solid; mp.: 86.7-87.3 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 10.18 (s, 1 H), 8.46 (d, *J* = 2.7 Hz, 1 H), 8.32 (d, *J* = 2.7 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 2.45 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 185.9, 156.3, 153.6, 146.2, 140.8, 133.0, 129.9, 128.8, 123.4, 119.1, 21.8;

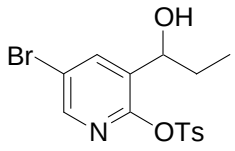
IR (KBr): 3062 (m), 1697 (vs), 1596 (m), 1578 (s), 1430 (vs), 1178 (vs), 724 (vs) cm^{-1};

MS (EI, 70 ev): 293 (M^+ (^{81}Br)-C_5H_4, 0.5%), 291 (M^+ (^{79}Br)-C_5H_4, 0.5%), 265 (51%), 263 (52%), 155 (41%), 91 (100%);

Anal. Calcd for $C_{13}H_{10}BrNO_4S$: C, 43.84; H, 2.83; N, 3.93;

Found: C, 43.76; H, 2.76; N, 3.87.

Synthesis of toluene-4-sulfonic acid 5-bromo-3-(1-hydroxy-propyl)-pyridin-2-yl ester (**2-45b**)



RHJ129D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) and propionaldehyde (0.60 mmol in 0.5 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 1:2) afforded the product **110b** (168 mg, 87%) as a white solid; mp.: 110.3-111.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.12 (d, *J* = 2.7 Hz, 1 H), 8.02 (d, *J* = 2.7 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.87-4.91 (m, 1 H), 2.44 (s, 3 H), 2.26 (bs, 1 H), 1.64-1.82 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H);

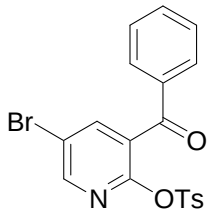
^{13}C NMR ($CDCl_3$, 75 MHz): 152.8, 147.2, 145.5, 140.3, 133.9, 133.5, 129.7, 128.7, 118.9, 68.9, 30.3, 21.7, 9.8;

IR (KBr): 3566 (vs), 3053 (m), 1595 (m), 1558 (m), 1372 (vs), 1207 (vs), 669 (vs) cm^{-1};

MS (EI, 70 ev): 386 (M^+, 0.01%), 358 (Br^{81}, 6%), 356 (Br^{79}, 6%), 294 (Br^{81}, 87%), 292 (Br^{79}, 87%), 155 (89%), 91 (100%);

HRMS (EI): calcd. for $C_{15}H_{15}BrNO_4S$ (M^+-H): 383.9905, **found**: 383.9868 (M^+-H).

Synthesis of toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester (**110c**)



RHJ138D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol), CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) and benzoyl chloride (0.75 mmol in 0.5 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **110c** (192 mg, 89%) as a white solid; mp.: 102.5-103.1 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.43 (d, *J* = 2.7 Hz, 1 H), 7.94 (d, *J* = 2.7 Hz, 1 H), 7.54-7.71 (m, 5 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 2.35 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 190.5, 152.4, 150.5, 145.4, 142.2, 135.6, 134.0, 133.1, 129.7, 129.4, 128.5, 128.3, 127.5, 117.9, 21.5;

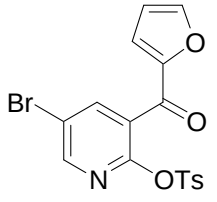
IR (KBr): 3060 (m), 1659 (vs), 1598 (s), 1572 (s), 1382 (vs), 1173 (vs), 689 (vs) cm^{-1};

MS (EI, 70 ev): 369 (M^+ (^{81}Br)-C_5H_4, 13%), 367 (M^+ (^{79}Br)-C_5H_4, 13%), 340 (14%), 288(31%), 155 (22%), 91 (100%);

Anal. Calcd for $C_{19}H_{14}BrNO_4S$: C, 52.79; H, 3.26; N, 3.24;

Found: C, 52.61; H, 2.90; N, 3.17.

Synthesis of toluene-4-sulfonic acid 5-bromo-3-(furan-2-carbonyl)-pyridin-2-yl ester (**110d**)



RHJ163D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol), CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) and 2-furoyl chloride (0.75 mmol in 0.5 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **110d** (176 mg, 83%) as a white solid; mp.: 133.0-134.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.42 (d, *J* = 2.2 Hz, 1 H), 8.01 (d, *J* = 2.2 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.65-7.66 (m, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 4.0 Hz, 1 H), 6.58 (dd, J_1 = 4.0 Hz, J_2 = 1.8 Hz, 1 H), 2.40 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 177.1, 152.6, 151.3, 150.8, 148.2, 145.6, 142.2, 133.5, 129.6, 128.6, 126.7, 121.4, 117.8, 112.9, 21.7;

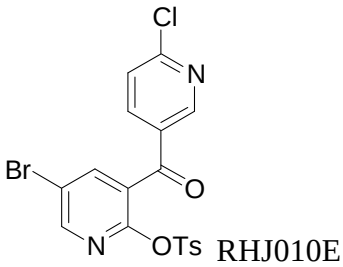
IR (KBr): 3079 (w), 1659 (vs), 1564 (w), 1584 (w), 1375 (vs), 1176 (s), 752 (vs) cm^{-1};

MS (EI, 70 ev): 359 (M^+ (^{81}Br)-C_5H_4, 3%), 357 (M^+ (^{79}Br)-C_5H_4, 3%), 331 (M^+ (^{81}Br)-C_7H_8, 43%), 329 (M^+ (^{79}Br)-C_7H_8, 43%), 274 (5%), 155 (17%), 91 (100%);

Anal. Calcd for $C_{17}H_{12}BrNO_5S$: C, 48.36; H, 2.86; N, 3.32;

Found: C, 48.14; H, 2.86; N, 3.26.

Synthesis of toluene-4-sulfonic acid 5-bromo-3-(6-chloro-pyridine-3-carbonyl)-pyridin-2-yl ester (**110e**)



RHJ010E

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (408 mg, 1.0 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 1.1 mmol), CuCN·2LiCl (1.10 mmol, 1.10 mL, 1.0 M in THF) and 6-chloronicotinoyl chloride (1.50 mmol in 1.0 mL of THF). Purification by flash chromatography afforded the product **110e** (351 mg, 75%) as a white solid; mp.: 171.7-172.2 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.61 (d, *J* = 2.2 Hz, 1 H), 8.50 (d, *J* = 2.2 Hz, 1 H), 8.07 (d, *J* = 2.7 Hz, 1 H), 7.95 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 2.42 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 188.5, 156.2, 152.5, 152.0, 151.0, 146.0, 142.9, 139.1, 132.9, 130.5, 129.7, 128.4, 126.1, 124.4, 118.5, 21.7;

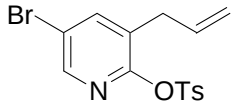
IR (KBr): 3058 (w), 1680 (vs), 1582 (vs), 1560 (w), 1421 (s), 1377 (vs), 1175 (vs) cm^{-1};

MS (EI, 70 ev): 406 (M^+ ($^{81}Br^{37}Cl$)-C_5H_4, 3%), 404 (M^+ ($^{79}Br^{37}Cl$ and $^{81}Br^{35}Cl$)-C_5H_4, 4%), 402 (M^+ ($^{79}Br^{35}Cl$)-C_5H_4, 1%), 376 (12%), 323 (30%), 155 (29%), 91 (100%);

Anal. Calcd for $C_{18}H_{12}BrClN_2O_4S$: C, 46.22; H, 2.59; N, 5.99;

Found: C, 45.93; H, 2.30; N, 5.85.

Synthesis of toluene-4-sulfonic acid 3-allyl-5-bromo-pyridin-2-yl ester (110f)



RHJ178D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol), allyl bromide (0.60 mmol in 0.5 mL of THF) and CuCN·2LiCl (2 mol%, 10 μL, 1.0 M in THF). Purification by flash chromatography (eluent: pentane: ether = 5:1) afforded the product **110f** (171 mg, 93%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.11 (d, *J* = 2.7 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 2.7 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 5.78-5.91 (m, 1 H), 5.07-5.20 (m, 2 H), 3.38 (d, *J* = 6.6 Hz, 2 H), 2.43 (s, 3 H);

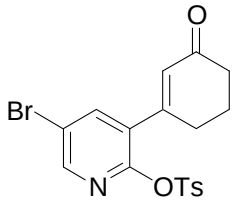
^{13}C NMR ($CDCl_3$, 75 MHz): 154.4, 146.4, 145.3, 142.4, 134.1, 133.4, 129.6, 129.2, 128.6, 118.4, 118.3, 33.5, 21.7;

IR (film): 2922 (m), 1640 (w), 1596 (w), 1557 (w), 1426 (s), 1376 (s), 1176 (vs), 1090 (s), 833 (s) cm^{-1};

MS (EI, 70 ev): 368 (M^+, 0.1%), 305 (M^+ (^{81}Br)-C_5H_4, 30%), 303 (M^+ (^{79}Br)-C_5H_4, 30%), 288 (50%), 155 (11%), 91 (100%);

HRMS (EI): calcd. for $C_{15}H_{15}BrNO_3S$ (M^++H, ^{79}Br): 367.9956, **found**: 367.9991 (M^++H, ^{79}Br).

Synthesis of toluene-4-sulfonic acid 5-bromo-3-(3-oxo-cyclohex-1-enyl)-pyridin-2-yl ester (110g)



RHJ139D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol), CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) and 3-iodo-cyclohex-2-enone (0.60 mmol in 1.0 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **110g** (177 mg, 84%) as a white solid; mp.: 108.5-109.3 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.24 (d, *J* = 2.2 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 2.2 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 6.01 (t, *J* = 1.3 Hz, 1 H), 2.64 (t, *J* = 6.0 Hz, 2 H), 2.41 (t, *J* = 6.6 Hz, 2 H), 2.41 (s, 3 H), 2.00-2.10 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 198.3, 154.8, 152.2, 148.7, 145.7, 140.9, 133.7, 130.4, 129.7, 129.5, 128.6, 118.2, 37.1, 29.2, 22.9, 21.6;

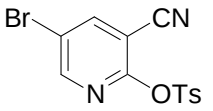
IR (KBr): 2952 (w), 1671 (vs), 1596 (m), 1419 (s), 1375 (s), 1172 (vs) cm^{-1};

MS (EI, 70 ev): 359 (M^+ (^{81}Br)-C_5H_4, 2%), 357 (M^+ (^{79}Br)-C_5H_6, 2%), 331 (M^+ (^{81}Br)-C_7H_8, 7%), 329 (M^+ (^{81}Br)-C_7H_8, 7%), 266 (21%), 155 (17%), 91 (100%);

Anal. Calcd for $C_{18}H_{16}BrNO_4S$: C, 51.19; H, 3.82; N, 3.32;

Found: C, 51.22; H, 3.92; N, 3.22.

Synthesis of toluene-4-sulfonic acid 5-bromo-3-cyano-pyridin-2-yl ester (**110h**)



RHJ137D

According to **TP6**, the reaction was carried out with 3, 5-dibromo-2-pyridyl 4-methylbenzenesulfonate **108** (204 mg, 0.5 mmol), *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) and TsCN (0.60 mmol in 1.0 mL of THF). Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **110h** (125 mg, 71%) as a white solid; mp.: 105.0-105.6 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.50 (d, *J* = 2.4 Hz, 1 H), 8.10 (d, *J* = 2.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.45 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 156.0, 152.8, 146.4, 145.4, 132.8, 129.9, 128.9, 117.3, 112.0, 103.1, 21.8;

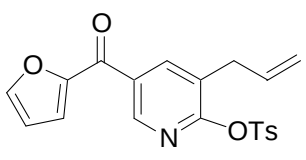
IR (KBr): 3078 (w), 2243 (m), 1595 (m), 1550 (m), 1429 (vs), 1386 (vs), 1192 (vs), 823 (vs) cm^{-1};

MS (EI, 70 ev): 290 (M^+ (^{81}Br)-C_5H_4, 10%), 288 (M^+ (^{79}Br)-C_5H_4, 10%), 155 (52%), 91 (100%);

Anal. Calcd for $C_{13}H_9BrN_2O_3S$: C, 44.21; H, 2.57; N, 7.93;

Found: C, 44.26; H, 2.56; N, 7.88.

Synthesis of toluene-4-sulfonic acid 3-allyl-5-(furan-2-carbonyl)-pyridin-2-yl ester (**112a**)



RHJ182D

According to **TP6**, the reaction was carried out with 3-allyl-5-bromo-2-pyridyl 4-methylbenzenesulfonate **110f** (184 mg, 0.5 mmol) and *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) at -30 ^{o}C for 7 h to form the Grignard **111** completely. THF (1.0 mL) and the solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added and the reaction mixture was stirred at –30 ^{o}C for 1 h, then warmed to rt and stirred for 1 h before quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 2:1) afforded the product **112a** (144 mg, 75%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.71 (d, *J* = 2.2 Hz, 1 H), 8.14 (d, *J* = 2.2 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 1.8 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 3.5 Hz, 1 H), 6.58 (dd, J_1 = 3.5 Hz, J_2 = 1.8 Hz, 1 H), 5.81-5.94 (m, 1 H), 5.04-5.15 (m, 2 H), 3.42 (d, *J* = 6.6 Hz, 2 H), 2.41 (s, 3 H);

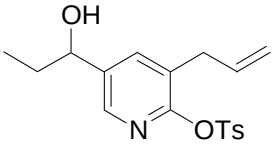
^{13}C NMR ($CDCl_3$, 75 MHz): 178.9, 157.8, 151.8, 147.5, 146.8, 145.4, 140.8, 134.0, 133.5, 131.4, 129.5, 128.7, 126.5, 120.7, 118.1, 112.6, 33.5, 21.6;

IR (film): 2923 (w), 1647 (m), 1596 (m), 1566 (m), 1377 (s), 1189 (vs), 816 (s) cm^{-1};

MS (EI, 70 ev): 383 (M^+, 0.01%), 319 (80%), 304 (93%), 290 (9%), 155 (9%), 91 (100%);

HRMS (EI): calcd. for $C_{20}H_{18}NO_5S$ (M^++H): 384,0906, **found**: 384.0908 (M^++H).

Synthesis of toluene-4-sulfonic acid 3-allyl-5-(1-hydroxy-propyl)-pyridin-2-yl ester (112b)



RHJ132F

The solution of propionaldehyde (0.60 mmol in 0.5 mL of THF) was added to the Grignard **111** and the reaction mixture was warmed to 25 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **112b** (139 mg, 80%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.99 (d, *J* = 2.2 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 2.2 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 5.78-5.94 (m, 1 H), 5.02-5.13 (m, 2 H), 4.50-4.61 (m,

1 H), 3.38 (d, *J* = 6.6 Hz, 2 H), 2.42 (s, 3 H), 2.25 (bs, 1 H), 1.61-1.79 (m, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H);

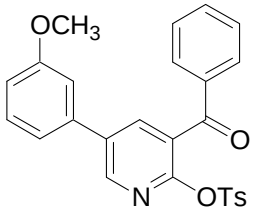
^{13}C NMR ($CDCl_3$, 75 MHz): 154.9, 145.0, 143.5, 139.0, 137.9, 134.4, 134.2, 129.5, 128.6, 126.7, 117.6, 72.8, 33.8, 31.8, 21.6, 9.8;

IR (film): 3411 (vs), 1714 (m), 1640 (m), 1597 (s), 1584 (s), 1416 (vs), 1307 (m) cm^{-1};

MS (EI, 70 ev): 347 (M^+, 0.01%), 330 (0.1%), 283 (49%), 268 (39%), 254 (100%), 155 (15%), 91 (82%);

HRMS (EI): calcd. for $C_{18}H_{22}NO_4S$ (M^++H): 348.1270, **found**: 348.1259 (M^++H).

Synthesis of toluene-4-sulfonic acid 3-benzoyl-5-(3-methoxy-phenyl)-pyridin-2-yl ester (114)



RHJ172D

A mixture of toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester **110c**: (216 mg, 0.5 mmol), 3-methoxylbenzeneboronic acid (152 mg, 1.0 mmol), TBAB (16 mg, 10 mol%), $Pd(dba)_2$ (14 mg, 5 mol%), tri (2-furyl) phosphine (12 mg, 10 mol%) in THF (2.0 mL) and water (0.5 mL) was refluxed under nitrogen for 12 h. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **114** (206 mg, 90%) as a white solid; mp.: 144.0-144.5 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.57 (d, *J* = 2.7 Hz, 1 H), 7.97 (d, *J* = 2.7 Hz, 1 H), 7.71 (d, *J* = 7.1 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 7.0 (t, *J* = 2.2 Hz, 1 H), 6.89 (dd, J_1 = 8.0 Hz, J_2 = 2.6 Hz, 1 H), 3.77 (s, 3 H), 2.34 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 192.3, 160.2, 153.1, 148.0, 145.3, 138.6, 137.1, 136.3, 135.6, 133.8, 133.7, 130.4, 129.9, 129.5, 128.6, 128.5, 126.2, 119.5, 114.1, 112.9, 55.4, 21.7;

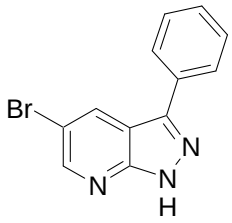
IR (KBr): 2968 (w), 1668 (vs), 1596 (vs), 1379 (s), 1428 (vs), 1180 (vs), 864 (s) cm^{-1};

HRMS calcd for $C_{26}H_{21}NNaO_5S$ (M^++Na): 482.1038, **found**: 482.1029 (M^++Na);

Anal. calcd for $C_{26}H_{21}NO_5S$: C, 67.96; H, 4.61; N, 3.05;

Found: C, 67.86; H, 4.49; N, 2.95.

Synthesis of 5-bromo-3-phenyl-*1H*-pyrazolo[3,4-b]pyridine (**115a**)



RHJ155D

The mixture of toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester **110c** (108 mg, 0.25 mmol) and hydrazine hydrate (0.1 mL) in toluene (1.0 mL) was stirred at 80 ^{o}C for 4 h. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 3:1) afforded the product **115a** (60 mg, 88%) as a white solid; mp.: 205.5-206.0 ^{o}C.

^{1}H NMR (DMSO-d_6, 300 MHz): 8.78 (d, *J* = 1.8 Hz, 1 H), 8.62 (d, *J* = 1.8 Hz, 1 H), 8.01 (d, *J* = 7.5 Hz, 2 H), 7.38-7.54 (m, 3 H);

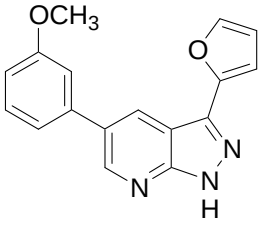
^{13}C NMR (DMSO-d_6, 75 MHz): 151.4, 149.5, 142.6, 132.7, 132.5, 129.3, 128.6, 126.9, 113.8, 112.5;

IR (KBr): 3430 (vs), 3195 (vs), 1596 (m), 1481 (m), 1371 (m), 1256 (s), 926 (s), 758 (s) cm^{-1};

MS (EI, 70 ev): 275 (M^+ (^{81}Br), 100%), 273 (M^+ (^{79}Br), 100%), 246 (7%), 193 (7%), 164 (6%);

HRMS (EI): calcd. for $C_{12}H_8BrN_3$ (M^+, ^{79}Br): 272.9902, **found**: 272.9903 (M^+, ^{79}Br).

Synthesis of 3-furan-2-yl-5-(3-methoxy-phenyl)-*1H*-pyrazolo[3,4-b]pyridine (115b)



RHJ176D

A mixture of toluene-4-sulfonic acid 5-bromo-3-(furan-2-carbonyl)-pyridin-2-yl ester **110d** (211 mg, 0.5 mmol), 3-methoxylbenzeneboronic acid (152 mg, 1.0 mmol), TBAB (16 mg, 10 mol%), $Pd(dba)_2$ (14 mg, 5 mol%), tri (2-furyl) phosphine (12 mg, 10 mol%) in THF (2.0 mL) and water (0.5 mL) was refluxed under nitrogen for 12 h. Hydrazine hydrate (0.5 mL) was added after the reaction mixture was cooled to room temperature and then it was refluxed for 6 h. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4

and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 2: 1) afforded the product **115b** (112 mg, 77%) as a white solid; mp.: 198.0-198.5 ^{o}C.

^{1}H NMR (DMSO-d_6, 300 MHz): 8.89 (d, *J* = 1.3 Hz, 1 H), 8.65 (d, *J* = 1.3 Hz, 1 H), 7.87 (s, 1 H), 7.30-7.46 (m, 3 H), 7.21 (d, *J* = 3.1 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz, 1 H), 6.70 (s, 1H), 3.86 (s, 3 H);

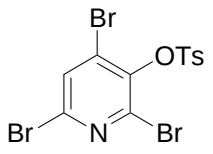
^{13}C NMR ($CDCl_3$, 75 MHz): 160.2, 152.2, 149.2, 148.2, 143.5, 139.6, 136.2, 130.5, 130.4, 127.9, 120.0, 113.5, 113.2, 112.1, 111.8, 108.1, 55.6;

IR (KBr): 3430 (s), 3132 (s), 1602 (s), 1509 (m), 1490 (m), 1476 (m), 1260 (s), 1219 (s) cm^{-1};

MS (EI, 70 ev): 291 (M^+, 100%), 262 (7%), 248 (11%), 219 (7%), 145 (12%);

HRMS (EI): calcd. for $C_{17}H_{13}N_3O_2$ (M^+): 291.1008, **found**: 291.1005 (M^+).

Synthesis of 2,4,6-tribromo-3-pyridyl-4-methylbenzenesulfonate (**116**)



RHJ124F

A solution of 2, 4, 6-tribromo-pyridin-3-ol (5.500 g, 16.6 mmol), TsCl (3.810 g, 20 mmol), NEt_3 (2.180 g, 22 mmol) and DMAP (10 mol %) in CH_2Cl_2 (60 mL) was stirred at 0 ^{o}C overnight. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane: ether = 3:1), providing **116** (6.254 g, 78%) as a white solid; m. p.: 103.0-103.6 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.87 (d, *J* = 8.2 Hz, 2 H), 7.67 (s, 1 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 2.46 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 146.4, 143.9, 137.3, 137.1, 133.9, 131.9, 130.8, 130.0, 128.7, 21.8;

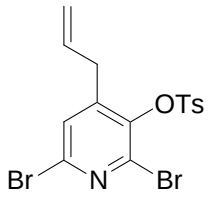
IR (KBr): 3090 (w), 1595(m), 1537(s), 1521(s), 1385(vs), 1312(vs), 1190(vs) cm^{-1};

MS (EI, 70 ev): 483 (M^+ ($^{79}Br^{79}Br^{79}Br$), 1%), 302 (2%), 197 (6%), 155 (100%), 91 (62%).

Anal. Calcd for $C_{12}H_8Br_3NO_3S$: C, 29.66; H, 1.66; N, 2.88

Found: C, 29.78; H, 1.78; N, 2.88.

Synthesis of toluene-4-sulfonic acid 4-allyl-2, 6-dibromo-pyridin-3-yl ester (**118a**)



RHJ129F

The solution of *i*-PrMgCl·LiCl (1.55 M in THF, 1.1 mmol) was slowly added to a solution of 2, 4, 6-tribromo-3-pyridyl-4-methylbenzenesulfonate **116** (486 mg, 1.0 mmol) in dry THF (3.0 mL) at -78 ^{o}C and the resulting mixture was stirred at this temperature for 40 min to complete the formation of the Grignard **117**. Allyl bromide (1.5 mmol in 1.0 mL of THF) and the solution of CuCN·2LiCl (1 mol%) were added in and the reaction mixture was stirred for 1 h then warmed to 25 °C. After 1 h the reaction mixuture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 5:1) afforded the product **118a** (402 mg, 90%) as a white solid; mp.: 82.0-83.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.87 (d, *J* = 8.2 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.34 (s, 1 H), 5.70-5.90 (m, 1 H), 5.10-5.30 (m, 2 H), 3.53 (d, *J* = 7.1 Hz, 2 H), 2.46 (s, 3 H);

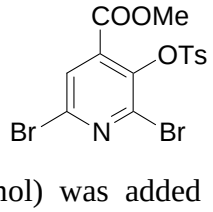
^{13}C NMR ($CDCl_3$, 75 MHz): 149.1, 146.3, 143.3, 137.4, 136.4, 133.3, 132.6, 130.0, 128.8, 128.7, 119.6, 34.8, 21.8;

IR (KBr): 1595(m), 1566(m), 1528(m), 1407(s), 1375(s), 1179(s), 1153(vs) cm^{-1};

MS (EI, 70 ev): 447 (M^+ (^{81}Br^{79}Br), 1.5%), 292 (11%), 155 (100%), 91 (87%);

HRMS (EI): calcd. for $C_{15}H_{13}Br_2NO_3S$ (M^+, ^{79}Br^{79}Br): 444.8983; **Found**: 444.8988 (M^+, ^{79}Br^{79}Br).

Synthesis of 2,6-dibromo-3-(toluene-4-sulfonyloxy)-isonicotinic acid methyl ester (**118b**)



RHJ133F

Methyl chloroformate (0.75 mmol) was added directly to the Grignard reagent **117** and warmed to room temperature. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na2SO4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 5:1) afforded the product **118b** (167 mg, 72%) as a white solid; mp.: 110.0-111.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.82 (s, 1 H), 7.72 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 3.94 (s, 3 H), 2.45 (s, 3 H);

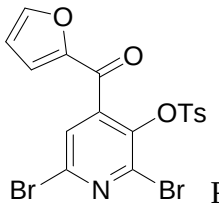
^{13}C NMR ($CDCl_3$, 75 MHz): 162.6, 146.6, 141.5, 137.7, 137.5, 132.6, 130.2, 128.7, 128.5, 53.5, 21.8;

IR (KBr): 1727(vs), 1596(m), 1529(m), 1431(m), 1389(vs), 1350(vs), 1268(s) cm^{-1};

MS (EI, 70 ev): 465 (M^+ ($^{81}Br^{79}Br$), 2%), 279 (3%), 155 (100%), 91 (87%);

HRMS (EI): calcd. for $C_{14}H_{11}Br_2NO_5S$ (M^+, $^{79}Br^{79}Br$): 462.8725; **Found**: 462.8733 (M^+, $^{79}Br^{79}Br$).

Synthesis of toluene-4-sulfonic acid 2,6-dibromo-4-(furan-2-carbonyl)-pyridin-3-yl ester (**118c**)



RHJ142F

The solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) was added to the Grignard reagent **117** at -78 ^oC and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added in and the reaction mixture was stirred at –30 ^oC for 1 h then warmed to rt and stirred for 1 h before it was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 5:1) afforded the product **118c** (180 mg, 72%) as a white solid; mp.: 153.5-154.0 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.67 (dd, J_1 = 1.8 Hz, J_2 = 0.9 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.57 (s, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 3.1 Hz, 2 H), 6.60 (dd, J_1 = 3.1 Hz, J_2 = 1.8 Hz, 1 H), 2.42 (s, 3 H);

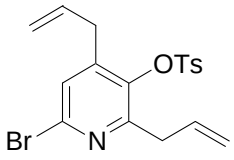
^{13}C NMR ($CDCl_3$, 75 MHz): 175.7, 150.6, 148.4, 146.5, 143.4, 140.6, 138.3, 137.8, 131.9, 130.0, 128.6, 127.4, 121.8, 113.1, 21.8;

IR (KBr): 1666(vs), 1560(m), 1522(m), 1460(s), 1391(vs), 1195(s) cm^{-1};

MS (EI, 70 ev): 501 (M^+ ($^{81}Br^{79}Br$), 0.2%), 346 (3%), 155 (88%), 91 (100%);

HRMS (EI): calcd. for $C_{17}H_{11}Br_2NO_5S$: 498.8725 (M^+, $^{79}Br^{79}Br$); **Found**: 498.8736 (M^+, $^{79}Br^{79}Br$).

Synthesis of toluene-4-sulfonic acid 2,4-diallyl-6-bromo-pyridin-3-yl ester (**120a**)



RHJ162F

The solution of *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was slowly added to a solution of toluene-4-sulfonic acid 4-allyl-2, 6-dibromo-pyridin-3-yl ester **118a** (224 mg, 0.5 mmol) in dry THF (2.0 mL) at -40 ^{o}C and the resulting mixture was stirred at this temperature for 1 h to complete the formation of the Grignard reagent **119**. Allyl bromide (0.8 mmol) and the solution of CuCN·2LiCl (1 drop) were added at this temperature and stirred for 1 h, then warmed to rt and stirred for 1 h before it was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na2SO4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 10:1) afforded the product **120a** (190 mg, 93%) as a white solid; mp.: 83.8-85.2 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.83 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 8.2 Hz, 2 H), 7.21 (s, 1 H), 5.67-5.93 (m, 2 H), 4.85-5.20 (m, 2 H), 3.25-3.38 (m, 4 H), 2.47 (s, 3 H);

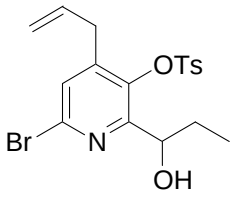
^{13}C NMR ($CDCl_3$, 75 MHz): 155.6, 147.0, 146.2, 142.8, 138.8, 133.7, 133.11, 133.09, 130.2, 128.1, 127.4, 119.0, 117.1, 37.1, 34.1, 21.7;

IR (KBr): 2978 (w), 1638 (m), 1597 (m), 1583 (m), 1542 (m), 1409 (s), 1422 (s), 1179 (s) cm^{-1};

MS (EI, 70 ev): 407 (M^+ (^{79}Br), 30%), 252 (100%), 155 (54%), 91 (100%);

HRMS (EI): calcd. for $C_{18}H_{18}BrNO_3S$ (M^+, ^{79}Br): 407.0191; **Found**: 407.0189 (M^+, ^{79}Br).

Synthesis of toluene-4-sulfonic acid 4-allyl-6-bromo-2-(1-hydroxy-propyl)-pyridin-3-yl ester (**112b**)



RHJ130F

The solution of propionaldehyde (0.60 mmol in 0.5 mL of THF) was added to the Grignard **119** and the reaction mixture was warmed to 25 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 1:1) afforded the product **112b** (134 mg, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.83 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 7.28 (s, 1 H), 5.65-5.84 (m, 1 H), 5.00-5.21 (m, 2 H), 4.40-4.53 (m, 1 H), 3.23-3.47 (m, 3 H), 2.46 (s, 3), 1.43-1.71 (m, 1 H), 0.75 (t, *J* = 7.3 Hz, 3 H);

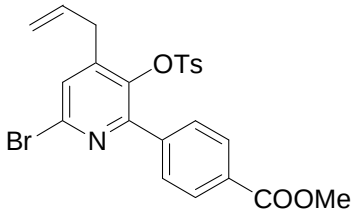
^{13}C NMR ($CDCl_3$, 75 MHz): 157.6, 147.6, 146.3, 141.3, 138.7, 133.0, 132.8, 130.2, 128.4, 127.9, 119.1, 69.7, 34.0, 30.0, 21.7, 9.6;

IR (KBr): 3457 (vs), 2934 (s), 1641 (m), 1596 (s), 1584 (s), 1544 (s), 1166 (m) cm^{-1};

MS (EI, 70 ev): 426(M^+ (^{79}Br), 0.5%), 398 (50%), 370 (9%), 240 (42%), 155 (100%), 91 (93%);

HRMS (EI): calcd. for $C_{18}H_{21}BrNO_4S$ (M^++H): 426.0375; **Found**: 426.0350 (M^++H).

Synthesis of 4-[4-allyl-6-bromo-3-(toluene-4-sulfonyloxy)-pyridin-2-yl]-benzoic acid methyl ester (**120c**)



RHJ136F

The solution of $ZnBr_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF) was added to Grignard reagent **119** at -40 °C and warmed to 0 ^oC and stirred for 20 min. The solution of methyl 4-iodobenzoate (144 mg, 0.55 mmol) in THF (0.5 mL), $Pd(dba)_2$ (14.4 mg, 5 mol%) and tri (2-furyl) phosphine (12 mg, 10 mol%) were added in and the reaction mixture was stirred overnight at room temperature then quenched as usual. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane: ether = 3:1) afforded the pure product **120c** (151 mg, 60%) as a white solid, mp: 138.0-138.5 ^oC.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.70 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 5.00-5.60 (m, 1 H), 5.11-5.30 (m, 2 H), 3.88 (s, 3 H), 3.61 (d, *J* = 6.6 Hz, 2 H), 2.25 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 166.5, 152.3, 149.0, 145.6, 142.9, 139.8, 139.1, 133.1, 132.3, 130.1, 129.5, 129.3, 129.0, 128.8, 127.9, 119.4, 52.2, 34.5, 21.5;

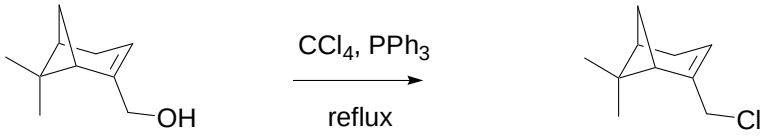
IR (KBr): 3437 (vs), 1720 (vs), 1578 (m), 1540 (m), 1386 (s), 1282 (vs), 1176 (vs) cm^{-1};

MS (EI, 70 ev): 503(M^+ (^{81}Br), 48%), 501 (47%), 348 (97%), 316 (75%), 208 (100%), 91 (50%);

HRMS (EI): calcd. for $C_{23}H_{20}BrNO_5S$ (M^+, ^{79}Br): 501.0246; Found: 501.0246 (M^+, ^{79}Br).

11. Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using Trisubstituted Allylic Zinc Reagents

Synthesis of 2-chloromethyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene (128a)



Triphenylphosphine (36.680 g, 140.0 mmol) was slowly added to a solution of 3(-) myrtenol (15.200 g, 100.0 mmol) in carbon tetrachloride (140.0 mL) and the resulting mixture was refluxed for 5 h. After the mixture was cooled, the pentane (250.0 mL) was added in. The suspension was filtered off and washed with pentane (100.0 mL). The solvent was removed under vacuum. Distillation (40 ^{o}C/2.0 mmHg) of the oil provided the compound **128a** (12.444 g, 73%) as a colourless oil. $[\alpha]_D^{20}$ = -40 (c = 0.8, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): 5.60 (s, 1 H), 3.94-4.01 (m, 2 H), 2.41 (dt, J_1 = 8.8 Hz, J_2 = 5.5 Hz, 1 H), 2.20-2.32 (m, 3 H), 2.06-2.11 (m, 1 H), 1.29 (s, 3 H), 1.16 (d, J = 8.8 Hz, 1 H), 0.82 (s, 3 H);

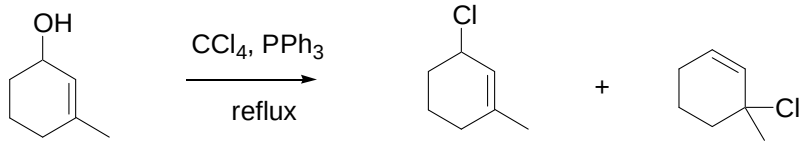
^{13}C NMR ($CDCl_3$, 150 MHz): 144.1, 122.4, 48.6, 44.2, 40.4, 38.0, 31.5, 31.2, 26.0, 21.1;

IR (neat): 2919 (m), 1650 (w), 1469 (m), 1429 (m), 1366 (m), 1256 (s) cm^{-1};

MS (EI, 70 ev): 172 (M^+, 1%), 170 (3%), 126 (13%), 91 (100%), 79 (15%);

HRMS (EI): calcd. for $C_{10}H_{15}Cl$ (^{35}Cl): 170.0862; **found**: 170.0849 (^{35}Cl).

Synthesis of 3-chloro-1-methyl-cyclohexene (128d + 128d')



Triphenylphosphine (14.700 g, 56.0 mmol) was slowly added to a solution of 3-methyl-cyclohex-2-enol (4.500 g, 40.0 mmol) in carbon tetrachloride (50.0 mL) and the resulting mixture was refluxed for 5 h. After the mixture was cooled, pentane (150.0 mL) was added in. The suspension was filtered off and washed with pentane (50.0 mL). The solvent was removed under vacuum. Distillation (40 ^{o}C/3.0 mmHg) of the oil provided the compound **128d** (3.130 g, 60%) as a colourless oil, as a ratio of 90: 10 mixture with **128d'**. The mixture was used in the subsequent step without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.50-5.60 (m, 1 H), 4.60-4.70 (m, 1 H), 1.80-2.10 (m, 6 H), 1.68 (s, 3 H);

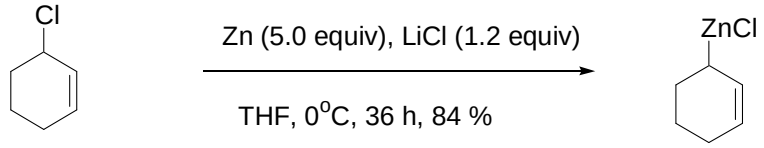
^{13}C NMR ($CDCl_3$, 75 MHz): 139.8, 122.6, 57.1, 32.0, 29.8, 23.7, 18.5;

IR (neat): 2934 (m), 1665 (m), 1444 (s), 1436 (w), 1222 (s) cm^{-1};

MS (EI, 70 ev): 132 (M^+ (^{37}Cl), 9%), 130 (3%), 95 (100%), 79 (29%), 67 (28%).

The spectral date is in accordance with that reported in the literature.[135]

Preparation of 2-cyclohexenylzinc chloride (129b)



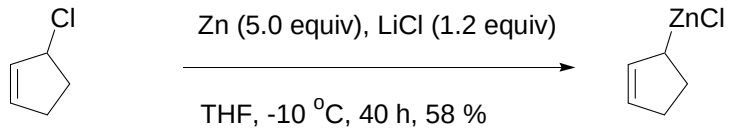
Zinc dust [136](3.20 g, 50.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (5.0 mL) and activated by addition of a few drops of 1,2-dibromoethane and TMSCl. A solution of 3-chloro-cyclohexene (1.17 g, 10.0 mmol) in THF (10.0 mL) was added in with syringe pump at 0 °C within 2 h. The resulting mixture was stirred under nitrogen at 0 °C for 36 h. The zinc suspension was to be settled using centrifuge machine. The concentration and the yield were determined as follows:

Element iodine (254 mg, 1.0 mmol) was placed into a dry 10 mL round-bottomed flask equipped with a magnetic stirrer bar and septum under nitrogen. Dry THF (5.0 mL) was added with syringe. The allylic zinc solution was added dropwise with syringe until the red colour disappeared. The volume of allylic zinc required can be noted and the following equation used to determine the molarity of the solution.

Molarity of allylic zinc reagent = 1/volume of allylic zinc reagent

The concentration of allylic zinc reagent: 0.60 mol/l; volume = 14.0 mL; yield: 84%.

Preparation of 2-cyclopentylzinc chloride (129c)



Zinc dust (3.20 g, 50.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (5.0 mL) and activated by addition of a few drops of 1, 2-dibromoethane and TMSCl. A solution of 3-chloro-cyclopentene (1.03 g, 10.0 mmol) in THF (10.0 mL) was added in with syringe pump at -10 °C within 2 h. The resulting mixture was stirred under nitrogen at -10 °C

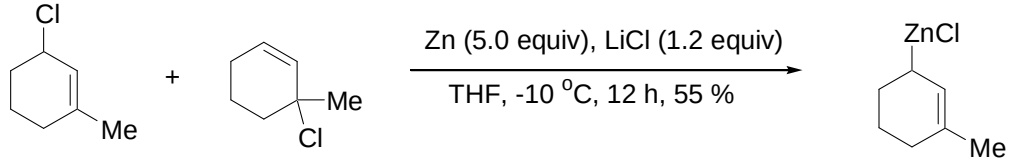
[135] T. Carrillo-Marquez, L. Caggiano, R. F. W. Jackson, U. Grabowska, A. Rae, M. J. Tozer, *Org. Biomol. Chem.*, **2005**, *3*, 4117.

[136] From Aldrich.

for 40 h. The zinc suspension was to be settled using centrifuge machine. The concentration and the yield were determined as the method shown above.

The concentration of allylic zinc reagent: 0.40 mol/l; volume = 14.5 mL; yield: 58%.

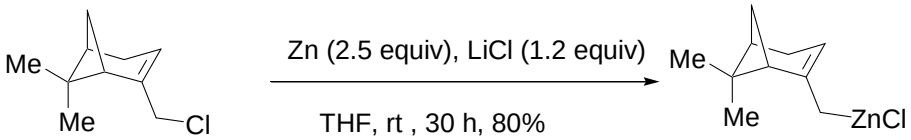
Preparation of 1-methyl-1-cyclohexenylzinc chloride (129d)



Zinc dust (3.20 g, 50.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (5.0 mL) and activated by addition of a few drops of 1,2-dibromoethane and TMSCl. A solution of 3-chloro-1-methyl-cyclohexene (mixture of 3-chloro-1-methyl-cyclohexeneand 3-chloro-3-methyl-cyclohexene, 1.30 g, 10.0 mmol) in THF (10.0 mL) was added in with syringe pump at -10 °C within 2 h. The resulting mixture was stirred under nitrogen at -10 °C for 12 h. The zinc suspension was to be settled using centrifuge machine. The concentration and the yield were determined as the method shown above.

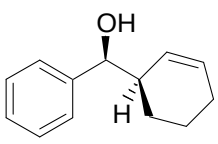
The concentration of allylic zinc reagent: 0.38 mol/l; volume = 14.5 mL; yield: 55%.

Preparation of 2-methyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-enylzinc chloride (129a)



Zinc dust (1.600 g, 25.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (5.0 mL) and activated by addition of a few drops of 1, 2-dibromoethane and TMSCl. A solution of 2-chloromethyl-6, 6-dimethyl-bicyclo[3.1.1]hept-2-ene (1.710 g, 10.0 mmol) in THF (10.0 mL) was added in with syringe pump at room temperature within 2 h. The resulting mixture was stirred under nitrogen at room temperature for 40 h. The zinc suspension was to be settled using centrifuge machine. The concentration and the yield were determined as the method shown above.

Synthesis of cyclohex-2-enyl-phenyl-methanol (130a)



RHJ142I

It was prepared from benzaldehyde (106 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride **129b** (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane:

ether = 10: 1) provided the pure compound **130a** (179 mg, 95%) as a colourless oil. dr = 90:10.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.20-7.40 (m, 5 H), 5.71-5.87 (m, 1 H), 5.29-5.42 (m, 1 H), 4.54 (d, *J* = 6.2 Hz, 1 H), 2.40-2.56 (m, 1 H), 2.04 (s, 1 H), 1.91-2.04 (m, 2 H), 1.64-1.80 (m, 2 H), 1.41-1.60 (m, 2 H);

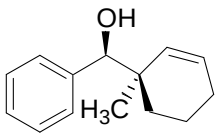
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 130.5, 128.4, 128.3, 127.6, 126.8, 77.6, 43.2, 25.5, 24.2, 21.4;

IR (neat): 3372 (s), 2925 (m), 1493 (m), 1451 (m), 1015 (m) cm^{-1};

MS (EI, 70 ev): 188 (M^+, 1%), 107 (100%), 79 (43%);

HRMS (EI): calcd. for $C_{13}H_{15}O$ (M^+-H): 187.1123; **found**: 187.1144 (M^+-H).

Synthesis of (1-methyl-cyclohex-2-enyl)-phenyl-methanol (130b)



RHJ154I

It was prepared from benzaldehyde (106 mg, 1.0 mmol) and 1-methyl-1-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 4: 1) provided the pure compound **130b** (198 mg, 98%) as a colourless oil. dr > 97:3.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.25-7.36 (m, 5 H), 5.86 (dt, J_1 = 10.2 Hz, J_2 = 3.7 Hz, 1 H), 5.49 (d, *J* = 10.2 Hz, 1 H), 4.48 (d, *J* = 2.2 Hz, 1 H), 1.99 (d, *J* = 2.2 Hz, 1 H), 1.91-1.98 (m, 2 H), 1.81-1.91 (m, 1 H), 1.47-1.76 (m, 2 H), 1.17-1.27 (m, 1 H), 0.93 (s, 3 H);

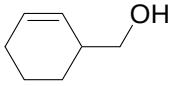
^{13}C NMR ($CDCl_3$, 75 MHz): 140.6, 133.7, 129.4, 127.9, 127.4, 127.2, 80.8, 40.4, 29.7, 25.1, 23.7, 18.8;

IR (neat): 3439 (w), 2930 (m), 1493 (w), 1452 (m), 1186 (m), 1022 (s) cm^{-1};

MS (EI, 70 ev): 184 (M^+-H_2O, 0.5%), 107 (100%), 96 (85%), 79 (59%), 67 (13%);

HRMS (EI): calcd. for $C_{14}H_{17}$ (M^+-OH): 185.1330; **found**: 185.1345 (M^+-OH).

Synthesis of cyclohex-2-enyl-methanol (130c)



It was prepared from formaldehyde (30 mg, 1.0 mmol) and cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 4: 1) provided the pure compound **130c** (100 mg, 89%) as a colourless oil

^{1}H NMR ($CDCl_3$, 300 MHz) 5.75-5.81 (m, 1 H), 5.53-5.59 (m, 1 H), 3.49 (dd, J_1 = 6.3 Hz, J_2 = 1.2 Hz, 2 H), 2.22-2.31 (m, 1 H), 1.92-2.00 (m, 2 H), 1.66-1.79 (m, 3 H), 1.46-1.58 (m, 1 H), 1.32-1.41 (m, 1 H);

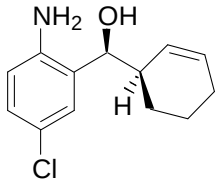
^{13}C NMR ($CDCl_3$, 75 MHz): 129.5, 127.7, 67.0, 38.2, 25.5, 25.2, 20.9;

IR (neat): 3310 (bs), 2922 (s), 1447 (w), 1434 (w) cm^{-1};

MS (EI, 70 ev): 112 (M^+, 2%), 94 (43%), 81 (100%), 77 (8%);

HRMS (EI): calcd. for $C_7H_{12}O$: 112.0888; found: 112.0894.

Synthesis of (2-amino-5-chloro-phenyl)-cyclohex-2-enyl-methanol (130d)



RHJ042J

It was from 2-amino-5-chloro-benzaldehyde (156 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 1: 1) provided the pure compound **130d** (213 mg, 90%) as a white solid, mp.: 112.0-112.5 ^oC. dr > 99:1 (determined by ^{1}H NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): 6.97-7.08 (m, 2 H), 6.55 (d, J = 8.8 Hz, 1 H), 5.72-5.83 (m, 1 H), 5.17-5.29 (m, 1 H), 4.43 (d, J = 7.9 Hz, 1 H), 3.00-4.31 (bs, 2 H), 2.61-2.74 (m, 1 H), 1.94-2.05 (m, 2 H), 1.69-1.93 (m, 2 H), 1.45-1.65 (m, 2 H);

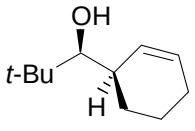
^{13}C NMR ($CDCl_3$, 75 MHz): 143.2, 130.4, 128.2, 128.00, 127.97, 127.5, 122.8, 117.9, 76.7, 39.6, 25.2, 24.9, 20.7;

IR (neat): 3384 (m), 3357 (m), 3162 (m), 1487 (s), 1420 (m), 1200 (m) cm^{-1};

MS (EI, 70 ev): 219 (M^+-H_2O, 100%), 191 (91%), 164 (48%), 140 (79%), 77 (29%);

HRMS (EI): calcd. for $C_{13}H_{15}ClNO$ (M^+-H): 236.0842; **found**: 236.0852 (M^+-H).

Synthesis of 2,2-Dimethyl-1-(1-methyl-cyclohex-2-enyl)-propan-1-ol (130e)



RHJ147I

It was prepared from pivaldehyde (86 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according **TP7**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130e** (270 mg, 96%) as a colourless oil. dr = 78 : 32.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.84-5.94 (m, 1 H), 5.60-5.70 (m, 1 H), 3.06 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1 H), 2.41-2.60 (m, 1 H), 1.31-2.07 (m, 7 H), 0.91 (s, 9 H). The following signals

are discernible for the minor isomer: 5.79-5.89 (m, 1 H), 5.37-5.50 (m, 1 H), 3.25 (t, *J* = 3.1 Hz, 1 H), 2.40-2.55 (m, 1 H), 1.31-2.07 (m, 7 H), 0.94 (s, 9 H).

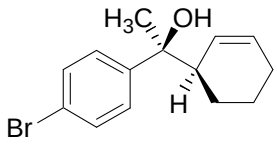
^{13}C NMR ($CDCl_3$, 75 MHz): 132.1, 162.4, 82.9, 36.3, 36.0, 30.4, 26.4, 25.0, 21.2. The following signals are discernible for the minor isomer: 131.6, 130.3, 82.0, 38.6, 35.3, 27.1, 24.7, 22.9, 21.9.

IR (neat): 3479 (m), 2952 (s), 2931 (s), 1479 (m), 1362 (m), 1090 (m) cm^{-1};

MS (EI, 70 ev): 168 (M, < 1%), 150 (< 1%), 111 (28%), 87 (100%), 67 (79%);

HRMS (EI): calcd. for $C_{11}H_{19}$ (M^+-OH): 151.1487; **found**: 151.1492 (M^+-OH).

Synthesis of 1-(4-bromo-phenyl)-1-cyclohex-2-enyl-ethanol (130f)



RHJ138I

It was prepared from 4-bromoacetophenone (199 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according **TP7**. Purification by flash chromatography (eluent: pentane: ether = 6: 1) provided the pure compound **130f** (270 mg, 96%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.42 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 5.85-5.97 (m, 1 H), 5.74 (d, *J* = 10.2 Hz, 1 H), 2.43-2.54 (m, 1 H), 1.87-2.00 (m, 2 H), 1.82 (s, 1 H), 1.63-1.76 (m, 1 H), 1.55 (s, 3 H), 1.33-1.45 (m, 2 H), 1.14-1.28 (m, 1 H);

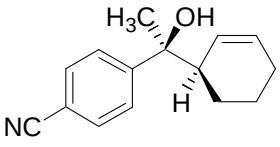
^{13}C NMR ($CDCl_3$, 100 MHz): 146.1, 132.0, 130.9, 127.1, 125.9, 120.2, 75.7, 46.4, 27.9, 25.1, 24.2, 21.8;

IR (neat): 3440 (m), 2929 (m), 1589 (w), 1485 (m), 1394 (m), 1076 (s) cm^{-1};

MS (EI, 70 ev): 280 (M^+ (^{79}Br), 0.05%), 201(100%), 199 (100%), 183 (7%);

HRMS (EI): calcd. for $C_{14}H_{16}Br$ (M^+(^{79}Br)-OH): 263.0435; **found**: 263.0438 (M^+(^{79}Br)-OH).

Synthesis of 4-(1-cyclohex-2-enyl-1-hydroxy-ethyl)-benzonitrile (130g)



RHJ152I

It was prepared from 4-acetylbenzonitrile (145 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 2: 1) provided the pure compound **130g** (220 mg, 97%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.55 (d, *J* = 8.3 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 2 H), 5.86-5.94 (m, 1 H), 5.72 (d, *J* = 10.5 Hz, 1 H), 2.43-2.53 (m, 1 H), 2.08 (s, 1 H), 1.84-1.94 (m, 2 H), 1.59-1.69 (m, 1 H), 1.54 (s, 3 H), 1.05-1.44 (m, 3 H);

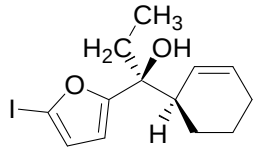
^{13}C NMR ($CDCl_3$, 75 MHz): 152.5, 132.3, 131.6, 126.0, 125.2, 118.8, 109.9, 75.7, 46.1, 27.8, 24.9, 24.1, 21.5;

IR (neat): 3481 (m), 2931 (m), 2227 (m), 1606 (m), 1372 (m) cm^{-1};

MS (EI, 70 ev): 227 (0.5%), 146 (100%), 130 (8%), 102 (7%);

HRMS (EI): calcd. for $C_{15}H_{18}NO$ (M^++H): 228.1388; **found**: 228.1388 (M^++H).

Synthesis of 1-cyclohex-2-enyl-1-(5-iodo-furan-2-yl)-propan-1-ol (130h)



RHJ183I

It was prepared from 1-(5-iodo-furan-2-yl)-propan-1-one (250 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 5: 1) provided the pure compound **130h** (316 mg, 95%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 600 MHz): 6.43 (d, *J* = 3.4 Hz, 1 H), 6.14 (d, *J* = 3.4 Hz, 1 H), 5.80-5.86 (m, 1 H), 5.69-5.75 (m, 1 H), 2.54-2.60 (m, 1 H), 1.89-1.96 (m, 2 H), 1.86 (q, *J* = 7.5 Hz, 2 H), 1.84 (s, 1 H), 1.68-1.74 (m, 1 H), 1.40-1.52 (m, 2 H), 1.25-1.32 (m, 1 H), 0.79 (t, *J* = 7.5 Hz, 3 H);

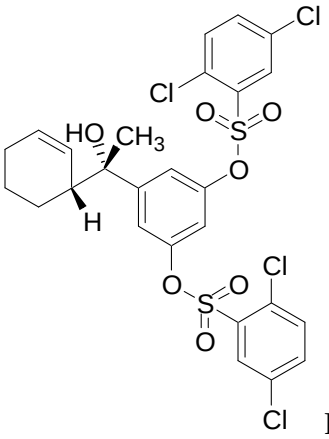
^{13}C NMR ($CDCl_3$, 150 MHz): 163.4, 130.9, 125.8, 120.6, 109.6, 85.3, 77.1, 44.3, 30.4, 25.0, 24.1, 21.9, 7.8;

IR (neat): 3464 (m), 2932 (m), 1486 (m), 1456 (m), 1095 (s) cm^{-1};

MS (EI, 70 ev): 314 (M^+-H_2O, 2%), 251 (100%), 221 (6%), 81 (9%);

HRMS (ESI): calcd. for $C_{14}H_{18}IO_4$ ([M+FA-H]$^-$): 377.0250; **found**: 377.0269 ([M+FA-H]$^-$);
calcd. for $C_{15}H_{20}IO_4$ ([M+FA-H]$^-$): 391.0406; **found**: 391.0429 ([M+FA-H]$^-$).

Synthesis of allylic alcohol 130i



RHJ078J

It was prepared from 3,5-bis(2,4-dichloro-benzenesulfonate)-acetophenone[137] (570 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 6: 1) provided the pure compound **130i** (600 mg, 92%) as a white solid, mp.: 149.6-150.8 ^{o}C. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.78 (d, *J* = 2.6 Hz, 2 H), 7.53 (s, 4 H), 7.03 (d, *J* = 2.6 Hz, 2 H), 6.85 (t, *J* = 2.6 Hz, 1 H), 5.85-5.96 (m, 1 H), 5.59 (d, *J* = 10.6 Hz, 1 H), 2.14-2.29 (m, 1 H), 1.50-2.00 (m, 4 H), 1.41 (s, 3 H), 1.19-1.36 (m, 1 H), 0.73-0.97 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 151.2, 149.0, 135.2, 134.1, 133.4, 133.3, 133.0, 132.1, 131.5, 124.7, 118.3, 114.5, 75.3, 46.2, 27.9, 25.0, 24.0, 21.7;

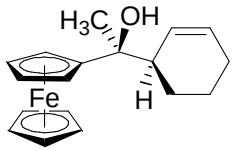
IR (neat): 3559 (m), 2930 (s), 1612 (w), 1588 (s), 1452 (s), 1434, 1394, 1384 cm^{-1};

MS (EI, 70 ev): 634 (M^{+}-H2O, 0.5%), 571 (100%), 360 (20%), 145 (30%);

Anal. Calcd for $C_{26}H_{22}C_{l4}O_7S_2$: C, 47.87; H, 3.40;

Found: C, 47.76; H, 3.46.

Synthesis of ferrocene allylic alcohol 130j



RHJ151I

It was prepared from acetylferrocene (228 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according **TP7**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130j** (288 mg, 93%) as a red solid, mp.: 83.1-84.4 ^{o}C. dr > 99:1.

[137] Prepared from 3,5-dihydroxyacetophenone and 2,5-dichlorobenzenesulfonylchloride as usual.

^{1}H NMR (C_6D_6, 400 MHz): 5.81-5.88 (m, 1 H), 5.67-5.75 (m, 1 H), 4.24-4.29 (m, 1 H), 3.99 (s, 5 H), 3.89-3.92 (m, 2 H), 3.86-3.88 (m, 1 H), 2.46-2.56 (m, 1 H), 2.09 (s, 1 H), 1.94-2.03 (m, 1 H), 1.76-1.85 (m, 2 H), 1.60-1.70 (m, 1 H), 1.49 (s, 3 H), 1.32-1.52 (m, 2 H);

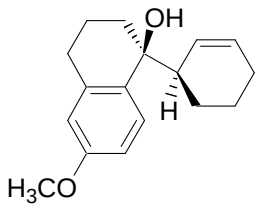
^{13}C NMR (C_6D_6, 100 MHz): 128.7, 128.6, 68.6, 68.5, 68.1, 67.6, 66.1, 47.8, 25.9, 25.5, 25.2, 22.6;

IR (film): 3545 (m), 2926 (m), 1446 (m), 1369 (m), 1318 (s) cm^{-1};

MS (EI, 70 ev): 292 (M^+-H_2O, 100%), 275 (10%), 225 (11%), 166 (9%), 121 (12%);

HRMS (EI): calcd. for $C_{18}H_{20}Fe$ (M^+-H_2O): 292.0914; found: 292.0906 (M^+-H_2O).

Synthesis of 1-cyclohex-2-enyl-6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ol (130k)



RHJ139I

It was prepared from 6-methoxy-3, 4-dihydro-*2H*-naphthalen-1-one (176 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the pure compound **130k** (250 mg, 97%) as a colourless oil. dr > 97:3.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.45 (d, J = 8.6 Hz, 1 H), 6.76 (dd, J_1 = 8.6 Hz, J_2 = 2.7 Hz, 1 H), 6.59 (d, J = 2.7 Hz, 1 H), 5.57-5.67 (m, 1 H), 4.97-5.06 (m, 1 H), 3.76 (s, 3 H), 2.84-2.93 (m, 1 H), 2.55-2.75 (m, 2 H), 1.65-2.08 (m, 9 H), 1.44-1.62 (m, 2 H);

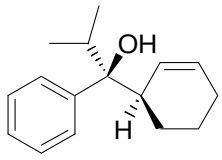
^{13}C NMR ($CDCl_3$, 100 MHz): 158.2, 139.7, 133.4, 128.9, 128.4, 127.8, 113.0, 112.7, 73.7, 55.0, 46.4, 33.1, 30.7, 25.3, 23.4, 22.3, 19.3;

IR (neat): 3446 (m), 2928 (s), 1607 (s), 1498 (s), 1253 (s) cm^{-1};

MS (EI, 70 ev): 240 (M^+-H_2O, 100%), 225 (9%), 211 (22%), 199 (33%), 159 (24%);

HRMS (EI): calcd. for $C_{17}H_{20}O$ (M^+-H_2O): 240,1514; **found**: 240.1520 (M^+-H_2O).

Synthesis of 1-cyclohex-2-enyl-2-methyl-1-phenyl-propan-1-ol (130l)



RHJ041J

It was prepared from 2-methyl-1-phenyl-propan-1-one (148 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. This reaction was carried out at -30

^{o}C for 12 h. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided the pure compound **130l** (216 mg, 94%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.22-7.47 (m, 5 H), 5.86-6.00 (m, 2 H), 2.85-3.05 (m, 1 H), 2.27-2.42 (m, 1 H), 1.83-2.03 (m, 2 H), 1.69-1.80 (m, 1 H), 1.63 (s, 1 H), 1.42-1.60 (m, 2 H), 1.17-1.33 (m, 1 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H);

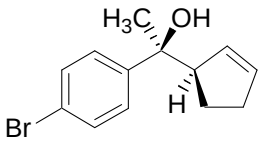
^{13}C NMR ($CDCl_3$, 75 MHz): 142.2, 131.3, 127.2, 126.6, 126.4, 126.1, 80.4, 41.6, 34.7, 25.2, 24.4, 22.2, 17.6, 16.8;

IR (neat): 3568 (w), 2933 (m), 1494 (w), 1468 (m), 1445 (m) cm^{-1};

MS (EI, 70 ev): 213 (M^+-OH, 1%), 187 (8%), 149 (100%), 105 (79%);

HRMS (EI): calcd. for $C_{16}H_{20}$ (M^+-H_2O): 212.1565; **found**: 212.1574 (M^+-H_2O).

Synthesis of 1-(4-bromo-phenyl)-1-cyclopent-2-enyl-ethanol (130m)



RHJ165I

It was prepared from 4-bromoacetophenone (199 mg, 1.0 mmol) and 2-cyclopentylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130m** (260 mg, 97%) as a colourless oil. dr > 99:1.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.43 (d, *J* = 7.9 Hz, 2 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 5.95-6.00 (m, 1 H), 5.71-5.76 (m, 1 H), 3.12-3.21 (m, 1 H), 2.14-2.35 (m, 2 H), 1.74 (s, 1 H), 1.44-1.69 (m, 5 H);

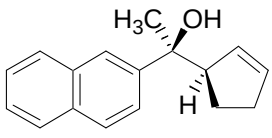
^{13}C NMR ($CDCl_3$, 75 MHz): 146.5, 135.8, 130.9, 129.4, 127.0, 120.2, 75.5, 57.2, 32.3, 29.1, 24.7;

IR (neat): 3458 (m), 2971 (m), 1611 (m), 1486 (s), 1075 (vs) cm^{-1};

MS (EI, 70 ev): 251 (M^+ (^{81}Br)-OH, 1%), 249 (M^+ (^{79}Br)-OH, 1%), 201 (100%), 183 (9%);

HRMS (EI): calcd. for $C_{13}H_{14}Br$ (M^+(^{79}Br)-OH): 249.0279; **found**: 249.0282 (M^+(^{79}Br)-OH).

Synthesis of 1-cyclopent-2-enyl-1-naphthalen-2-yl-ethanol (130n)



RHJ163I

It was prepared from 1-naphthalen-2-yl-ethanone (170 mg, 1.0 mmol) and 2-cyclopentylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 6: 1) provided the pure compound **130n** (236 mg, 99%) as a colourless oil. dr > 99:1.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.96 (s, 1 H), 7.80-7.87 (m, 3 H), 7.55 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.42-7.50 (m, 2 H), 5.99-6.03 (m, 1 H), 5.80-5.85 (m, 1 H), 3.32-3.41 (m, 1 H), 2.17-2.40 (m, 2 H), 1.90 (s, 1 H), 1.65 (s, 3 H), 1.58-1.68 (m, 2 H);

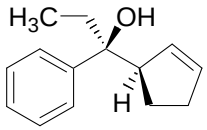
^{13}C NMR ($CDCl_3$, 75 MHz): 144.9, 135.5, 133.1, 132.1, 129.7, 128.1, 127.6, 127.4, 125.9, 125.5, 123.8, 123.5, 75.9, 57.1, 32.3, 29.1, 24.8;

IR (neat): 3456 (m), 2969 (m), 1600 (w), 1505 (m), 1125 (m), 817 (s) cm^{-1};

MS (EI, 70 ev): 238 (M^+, 1%), 220 (23%), 205 (10%), 171 (100%), 155 (25%);

HRMS (EI): calcd. for $C_{17}H_{18}O$: 238.1358; **found**: 238.1322.

Synthesis of 1-cyclopent-2-enyl-1-phenyl-propan-1-ol (130o)



RHJ169I

It was prepared from 1-phenyl-propan-1-one (134 mg, 1.0 mmol) and 2-cyclopentylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130o** (200 mg, 99%) as a colourless oil. dr > 99:1.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.36-7.41 (m, 2 H), 7.28-7.34 (m, 2 H), 7.17-7.23 (m, 1 H), 5.97-6.02 (m, 1 H), 5.80-5.86 (m, 1 H), 3.20-3.35 (m, 1 H), 2.10-2.38 (m, 2 H), 1.80-2.00 (m, 2 H), 1.44-1.66 (m, 2 H), 1.54 (s, 1 H), 0.68 (t, J = 7.5 Hz, 3 H);

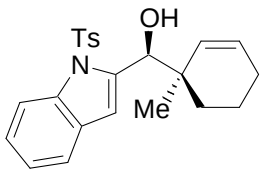
^{13}C NMR ($CDCl_3$, 75 MHz): 144.9, 135.8, 129.5, 127.7, 126.0, 125.8, 78.5, 56.6, 34.2, 32.1, 24.8, 7.9;

IR (neat): 3569 (m), 2934 (m), 1494 (m), 1446 (m), 1169 (m), 964 (m), 751 (s) cm^{-1};

MS (EI, 70 ev): 184 (M^+, < 1%), 135 (100%), 105 (12%), 77 (9%), 57 (33%);

HRMS (EI): calcd. for $C_{14}H_{17}$ (M^+-OH): 185.1330; **found**: 185.1305 (M^+-OH).

Synthesis of (1-methyl-cyclohex-2-enyl)-[1-(toluene-4-sulfonyl)-*1H*-indol-3-yl]-methanol (130p)



RHJ186I

It was prepared from 1-(toluene-4-sulfonyl)-*1H*-indole-3-carbaldehyde (299 mg, 1.0 mmol) and 1-methyl-1-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 2: 1) provided the pure compound **130p** (345 mg, 87%) as a white solid, mp.: 117.5-119.0 ^{o}C. dr = 95:5.

^{1}H NMR ($CDCl_3$, 600 MHz): 7.95 (d, *J* = 8.4 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.53 (s, 1 H), 7.26 (dt, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1 H), 7.15-7.21 (m, 3 H), 5.82-5.87 (m, 1 H), 5.40 (d, *J* = 10.1 Hz, 1 H), 4.76 (d, *J* = 1.8 Hz, 1 H), 2.31 (s, 3 H), 1.88-2.00 (m, 3 H), 1.79-1.87 (m, 1 H), 1.63-1.71 (m, 1 H), 1.50-1.58 (m, 2 H), 1.25-1.32 (m, 1 H), 0.96 (s, 3 H);

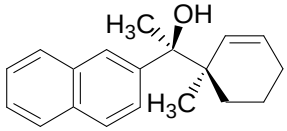
^{13}C NMR ($CDCl_3$, 150 MHz): 144.8, 135.2, 134.8, 133.2, 130.5, 129.9, 129.8, 126.8, 124.5, 124.4, 123.0, 122.9, 121.1, 113.5, 74.4, 40.9, 30.2, 25.1, 23.8, 21.5, 19.0;

IR (neat): 3562 (w), 2930 (w), 1598 (w), 1446 (m), 1363 (m), 1166 (s) cm^{-1};

MS (EI, 70 ev): 395 (M^+, <1%), 300 (100%), 155 (28%), 91 (39%);

HRMS (ESI): calcd. for $C_{24}H_{26}NO_5S$ ($[M+FA-H]^-$): 440.1532; **found**: 440.1541 ($[M+FA-H]^-$).

Synthesis of 1-(1-methyl-cyclohex-2-enyl)-1-naphthalen-2-yl-ethanol (130q)



RHJ167I

It was prepared from 1-naphthalen-2-yl-ethanone (170 mg, 1.0 mmol) and 1-methyl-1-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 8: 1) provided the pure compound **130q** (263 mg, 99%) as a colourless oil. dr > 99:1.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.96 (s, 1 H), 7.77-7.89 (m, 3 H), 7.68 (dd, , J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1 H), 7.43-7.51 (m, 2 H), 5.81-5.94 (m, 2 H), 2.07 (s, 1 H), 1.85-1.98 (m, 3 H), 1.75 (s, 3 H), 1.42-1.72 (m, 2 H), 1.11 (s, 3 H), 1.02-1.11 (m, 1 H);

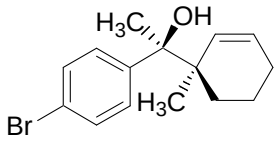
^{13}C NMR ($CDCl_3$, 75 MHz): 142.8, 132.6, 132.1, 131.9, 130.0, 128.2, 127.2, 126.2, 125.9, 125.8, 125.6, 125.5, 78.4, 43.0, 30.8, 25.3, 24.9, 23.4, 19.5;

IR (neat): 3470 (w), 2936 (m), 1599 (w), 1374 (m), 1125 (m), 819 (s) cm^{-1};

MS (EI, 70 ev): 248 (M^+-H_2O, 1%), 171 (100%), 155 (15%), 177 (23%);

HRMS (EI): calcd. for $C_{19}H_{21}$ (M^+-OH): 249.1643; **found**: 249.1639 (M^+-OH).

Synthesis of 1-(4-bromo-phenyl)-1-(1-methyl-cyclohex-2-enyl)-ethanol (130r)



RHJ155I

It was prepared from 4-bromoacetophenone (199 mg, 1.0 mmol) and 1-methyl-1-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130r** (292 mg, 99%) as a colourless oil. dr > 98:2.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.40 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 5.81-5.87 (m, 1 H), 5.67-5.72 (m, 1 H), 1.93 (s, 1 H), 1.78-1.93 (m, 2 H), 1.59-1.77 (m, 2 H), 1.56 (s, 3 H), 1.36-1.53 (m, 1 H), 0.98 (s, 3 H), 0.93-1.92 (m, 1 H);

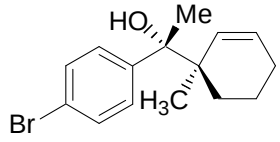
^{13}C NMR ($CDCl_3$, 75 MHz): 144.2, 131.5, 130.3, 130.1, 129.0, 120.5, 78.0, 42.7, 30.6, 25.0, 24.9, 23.2, 19.4;

IR (neat): 3476 (m), 2937 (m), 1589 (w), 1486 (s), 1368 (m), 1076 (s) cm^{-1};

MS (EI, 70 ev): 276 (M^+-H_2O, 0.5%), 201 (^{81}Br, 100%), 199 (^{79}Br, 100%), 185 (9%), 95 (21%);

HRMS (EI): calcd. for $C_{15}H_{18}Br$ (M^+ (^{79}Br)-OH): 277.0592; **found**: 277.0589 (M^+ (^{79}Br)-OH).

1-(4-Bromo-phenyl)-1-(1-methyl-cyclohex-2-enyl)-ethanol (130r')



RHJ086J

The solution of CH_3MgCl (0.44 mL, 2.5 M in THF) was added to the solution of ketone **132** (200 mg, 1.0 mmol) in THF (2.0 mL) at -20 ^{o}C and the resulting mixture was stirred overnight at this temperature. Quenched as usual and purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the starting material ketone **132** (60 mg) and pure desired compound **130r'** (184 mg, 90%) as a colourless oil. dr = 80:20.

^{1} H NMR ($CDCl_3$, 400 MHz): 7.40 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 5.75-5.82 (m, 1 H), 5.47-5.53 (m, 1 H), 1.42-2.00 (m, 6 H) 1.52 (s, 3 H),1.29-1.36 (m, 1 H), 0.93 (s, 3 H). The following signals are discernible for the minor isomer: 5.81-5.87 (m, 1 H), 5.67-5.72 (m, 1 H), 1.56 (s, 3 H), 0.98 (s, 3 H).

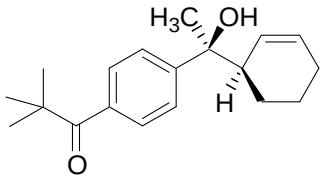
^{13}C NMR ($CDCl_3$, 100 MHz): 144.9, 131.8, 130.8, 130.0, 129.2, 128.95, 120.4, 78.2, 42.7, 24.8, 24.6, 22.8, 19.3. The following signals are discernible for the minor isomer: 144.2, 131.5, 130.3, 130.1, 129.0, 120.5, 78.0, 42.7, 30.6, 25.0, 24.9, 23.2, 19.4.

IR (neat): 3471 (m), 2914 (s), 1729 (s), 1486 (m), 1471 (m), 1392 (m) cm^{-1};

MS (EI, 70 ev): 276 (M^+-H_2O, 0.5%), 201 (^{81}Br, 100%), 199 (^{79}Br, 100%), 185 (9%), 95 (21%);

HRMS (EI): calcd. for $C_{15}H_{17}Br$ (M^+ (^{79}Br)-H_2O): 276.0514; **found**: 276.0519 (M^+ (^{79}Br)-H_2O).

Synthesis of 1-[4-(1-cyclohex-2-enyl-1-hydroxy-ethyl)-phenyl]-2,2-dimethyl-propan-1-one (130s)



RHJ048J

It was prepared from 1-(4-acetyl-phenyl)-2, 2-dimethyl-propan-1-one (204 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 6: 1) provided the pure compound **130s** (260 mg, 91%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.68 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 5.87-5.96 (m, 1 H), 5.71-5.81 (m, 1 H), 2.45-2.58 (m, 1 H), 1.86-2.00 (m, 2 H), 1.80 (s, 1 H), 1.59-1.74 (m, 1 H), 1.58 (s, 3 H), 1.12-1.47 (m, 3 H), 1.34 (s, 9 H);

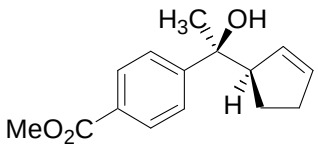
^{13}C NMR ($CDCl_3$, 75 MHz): 208.6, 150.2, 136.3, 132.2, 127.9, 125.8, 124.9, 76.0, 46.3, 44.1, 28.1, 28.0, 25.1, 24.2, 21.8;

IR (neat): 3486 (bs, m), 2930 (s), 1668 (vs), 1604 (s), 1276 (s) cm^{-1};

MS (EI, 70 ev): 287 (M^++H, 0.5%), 269 (0.5%), 229 (8%), 205 (100%), 148 (19%);

HRMS (EI): calcd. for $C_{19}H_{24}O$ (M^+-H_2O): 268.1827; **found**: 268.1845 (M^+-H_2O).

Synthesis of 4-(1-cyclopent-2-enyl-1-hydroxy-ethyl)-benzoic acid methyl ester (130t)



RHJ162I

It was prepared from 4-acetyl-benzoic acid methyl ester (178 mg, 1.0 mmol) and 2-cyclopentylzinc chloride (1.2 mmol) according to **TP7**. This reaction was carried out in THF (5.0 mL). Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the pure compound **130t** (236 mg, 96%) a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.96 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 8.5 Hz, 2 H), 5.95-6.00 (m, 1 H), 5.72-5.77 (m, 1 H), 3.87 (s, 3 H), 3.17-3.25 (m, 1 H), 2.10-2.33 (m, 2 H), 1.87 (s, 1 H), 1.46-1.65 (m, 2 H), 1.53 (s, 3 H);

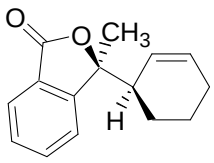
^{13}C NMR ($CDCl_3$, 75 MHz): 167.0, 152.7, 135.9, 129.3 (2 X C), 128.1, 125.2, 75.8, 57.1, 51.9, 32.2, 29.0, 24.6;

IR (neat): 3499 (m), 2951 (m), 1705 (s), 1609 (m), 1436 (m), 1406 (m), 1276 (vs) cm^{-1};

MS (EI, 70 ev): 228 (M^+-H_2O, 1%), 179 (100%), 163 (8%), 137 (9%), 77 (9%);

HRMS (EI): calcd. for $C_{15}H_{19}O_3$ (M^++H): 247.1334; **found**: 247.1349 (M^++H).

Synthesis of 3-cyclohex-2-enyl-3-methyl-*3H*-isobenzofuran-1-one (130u)



RHJ015J

It was prepared from 2-acetyl-benzoic acid methyl ester (178 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. This reaction was carried out at -78 ^oC for 1 h then warmed to room temperature for 1 h before quenching with water. Purification by flash chromatography (eluent: pentane: ether = 10: 1) provided the pure compound **130u** (221 mg, 97%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.82 (d, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 5.68-5.77 (m, 1 H), 5.60 (d, *J* = 9.7 Hz, 1 H), 2.60-2.72 (m, 1 H), 1.82-1.94 (m, 2 H), 1.67-1.79 (m, 1 H), 1.64 (s, 3 H), 1.36-1.62 (m, 2 H), 1.18-1.32 (m, 1 H);

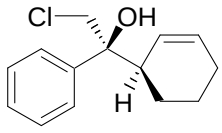
^{13}C NMR ($CDCl_3$, 75 MHz): 170.0, 153.2, 133.8, 130.4, 128.8, 126.3, 125.6, 124.6, 121.5, 89.2, 43.7, 24.7, 24.3, 23.8, 21.8;

IR (neat): 2933 (m), 1750 (vs), 1597 (w), 1613 (w), 1466 (m), 1449 (m), 1116 (s) cm^{-1};

MS (EI, 70 ev): 229 (M^++H, 0.5%), 147 (100%), 91 (35%);

HRMS (EI): calcd. for $C_{15}H_{17}O_2$ (M^++H): 229.1229; **found**: 229.1241 (M^++H).

Synthesis of 2-chloro-1-cyclohex-2-enyl-1-phenyl-ethanol (130v)



RHJ003J

It was prepared from 2-chloro-1-phenyl-ethanone (161 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash

chromatography (eluent: pentane: ether = 5: 1) provided the pure compound **130v** (230 mg, 97%) as a colourless oil. dr > 99:1.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.28-7.51 (m, 5 H), 5.85-5.93 (m, 1 H), 5.70-5.85 (m, 1 H), 3.99-4.20 (m, 2 H), 2.70-2.82 (m, 1 H), 2.58 (s, 1 H), 1.84-2.10 (m, 2 H), 1.69-1.80 (m, 1 H), 1.29-1.66 (m, 3 H);

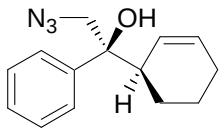
^{13}C NMR ($CDCl_3$, 75 MHz): 141.9, 131.1, 127.9, 127.1, 126.0, 125.4, 77.9, 52.4, 44.3, 24.9, 24.3, 21.8;

IR (neat): 3550 (m), 1495 (m), 1446 (s), 1433 (m), 1054 (m) cm^{-1};

MS (EI, 70 ev): 219 (M^+-H_2O, 0.1%), 155 (100%), 105 (8%), 91 (9%), 77 (32%);

HRMS (EI): calcd. for $C_{14}H_{16}Cl$ (M^+-OH): 219.0941; **found**: 219.0924 (M^+-OH).

Synthesis of 2-azido-1-cyclohex-2-enyl-1-phenyl-ethanol (130w)



RHJ009J

It was prepared from 2-azido-1-phenyl-ethanone (161 mg, 1.0 mmol) and 2-cyclohexenylzinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 5: 1) provided the pure compound **130w** (226 mg, 93%) as a colourless oil. dr > 99:1.

^{1} H NMR ($CDCl_3$, 300 MHz): 7.20-7.50 (m, 5 H), 5.84-5.96 (m, 1 H), 5.70-5.80 (m, 1 H), 3.74 (s, 2 H), 2.57-2.71 (m, 1 H), 2.33 (bs, 1 H), 1.83-2.00 (m, 2 H), 1.62-1.75 (m, 1 H), 1.34-1.49 (m, 2 H), 1.17-1.31 (m, 1 H);

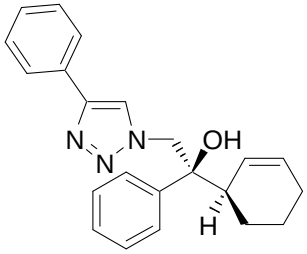
^{13}C NMR ($CDCl_3$, 75 MHz): 142.4, 132.1, 128.1, 127.1, 125.6, 125.2, 78.3, 59.2, 43.7, 24.9, 24.0, 21.6;

IR (neat): 3547 (w), 2130 (vs), 1495 (w), 1446 (m) cm^{-1};

MS (EI, 70 ev): 197 (M^+-H_2O-N_2, 95%), 169 (100%), 115 (8%);

HRMS (ESI):calcd. for $C_{15}H_{18}N_3O_3$ ([M+FA-H]$^-$): 288.1348; **found**: 288.1375 ([M+FA-H]$^-$);
calcd. for $C_{16}H_{20}N_3O_3$ ([M+AA-H]$^-$): 302.1505; **found**: 302.1535 ([M+AA-H]$^-$).

Synthesis of 1-cyclohex-2-enyl-1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanol (133a)



RHJ014J

The 2-cyclohexenylzinc chloride **129b** (2.0 mL, 1.2 mmol, 0.6 M in THF) was added to the solution of 2-azido-1-phenyl-ethanone (161 mg, 1.0 mmol) and ethynyl-benzene (153 mg, 1.5 mmol) in THF (2.0 mL) at -78 ^{o}C and the resulting mixture was stirred for 1 h at this temperature. The solution of CuCN·2LiCl (0.05 mL, 1.0 M in THF) was added and the reaction mixture was stirred overnight at room temperature. After quenching with water (10 mL), the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 10: 1 then ether: CH_2Cl_2 = 1: 1) provided the pure compound **133a** (325 mg, 94%) as a white solid, mp.: 161.0-162.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.69 (t, *J* = 1.76 Hz, 1 H), 7.67 (s, 1 H), 7.20-7.42 (m, 9 H), 6.00-6.12 (m, 1 H), 5.91 (d, *J* = 11.5 Hz, 1 H), 4.96 (d, *J* = 14.1 Hz, 1 H), 4.80 (d, *J* = 14.1 Hz, 1 H), 3.09 (s, 1 H), 2.74-2.87 (m, 1 H), 1.95-2.08 (m, 2 H), 1.68-1.82 (m, 1 H), 1.27-1.55 (m, 3 H);

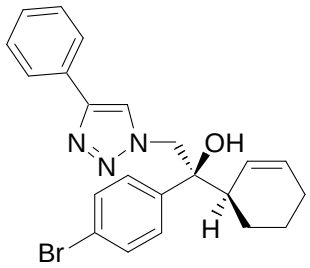
^{13}C NMR ($CDCl_3$, 75 MHz): 147.0, 141.2, 133.3, 130.5, 128.7, 128.2, 127.9, 127.3, 125.64, 125.58, 124.7, 121.1, 78.1, 58.6, 43.7, 25.0, 24.2, 21.6;

IR (neat): 3345 (m), 2932 (m), 1469 (m), 1446 (m), 1084 (m) cm^{-1};

MS (EI, 70 ev): 345 (M^+, 1%), 264 (34%), 218 (10%), 182 (12%), 159 (83%), 105 (100%);

HRMS (EI): calcd. for $C_{22}H_{23}N_3O$ (M^+): 345.1841; **found**: 345.1847 (M^+).

Synthesis of 1-(4-bromo-phenyl)-1-cyclohex-2-enyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanol (133b)



RHJ019J

The 2-cyclohexenylzinc chloride **129b** (2.0 mL, 1.2 mmol, 0.6 M in THF) was added to the solution of 2-azido-1-(4-bromo-phenyl)-ethanone (240 mg, 1.0 mmol) and ethynyl-benzene (153 mg, 1.5 mmol) in THF (2.0 mL) at -78 ^{o}C and the resulting mixture was stirred for 1 h at this temperature. The solution of CuCN·2LiCl (0.05 mL, 5 mol%, 1.0 M in THF) was added and the reaction mixture was stirred overnight at room temperature. After quenching with water (10 mL), the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo*.

Purification by flash chromatography (eluent: pentane: ether = 10: 1 then ether: CH_2Cl_2 = 1: 1) provided the pure compound **133b** (400 mg, 94%) as a white solid, mp.: 157.0-158.5 ^oC.

^{1}H NMR ($CDCl_3$, 600 MHz): 7.66 (d, *J* = 7.6 Hz, 2 H), 7.51 (s, 1 H), 7.32-7.41 (m, 4 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 5.99-6.05 (m, 1 H), 5.81 (d, *J* = 10.1 Hz, 1 H), 4.84 (d, *J* = 14.1 Hz, 1 H), 4.77 (d, *J* = 14.1 Hz, 1 H), 3.19 (s, 1 H), 2.68-2.76 (m, 1 H), 1.87-2.02 (m, 2 H), 1.64-1.75 (m, 1 H), 1.36-1.48 (m, 2 H), 1.18-1.30 (m, 1 H), ;

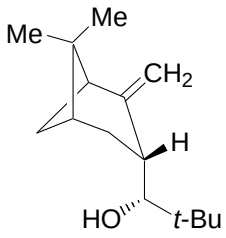
^{13}C NMR ($CDCl_3$, 150 MHz): 147.2, 140.2, 133.8, 131.3, 130.3, 128.8, 128.1, 127.5, 125.6, 124.2, 121.4, 121.0, 77.9, 58.2, 43.8, 25.0, 24.1, 21.4;

IR (neat): 3327 (m), 2939 (m), 1609 (m), 1590 (m), 1487 (m), 1466 (m), 1005 (s) cm^{-1};

MS (EI, 70 ev): 425 (M^+ (^{81}Br), 1%), 423 (M^+ (^{79}Br), 1%), 342 (18%), 296 (6%), 183 (88%), 159 (100%), 130 (42%);

HRMS (EI): calcd. for $C_{22}H_{22}BrN_3O$ (M^+, ^{79}Br): 423.0946; **found**: 423.0926 (M^+, ^{79}Br).

Synthesis of 1-(6,6-dimethyl-2-methylene-bicyclo[3.1.1]hept-3-yl)-2,2-dimethyl-propan-1-ol (135a)



RHJ106I, RHJ097I

It was prepared from 2, 2-dimethyl-propionaldehyde (86 mg, 1.0 mmol) and ((6, 6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)zinc chloride (1.2 mmol) according to **TP7**. Purification by flash chromatography (eluent: pentane: ether = 3: 1) provided the pure compound **135a** (200 mg, 90%) a colourless oil. dr > 99:1. $[\alpha]_D^{20}$ = -+8.4 (c = 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): 4.94 (s, 1 H), 4.62 (s, 1 H), 3.08 (t, *J* = 5.4 Hz, 1 H), 2.57 (t, *J* = 7.5 Hz, 1 H), 2.47 (d, *J* = 5.3 Hz, 1 H), 2.33 (d, *J* = 5.0 Hz, 1 H), 2.22-2.29 (m, 1 H), 2.06-2.14 (m, 1 H), 1.95 (q, *J* = 5.5 Hz, 1 H), 1.63 (dd, J_1 = 13.8 Hz, J_2 = 4.4 Hz, 1 H), 1.35 (d, *J* = 10.2 Hz, 1 H), 1.23 (s, 3 H), 0.91 (s, 9 H), 0.72 (s, 3 H);

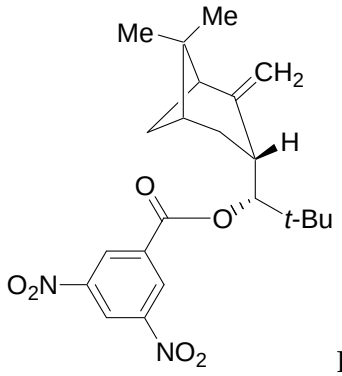
^{13}C NMR ($CDCl_3$, 150 MHz): 153.7, 111.9, 83.6, 51.7, 41.4, 40.5, 37.3, 36.4, 33.5, 25.77, 25.75, 25.6, 21.6;

IR (neat): 3532 (m), 2920 (s), 2948 (s), 1630 (m), 1479 (m), 1458 (m), 1364 (s), 1076 (s) cm^{-1};

MS (EI, 70 ev): 222 (M^+, 1%), 189 (5%), 165 (8%), 147 (9%), 136 (39%), 121 (30%), 93 (100%), 69 (23%);

HRMS (EI): calcd. for $C_{15}H_{27}O$ (M^++H): 223.2062; **found**: 223.2077 (M^++H).

Synthesis of 3,5-dinitro-benzoic acid 1-(6,6-dimethyl-2-methylene-bicyclo[3.1.1]hept-3-yl)-2,2-dimethyl-propyl ester (136)



RHJ107I

A solution of 1-(6, 6-dimethyl-2-methylene-bicyclo[3.1.1]hept-3-yl)-2,2-dimethyl-propan-1-ol **135a** (44 mg, 0.2 mmol), 3,5-dinitro-benzoyl chloride (69 mg, 0.3 mmol), NEt_3 (61 mg, 0.6 mmol) and DMAP (10 mol %) in CH_2Cl_2 (10 mL) was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (30 mL) and then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane: ether = 8: 1), providing **136** (71 mg, 85%) as a white solid; mp.: 171.5-172.8 ^oC. $[\alpha]_D^{20}$ = -59.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 300 MHz): 9.17 (t, *J* = 2.0 Hz, 1 H), 9.11 (d, *J* = 2.0 Hz, 2 H), 4.93 (d, *J* = 8.8 Hz, 1 H), 4.62-4.70 (m, 2 H), 2.92 (t, *J* = 8.5 Hz, 1 H), 2.06-2.34 (m, 3 H), 1.91-2.02 (m, 1 H), 1.69-1.82 (m, 1 H), 1.54 (d, *J* = 9.7 Hz, 1 H), 1.19 (s, 3 H), 1.07 (s, 9 H), 0.70 (s, 3 H);

^{13}C NMR ($CDCl_3$, 75 MHz): 161.6, 150.5, 148.6, 134.7, 129.4, 122.0, 112.7, 87.5, 51.9, 40.9, 40.5, 36.2, 35.4, 32.9, 26.5, 26.1, 25.5, 21.8;

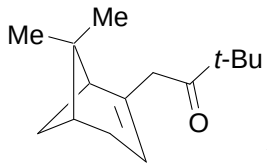
IR (neat): 2912 (m), 1719 (s), 1628 (w), 1542 (vs), 1482(w), 1460 (w), 1339 (vs), 1279 (s) cm^{-1};

MS (EI, 70 ev): 401 (M^+-CH_3, 0.5%), 330 (25%), 194 (80%), 105 (90%), 91 (100%);

Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73;

Found: C, 63.24; H, 6.56, N, 6.70.

Synthesis of 1-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-3,3-dimethyl-butan-2-one (135b)



RHJ127I

The ((6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)zinc chloride (2.0 mL, 1.2 mmol, 0.6 M in THF) was added to the solution of 2,2-dimethyl-propionitrile (83 mg, 1.0 mmol) in THF (2.0 mL) at 0 ^{o}C and the resulting mixture was stirred for 0.5 h at 0 ^{o}C then stirred for 4 h at room temperature. The solution of HCl (2.0 mL, 1.0 M in water) was added and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 x 30 mL). The combined extracts were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane: ether = 100: 1) provided the pure compound **135b** (200 mg, 91%) as a colourless oil. $[\alpha]_D^{20}$ = -31.8 (c = 0.9, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): 5.25 (s, 1 H), 3.20 (d, *J* = 16.8 Hz, 1 H), 3.14 (d, *J* = 16.8 Hz, 1 H), 2.36 (dt, J_1 = 8.8 Hz, J_2 = 5.7 Hz, 1 H), 2.13-2.30 (m, 2 H), 2.01-2.08 (m, 1 H), 1.96 (t, *J* = 5.7 Hz, 1 H), 1.19-1.27 (m, 1 H), 1.24 (s, 3 H), 1.12 (s, 9 H), 0.83 (s, 3 H);

^{13}C NMR ($CDCl_3$, 150 MHz): 213.7, 142.3, 120.4, 46.2, 44.7, 44.3, 40.5, 38.0, 31.8, 31.4, 26.5, 26.3, 21.0;

IR (neat): 2913 (s), 1710 (vs), 1603 (w), 1477 (m), 1364 (s), 1060 (s) cm^{-1};

MS (EI, 70 ev): 220 (5%), 177 (5%), 163 (10%), 135 (25%), 91 (22%), 57 (100%);

HRMS (EI): calcd. for $C_{15}H_{24}O$ (M^+): 220.1827; **found**: 220.1818 (M^+).

12. Curriculum Vitae

Name: Hongjun Ren
Date of Birth: April, 24th 1975
Nationality: Chinese
Place of birth: Jiangsu, China
Gender: Male
Marital Status: Single
Mother language: Chinese. Other language: English.

EDUCATION

Aug./2003- Dec./2006	**Ludwig-Maximilians-Universität (München)** **Department Chemie und Biochemie** Ph.D. under the supervision of Prof. Dr. Paul Knochel	Germany
Sep./1998 - May./2001	**Zhejiang University** **Department of Chemistry** Master of Science Degree in Chemistry Supervisor: Prof. Dr. Yanguang Wang	Hangzhou, China
Sep./1994 - Jun./1998	**Zhejiang University** **Department of Chemistry** Bachelor of Science Degree in Chemistry Supervisor: Prof. Dr. Yuanjiang Pan	Hangzhou, China

EXPERIENCE

Jun./2001 - Jul./2003	**Shanghai Institute of Organic Chemistry, CAS, Shanghai, P. R. China** Research assistant in Shengming Ma's group.

PUBLICATIONS

1) A Novel Synthesis of Aryl-unsaturated Amides
   Hongjun Ren and Yanguang Wang*, *Synth. Commun.* **2001**, *31*, 73;
2) Highly Regio- and Stereoselective Halohydroxylation Reaction of 1, 2-allenyl Phenyl Sulfoxides. Reaction Scope, Mechanism and the Corresponding Pd- or Ni-Catalyzed Selective Coupling Reactions
   Shengming Ma*, **Hongjun Ren** and Qi Wei, *J. Am. Chem. Soc*. **2003**, *125*, 4817;
3) Highly Region- and Stereoselective $PdCl_2(MeCN)_2$-Catalyzed Cross Coupling of 1,2-

allenylic Sulfoxides with Allyl Bromide

Shengming Ma*, Qi Wei and **Hongjun Ren,** *Tetrahedron Lett.* **2004**, 3517;

4) Stereoselective Preparation of Functionalized Acyclic Alkenylmagnesium Reagents Using *i*-PrMgCl·LiCl

Hongjun Ren, Arkady Krasovskiy and Paul Knochel*, *Org. Lett*. **2004**, *6*, 4215;

5) Preparation of Cyclic Alkenylmagnesium Reagents *via* an Iodine/Magnesium Exchange

Hongjun Ren, Arkady Krasovskiy and Paul Knochel*, *Chem. Comm.* **2005**, 543;

6) Chemoselective Benzylic C-H Activations for the Preparation of Condensed *N*-Heterocycles

Hongjun Ren, Paul Knochel*, *Angew. Chem., Int. Ed.* **2006**, *45*, 3462;

7) Magnesiated Unsaturated Silylated Cyanohydrins as Synthetic Equivalents of Aromatic and Heterocyclic Grignard Reagents Bearing a Ketone or an Aldehyde

Ching-Yuan Liu, **Hongjun Ren**, and Paul Knochel*, *Org. Lett*. **2006**, *8*, 617;

8) Regioselective Functionalization of Trisubstituted Pyridines Using a Bromine-Magnesium Exchange

Hongjun Ren, Paul Knochel*, *Chem. Comm.* **2006**, 726;

9) Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using Trisubstituted Allylic Zinc Reagents

Hongjun Ren and Paul Knochel*, manuscript in preparation;

10) Chemoselective Benzylic sp3 C-H Bond activation and Domino C-H Activation for Preparation of Condensed *N*-Heterocycles

Hongjun Ren, Zhuo Li and Paul Knochel*, manuscript in preparation.

CONFERENCES AND POSTER

1. **"***Stereoselective Preparation of Functionalized Alkenylmagnesium Reagents Using iPrMgCl·LiCl***";** Poster, 13th IUPAC International Symposium on Organometallic Chemistry directed toward Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17th-21th, July, 2005.
   13th OMCOS Poster Awards (2005, Geneva)
2. *"Chemoselective Benzylic C-H Activations for the Preparation of Condensed N-Heterocycles"*; Poster, Industrietag, München, Germany, 6th, October, 2006.

München, den 19.12.2006