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Preparation of New Functionalized Organomagnesium Reagents using a Low Temperature Halogen-Magnesium Exchange

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Preparation of New Functionalized Organomagnesium Reagents using a Low Temperature Halogen-Magnesium Exchange

von

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aus

Hanoi, Vietnam

München, 2003

Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

München, am 11. November 2003

Viet Anh Vu

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2. Gutachter: Prof. Dr. Heinz Langhals

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1. Vu, V. A.; Bérillon, L.; Knochel, P. "New Functionalized Alkenylmagnesium Reagents Bearing an Oxygen Function in the beta-Position. Preparation and Reaction of 5-Magnesiated-1,3-Dioxin-4-one Derivatives" *Tetrahedron Lett*. **2001**, *42*, 6847.

2. Knochel, P.; Hupe, E.; Dohle, W.; Lindsay, D. M.; Bonnet, V.; Boudier, A.; Kopp, F.; Demay, S.; Seidel, N.; Calaza, I.; Vu, V. A.; Monguchi, Y.; Sapountzis, I.; Wendicke, S.; Bunlaksananusorn, T. "Functionalized Main Group Organometallics for Organic Synthesis" *Pure Appl. Chem*. **2002**, *47*, 11.

3. Thibonnet, J.; Vu, Viet Anh; Berillon, L.; Knochel. P. "Alkenylmagnesium Reagents *via* a Halide-Magnesium Exchange" *Tetrahedron* **2002**, *58*, 4787.

4. Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. "Practical Synthetic Procedures: Preparation and Reactions of Functionalized Arylmagnesium Reagents" *Synthesis* **2002**, *4*, 565.

5. Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. "Preparation of new functionalized cyclopropylmagnesium reagents" *Angew. Chem.* **2002**, *114,* 361; *Angew. Chem. Int. Ed*. **2002**, *41*, 351.

6. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. "Highly Functionalized Magnesium Organometallics Prepared *via* a Halogen-Metal Exchange" *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed*. **2003,** *42***,** 4302.

7. Vu, V. A; Marek, I.; Knochel, P. "Stereoselective Preparation of Functionalized Unsaturated Lactones and Esters *via* Functionalized Magnesium Carbenoids" *Synthesis* **2003**, 1797.

Table of Contents

Introduction

1. Organometallic reagents in organic synthesis

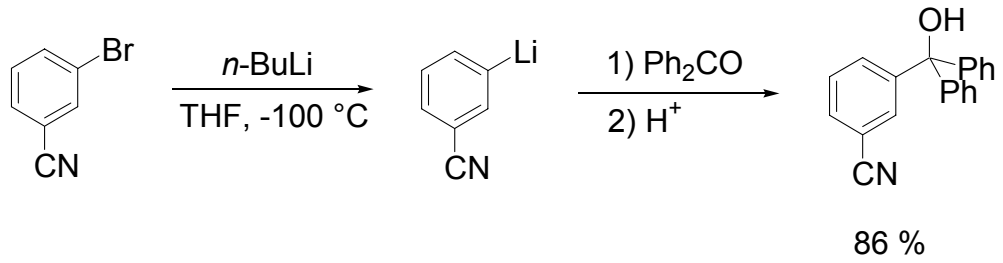
Polyfunctional organometallic compounds provide a general entry into complex molecules and their extensive applications in total synthesis of natural products have been described.[1] In the last 20 years, organometallic compounds of various metals (Li, Mg, B, Zn, Sn, etc.) have been prepared. Their reactivity generally increases with the ionic character of the carbon-metal bond and with the difference in electronegativity between the metal center and the carbon atom (Figure 1).[2]

increasing reactivity of the respective organometallic species

Figure 1. Electronegativity differences between the metal and carbon

The polar organolithium species display high reactivity towards most functional groups in organic synthesis and the generation of polyfunctional organolithiums is possible only by generating these at very low temperature or in the presence of the electrophile (Barbier reaction).[3] Parham showed that functionalized organolithium reagents, bearing cyano-, amide-, *t*-butylester-substituents, can be prepared by a bromine-lithium exchange at -100 °C and quenched with various electrophiles (Scheme 1).[4]

[1] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, Verlag Chemie, Weinheim, **1996**.
[2] Negishi, E. *Organometallics in Organic Synthesis*, Wiley, New York, **1980**.
[3] Blomberg, C. *The Barbier Reaction and Related One-Step Processes*, Springer-Verlag, **1993**.
[4] a) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem*. **1975**, *40*, 2394; b) Parham, W. E.; Jones, L. D. *J. Org. Chem*. **1976**, *41*, 1187; c) Parham, W. E.; Jones, L. D. *J. Org. Chem*. **1976**, *41*, 2704; d) Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 260; e) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.



Scheme 1. A functionalized organolithium reagent prepared by low-temperature bromine- lithium exchange.

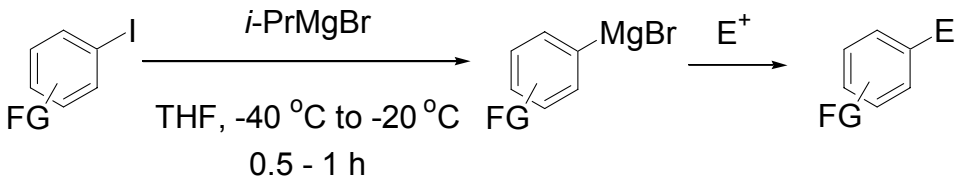
All of the previously described organolithium reagents are relatively unstable,[5] thus, making them difficult to handle especially in large quantities used in industry.

On the other side of the reactivity spectra are zinc, tin and boron, which form covalent bonds with carbon and show low reactivity towards many electrophilic reagents but tolerate many functional groups. The presence of low lying orbitals which facilitate transmetallation reaction is decisive for synthetic applications of these non-polar organometallics.[6]

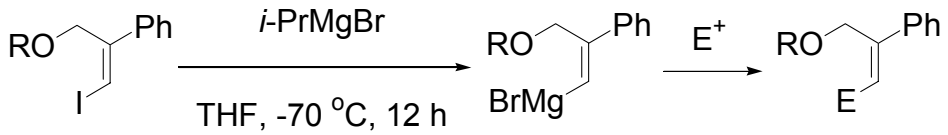
Organomagnesium reagents, like organolithium reagents, have a highly polar carbon-metal bond which makes them rather reactive towards electrophiles. However, these species are more stable and tolerate most functional groups, provided reactions are carried out below -10 °C. Although the application of organomagnesium reagents in organic synthesis would be possible, only few methods for generating functionalized organomagnesium species have been described.[7] In this context, the use of Rieke magnesium proved not to be general, since most polar functional groups coordinate to the surface of the activated magnesium and thereby inhibit the oxidative addition of the metal into the carbon-halogen bond.[8] Recently, a more general method using a halide-

[5] For a study of the stability of common organolithium reagents, see: Stanetty, P.; Mihovilovic, M. *J.Org. Chem*. **1997**, *62*, 1514.
[6] Boudier, A. ; Bromm, L. O. ; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.
[7] Ficini, J. ; Sarrade-Loucheur, G.; Normant, H. *Bull. Soc. Chim. Fr.* **1962**, 1219.
[8] a) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; b) Rieke, R. D. *Science* **1989**, *246*, 1260; c) Lee, J.; Vélarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

magnesium exchange reaction has been developed by Knochel for the preparation of polyfunctional aryl-, heteroaryl- or alkenylmagnesium compounds (Scheme 2).[9]



Functional group (FG) = Br, $CONR_2$, CN, CO_2Et, CO_2t-Bu;
E^+ = aldehyde, allyl bromide

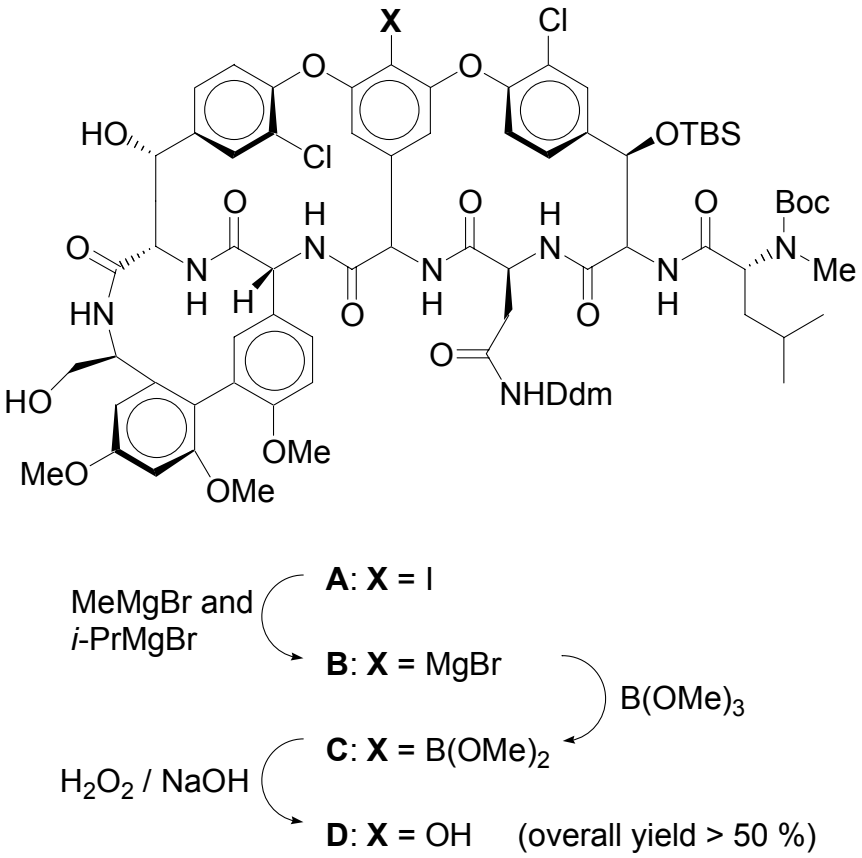


R = Me, 3-cyanobenzyl, N,N-dimethylcarbamoyl, 4-carbethoxybenzyl
E^+ = PhCHO, TosCN, PhSSPh

Scheme 2. Synthesis of functionalized Grignard reagents by low temperature iodine-magnesium exchange

Many other research groups have applied this methodology to the synthesis of complex natural product. In the course of the synthesis of the antibiotic vancomycin by Nicolaou et al., the iodine-magnesium exchange was used to perform a difficult oxidation reaction (Scheme 3).[10]

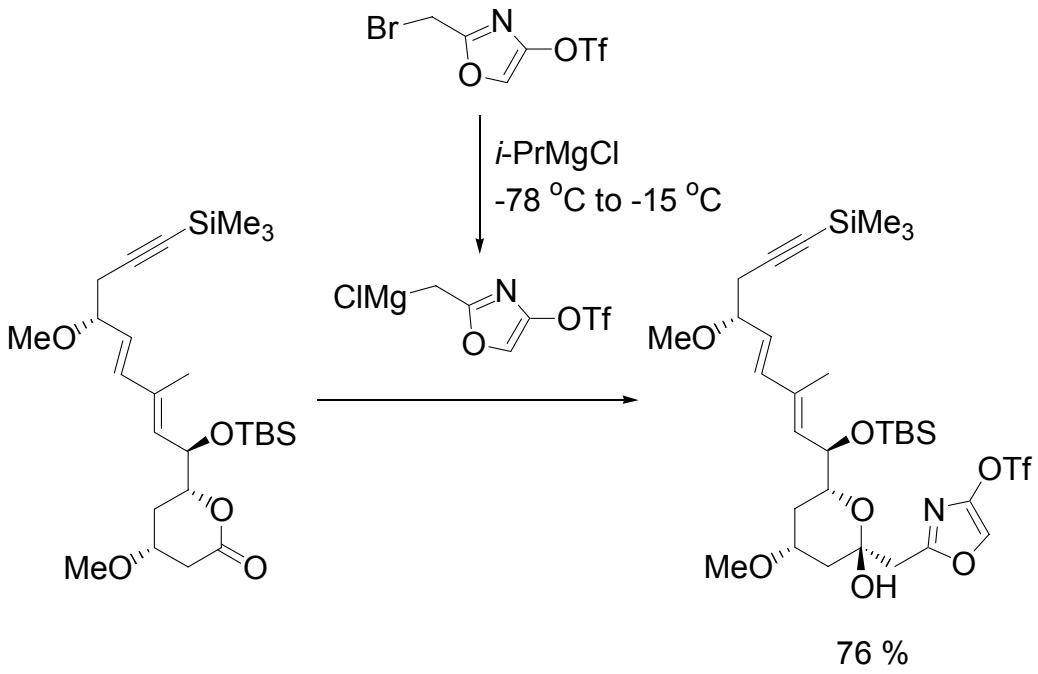
[9] a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.
[10] Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Kanbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem.* **1998**, *110*, 2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2717.



Scheme 3. Formation of a functionalized arylmagnesium compound using iodine-magnesium exchange reaction in the synthesis of vancomycin. Ddm = 4,4'-dimethoxydiphenyl methyl, TBS = *t*-butyldimethylsilyl.

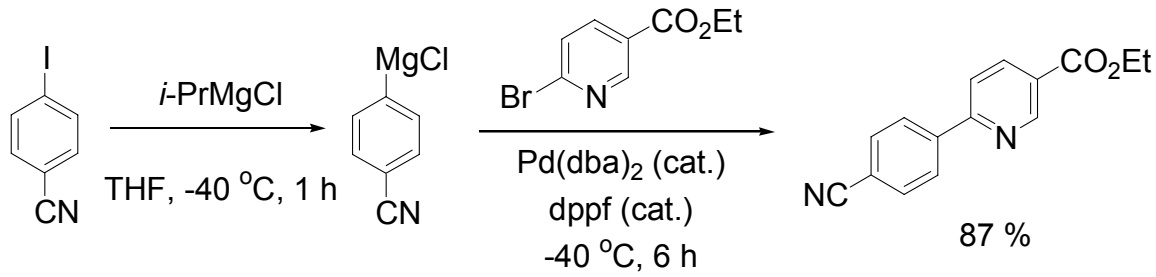
Another impressive use of a halogen-magnesium exchange reaction in a total synthesis of (+)-phorboxazole A has been provided recently by by Smith III et al. (Scheme 4).[11]

[11] Smith, III A. B.; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123,* 10942.



Scheme 4. Bromine-magnesium exchange in the synthesis of a (+)-phorboxazole A intermediate.

Based on this novel methodology, an array of applications of Grignard reagents in palladium-catalyzed[12] cross-coupling reactions has been developed (Scheme 5).



Scheme 5. Synthesis of functionalized pyridines by palladium-catalyzed cross-coupling of functionalized arylmagnesium chlorides.

The scope of organomagnesium reagents in organic synthesis can be expanded because the transmetallation from magnesium species to zinc species can be easily done through

[12] a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2000**, *56* ,1349; b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669; c) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

the addition of $ZnBr_2$ (as a solution in THF).[13] The organozinc reagents generated by this method can be used in cross-coupling reactions. This reaction is useful for the synthesis of complex molecules. For example, the palladium-catalyzed Negishi cross-coupling reaction has found application as a key step in the synthesis of the terpenoid mokupalide, where it exhibits high stereoselectivity (E:Z > 98: 2) (Figure 2, Scheme 6).

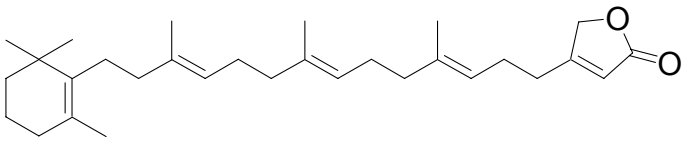
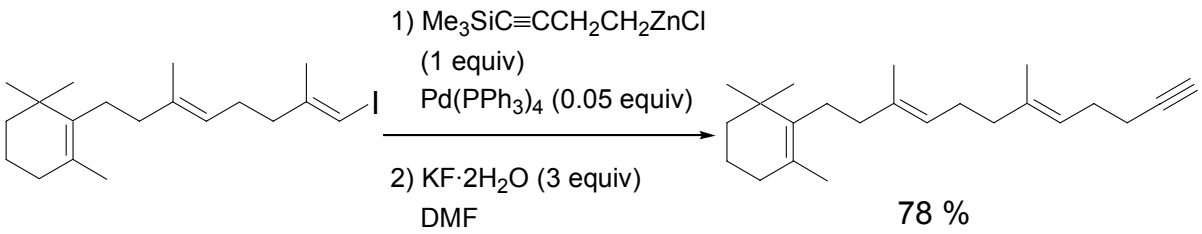


Figure 2. Natural product mokupalide



Scheme 6. A key step in the synthesis of the triterpenoid mokupalide is the Negishi cross-coupling reaction.

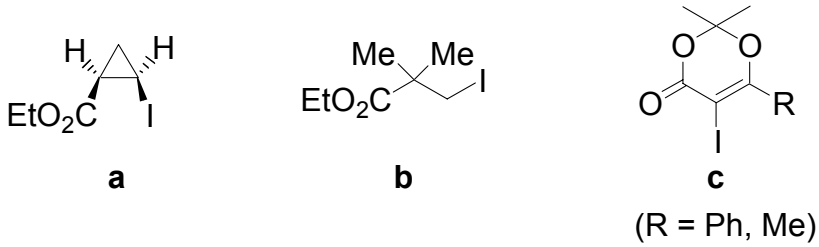
Thus, the access to new functionalized Grignard reagents will considerably expand the current scope of organomagnesium reagents in organic synthesis.

[13] Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201.

2. Objectives

The aim of this thesis is the preparation of new functionalized organomagnesium reagents, which are available using a low temperature halogen-magnesium exchange. [9]

In the first part, the preparation of novel functionalized cyclopropylmagnesium, alkylmagnesium and alkenylmagnesium reagents are studied, starting from the corresponding iodides **a**, **b** and **c** (Scheme 7).

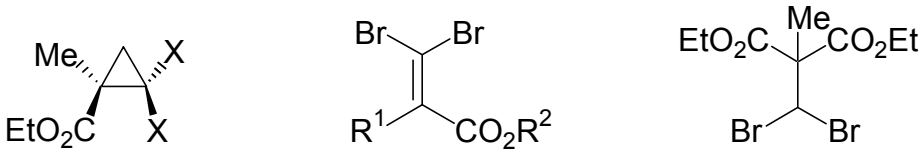


a **b** **c**

(R = Ph, Me)

Scheme 7. Starting materials for proposed iodine-magnesium exchange reactions.

Magnesium carbenoids are an important class of organometallic reagents.[14] Therefore, the possibility of a stereoselective preparation of new cyclopropyl, alkenyl and alkyl carbenoids bearing an ester group is examined in a second part starting from the corresponding dihalides **d**, **e**, **f**. The coordination of the magnesium atom through the oxygen of the carbonyl group is considered as being of importance in such systems (Scheme 8).



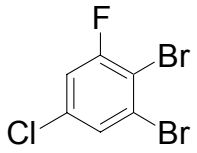
d **e** **f**

(X = I, Br) (R^1 = Ph, Me) (R^2 = Et, Me)

Scheme 8. Starting materials for halogen-magnesium exchange reactions for the generation of functionalized magnesium carbenoids.

[14] a) Hoffmann, R. W.; Kusche, A. *Chem. Ber*. **1994**, *127*, 1311; b) Satoh, T.; Koji, T.; Ota, H.; Somega, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557; c) Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem* **1998**, *110,* 869; *Angew. Chem. Int. Ed.* **1998,** *37,* 824; d) Hoffmann, R. W.; Kusche, A. *Chem. Ber*. **1994,** *127*, 1311.

In the last part of the thesis, the regioselective halogen-magnesium exchange on dibromoarene **g** is discussed, which is facilitated by inductive effects (Scheme 9).



g

Scheme 9. Proposed regioselective halogen-magnesium exchange reaction facilitated by inductive effects.

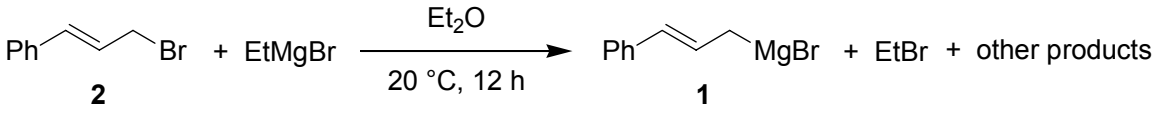
Results and discussion

1. Preparation of new functionalized organomagnesium reagents

1.1 Introduction

Grignard reagents are standard carbanionic reagents in organic synthesis and have found many applications.[15] However, the preparation and the scope of their application have been limited because of their low functional group tolerance. The use of activated magnesium for the low temperature synthesis of functionalized Grignard reagents has recently been reported by Rieke[8] but lacks of generality since most functional groups deactivate the surface of the magnesium and inhibit the reaction. Thus, the halogen-magnesium exchange provides an efficient alternative when performed at low temperature.

The first example of a bromine-magnesium exchange reaction was briefly demonstrated in 1931 by Prévost[16] who observed the formation of cinnamylmagnesium bromide **1** by reacting cinnamyl bromide **2** and ethylmagnesium bromide (Scheme 10).

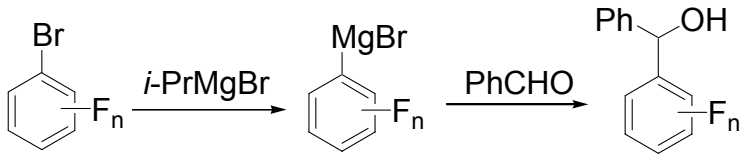


Scheme 10. First example of a halogen-magnesium exchange.

A similar transformation was performed by Urion[17] a few years later with the reaction of cyclohexyl bromide and ethylmagnesium bromide. Electron-withdrawing groups are often necessary for a fast bromine-magnesium exchange. For example, a significant rate difference is observed for the bromine-magnesium exchange in the case of fluorinated bromobenzene derivatives **3a-d** (Scheme 11).[18] Whereas bromopentafluorobenzene **3a**

[15] Silverman, G. S. and Rakita, P. E. *Handbook of Grignard-Reagents*, Marcel Dekker: New York, **1996**.
[16] Prevost, C. *Bull. Soc. Chim. Fr*. **1931**, 1372.
[17] Urion, E. *Comptes rendus* **1934**, *198*, 1244.
[18] Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

reacts with *i*-PrMgBr at -78 °C within 0.5 h, 1-bromo-2,4,5-trifluorobenzene **3b** requires a reaction temperature of -10 °C and a reaction time of 1 h.



3a-d **4a-d** **5a-d**

Substrates	T (°C) / t (h)	Yield
3a : 2,3,4,5,6-pentafluoro	-78 / 0.5	**5a** : 88 %
3b : 2,4,5-trifluoro	-10 / 1	**5b** : 85 %
3c : 2,5-difluoro	rt / 2	**5c** : 75 %
3d : 3-fluoro	rt/ 3	**5d** : 50 %

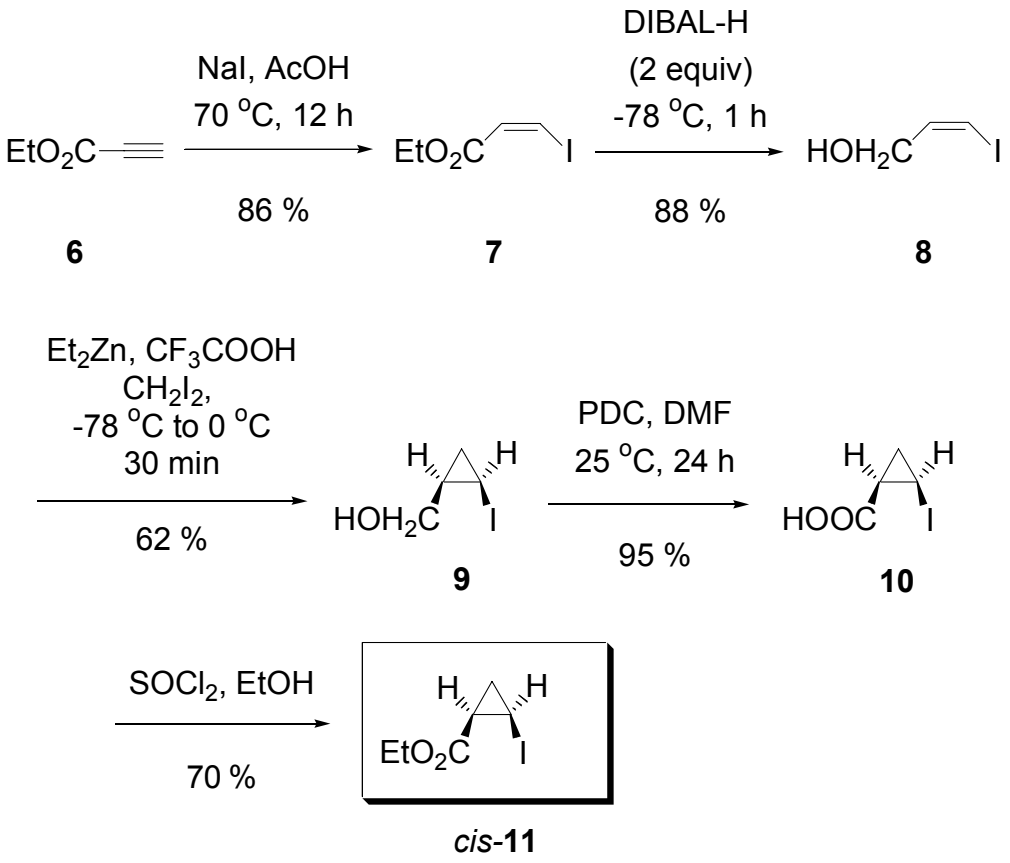
Scheme 11. Rate of the bromine-magnesium exchange.

The iodine-magnesium exchange is much faster and does not require such activating groups. Thus, an inactivated aryl iodide, such as 1-naphthyl iodide reacts at room temperature within 0.5 h using a stoichiometric amount of i-Pr_2Mg.[9]

1.2 Preparation of functionalized cyclopropylmagnesium reagents

The iodine-magnesium exchange is a fast reaction for aromatic iodides bearing electron-withdrawing groups. However it is considerably slower for alkyl iodides, where competitive substitution and elimination reactions can occur. Therefore, we have directed our first studies towards cyclopropanic molecules, where substitution and

elimination side reactions are less likely to occur.[19,20] The preparation of the starting material for the exchange reaction is shown in Scheme 12 and adapted from the literature.[21]



Scheme 12. Preparation of *cis*-2-iodocyclopropanecarboxylate.

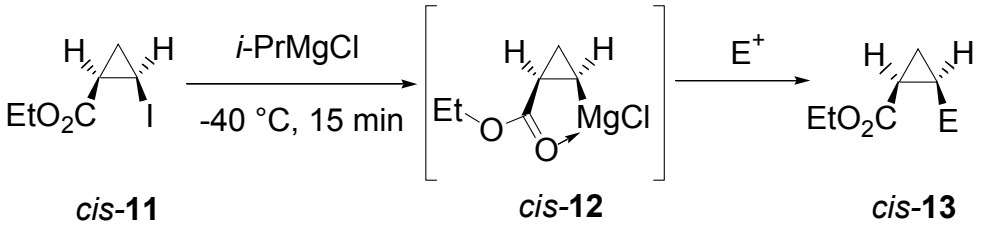
The *cis*-2-iodocyclopropanecarboxylate (*cis*-**11**) was treated with *i*-PrMgCl (1.1 equiv) in THF at -40 °C for 15 min affording the corresponding *cis*-cyclopropylmagnesium chloride (*cis*-**12**). This compound exhibits an excellent stability, most likely due to the presence of the ester group, which stabilizes through coordination to Mg as well as inductive effects. It can be trapped with retention of configuration with a range of

[19] a) Hamdouchi, C.; Topolski, M.; Goedken, V.; Walborsky, H. M. *J. Org. Chem*. **1993**, *58*, 3148; b) Boche, G.; Schneider, D. R. *Tetrahedron Lett*. **1978**, 2327; c) Boche, G.; Schneider, D.R.; Wintermayr, H. *J. Am. Chem. Soc*. **1980**, *102*, 5697; d) Boche, G. ; Walborsky, H. M. *Cyclopropane Derived Reactive Intermediates*, John Wiley and Sons, London, **1990**.

[20] a) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev*. **2000**, *100*, 93; b) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20; c) de Meijere, A. *Chem. Ber*. **1987**, *23*, 865; d) de Meijere, A. *Angew. Chem*. **1979**, *91*, 867; *Angew. Chem. Int. Ed.* **1979**, *18*, 809.

[21] a) Beruben, D; Marek, I; Normant, J.F; Platzert, N. *J. Org. Chem.* **1995**, *60,* 2488; b) Moss, R. A.;Wilk, B.; Krogh-Jespersen, K; Westbrook, J. D. *J. Am. Chem. Soc*. **1989**, *111*, 6729; c) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621.

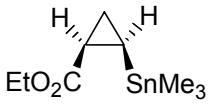
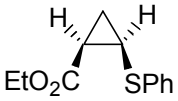
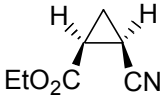
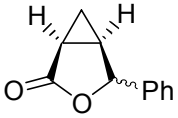
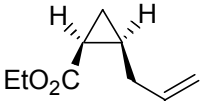
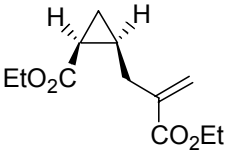
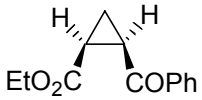
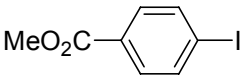
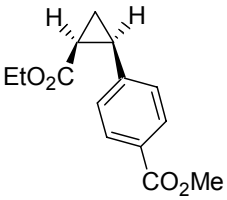
electrophiles either directly (reaction with Me_3SnCl, PhSSPh, tosyl cyanide,[22] aldehydes) or after transmetallation to copper (reaction with allylic bromides and chlorides)[23] or palladium (reaction with functionalized aryl iodides) leading to products of type *cis*-**13** (Scheme 13 and Table 1).



Scheme 13. Stereoselective preparation of a functionalized cyclopropylmagnesium reagent *via* an iodine-magnesium exchange.

In the case of the reaction with benzaldehyde, a spontaneous lactonization occurs leading to the lactone **13d** as a separable mixture of two diastereoisomers in the ratio of 65:35 (entry 4 of Table 1). In the presence of CuCN·2LiCl,[24] a smooth reaction proceeds with allyl bromide, ethyl (2-bromomethyl)acrylate[25] or benzoyl chloride (entries 5-7). A fast Negishi cross-coupling reaction[26] takes place after transmetallation to the corresponding zinc reagent with $ZnBr_2$. In the presence of *bis*-dibenzylideneacetonepalladium(0)[13] ($Pd(dba)_2$) and *tris*-*o*-furylphosphine[27] (tfp), an efficient cross-coupling takes place leading to the diester **13h** in 92 % yield (25 °C, 6 h, entry 8).

[22] Klement, I.; Lennick, K. ; Tucker, C. E.; Knochel, P. *Tetrahedron Lett*. **1993**, *34*, 4623.
[23] Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Organic Reactions* Ed. Overman, L. E. Vol. 58, **2001**, John Wiley and Sons.
[24] Knochel, P. ; Yeh, M. C. P. ; Berk, S. C. ; Talbert, J. *J. Org. Chem*. **1988**, *53*, 2390.
[25] Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
[26] a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
[27] a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585; b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem*. **1994**, *59*, 5905.

Entry	Electrophile	Product of type *cis*-**13**		Yield (%)[a]
1	Me_3SnCl		*cis*-**13a**	67
2	PhSSPh		*cis*-**13b**	52
3	TosCN		*cis*-**13c**	67
4	PhCHO		*cis*-**13d**	90[b]
5	allyl bromide		*cis*-**13e**	75[c]
6	ethyl (2-bromomethyl) acrylate		*cis*-**13f**	81[c]
7	PhCOCl		*cis*-**13g**	73[d]
8			*cis*-**13h**	92[e]

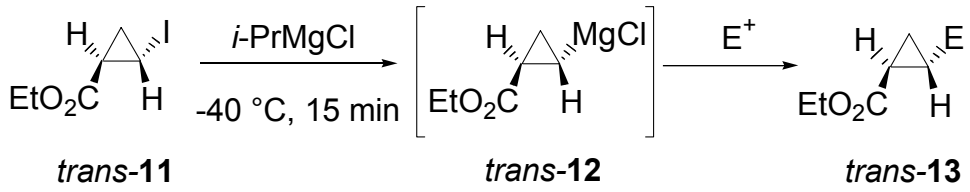
[a] Isolated yield of analytically pure product. [b] D.r. = 65:35. [c] Reaction performed in the presence of CuCN·2LiCl (10 mol %). [d] Reaction performed after a transmetallation to the corresponding copper reagent by adding CuCN·2LiCl (1.0 equiv). [e] Product obtained from Negishi cross-coupling reaction.

Table 1. Reactions of functionalized magnesium reagent *cis*-**11** with electrophiles leading to products of type *cis*-**13**.

Trans-iodoester of **11**[28] was also converted to the corresponding Grignard reagent *trans*-**12** after treatment with *i*-PrMgCl (1.1 equiv) in THF at -40 °C for 15 min

[28] See experimental section.

(Scheme 14). It can be trapped with retention of configuration with a range of electrophiles either directly (reaction with Me_3SnCl or PhCOPh) or after transmetallation to copper (reaction with allylic bromides) or palladium (reaction with functionalized aryl iodides) leading to products of type *trans*-**13** (Scheme 14 and Table 2).

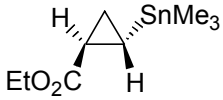
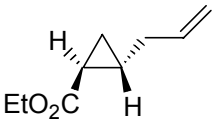
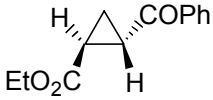
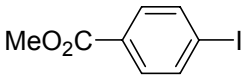
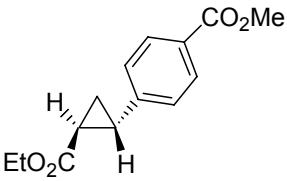
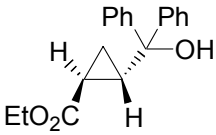


trans-**11** *trans*-**12** *trans*-**13**

Scheme 14. Stereoselective synthesis of a functionalized cyclopropylmagnesium reagent *via* an iodine-magnesium exchange.

No lactonization was observed during the reaction with benzophenone, and alcohol *trans*-**13i** was obtained (entry 5 of Table 2). This shows the configurational stability of the functionalized *trans*-isomer of compound **11**.

The stereochemistry of the products was determined by NOESY, ^{1}H and ^{13}C experiments.

Entry	Electrophile	Product of type *trans*-**13**		Yield (%)[a]
1	Me_3SnCl		*trans*-**13a**	85
2	allyl bromide		*trans*-**13e**	71[b]
3	PhCOCl		*trans*-**13g**	65[c]
4			*trans*-**13h**	85[d]
5	PhCOPh		*trans*-**13i**	66

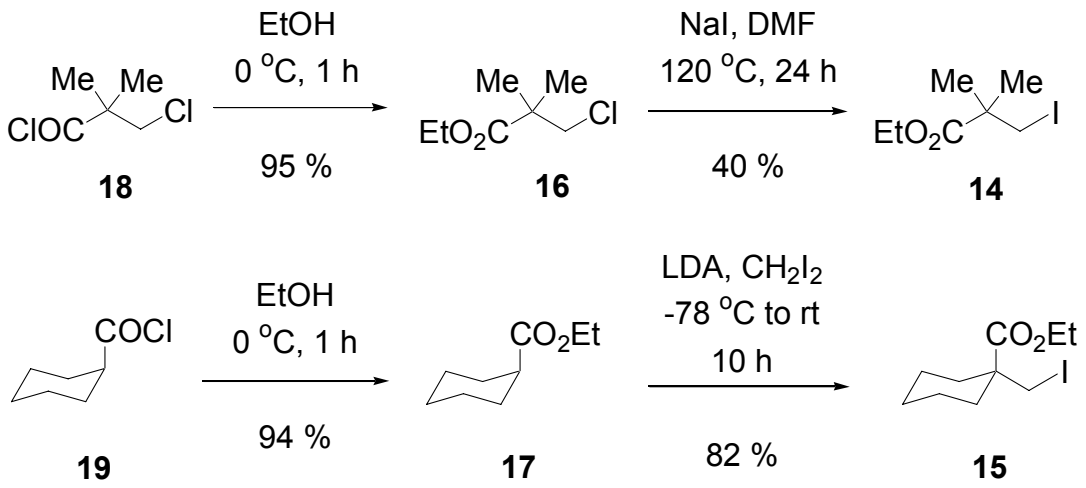
[a] Isolated yield of analytically pure product. [b] Reaction performed in the presence of CuCN·2LiCl (10 mol %). [c] Reaction performed after a transmetallation to the corresponding copper reagent by adding CuCN·2LiCl (1.0 equiv). [d] Product obtained from Negishi cross-coupling reaction.

Table 2. Reactions of functionalized magnesium reagents *trans*-**11** with electrophiles leading to products of type *trans*-**13**.

In summary, the formation of functionalized cyclopropyl organometallic reagents of type **12** by iodine-magnesium exchange reactions is stereoselective. Their reaction with electrophiles furnishes the expected product of type **13** with retention of configuration.

1.3 Preparation of new functionalized alkylmagnesium reagents

Although the preparation of polyfunctionalized alkylmagnesium reagents may be envisioned, only a few examples have been reported.[29] The difficulties arise from the higher reactivity of the resulting alkylmagnesium compounds relative to that of alkenyl-, aryl-, or heteroarylmagnesium species. As shown in Section 1.2, a range of functionalized cyclopropylmagnesium compounds can be prepared by iodine-magnesium exchange. In this Section, the preparation of functionalized alkylmagnesium species is studied. Alkyl iodides bearing an ester functionality **14** and **15** were choosen as starting materials (Scheme 15). Esters **16** and **17** were prepared starting from commercially available acyl chlorides **18** and **19** in 95 % and 94 % yield, respectively. The iodo-ester **14** was furnished in 40 % yield using Finkelstein reaction[30] with DMF as solvent and reflux at 120 °C for 24 h. The treatment of ester **17** with LDA in THF at -78 °C for 30 min follow by adding CH_2I_2 and warming up to rt for 10 h lead to the iodo-ester **15** in 82 % yield.[31]

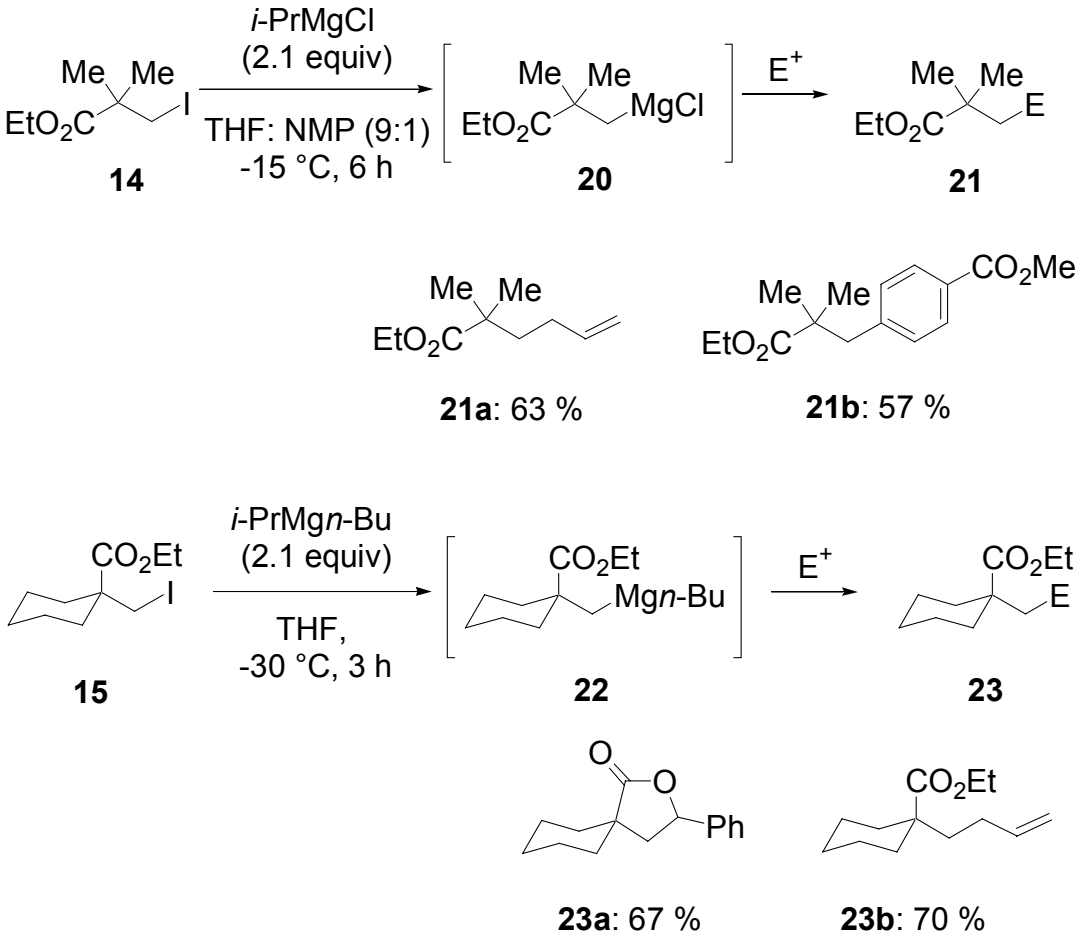


Scheme 15. Preparation of iodo-esters **14** and **15**.

The iodine-magnesium exchange reaction of ester **14** was complete after 6 h using 2.1 equiv of *i*-PrMgCl in a mixture of THF/NMP (9/1) (Scheme 16). In the presence of

[29] Inoue, A.; Shinokubo, H; Oshima, K. *Org. Lett*. **2000**, *2*, 651.
[30] Finkelstein, H. *Chem. Ber.* **1910**, *43* 1528.
[31] Komatsu, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *Heterocycles* **1985**, *23*, 677.

10 mol % CuCN·2LiCl, a smooth reaction proceeds with allyl bromide to give the allylated product **21a** in 63 % yield. A fast Negishi-cross-coupling reaction takes place after transmetallation to the corresponding zinc reagent with $ZnBr_2$. In the presence of $Pd(dba)_2$ and tfp, an efficient cross-coupling reaction is achieved leading to diester **23b** in 57 % yield. Trapping Grignard reagent **20** with other electrophiles, such as benzaldehyde, benzoyl chloride and benzophenone did not give expected products, only the hydrolysis product of **20** was observed.



Scheme 16. Preparation of alkylmagnesium reagents bearing an ester functionality.

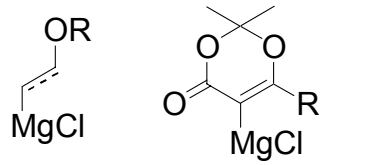
The exchange reaction using iodo-ester **15** did not proceed using *i*-PrMgCl. However, the application of 2 equiv of *i*-PrMg*n*-Bu in THF at -30 °C lead to the generation of Grignard reagent **22** after 3 h. By trapping reagent **22** with benzaldehyde, the lactone **23a** was formed in 67 % yield. Allylation of Grignard reagent **22** in the presence of catalytic amount of copper(I) gave ester **23b** in 70 % yield. Transmetallation of **22** to a

copper species and then acylation using benzoyl chloride failed to give the expected product, the hydrolysis product of Grignard reagent **22** was observed.

1.4 Preparation of functionalized alkenylmagnesium reagents bearing an oxygen function in the β-position

The synthesis of alkenylmagnesium halides bearing an oxygen functionality in the β-position, such as reagent **24**, is usually not possible since fast β-elimination can occur.[32] The preparation of such organometallic compounds is possible only in special cases.[33,34] Various functionalized alkenylmagnesium compounds[35] bearing an electrophilic group in the α-position can be readily prepared *via* a bromine-magnesium exchange at low temperature. It was anticipated that sensitive β-alkoxymagnesium compounds could be accessed *via* a fast iodine-magnesium exchange. β-Alkoxymagnesium derivatives of type **25** were chosen (Scheme 17). The corresponding 5-magnesiated-1,3-oxazin-4-one derivatives are not only interesting as examples of β-alkoxy-Grignard reagents. This functionalization of the position 5 of such heterocycles with electrophiles leads to products with a potential use as pharmaceutical and agrochemical intermediates.[36]

[32] a) Gurien, H. *J. Org. Chem*. **1963**, *28*, 878; b) Ficini, J.; Depezay J. C. *Bull. Soc. Chim. Fr*. **1966**, 3878; c) Mann, F. G.; Stewart, F. H. C. *J. Chem. Soc*. **1954**, 2826; d) Reichstein, T.; Baud, J. *Helv. Chim. Acta* **1937**, *20*, 892.
[33] For the behaviour of β-aminomagnesium reagents, see: a) Ficini, J.; Sarrade-Loucheaur, G.; Normant, H. *Bull. Soc. Chim. Fr.* **1962**, 1219; b) Ficini, J.; Depezay, J. C. *Bull. Soc. Chim. Fr*. **1966**, 3878; c) Calaza, M. I.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc*. **2001**, *123*, 2095; d) Foubelo, F.; Gutierrez, A.; Yus, M. *Synthesis* **1999**, 503; e) Schwerdtfeger, J.; Kolczewski, S.; Weber, B.; Fröhlich, R. ; Hoppe, D. *Synthesis* **1999**, 1573.
[34] a) Ficini, J.; Depezay, J. C. *Tetrahedron Lett*. **1969**, *54*, 4795; b) Rychnovsky, S. D.; Griesgraber, G.; Kim, J. *J. Am. Chem. Soc*. **1994**, *116*, 2621.
[35] Thibonnet, J.; Knochel, P. *Tetrahedron Lett*. **2000**, *41*, 3319.
[36] a) Iwaoka, T.; Murohashi, T.; Katagiri, N.; Sato, M.; Kaneko, C. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1393; b) Hayashizaki, K.; Usui, Y.; Tsutsumi, Y.; Go, A. *Jpn. Kokai Tokkyo Koho* **1995**, 11pp., CAN 123:256690.

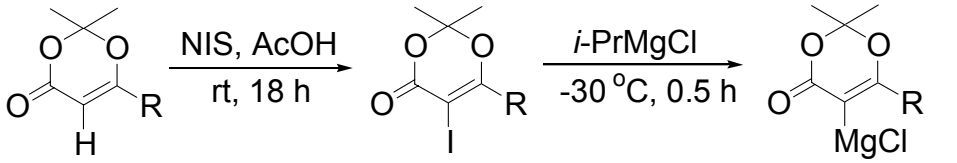


24

25a: R = Ph
25b: R = Me

Scheme 17. Alkenylmagnesium reagents bearing an oxygen functionality in the β-position.

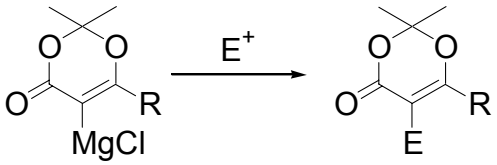
In order to synthesis the starting material, iodination of the readily available 1,3-dioxin-4-ones **26a/b** with *N*-iodosuccinimide (NIS) in acetic acid[36,37] furnishes the 5-iodo-1,3-dioxin-4-ones **27a/b** in 70-85 % yield. Treatment of **27a/b** with *i*-PrMgCl (1.1 equiv) in THF at –30 °C for 0.5 h results in a complete conversion to the corresponding Grignard reagents **25a/b** (Scheme 18).



26a: R = Ph
26b: R = Me

27a: R = Ph : 85 %
27b: R = Me : 70 %

25a: R = Ph
25b: R = Me



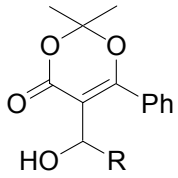
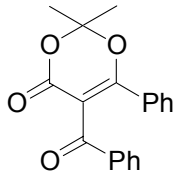
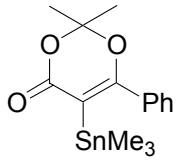
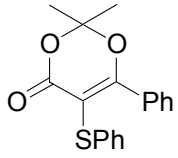
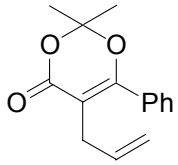
25a - b

28

Scheme 18. Preparation of alkenylmagnesium reagents bearing an oxygen function in the β-position.

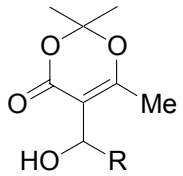
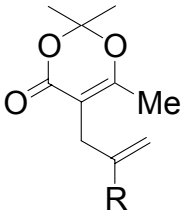
[37] Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bul.* **1983**, *31*, 1896.

Although the stability of **25a/b** was found to be limited, these *β*-alkoxy alkenylmagnesium species could be reacted with a range of electrophiles leading to products of type **28** (Scheme 18 and Table 3). Thus, the reaction of **25a** and **25b** with benzaldehyde or an aliphatic aldehyde such as cyclohexanecarbaldehyde furnishes the expected addition products **28a/b** and **28g**/**h** in 57-81 % yield (entries 1, 2, 7 and 8). The acylation of **25a** is best performed by converting the Grignard reagent **25a** to the corresponding copper reagent by transmetallation with the THF-soluble copper salt[24] CuCN·2LiCl (-30 °C; 0.5 h) followed by the addition of benzoyl chloride (-15 °C; 3 h). The unsaturated ketoester **28c** was isolated in 83 % yield (entry 3). The allylation of **25a/b** can be performed simply by adding a catalytic amount of CuCN·2LiCl (10 mol %) and then allyl bromide leading to the expected allylated products **28f, 28i** and **28j** in 65-81 % yield (entries 6, 9 and 10). Finally, electrophiles Me_3SnCl and PhSSPh react smoothly, furnishing the organotin-derivative **28d** (59 %; entry 4) and the thioether **28e,** respectively (68 %; entry 5).

Entry	Grignard reagent	Electrophile	Product of type **28**	Yield (%)[a]
1	**25a**	PhCHO	 **28a** : R = Ph	81
2	**25a**	*c*-HexCHO	**28b** : R = *c*-Hex	64
3	**25a**	PhCOCl	 **28c**	83[b]
4	**25a**	Me_3SnCl	 **28d**	59
5	**25a**	PhSSPh	 **28e**	68
6	**25a**	allyl bromide	 **28f**	81[c]

[a] Isolated yield of analytically pure product. [b] Reaction performed after a transmetallation to the corresponding copper reagent by adding CuCN·2LiCl (1.0 equiv). [c] Reaction performed in the presence of CuCN·2LiCl (10 mol %).

Table 3. 5-Substituted 1,3-dioxin-4-ones of type **28** obtained by reaction of Grignard reagent **25a/b** with various electrophiles.

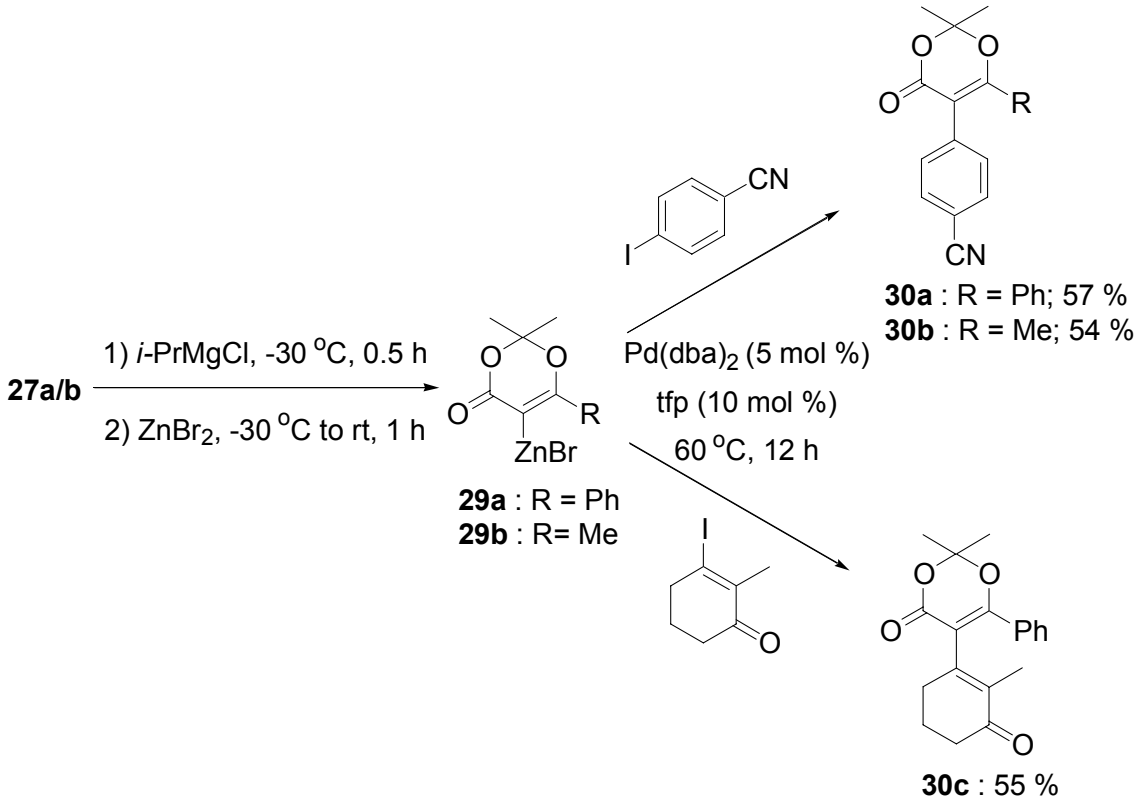
Entry	Grignard reagent	Electrophile	Product of type **28**	Yield (%)[a]
7	**25b**	PhCHO	 **28g** : R = Ph	76
8	**25b**	*c*-HexCHO	**28h** : R = *c*-Hex	57
9	**25b**	allyl bromide	 **28i** : R = H	77[b]
10	**25b**	ethyl (2-bromomethyl) acrylate	**28j** : R = CO_2Et	65[b]

[a] Isolated yield of analytically pure product. [b] Reaction performed in the presence of CuCN·2LiCl (10 mol %).

Table 3 (cont.). 5-Substituted 1,3-dioxin-4-ones of type **28** obtained by the reaction of the Grignard reagent **25a/b** with various electrophiles.

A palladium(0)-catalyzed cross-coupling[26] with aryl or alkenyl iodides is accomplished by transmetallation of the sensitive organomagnesium derivatives **25a/b** to the corresponding organozinc species **29a/b** by adding $ZnBr_2$ (1.0 equiv). In the presence of $Pd(dba)_2$ (5 mol %) and tfp (10 mol %), the cross-coupling products **30a-c** are isolated in acceptable yields (60 °C; 12 h; 54-57 %). Remarkably, the *β*-alkoxy-organozinc reagents **29** do not significantly undergo an elimination reaction at 60 °C (12 h reaction time) showing that the elimination rate depends strongly on the ionic character of the carbon-metal bond[38] (Scheme 19).

[38] Knochel, P.; Perea Almena, J. J.; Jones**,** P. *Tetrahedron,* **1998,** *54***,** 8275.

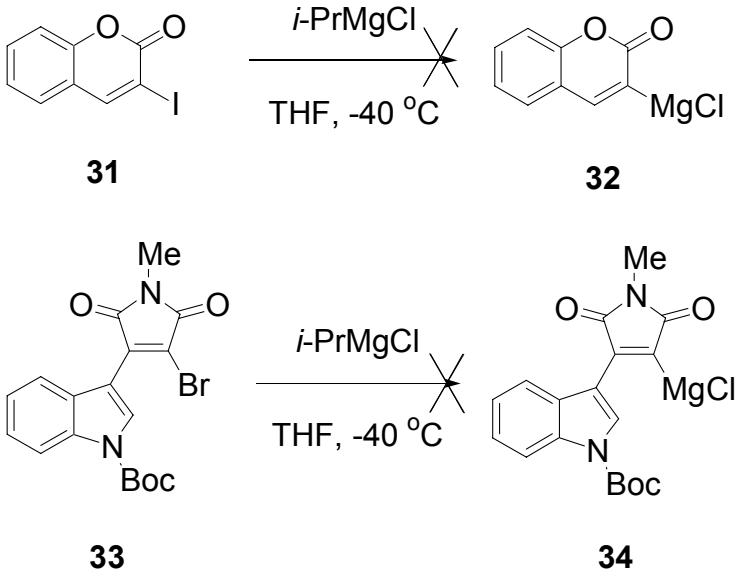


Scheme 19. Transmetallation and Negishi cross-coupling of the organomagnesium species type **25a/b**.

In summary, it was shown that the mild reaction conditions required for the iodine-magnesium exchange allows the generation of a *β*-alkoxy alkenylmagnesium derivative, which is sufficiently stable at low temperature (-30 °C) to react with aldehydes. A transmetallation to copper provides the corresponding copper reagents, which can be smoothly acylated or allylated. Finally, by transmetallation to organozinc species, very stable *β*-alkoxyalkenylzinc reagent are obtained, which undergo Negishi cross-coupling reactions at 60 °C in satisfactory yields.

1.5 Attempts to prepare new functionalized alkenylmagnesium reagents

Attempts to generate new functionalized alkenylmagnesium reagents using halogen-magnesium exchange reaction failed. As shown in Scheme 20, the exchange reaction using 3-iodocoumarin **31** did not proceed even under a variety of reaction conditions (e.g. changing solvent to Et_2O or THF/NMP (9:1), using *i*-PrMg*n*-Bu[39] instead of *i*-PrMgCl).



31 **32**

33 **34**

Scheme 20. Attempts to prepare new functionalized alkenylmagnesium reagents.

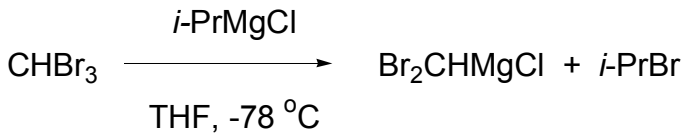
A negative result was also obtained using compound **33**. Instead of an exchange reaction, addition of the Grignard reagent to the carbonyl group occured.

[39] For more detailed information, see the experimental section

2. Preparation and reaction of functionalized magnesium carbenoids

2.1 Introduction

The preparation of a magnesium carbenoid was first demonstrated by Villiéras using a halogen-magnesium exchange reaction under mild conditions (Scheme 21).[40]

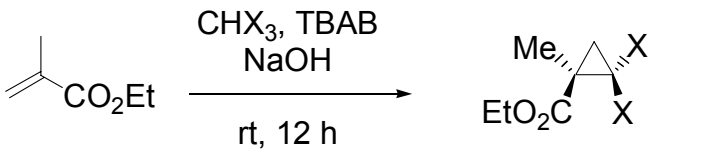


Scheme 21. Low temperature carbenoid preparation by bromine-magnesium exchange reaction.

Since magnesium carbenoids are an important class of reagents,[14] the formation of such carbenoids[41] bearing an ester function is examined.

2.2 Preparation of functionalized cyclopropyl carbenoids

The synthesis of the starting materials for the exchange reactions was accomplished using phase-transfer catalyzed cyclopropanation reaction, shown in Scheme 22.[42]

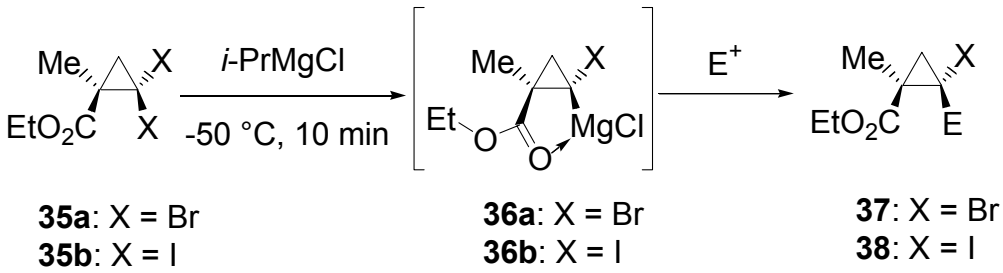


35a: X = Br, 46 %
35b: X = I, 30 %

Scheme 22. Preparation of dibromocyclopropanecarboxylic acid ethyl ester **35a/b**.

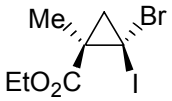
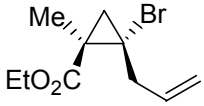
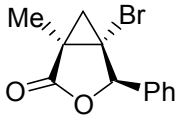
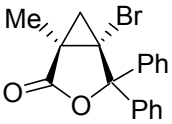
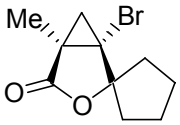
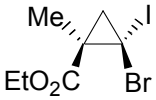
[40] Villiéras, J. *Bull. Soc. Chim. Fr*. **1967**, 1520.
[41] Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820.
[42] a) Baird, M. S.; Baxter, A. G. W. *J. Chem. Soc. Perkin 1* **1979**, 2317; b) Baird, M.S.; Gerrard, M. E. *J. Chem. Res. (S)* **1986**, 114.

The dibromocyclopropanecarboxylic acid ethyl ester (**35a**) was treated with *i*-PrMgCl (1.1 equiv) in THF, resulting in the formation of a 65:35 mixture of diastereomeric carbenoids as indicated by quenching experiments with electrophiles. The major diastereoisomer was Grignard reagent **36a**. The ratio of diastereomers did not significantly change under the reaction condition. However, by performing the bromine-magnesium exchange in Et_2O (-50 °C, 10 min), a completely stereoselective exchange was observed resulting in the formation of the *cis*-magnesium carbenoid **36a** (d.r. > 99:1). This carbenoid can be stereoselectively trapped by several electrophiles (Scheme 23 and Table 4).



Scheme 23. Stereoselective preparation of cyclopropylmagnesium carbenoids.

Thus, the reaction of ester-substituted carbenoid **36a** with iodine furnishes stereoselectively the iodobromocyclopropane **37a** in 85 % yield (entry 1). Similarly, quenching of **36a** with allyl bromide, furnishes the expected allylated product **37b** in 64 % yield. The reaction of **36a** with various aldehydes or ketones proceeds readily and leads to the lactones **37c-e** in 60-61 % yield. The reaction with benzaldehyde was highly diastereoselective (d.r. = 92:8) leading to product **37c** in 60 % yield. (major isomer depicted in entry 3). Its molecular structure was verified by X-ray analysis (Figure 3).

Entry	Grignard reagent	Electrophile	Product of type **37** and **38**		Yield (%)[a]
1	**36a**	I_2		**37a**	85
2	**36a**	allyl bromide		**37b**	64[b]
3	**36a**	PhCHO		**37c**	60[c]
4	**36a**	Ph_2CO		**37d**	61
5	**36a**	C_5H_8O		**37e**	61
6	**36b**	$(BrCl_2C)_2$		**38a**	80

[a] Isolated yield of analytically pure product. [b] Reaction performed in the presence of CuCN·2LiCl (10 mol %). [c] D.r. = 92:8.

Table 4. Reactions of functionalized magnesium carbenoid type **36** with electrophiles.

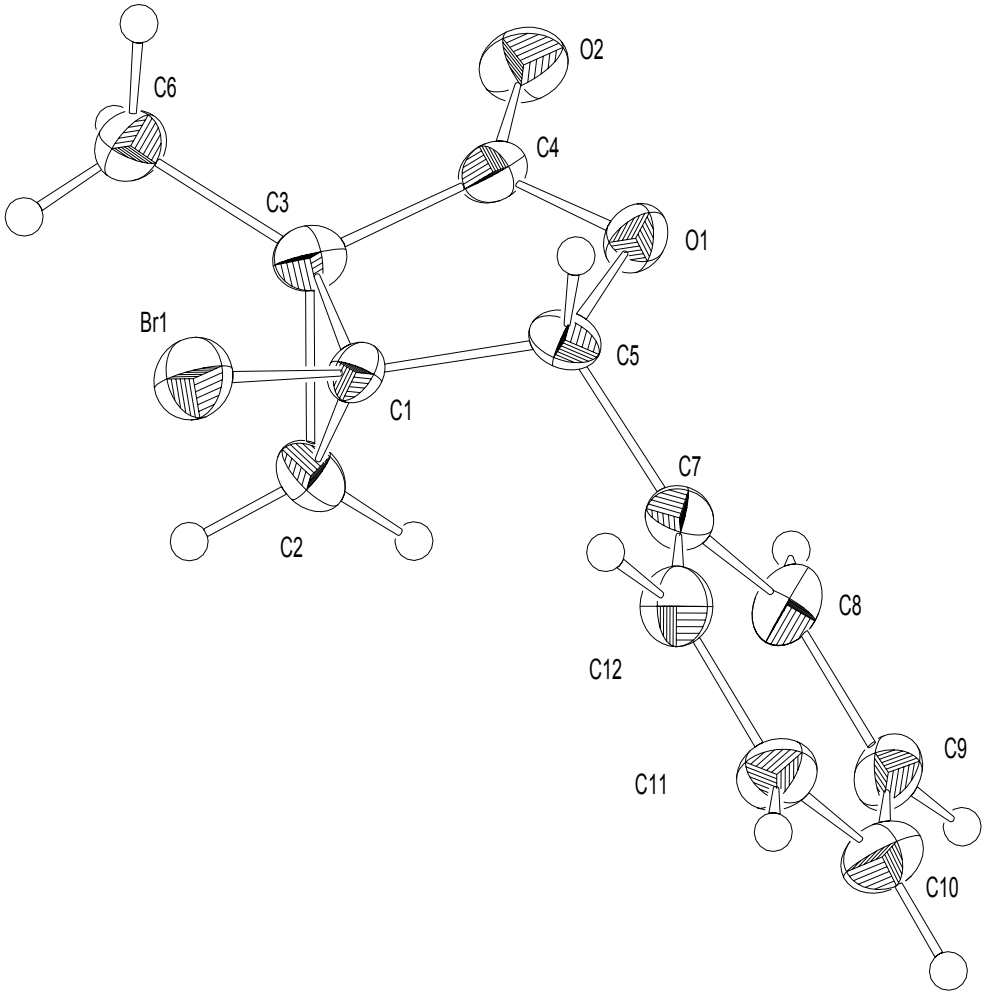
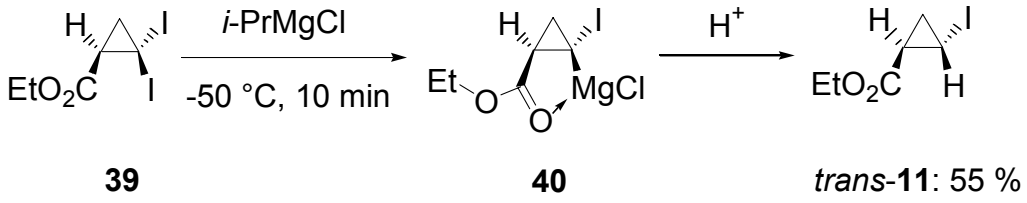


Figure 3. Crystal structure of the major isomer of compound **37c**

Interestingly, the reaction of carbenoid **36b** generated by the reaction of *i*-PrMgCl from the diiodocyclopropanecarboxylic acid ethyl ester (**35b**) at -50 °C in Et_2O is also highly diastereoselective. After trapping the carbenoid **36b** with 1,2-dibromotetrachloroethane, the diastereomeric iodobromocyclopropane **38a** is formed in 80 % yield (compare entries 1 and 6). *Trans*-iodo **11**, the starting material in Section 1.2, was obtained by this method (Scheme 24).

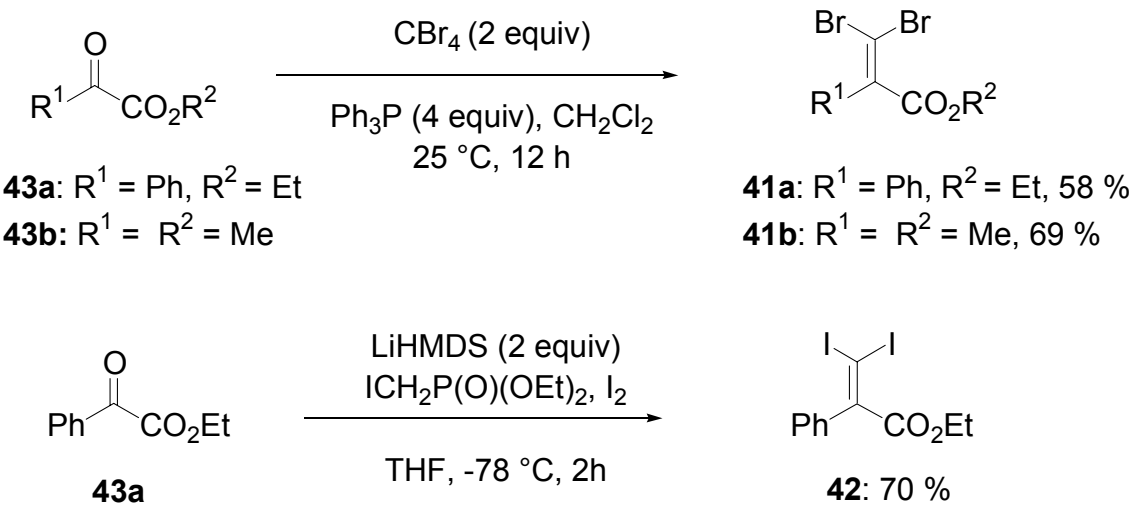


Scheme 24. Preparation of *trans*-iodo **11** using an iodine-magnesium exchange reaction.

2.3 Preparation of alkenyl carbenoids

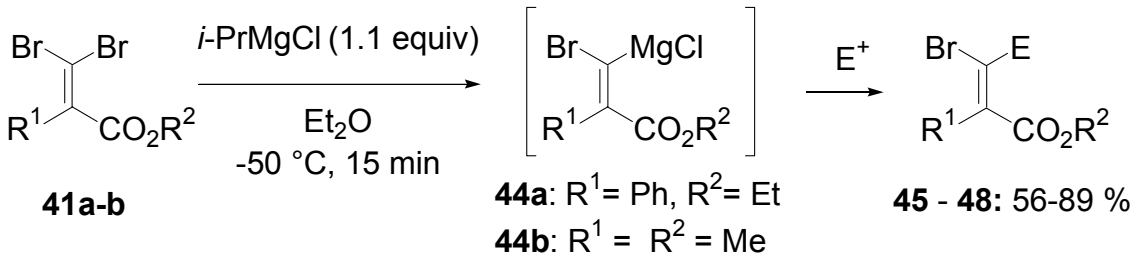
Functionalized carbenoids are potentially important intermediates for organic synthesis.[43] A new stereoselective synthesis of unsaturated lactones and esters starting from dibromoesters **41a/b** and the diiodoester **42** (Scheme 25) was reported. Thus, the reaction of ethyl phenylglyoxylate **43a** or methyl pyruvate **43b** with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 (12 h, 25 °C) furnished the corresponding dibromoester **41a** and **41b** in 58 % and 69 % yield, respectively.[44] The diiodoester **42** was also prepared from ethyl phenylglyoxylate (**43a**) using a method developed by Duhamel.[45] Thus, the treatment of **43a** with an *in situ* generated lithiated diiodophosphonate at –78 °C furnished the expected product **42** in 70 % yield (Scheme 25).

[43] (a) Mueller, A., Marsch, M.; Harms, K.; Lohrenz, J. C. W.; Boche, G. *Angew. Chem*. **1996**, *108*, 1639; *Angew. Chem. Int. Ed.* **1996**, *35*, 1518. (b) Hoffmann, R.W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049. (c) Villieras, J.; Kirschleger, B.; Tarhouni, R.; Rambaud, M. *Bull. Soc. Chim. Fr*. **1986**, *3*, 470.
[44] Colson, P.J.; Hegedus, L.S. *J. Org. Chem.* **1993**, *58*, 5918.
[45] (a) Bonnet, B.; Le Gallic, Y.; Plé, G; Duhamel, L. *Synthesis* **1993**, 1071. (b) Larock, R.C.; Doty, M.J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

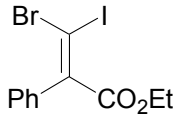
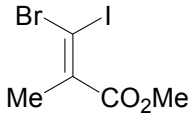
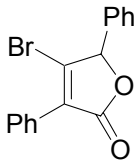
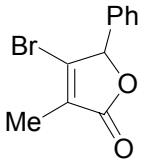
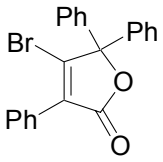
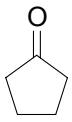
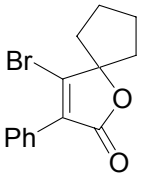


Scheme 25. Preparation of dibromoesters **41a/b** and diiodoester **42**.

The reaction of **41a/b** with *i*-PrMgCl (1.1 equiv) in Et_2O at –50 °C for 15 min provided the expected magnesium carbenoids **44a/b** which can be reacted with several electrophiles. Reaction with iodine, benzaldehyde, benzophenone or cyclopentanone providing the corresponding unsaturated esters **45a/b** in 89 % yield or in the case of reaction with carbonyl compounds to the unsaturated bromolactones **46a/b**, **47** and **48** in 56 – 79 % yield (Scheme 26 and Table 5).



Scheme 26. Generation and reaction of magnesium carbenoids **44a/b**.

Entry	Grignard reagent	Electrophile	Product of type **45 - 48**		Yield (%)[a]
1	**44a**	I_2		**45a**	89
2	**44b**	I_2		**45b**	89
3	**44a**	PhCHO		**46a**	56
4	**44b**	PhCHO		**46b**	56
5	**44a**	PhCOPh		**47**	79
6	**44a**			**48**	71

[a]Isolated yield of analytically pure product;

Table 5. Reaction of functionalized magnesium carbenoid type **44** with electrophiles.

The crystal structure of product **46a**, highlighting the lactone ring is shown in Figure 4. The bond length between C1 and C2 is shorter than the bond length between C1 and C4, which clearly indicate the existing of the double bond between C1 and C2.[46]

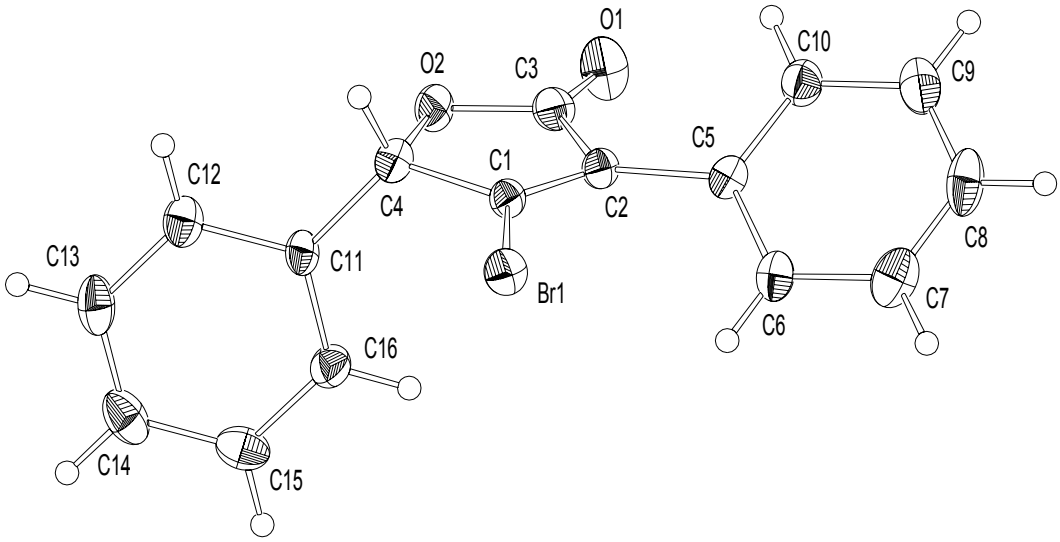
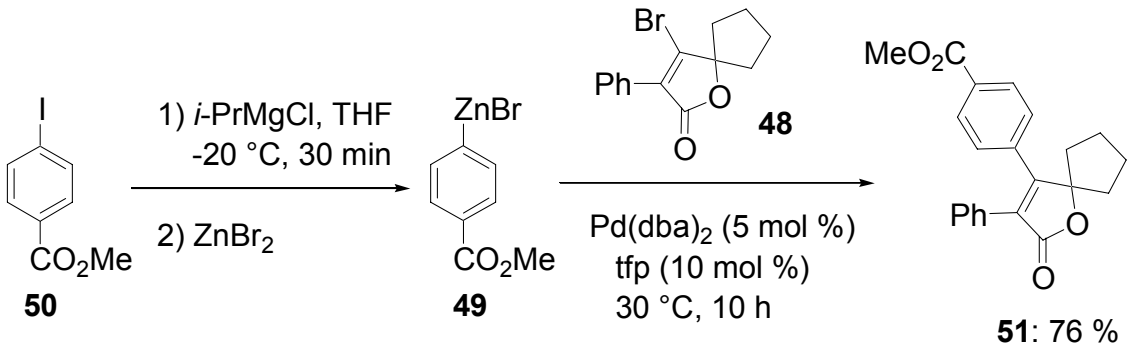


Figure 4. Crystal structure of compound **46a.**

To extend the scope to the synthesis of more complex, polyfunctional molecules, the bromolactone **48** can be further functionalized using a Negishi cross-coupling reaction as an example. The functionalized arylzinc bromide **49** was prepared from methyl 4-iodobenzoate **50** *via* an iodine-magnesium exchange and a transmetallation with zinc bromide. The reaction of bromide **48** with this arylzinc bromide **49** furnished, in the presence of catalytic amounts of $Pd(dba)_2$ (5 mol %) and tfp (10 mol %) at 30 °C after a reaction time of 10 h, the desired cross-coupling product **51** in 76 % yield (Scheme 27).

[46] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907.

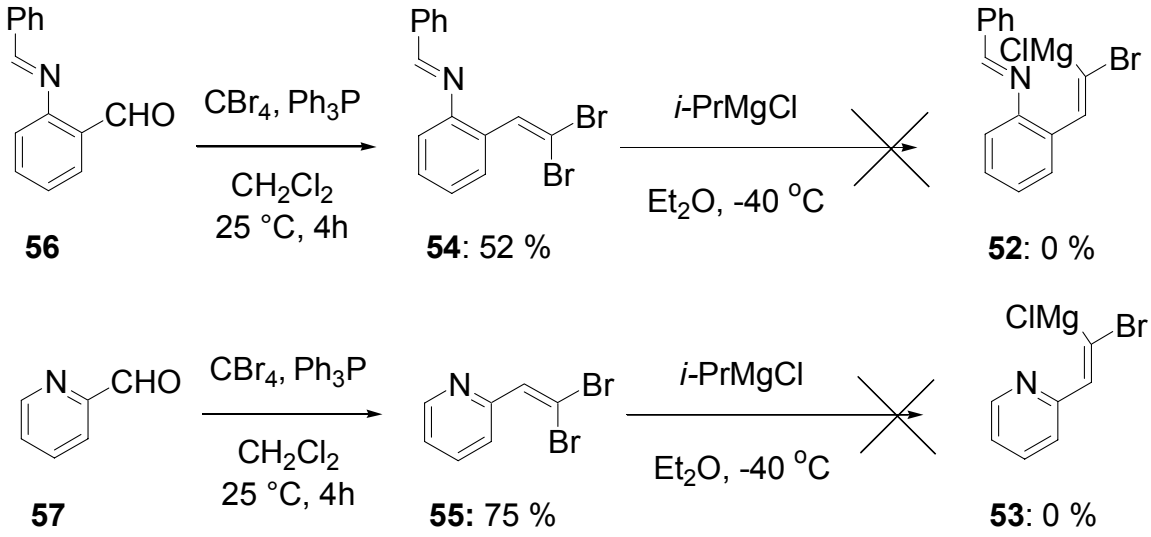


Scheme 27. Negishi cross-coupling reaction leading to the unsaturated lactone **51.**

Attempts to generate organometallic species from bromide **48** through bromine-metal exchange reactions failed with *i*-PrMgCl as well as with cuprate Bu_2CuLi.

2.4 Attempts to prepare alkenyl carbenoids

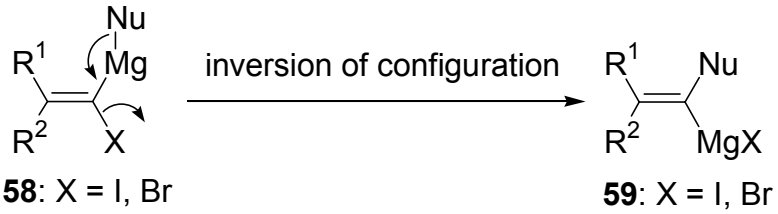
An extension of the selective halogen magnesium exchange reaction to prepare further new alkenyl carbenoids was not successful in the case of imine **52** and pyridine derivative **53**. Because of the starting materials dibromo **54** and **55** exist in the form as shown in Scheme 28, the expected chelation of magnesium by the nitrogen atom could not assist a reaction with the Grignard reagent.



Scheme 28. Attempt to preparare alkenyl carbenoids.

2.5 Preparation of alkenyl Grignard reagents from alkenyl carbenoids

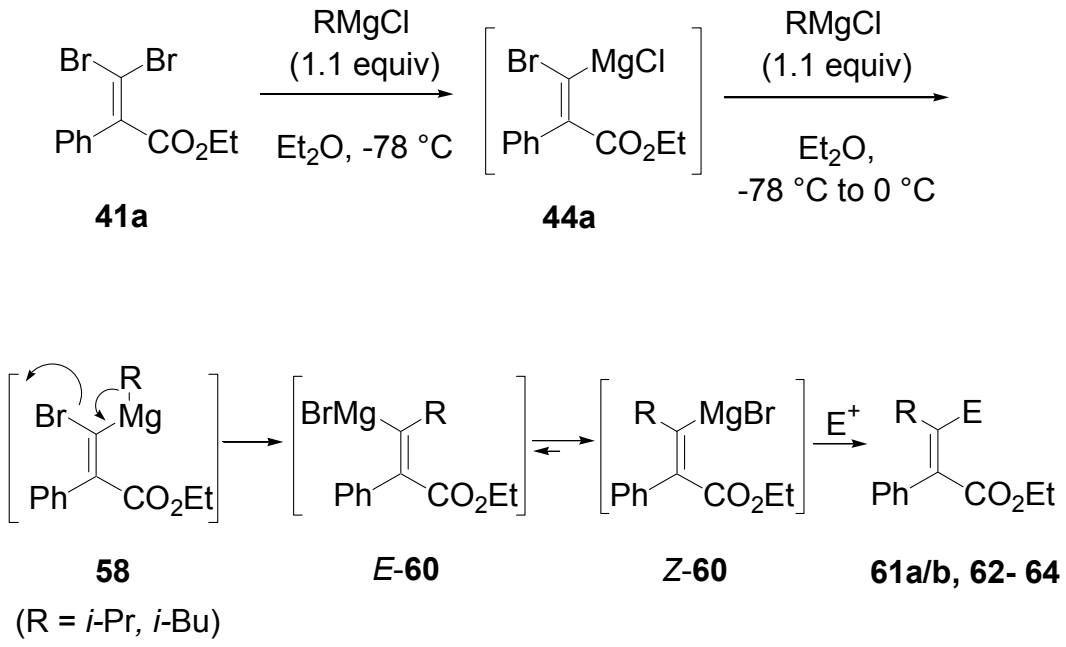
The electrophilic reactivity of magnesium carbenoids was also examined. It is well known in the literature that a 1,2-migration can occur when a carbenoid species of type **58** are bearing a nucleophilic substituent (Nu). This leads to products of type **59** with inversion of configuration at the carbenoid center (Scheme 29).[47]



Scheme 29. 1,2-Migration of magnesium carbenoids.

Herein, related 1,2-migration reactions proceeding formally with retention of configuration are reported. Thus, the reaction of dibromoester **41a** with two equivalents of an alkylmagnesium reagent, such as *i*-PrMgCl or *i*-BuMgCl in Et_2O provided after reaction with an electrophile the products **61a/b**, **62-64** in which formally the 1,2-migration has occurred with retention of configuration. The isolated yields of the products are good (56 – 73 %) and the stereoselectivity of the resulting open-chain unsaturated esters is excellent. For the allylated products **61a/b**, the *E/Z* ratio is > 1:99 (Scheme 30).

[47] (a) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc*. **1988***, 110*, 646; (b) Miller, J. A. *J. Org. Chem.* **1989***, 54*, 998; (c) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6039; (d) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc*. **1989***, 111*, 6474; (e) Knochel, P.; Rao, A. S. *J. Am. Chem. Soc*. **1990***, 112*, 6146; (f) Harada, T.; Kotani, Y.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1573; (g) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993***, 58*, 4897; (h) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem.* **2001**, *113*, 812; *Angew. Chem. Int. Ed. Engl*. **2001**, *40*, 790; (i) Kurahashi, T.; Hata, T.; Masai, H.; Kitagawa, H.; Shimizu, M.; Hiyama, T. *Tetrahedron* **2002**, *58*, 6381.

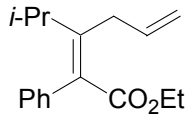
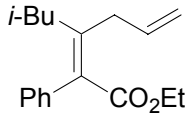
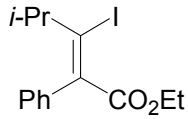
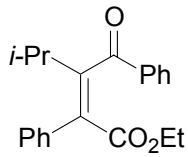
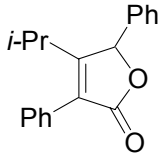


Scheme 30. 1,2-Migration of magnesium carbenoid with formal retention of configuration.

The retention of configuration of the 1,2-migration is best explained by a 1,2-migration occurring with an inversion followed by an isomerization. This isomerization is driven by a potential coordination through the oxygen atom of the ester group. Thus, the bromine-magnesium exchange of **41a** might proceed as shown in Scheme 30, leading to the corresponding magnesium carbenoid **44a** which transfers an alkyl group (*i*-Pr or *i*-Bu). This provides the intermediate type **58** and subsequently *E*-magnesium reagent *E*-**60**. Under the reaction conditions (–78 °C to 0 °C), the *E*-alkenylmagnesium compound *E*-**60** isomerizes to the thermodynamically more stable *Z*-alkenylmagnesium species *Z*-**60,** which is stabilized by additional coordination of the magnesium atom through the oxygen atom of the ester functionality.

Thus, reaction of *Z*-**60** with electrophiles like iodine, benzaldehyde provides the corresponding unsaturated ester and lactone **62** and **64** in 82 % and 56 % yield, respectively (entries 3 and 5, Table 6). The allylation of *Z*-**60** can be performed by adding a catalytic amount of CuCN·2LiCl (10 mol %), leading to the expected allylated products **61a/b** in 75 and 73 % yield, respectively (entries 1 and 2). The acylation of *Z*-**60** is best performed by converting the Grignard reagent *Z*-**60** to the corresponding copper reagent by transmetallation with CuCN·2LiCl[24] (-30 °C; 0.5 h) followed by the

addition of benzoyl chloride (-15 °C; 3 h), leading to the unsaturated ketoester **63** in 61 % yield (entry 4).

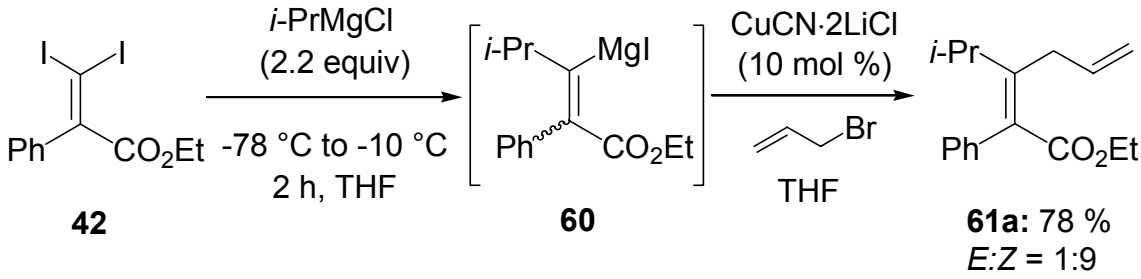
Entry	Electrophile	Product of type **61** - **64**		Yield (%)[a]
1	allyl bromide		**61a**	75[b]
2	allyl bromide		**61b**	73[b]
3	I_2		**62**	82
4	PhCOCl		**63**	61[c]
5	PhCHO		**64**	56

[a] Isolated yield of analytically pure product. [b] Reaction performed in the presence of CuCN·2LiCl (10 mol %). [c] Reaction performed after a transmetallation to the corresponding copper reagent by adding CuCN·2LiCl (1.0 equiv).

Table 6. Reaction of functionalized alkenylmagnesium species **60** with electrophiles.

Interestingly, by performing the reaction of **42** in THF, which is a stronger donor solvent compared to Et_2O, a mixture of diastereomers (*E/Z* = 1:9) was obtained after an allylation reaction performed with allyl bromide (1.1 equiv) in the presence of catalytic amounts of CuCN·2LiCl[10] (Scheme 31). A less selective reaction is observed because

Grignard species in THF solution have less open coordination sites to get coordinated by oxygen atom of the carbonyl group of the ester function.[48]



Scheme 31. Copper-catalyzed allylation in THF.

In summary, it was shown that the bromine-magnesium exchange reaction on β-dibromoesters of type **41**, in the presence of two equivalents of an alkylmagnesium reagent, allows the elaboration of steroselectively functionalized α,β-unsaturated esters and lactones.

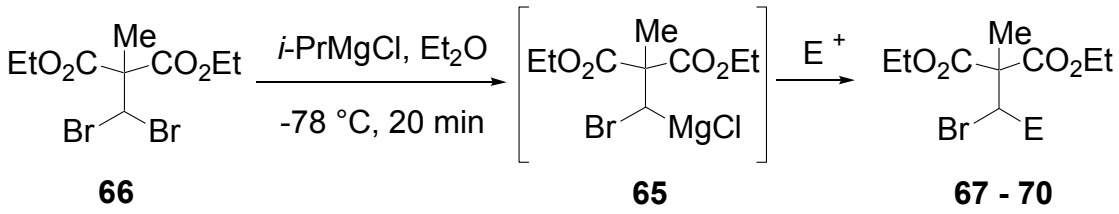
2.6 Preparation of functionalized alkyl carbenoids.

The preparation of non-functionalized alkyl carbenoids was reported.[49] Since the ester functionality can potentially coordinate the magnesium intermediate (Section 1.2), the formation of functionalized alkyl carbenoid of type **65** from dibromo diester **66** was studied.

Compound **66** was prepared according to literature starting from commercially available diethyl methyl malonate.[50]

The reaction of dibromide **66** with *i*-PrMgCl in Et_2O at – 78 °C for 20 min provided the expected magnesium carbenoids **65,** which can be trapped using several electrophiles, such as iodine, benzaldehyde or valeraldehyde (Scheme 32).

[48] Richey, H. G. (ed) *Grignard Reagents New Development,* Wiley, New York, **2000**.
[49] Hoffmann, R.W.; Knopff, O.; Kusche, A. *Angew. Chem.* **2000**, *112,* 1521; *Angew. Chem. Int. Ed.* **2000,** *39*, 1462.
[50] Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.

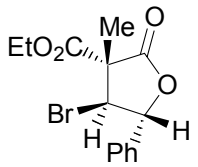
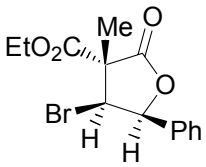
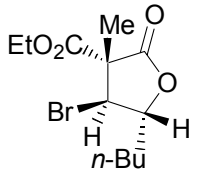
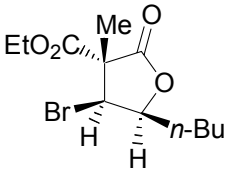
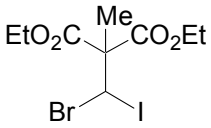
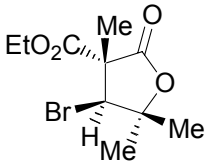


66 **65** **67 - 70**

Scheme 32. Generation and reaction of magnesium carbenoid **65**.

In the reaction of magnesium carbenoid **65** with carbonyl compounds, the major diastereoisomer of saturated bromolactones **67** and **68** were isolated in 55 – 65 % yield with a good diastereomeric excess. Only two diastereoisomers were detected by GC and NMR. The structures of the major and minor diastereoisomers were determined by NOESY NMR and are shown in entries 1 and 2 of Table 7.

When organomagnesium reagent **65** was reacted with iodine, compound **69** was isolated in 80 % yield (entry 3). When acetone was use as an electrophile, only one diastereoisomer of saturated bromolactone **70** was form in 60 % yield (entry 4). The absolute structure of **70** was determined by NOESY NMR.

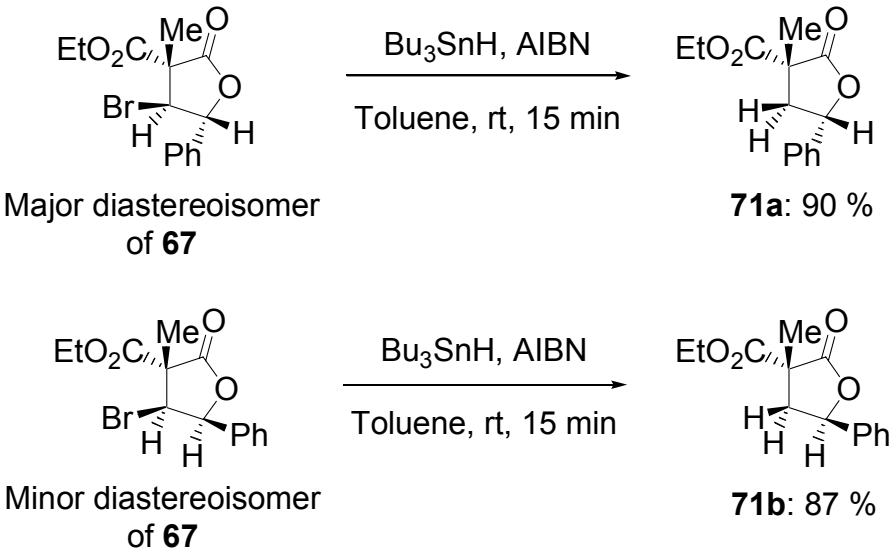
Entry	Electrophile	Product of type **67** - **70**			Yield (%)[a]	d.r.[b]
1	PhCHO	 Major diastereoisomer	 Minor diastereoisomer	**67**	65[c]	6:1
2	*n*-BuCHO	 Major diastereoisomer	 Minor diastereoisomer	**68**	55[c]	7:1
3	I_2			**69**	80	
4	Acetone			**70**	60	99:1

[a] Isolated yield of analytically pure product. [b] Determined by GC and NMR. [c] Isolated yield of major diastereoisomer.

Table 7. Reactions of functionalized magnesium carbenoid **65** with electrophiles.

To strongly confirm the stereochemistry of the lactone **67**, both major and minor diastereoisomers were debrominated using Bu_3SnH with catalytic amount of AIBN to give **71a/b**.[51] The absolute structure of **71a/b** were determined by NOESY NMR (Scheme 33).

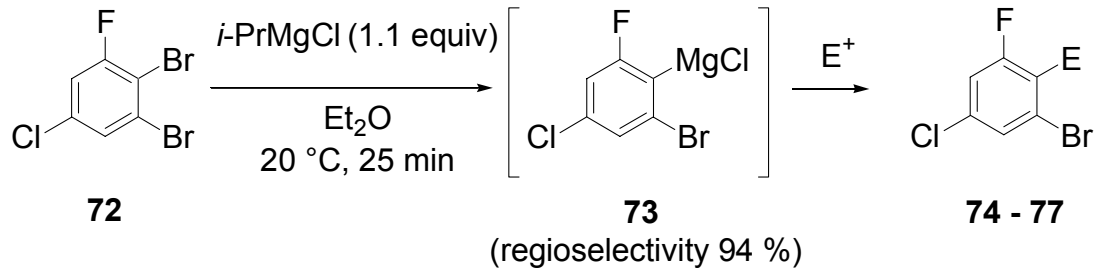
[51] Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson , G.; Lavallée, J.-F.; Slassi; A.; Jung, G.; Rancourt, J.; Durkin; K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166.



Scheme 33. Debromination of compound **67**.

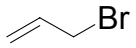
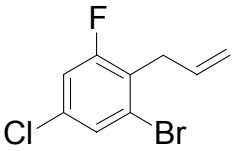
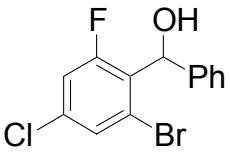
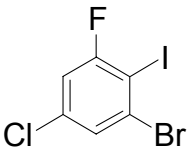
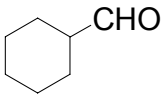
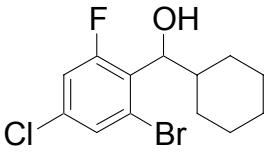
3. Selective bromine-magnesium exchange through inductive effect

In addition to assistance *via* chelation, inductive effects may be used for performing selective halogen-magnesium exchange reaction. The commercially available 1-fluoro-2,3-dibromo-5-chlorobenzene (**72**) was selected as substrate. It reacts in Et_2O with *i*-PrMgCl (20 °C, 25 min) with a good regioselectivity (94 %), providing the magnesium reagent **74** generated *via* a bromine-magnesium exchange reaction of the bromine in *ortho*-position to the fluoro-substituent (Scheme 34).



Scheme 34. Selective bromine-magnesium exchange through inductive effect.

The Grignard reagent **73** can be allylated in the presence of a catalytic amount of CuCN·2LiCl[24] leading to the allylbenzene derivative **74** in 85 % yield (entry 1, Table 8). Similarly, the reaction with benzaldehyde leads to the benzhydryl alcohol **75** in 62 % yield (entry 2). Interestingly, the trapping of Grignard reagent **73** with iodine furnishes the tetrahalobenzene (**76**) bearing four different halogen atoms in 87 % yield (entry 3). The reaction of the magnesium compound **73** with cyclohexanecarboxaldehyde leads to the alcohol **77** in 61 % yield (entry 4). Compounds **74** – **76** were obtained as a inseparable mixture of two isomers: The major isomer (94 %) were compounds **74** – **76**, and the minor isomers were the products generated through a bromine-magnesium exchange reaction with the bromine in *meta*-position to the fluoro-substituent. Only compound **77** was isolated as a single regioisomer.

Entry	Electrophile	Major isomer	Yield (%)[a]	Ratio of isomers
1		 **74**	85[b]	94:6
2	PhCHO	 **75**	62	94:6
3	I_2	 **76**	87	94:6
4		 **77**	61[c]	99:1

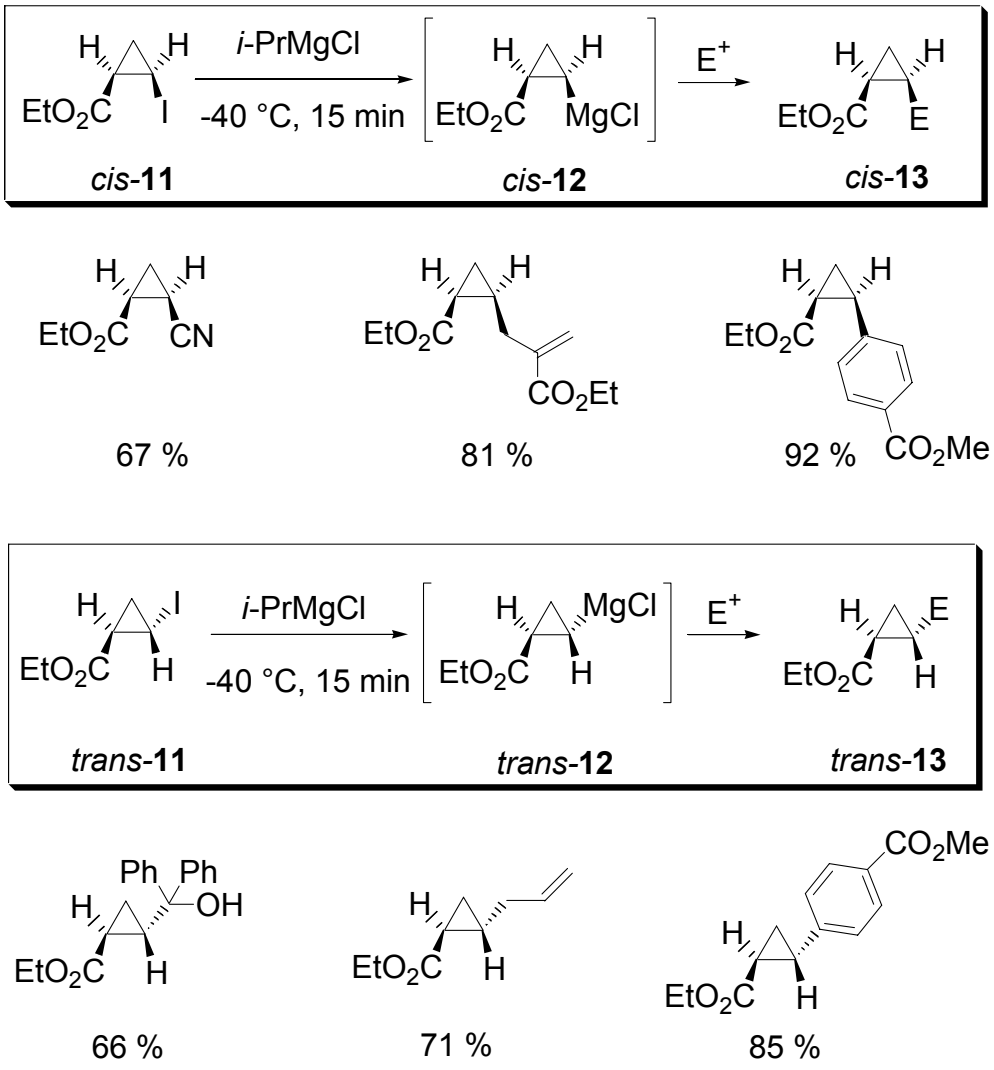
[a] Yield of the mixture of two isomers. [b] This reaction was performed in the presence of 10 mol % of CuCN·2LiCl. [c] Isolated yield of analytically pure product.

Table 8. Reactions of arylmagnesium species of type **73** with electrophiles.

4. Summary

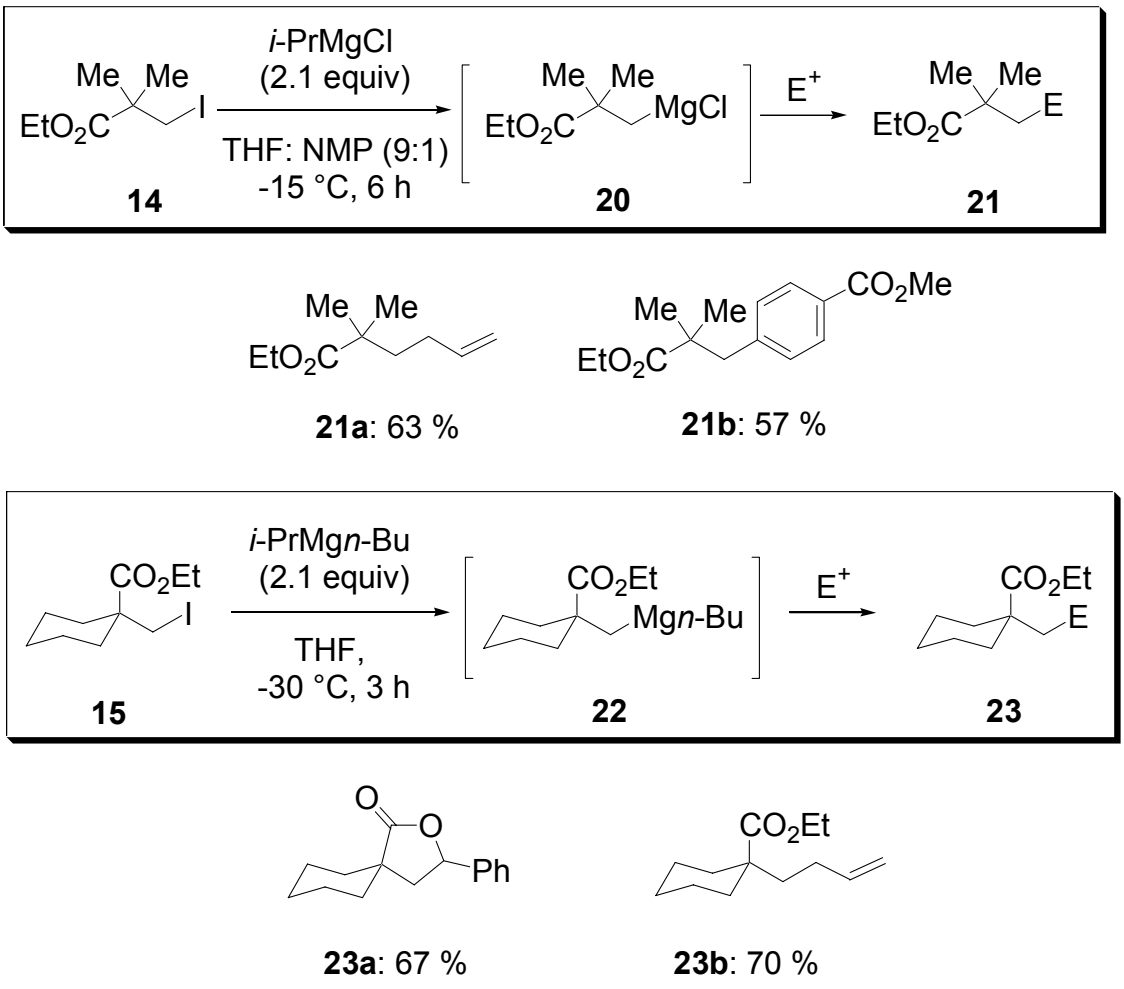
This work focuses on the preparation of new functionalized organomagnesium reagents using low temperature halogen-magnesium exchange reactions.

In the first part, the preparation of new functionalized cyclopropylmagnesium reagents is described. The formation of these species of the general structure **12**, using an iodine-magnesium exchange reaction, is stereoselective. Their reactions with electrophiles furnish the expected product of the general structure **13** with retention of configuration (Scheme 35).



Scheme 35. Stereoselective generation and reaction of functionalized cyclopropylmagnesium reagents *via* iodine-magnesium exchange reactions.

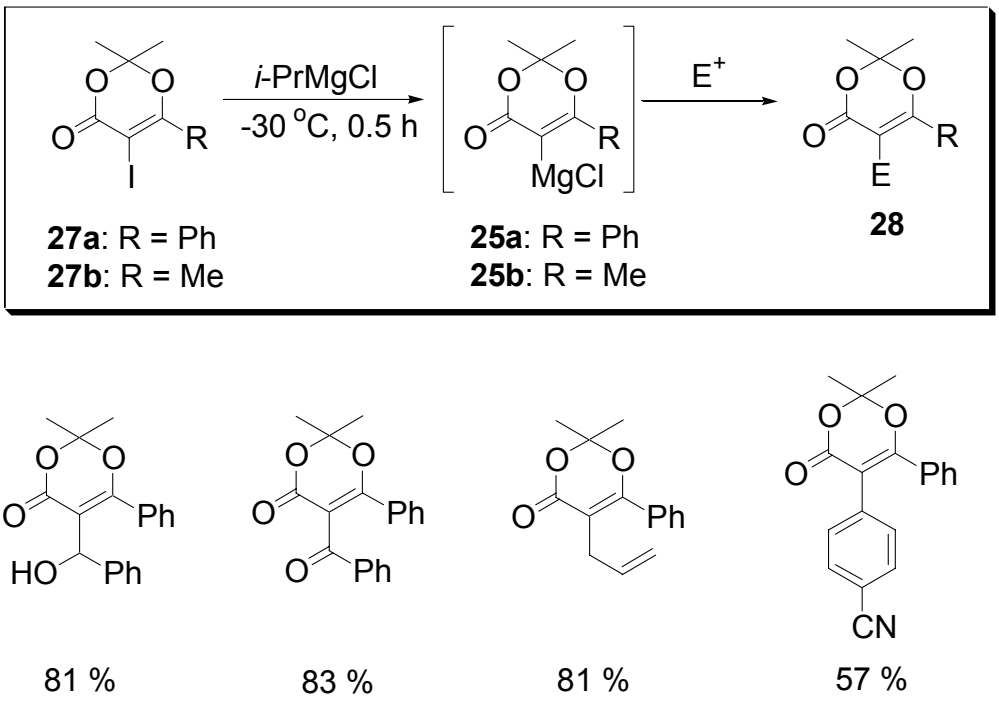
The alkylmagnesium species bearing an ester functionality can be generated using a low temperature iodine-magnesium exchange reaction (Scheme 36). Grignard reagents **20** and **22** are allylated in the presence of a catalytic amount of CuCN•2LiCl to give the desired products in good yields. Lactone **23a** is formed by trapping with benzaldehyde. A palladium(0)-catalyzed cross-coupling reaction with aryl iodides is accomplished through transmetallation of the sensitive organomagnesium derivative **20** to the corresponding organozinc species. In the presence of $Pd(dba)_2$ (5 mol %) and tfp (10 mol %), the cross-coupling product **21b** is isolated in an acceptable yield.



Scheme 36. Preparation of alkylmagnesium reagents bearing an ester functionality.

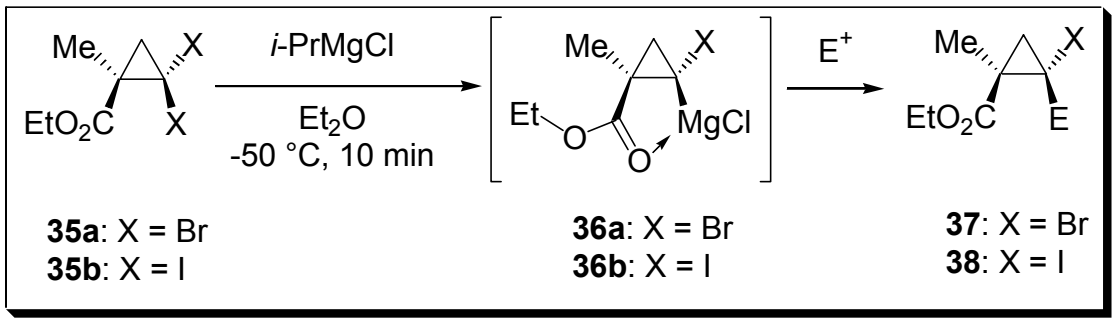
The generation of a *β*-alkoxy alkenylmagnesium derivative is also realized under the mild reaction conditions developed for the iodine-magnesium exchange reaction. The *β*-alkoxy alkenylmagnesium derivatives of type **25** are sufficiently stable at low

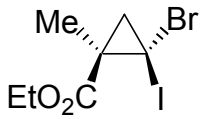
temperature (-30 °C) to react cleanly with different aldehydes. A transmetallation to copper provides the corresponding copper reagent, which can be smoothly acylated or allylated. Finally, transmetallation to organozinc species yields a very stable *β*-alkoxyalkenylzinc reagent, which undergoes Negishi cross-coupling reactions at 60 °C in satisfactory yields (Scheme 37).



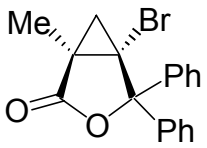
Scheme 37. Preparation and reaction of alkenylmagnesium reagents bearing an oxygen functionality in the *β*-position.

Since magnesium carbenoids are an important class of organometallic reagents, the possibility of a stereoselective preparation of new cyclopropyl and alkyl carbenoids bearing an ester group was examined in a second part. The coordination of the magnesium atom through the oxygen of the ester group is considered to be of major importance (Scheme 38).

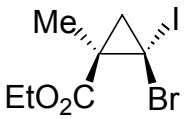




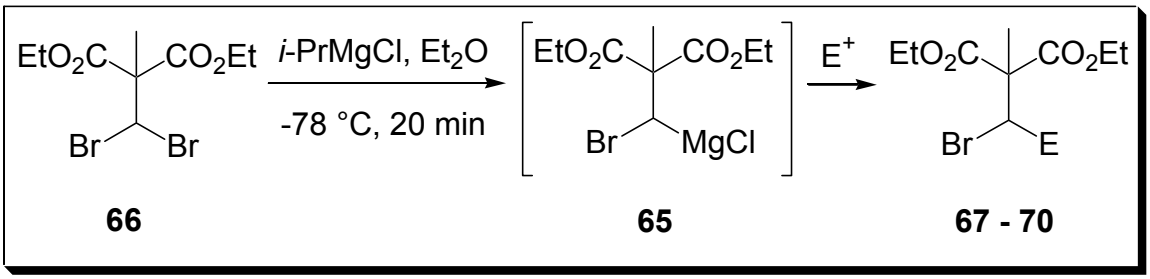
85 %

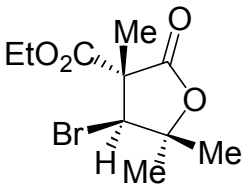


61 %

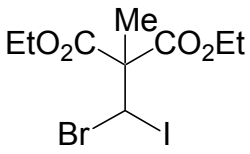


80 %





60 %
(d.r = 99:1)

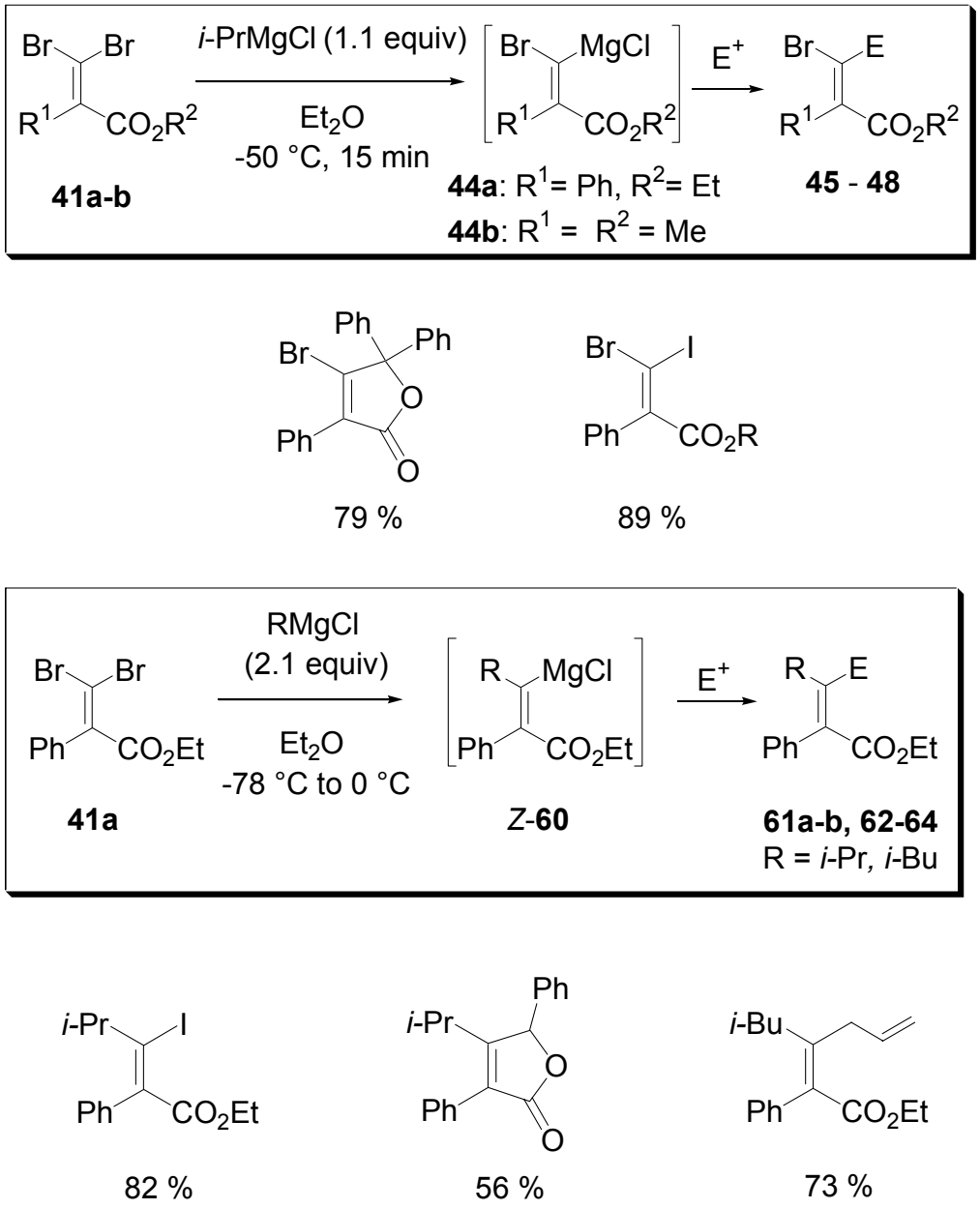


80 %

Scheme 38. Generation of functionalized cyclopropyl and alkyl magnesium carbenoids and their subsequent reactions.

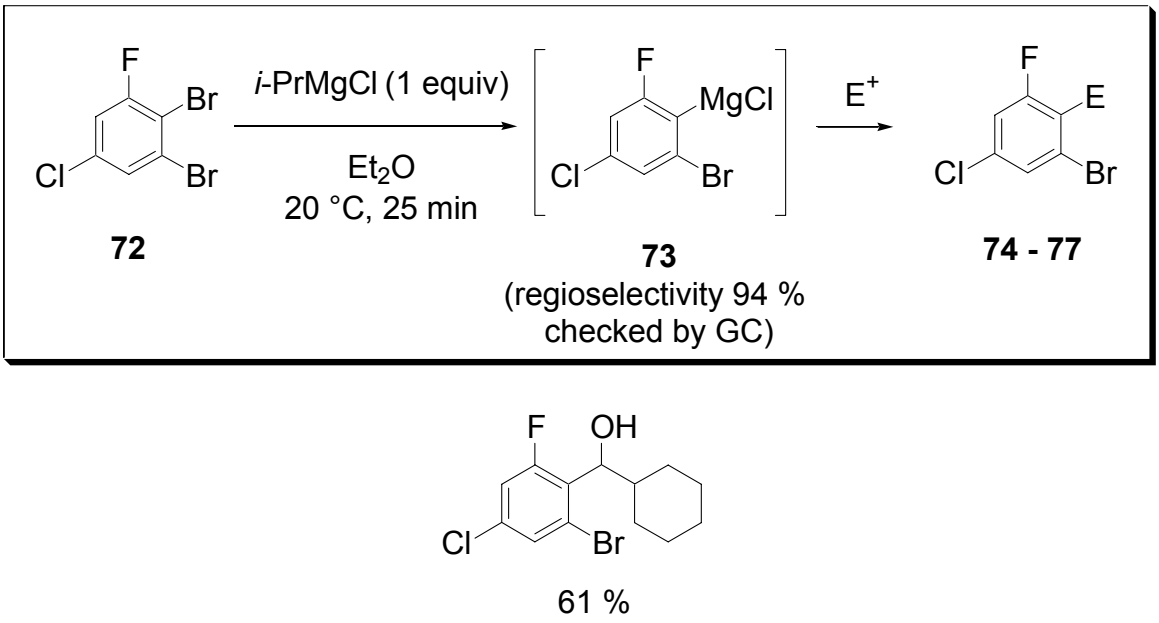
Furthermore, alkenylmagnesium carbenoids of the general structure **44** can be generated through a bromine-magnesium exchange reaction using one equivalent of *i*-PrMgCl in Et_2O. Interestingly, the bromine-magnesium exchange reaction on *β*-dibromoester **41**, in the presence of two equivalents of an alkylmagnesium reagent in Et_2O, allows for the

stereoselective preparation of functionalized α,β-unsaturated ester and lactones (Scheme 39).



Scheme 39. Stereoselective preparation and reaction of functionalized α,β-unsaturated esters and lactones starting from β-dibromoester **41**.

In the last part, a regioselective bromine-magnesium exchange reaction on a dibromoarene is presented using inductive electronic effects (Scheme 40).



Scheme 40. A regioselective bromine-magnesium exchange reaction using inductive electronic effects.

An extension of this low temperature halogen-magnesium exchange reaction might be of importance for the preparation of polyfunctional, more complex molecules.

Experimental section

1. General conditions

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

Solvents

Solvents were dried according to standard methods by distillation over drying agents stated below and were stored under argon. CH_2Cl_2, DMF and pentane over CaH_2, Et_2O and THF over Na/benzophenone, pyridine and triethylamine over KOH, toluene over Na.

Reagents

- Reagents of > 98 % purity were used as obtained.
- 1 M CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 0.1 mol) and LiCl (8.48 g, 0.2 mol) in a Schlenk flask *in vacuo* for 4 h at 120 °C. After cooling to rt, dry THF (100 mL) was added and stirring was continued until the salts were completely dissolved.
- 1 M $ZnBr_2$ solution was prepared by drying $ZnBr_2$ (22.5 g, 0.1 mol) *in vacuo* for 5 h at 150 °C. After cooling to rt, dry THF (100 mL) was added and stirring was continued until the salt was dissolved.
- *n*-Butyllithium was used as a 1.5 M solution in hexane.
- Diisopropylamine was distilled from CaH_2.

The following reagents were prepared according to literature procedures: palladium(II)*bis*(dibenzylideneacetone),[52] tri-*o*-furylphosphine,[53] *cis*-2-iodo-cyclopropanecarboxylic acid ethyl ester (*cis*-**11**),[21] 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (**22a**),[36,37] 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one (**22b**),[36,37] 3-iodo-

[52] Takahashi, Y.; Ito, T.; Sakai, S. *Chem. Comm.* **1970**, 1065.
[53] Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc. Perkin Trans. II*, **1972**, 63.

chromen-2-one (**26**),[54] 2,2-dibromo-1-methyl-cyclopropanecarboxylic acid ethyl ester (**30a**),[42] 2,2-diiodo-1-methyl-cyclopropanecarboxylic acid ethyl ester (**30b**),[42] 3,3-dibromo-2-phenyl-acrylic acid ethyl ester(**36a**),[44] 3,3-dibromo-2-methyl-acrylic acid methyl ester (**36b**),[44] 3,3-diiodo-2-phenyl-acrylic acid ethyl ester (**37**),[45] 2-(2,2-dibromo-vinyl)-pyridine (**50**),[55] 2-dibromomethyl-2-methyl-malonic acid diethyl ester (**61**).[50]

Content determination of organometallic reagents

Organolithium and organomagnesium solutions were titrated using the method of Paquette.[56]

Chromatography

- Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The chromatograms were viewed under UV light and/or by treatment of the TLC plate with one of the solutions given below followed by heating with a heat gun:

  - $KMnO_4$ (3.0 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).

  - Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

- Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm) from Merck.

- Gas chromatography (GC): Hewlett-Packard 5890 Series II.

  - Column A: 5 % phenylmethylpolysiloxane (HP Ultra 2) 12 m x 0.2 mm

  - Column B: 5 % phenylmethylpolysiloxane (HP 5) 5 m x 0.25 mm

  The compounds were detected with a flame ionization detector.

[54] Fukuyama, N; Nishino, H; Kurosawa, K. *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 4363.
[55] Uenishi, J; Kawahama, R; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998,** *63*, 8965.
[56] Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

Analytical data

- Melting points were determined on a Büchi B-540 apparatus and are uncorrected.
- NMR spectra were recorded on Brucker ARX 200, AC 300 or WH 400 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.27, δ_C: 77.0. For the characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) as well as br (broad).
- Infrared spectra were recorded from 4000 - 400 cm^{-1} on a Nicolet 510 or a Perkin-Elmer 281 spectrophotometer. Samples were measured either as a film between sodium chloride plates or (for solids) as potassium bromide tablets. The absorption bands are reported in wave numbers (cm^{-1}). For the band characterization the following abbreviations were applied: s (strong), m (medium), w (weak).
- Electron impact mass (EI, 70 eV) spectra were recorded on a Varian MAT CH 7A instrument. High resolution mass spectra (HRMS) were recorded on a Varian MAT 711 instrument. Additionally, for the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

  - Column C: 5 % phenylmethylpolysiloxane (HP 5) 30 m x 0.25 mm
- Elemental analysis was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of Department für Chemie und Pharmazie, Ludwig-Maximilians-Universität Munich.
- The stereochemistry of the products was determined by NOESY, HMBC, ^1H and ^{13}C NMR experiments.

2. Typical procedures (TP)

2.1 TP 1: Typical procedure for the halogen-magnesium exchange on mono halide substituted substrates

A solution of *i*-PrMgCl (1.05 mmol) in THF (1.6 M, 0.65 mL) was added dropwise over 5 min to a stirred solution of mono halide substrate (1 mmol) in THF (3 mL) at - 30 °C under argon. The resulting solution was then stirred until the exchange reaction was complete (GC monitoring) and the electrophile (1.20 mmol) was added. The reaction mixture was allowed to warm up to rt, quenched with brine (20 mL) and extracted with Et_2O (3 x 40 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to give the product.

2.2 TP 2: Typical procedure for the halogen-magnesium exchange on di halide substituted substrates

A solution of *i*-PrMgCl (1.05 mmol) in Et_2O (2 M, 0.52 mL) was added dropwise over 5 min to a stirred solution of the di halide substrate (1 mmol) in Et_2O (3 mL) at - 50 °C under argon. The resulting solution was then stirred until the exchange reaction was complete (GC monitoring) and the electrophile (1.20 mmol) was added. The reaction mixture was allowed to warm up to rt, quenched with brine (20 mL) and extracted with Et_2O (3 x 40 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to give the product.

2.3 TP 3: Typical procedure for the palladium-catalyzed cross-coupling reactions

A dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with a halide substrate (1.0 mmol) in dry THF (2 mL) and cooled to - 30 °C. *i*-PrMgCl (1.1 mmol) in THF (1.6 M, 1.45 mL) was then added slowly. The resulting solution was then stirred until the exchange reaction was complete (GC monitoring) and a $ZnBr_2$ solution (0.73 mL, 1.5 M in THF, 1.1 mmol) was added. The reaction mixture was allowed to warm to rt to form the zinc reagent. Another dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd(dba)_2$ (29 mg, 0.05 mmol) and tfp (23 mg, 0.1 mmol) in dry THF (1 mL). The initial red color disappeared after 2 min leading to a yellow solution that confirmed the formation of the active catalyst. Aryl iodide (0.7 mmol) was added, followed by the prepared zinc reagent. The reaction mixture was stirred at rt for 16 h, then quenched with saturated, aqueous NH_4Cl (2 mL), poured into water (50 mL) and extracted with Et_2O (3 x 40 mL). The combined organic fractions were washed with brine (70 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to yield the cross-coupling product.

3. Synthesis of organomagnesium reagents

3.1 Synthesis of *i*-propylpmagnesium chloride

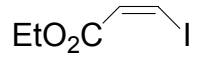
A dried, three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (3.7 g, 150 mmol). A small amount of THF was added to cover the magnesium, and *iso*propyl chloride (7.8 g, 100 mmol) in THF (150 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete the reaction mixture was stirred at rt for 10 h. The excess magnesium was removed by filtration and the molarity was determined by the method of Paquette.[56] Generally, yields between 90 and 95 % were obtained.

3.2 Synthesis of *i*-propyl*n*-butylmagnesium

A dried, three-necked flask equipped with an argon inlet, a magnetic stirring bar, a dropping funnel and a thermometer was charged with a solution of *i*-PrMgCl (20 mmol, 1.6 M in THF, 12.5 mL). A solution of *n*-butyl lithium (22 mmol, 1.5 M in hexane, 14.6 mL) was added slowly over 30 minutes. The reaction mixture was stirred at rt for 10 h. Thereafter, the stiring was stopped and the mixture was allowed to stay for additional 5 hours. The clear solution was separated from the precipitate. The molarity was determined by the method of Paquette.[56]

4. Preparation of functionalized cyclopropylmagnesium reagents

Synthesis of *Z*-3-iodo-acrylic acid ethyl ester (7)[21a]



A 250 mL round-bottomed flask equipped with a magnetic stirring bar and an argon gas inlet was charged with 22.5 g (0.15 mol) of dry sodium iodide and 100 mL of glacial acetic acid. To the stirred solution was added 10.1 mL portion (0.1 mol) of ethyl propiolate (**6**) and the resulting mixture was heated at 70 °C during 12 h. The brown solution was cooled to room temperature and 100 mL of water and 100 mL of ether were added. The organic layer was separated and the aqueous layer extracted twice with 20 mL of ether. The combined organic layers were treated with 3 M aqueous potassium hydroxide (ca. 150 mL per portions of 50 mL) until the aqueous phase become neutral (pH = 7), washed with 50 mL of brine, and dried over anhydrous magnesium sulfate. After rotary evaporation of the solvent, the residual brown oil was distilled to give **7** (19.4 g, 86 % yield) as a yellow oil.

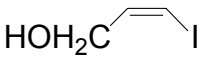
Bp = 62 °C.

IR (KBr): 2982 (m), 1726 (s), 1600 (m), 1323 (m), 1199 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 8.9 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 4.18 (q, J = 7.1Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.9, 130.3, 95.0, 61.1, 14.6.

Synthesis of *Z*-3-iodo-prop-2-en-1-ol (8)[21a]



A 100 mL, dry four-necked, round bottomed flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum, and an argon gas inlet was charged with 11.3 g (50 mmol) of *Z*-3-iodo-acrylic acid ethyl ester (**7**) and 100 mL of anhydrous dichloromethane. The stirred solution was cooled to -78 °C by mean of a liquid nitrogen bath, and 100 mL (100 mmol) of a 1 M solution of diisobutyl aluminium hydride in

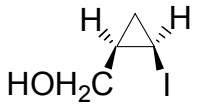
hexane was added dropwise via a syringe at such a rate that the temperature did not exceed -75 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The hydrolysis was carried out at -20 °C by dropwise addition of 50 mL of 1 M aqueous solution of hydrochloric acid, followed by addition of 100 mL of ether. The organic layer was separated, the aqueous one extracted with two portions of 20 mL of ether, and the combined extracts were dried over magnesium sulfate. After rotary evaporation of the solvents, the residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording **8** (8.05 g, 88 % yield) as a yellow oil.

IR (KBr): 3326 (br), 2922 (w), 2869 (w), 1608 (m), 1279 (m), 1042 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (dt, J = 7.6 Hz, J = 5.5, 1H), 6.30 (d, J = 7.6 Hz, 1H), 4.17 (d, J = 5.5 Hz, 2H), 1.85 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 140.3, 83.0, 66.1.

Synthesis of *cis*-(2-iodo-cyclopropyl)-methanol (9)[21c]

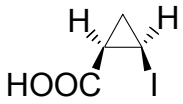


To freshly distilled CH_2Cl_2 (50 mL) was added Et_2Zn (1.0 M in hexanes) (53 mL, 53 mmol) under argon. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (4.11 mL, 53 mmol) in CH_2Cl_2 (10 mL) was then dripped very slowly into the reaction mixture via syringe. Upon stirring for 20 min, a solution of CH_2I_2 (4.33 mL, 53 mmol) in CH_2Cl_2 (10 mL) was added. After an additional 20 min stirring, a solution of *Z*-3-iodo-prop-2-en-1-ol (**8**) (4.43 g, 24.1 mmol) in CH_2Cl_2 (10 mL) was added and the ice bath was removed. After an additional 30 min stirring, the reaction mixture was quenched with sat. aqueous NH_4Cl and hexanes (50 mL) and the layers separated. The aqueous layer was extracted with hexanes. The combined organic layers were washed with sat. $NaHCO_3$, H_2O, and brine, then dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography on silica gel (pentane/Et_2O 1:4) affording ***cis*-9** (2.96 g, 62 % yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (dd, J = 11.8 Hz, J = 5.0 Hz, 1H), 3.51 (dd, J = 11.8 Hz, J = 8.8 Hz, 1H), 2.63 (dt, J = 7.3 Hz, J = 5.0 Hz, 1H), 1.81 (s, 1H), 1.39-1.30 (m, 1H), 1.04-0.90 (m, 1H), 0.69 (dt, J = 6.4Hz, J = 5.0 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 68.4, 18.0, 14.1, 10.0.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid (10)[21b]



A 50 mL, dry round bottomed flask equipped with a mechanical stirrer, a rubber septum, and an argon gas inlet was charged with *cis*-(2-iodo-cyclopropyl)-methanol **(*cis*-9)** (3.3 g, 16.7 mmol) and 25.8 g (68.8 mmol) pyridinium dichromate dissolved in 50 mL of dry DMF. The reaction mixture was stirred for 24 h at 25 °C. After this time, the reaction mixture was poured into 80 mL of water, and the solution was acidified with 3 N HCl to pH 2.5. The water solution was extracted 3 times with 30 mL portions of Et_2O. The combined ethereal solution was washed twice with 20 mL of water. The combined organic layers were washed with brine, then dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording ***cis*-10** (3.34 g, 95 % yield) as white crystals.

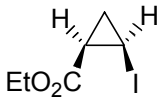
Mp = 65 °C.

IR (KBr): 3041 (w), 1700 (s), 1652 (m), 1460 (m), 1425 (m), 1225 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 2.90 (dt, J = 8.0 Hz, J = 6.7Hz, 1H), 1.93 (dt, J = 8.1 Hz, J = 6.3 Hz, 1H), 1.61 (dt, J = 8.1 Hz, J = 6.2 Hz, 1H), 1.44 (q, J = 6.4 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 175.5, 19.3, 17.5, 14.3.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid ethyl ester (*cis*-11)[21b]



A mixture of *cis*-2-iodo-cyclopropanecarboxylic acid (***cis*-10**) (1.91 g, 9 mmol), thyonylchloride (1.3 mL, 18 mmol) and 3 drops of DMF was refluxed at 50 °C for 1 h. After that, thionylchloride was removed by vacuum pump with an extra liquid nitrogen trap and the mixture was cooled to 0 °C. EtOH (0.8 mL, 13.5 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. After this time, the reaction mixture was poured into 20 mL of water and Et_2O (20 mL) and the layers separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$, H_2O, and brine, then dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***cis*-11** (1.51 g, 70 % yield) as a yellow oil.

IR (KBr): 2982 (w), 1731 (s), 1381 (m), 1179 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.21-4.11 (m, 2H), 2.74 (dt, J = 8.1 Hz, J = 6.5 Hz, 1H), 1.80 (dt, J = 8.2 Hz, J = 6.5 Hz, 1H), 1.48-1.30 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

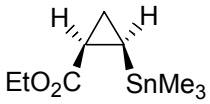
^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 60.2, 18.3, 15.3, 13.4, - 15.6.

MS (EI) 240 (100), 195 (63), 167 (30).

$C_6H_9IO_2$ HRMS Calcd. 239.9647

Found 239.9644.

Synthesis of *cis*-2-trimethylstannanyl-cyclopropanecarboxylic acid ethyl ester (*cis*-13a)



The reaction was carried out according to TP 1 using ***cis*-11** (245 mg, 1.02 mmol), *i*-PrMgCl (0.69 mL, 1.12 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), Me_3SnCl (1.53 mL, 1 M in THF, 1.53 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 2:1) affording ***cis*-13a** (191 mg, 67 % yield) as a yellow oil.

IR (KBr): 2925 (m), 1717 (s), 1381 (m), 1192 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.01 (q, J = 7.1 Hz, 2H), 1.76-1.69 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.13-1.06 (m, 1H), 0.82-0.73 (m, 2H), 0.00 (s, 9H).

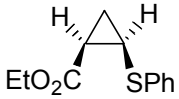
^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.0, 60.9, 32.3, 30.0, 23.0, 16.6, 14.7, 13.5, 8.0, -8.4.

MS (EI) 277 (3), 263 (100), 233 (13), 165 (40), 135 (10).

$C_9H_{18}O_2Sn$ HRMS Calcd. 278.0329

Found 278.0360.

Synthesis of *cis*-2-phenylsulfanyl-cyclopropanecarboxylic acid ethyl ester (*cis*-13b)



The reaction was carried out according to TP 1 using ***cis*-11** (158 mg, 0.65 mmol), *i*-PrMgCl (0.44 mL, 0.72 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), PhSSPh (215 mg in 3 mL THF, 0.98 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***cis*-13b** (76 mg, 52 % yield) as a yellow oil.

IR (KBr): 3448 (w), 2981 (m), 1731 (s), 1381 (m), 1180 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.13 (m, 5H), 4.07 (q, J = 7.1 Hz, 2H), 2.71 (dt, J = 6.9 Hz, J = 7.8 Hz, 1H), 2.25 (dt, J = 6.7 Hz, J = 7.8 Hz, 1H), 1.50-1.43 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 137.5, 129.1, 127.9, 125.9, 61.2, 22.5, 14.5, 13.6.

MS (EI) 222 (100), 177 (31), 149 (96), 116 (25), 109 (18).

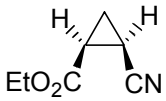
$C_{12}H_{14}O_2S$ HRMS Calcd. 222.0715

Found 222.0711

$C_{12}H_{14}O_2S$ Calcd. C 64.83 H 6.35 S 14.42

Found: C 64.87 H 6.39 S 14.67.

Synthesis of *cis*-2-cyano-cyclopropanecarboxylic acid ethyl ester (*cis*-13c)



The reaction was carried out according to TP 1 using ***cis*-11** (334 mg, 1.39 mmol), *i*-PrMgCl (0.94 mL, 1.53 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), *p*-toluenesulphonyl cyanide (377 mg in 3 mL THF, 2.08 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording ***cis*-13c** (131 mg, 67 % yield) as a colorless oil.

IR (KBr): 3449 (w), 2986 (m), 2246 (m), 1731 (s), 1385 (m), 1199 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27 (q, J = 7.1 Hz, 2H), 2.16-2.09 (m, 1H), 1.85 (dd, J = 8.1 Hz, J = 6.7 Hz, 1H), 1.69 (dt, J = 5.0 Hz, J = 6.5 Hz, 1H), 1.43 (dd, J = 8.1 Hz, J = 5.0 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H).

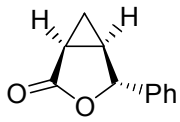
^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 118.0, 62.1, 20.4, 14.5, 13.6, 6.0.

MS (EI) 139 (11), 112 (60), 94 (100), 67 (30).

$C_7H_9NO_2$ HRMS Calcd. 139.1519

Found 139.1547.

Synthesis of 4-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (*cis*-13d)



The reaction was carried out according to TP 1 using ***cis*-11** (107 mg, 0.44 mmol), *i*-PrMgCl (0.30 mL, 0.49 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), benzaldehyde (71 mg, 0.66 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording ***cis*-13d** (71 mg, 90 % yield) as two diastereoisomers in a ratio of 65:35.

Diastereoisomer 1: 46 mg (59 %), yellow oil.

IR (KBr): 3492 (w), 2924 (m), 1765 (s), 1455 (m), 1180 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.29 (m, 5H), 5.27 (s, 1H), 2.23-2.14 (m, 2H), 1.30 (dd, J = 7.6 Hz, J = 4.9 Hz, 1H), 1.01 (dt, J = 3.5 Hz, J = 4.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.3, 140.1, 129.2, 126.0, 82.0, 25.1, 18.2, 13.3.

MS (EI): 174 (100), 145 (10), 129 (36), 117 (36), 104 (22).

$C_{11}H_{10}O_2$ HRMS Calcd. 174.0681

Found 174.0678

Diastereoisomer 2: 25 mg (31 %), yellow solid.

Mp = 110 °C.

IR (KBr): 3318 (w), 2920 (m), 1770 (s), 1452 (m), 1191 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.23 (m, 5H), 5.65 (d, J = 4.8 Hz, 1H), 2.52-2.45 (m, 1H), 2.18-2.12 (m, 1H), 1.05 (dd, J = 7.6 Hz, J = 5.2 Hz, 1H), 0.82-0.78 (m, 1H).

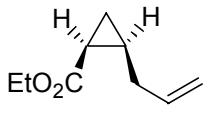
^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.0, 137.8, 129.2, 126.0, 82.0, 22.6, 19.6, 13.3.

MS (EI) 174 (100), 145 (12), 129 (17), 115 (16), 104 (32).

$C_{11}H_{10}O_2$ HRMS Calcd. 174.0681

Found 174.0668

Synthesis of *cis*-2-allyl-cyclopropanecarboxylic acid ethyl ester (*cis*-13e)



The reaction was carried out according to TP 1 using ***cis*-11** (210 mg, 0.87 mmol), *i*-PrMgCl (0.59 mL, 0.96 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), CuCN·2LiCl (0.17 mL, 1.0 M in THF, 0.17 mmol), allyl bromide (157 mg, 1.31 mmol)

to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***cis*-13e** (102 mg, 75 % yield) as a colorless oil.

IR (KBr): 2981 (m), 1726 (s), 1381 (m), 1180 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.82-5.69 (m, 1H), 5.03-4.87 (m, 2H), 4.05 (q, J = 7.1 Hz, 2H), 2.34-2.10 (m, 2H), 1.69-1.62 (m, 1H), 1.30-1.23 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H), 1.00-0.87 (m, 2H).

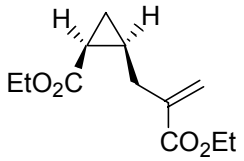
^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 137.8, 115.1, 60.6, 31.4, 20.9, 18.4, 14.7.

MS (EI) 155 (12), 125 (33), 109 (100), 107 (9).

$C_9H_{14}O_2$ HRMS Calcd. 154.0994

Found 154.0980

Synthesis of *cis*-2-(2-Ethoxycarbonyl-allyl)-cyclopropanecarboxylic acid ethyl ester (*cis*-13f)



The reaction was carried out according to TP 1 using ***cis*-11** (186 mg, 0.77 mmol), *i*-PrMgCl (0.52 mL, 0.85 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), CuCN·2LiCl (0.15 mL, 1.0 M in THF, 0.15 mmol), 2-bromomethyl-acrylic acid ethyl ester (225 mg, 1.16 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 4:1) affording ***cis*-13f** (143 mg, 81 % yield) as a colorless oil.

IR (KBr): 2982 (m), 1722 (s), 1404 (m) 1179 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.09 (s, 1H), 5.54 (q, J = 1.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.04 (q, J = 7.1 Hz, 2H), 2.61-2.38 (m, 2H), 1.68 (dd, J = 7.8 Hz, J = 5.6 Hz, 1H), 1.47-1.34 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.17(t, J = 7.1 Hz, 3H), 1.04-0.91 (m, 2H).

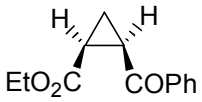
^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.1, 167.4, 140.5, 125.2, 61.0, 60.7, 29.6, 20.4, 18.6, 14.7, 14.6, 13.7.

MS (EI) 226 (13), 181 (100), 152 (49), 123 (16), 107 (28).

$C_{12}H_{18}O_4$ HRMS Calcd. 226.1205

Found 226.1220.

Synthesis of *cis*-2-benzoyl-cyclopropanecarboxylic acid ethyl ester (*cis*-13g)



The reaction was carried out according to TP 1 using ***cis*-11** (166 mg, 0.69 mmol), *i*-PrMgCl (0.46 mL, 0.76 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), CuCN·2LiCl (0.76 mL, 1.0 M in THF, 0.76 mmol), benzoyl chloride (145 mg, 1.03 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***cis*-13g** (111 mg, 73 % yield) as a colorless oil.

IR (KBr): 3621 (w), 2982 (m), 1731 (s), 1597 (m), 1354 (s), 1227 (s) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97-7.94 (m, 2H), 7.51-7.35 (m, 3H), 3.90 (q, J = 7.1 Hz, 2H), 2.71 (dd, J = 6.8 Hz, J = 8.0 Hz, 1H), 2.22 (dd, J = 6.4 Hz, J = 8.2 Hz, 1H), 1.83 (dt, J = 4.7 Hz, J = 6.6 Hz, 1H), 1.28 (dt, J = 4.7 Hz, J = 8.1 Hz, 1H), 0.97 (t, J = 7.1 Hz, 3H).

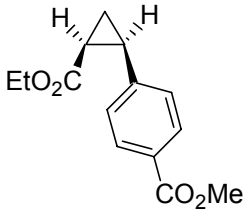
^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.9, 170.4, 137.5, 133.5, 128.9, 128.7, 61.2, 26.6, 23.5, 14.3, 12.0.

MS (EI) 218 (3), 173 (23), 145 (17), 105 (100).

$C_{13}H_{14}O_3$ HRMS Calcd. 218.0943

Found 218.0948.

Synthesis of 4-[(1*S*, 2*R*)-2-ethoxycarbonyl-cyclopropyl)]-benzoic acid methyl ester (*cis*-13h):



The reaction was carried out according to TP 3 using ***cis*-11** (274 mg, 1.14 mmol), *i*-PrMgCl (0.77 mL, 1.25 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), $ZnBr_2$ (0.76 mL, 1.6 M in THF, 1.25 mmol), $Pd(dba)_2$ (27.3 mg, 5 mol %), tfp (22.0 mg, 10 mol %) and 4-iodo-benzoic acid methyl ester (245 mg, 0.95 mmol). The residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***cis*-13h** (215 mg, 92 % yield) as a yellow oil.

IR (KBr): 3430 (w), 2983 (m), 1724 (s), 1611 (m), 1280 (s), 1158 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88-7.84 (m, 2H), 7.27-7.24 (m, 2H), 3.82 (s, 3H), 3.80 (q, J = 7.1 Hz, 2H), 2.52 (q, J = 8.5 Hz, 1H), 2.10-2.02 (m, 1H), 1.68 (dt, J = 7.5 Hz, J = 5.3 Hz, 1H), 1.30 (dd, J = 7.8 Hz, J = 5.1 Hz, 1H), 0.91 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 167.4, 142.5, 129.6, 128.9, 60.7, 52.4, 25.7, 22.6, 14.5, 11.8.

MS (EI) 248 (78), 217 (24), 193 (41), 175 (39), 115 (57).

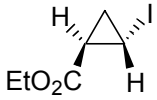
$C_{14}H_{16}O_4$ HRMS Calcd. 248.1049

Found 248.1050.

$C_{14}H_{16}O_4$ Calcd. C 67.73 H 6.50

Found C 68.06 H 6.44.

Synthesis of *trans*-2-iodo-cyclopropanecarboxylic acid ethyl ester (*trans*-11)



The reaction was carried out according to TP 2 using **39** (5 g, 13.6 mmol), *i*-PrMgCl (7.5 mL, 15 mmol, 2 M in Et_2O) (exchange at -60 °C, 5 min) and acetic acid (10 mL, 0.5 N) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/ Et_2O 5:1) affording ***trans*-11** (1.79 g, 55 % yield) as a pink oil.

IR (KBr): 2981 (w), 1726 (s), 1478 (m), 1180 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.17 (q, J = 7.1 Hz, 2H), 2.82-2.76 (m, 1H), 2.03-1.96 (m, 1H), 1.65 (dt, J = 5.7 Hz, J = 8.1 Hz, 1H), 1.35-1.26 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H).

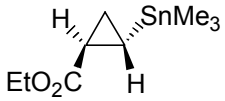
^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.3, 61.5, 25.0, 20.0, 14.6, -12.1.

MS (EI) 240 (100), 195 (52), 167 (30).

$C_6H_9IO_2$ HRMS Calcd. 239.9647

Found 239.9652.

Synthesis of *trans*-2-trimethylstannanyl-cyclopropanecarboxylic acid ethyl ester (*trans*-13a)



The reaction was carried out according to TP 1 using ***trans*-11** (174 mg, 0.72 mmol), *i*-PrMgCl (0.49 mL, 0.79 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), Me_3SnCl (0.79 mL, 1 M in THF, 0.79 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 2:1) affording ***trans*-13a** (172 mg, 85 % yield) as a colorless oil.

IR (KBr): 2981 (m), 1725 (s), 1379 (m), 1177 (s) cm^{-1}.

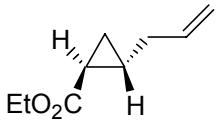
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.16-4.07 (m, 2H), 1.51-1.47 (m, 1H), 1.31-1.26 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3H), 0.79-0.74 (m, 1H), 0.62-0.56 (m, 2H), 0.06 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8, 60.3, 16.7, 14.3, 12.9, 5.9, -10.8.

MS (EI) 263 (100), 217 (49), 165(68), 135 (20).

$C_9H_{18}O_2Sn$	Calcd.	C 39.03	H 6.55
	Found	C 39.05	H 6.83.

Synthesis of *trans*-2-allyl-cyclopropanecarboxylic acid ethyl ester (*trans*-13e)



The reaction was carried out according to TP 1 using ***trans*-11** (182 mg, 0.75 mmol), *i*-PrMgCl (0.52 mL, 0.83 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), CuCN·2LiCl (0.07 mL, 1.0 M in THF, 0.07 mmol), allyl bromide (136 mg, 1.14 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) affording ***trans*-13e** (83 mg, 71 % yield) as a colorless oil.

IR (KBr): 2981 (m), 1727 (s), 1178 (s) cm^{-1}.

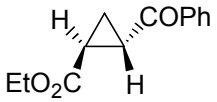
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.82-5.67 (m, 1H), 5.06-4.90 (m, 2H), 4.05 (q, J = 7.1 Hz, 2H), 2.06-1.96 (m, 2H), 1.44-1.30 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 1.15-1.08 (m, 1H), 0.71-0.62 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.7, 136.5, 116.0, 60.7, 36.8, 21.8, 20.1, 15.2, 14.6.

MS (EI) 155 (95), 125 (15), 109 (100), 107 (34).

$C_9H_{14}O_2$	HRMS	Calcd.	155.1072 $[M+H]^+$
		Found	155.1063.

Synthesis of *trans*-2-benzoyl-cyclopropanecarboxylic acid ethyl ester (*trans*-13g)



The reaction was carried out according to TP 1 using ***trans*-11** (57 mg, 0.23 mmol), *i*-PrMgCl (0.16 mL, 0.26 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), CuCN·2LiCl (0.26 mL, 1.0 M in THF, 0.26 mmol), benzoyl chloride (49 mg, 0.35 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) affording ***trans*-13g** (33 mg, 65 % yield) as a colorless oil.

IR (KBr): 3437 (w), 2982 (m), 1729 (s), 1597 (m), 1333 (s), 1224 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97-7.93 (m, 2H), 7.55-7.38 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 3.15-3.09 (m, 1H), 2.34-2.28 (m, 1H), 1.58-1.49 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H).

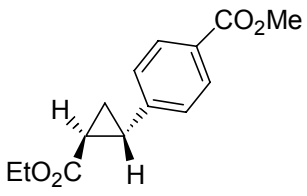
^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.4, 172.7, 137.4, 133.7, 129.0, 128.6, 61.5, 26.3, 25.0, 18.2, 14.5.

MS (EI) 218 (1), 173 (26), 144 (38), 115 (9).

$C_{13}H_{14}O_3$ HRMS Calcd. 218.0943

Found 218.0943.

Synthesis of 4-[(1*R*, 2*R*)-2-ethoxycarbonyl-cyclopropyl)]-benzoic acid methyl ester (*trans*-13h)



The reaction was carried out according to TP 3 using ***trans*-11** (241 mg, 1.00 mmol), *i*-PrMgCl (0.69 mL, 1.10 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), $ZnBr_2$ (0.73 mL, 1.5 M in THF, 1.10 mmol), $Pd(dba)_2$ (12 mg, 5 mol %), tfp (9.7 mg, 10 mol

%), and 4-iodo-benzoic acid methyl ester (219 mg, 0.83 mmol). The residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***trans*-13h** (177 mg, 85 % yield) as a yellow solid.

Mp = 75 °C.

IR (KBr): 3425 (w), 1724 (s), 1611 (m), 1282 (s), 1194 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89-7.86 (m, 2H), 7.10-7.05 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.52-2.44 (m, 1H), 1.92-1.85 (m, 1H), 1.62-1.55 (m, 1H), 1.31-1.24 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H).

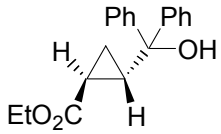
^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.3, 167.2, 146.1, 130.2, 128.7, 126.4, 61.3, 52.4, 26.4, 25.1, 17.9, 14.6.

MS (EI) 248 (96), 220 (22), 217 (28), 203 (16), 193 (58), 175 (64), 165 (21), 143 (27), 131 (36), 115 (100).

$C_{14}H_{16}O_4$ HRMS Calcd. 248.1049

Found 248.1034.

Synthesis of (1*R*, 2*R*)-2-(hydroxy-diphenyl-methyl)-cyclopropanecarboxylic acid ethyl ester (*trans*-13i)



The reaction was carried out according to TP 1 using ***trans*-11** (229 mg, 0.95 mmol), *i*-PrMgCl (0.65 mL, 1.05 mmol, 1.6 M in THF) (exchange at -40 °C, 15 min), benzophenone (260 mg, 1.43 mmol, dissolved in 2 mL Et_2O) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording ***trans*-13i** (188 mg, 66 % yield) as a white solid.

Mp = 62 °C

IR (KBr): 3453 (s), 1699 (s), 1447 (m), 1193 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.17 (m, 10H), 4.05 (q, J = 7.1 Hz, 2H), 2.22-2.14 (m, 1H), 1.94 (s, 1H), 1.75 (dt, J = 4.8 Hz, J = 8.4 Hz, 1H), 1.22-1.04 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.5, 146.8, 128.9, 128.5, 127.8, 126.9, 60.9, 32.2, 18.1, 15.6, 14.7, 12.3.

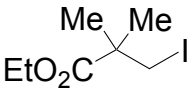
MS (EI) 279 (2), 251 (3), 196 (100), 183 (11), 105 (23).

$C_{19}H_{20}O_3$ HRMS Calcd. 279.1385 $[M\text{-}OH]^+$

Found 279.1345.

5. Preparation of functionalized alkylmagnesium reagents

Synthesis of 3-iodo-2,2-dimethyl-propionic acid ethyl ester (14)[30]



A 100 mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with 3-chloro-2,2-dimethyl-propionic acid ethyl ester **16** (5.95 g, 30 mmol) and DMF (60 mL). Sodium iodide (9 g, 60 mmol) was added to the clear solution and the mixture was refluxed at 120 °C for 24 h. After completion of the reaction the DMF was evaporated *in vacuo*. The residue was taken up in Et_2O (100 mL) and washed with a saturated aqueous solution of sodium thiosulfate (3 x 30 mL). The ethereal phase was dried over $MgSO_4$, filtered and concentrated. The resulting yellow oil was purified by flash column chromatography on silica gel (pentane/Et_2O 7:1) affording **14** (3 g, 40 % yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (q, J = 7.1 Hz, 2H), 3.28 (s, 2H), 1.26 (s, 6H), 1.21 (t, J = 7.1 Hz, 3H).

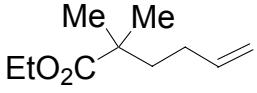
^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.9, 61.3, 43.6, 25.8, 16.9, 14.6.

MS (EI) 256 (15), 183 (49), 129 (100), 101 (11), 73 (42), 55 (58), 41 (26).

$C_7H_{13}IO_2$ HRMS Calcd. 255.9960

Found 255.9970.

Synthesis of 2,2-dimethyl-hex-5-enoic acid ethyl ester (21a)



The reaction was carried out according to TP 1 using **14** (170 mg, 0.66 mmol) dissolved in a mixture of 3 mL THF and 0.3 mL NMP, *i*-PrMgCl (0.69 mL, 1.39 mmol, 2 M in THF) (exchange at -15 °C, 6 h), CuCN·2LiCl (0.06 mL, 1.0 M in THF, 0.06 mmol), allyl bromide (95 mg, 0.79 mmol) to give a crude residue, which was purified by flash

column chromatography on silica gel (pentane/Et_2O 3:1) affording **21a** (70 mg, 63 % yield) as a colorless oil.

IR (KBr): 2924 (w), 2856 (m), 1728 (m), 1443 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 1H), 5.03-4.91 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.02-1.95 (m, 2H), 1.63-1.59 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.17 (s, 6H).

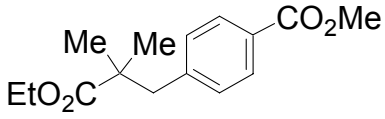
^{13}C-NMR (75 MHz, $CDCl_3$): δ 177.8, 138.6, 114.4, 60.2, 39.8, 29.3, 25.1, 14.2.

MS (EI) 170 (2), 116 (95), 97 (54), 88 (75), 73 (22), 55 (100), 41 (43).

$C_{10}H_{18}O_2$ HRMS Calcd. 170.1307

Found 170.1281.

Synthesis of 4-(2-ethoxycarbonyl-2-methyl-propyl)-benzoic acid methyl ester (21b)



The reaction was carried out according to TP 3 using **14** (199 mg, 0.77 mmol) dissolved in a mixture of 3 mL THF and 0.3 mL NMP, *i*-PrMgCl (0.81 mL, 1.61 mmol, 2 M in THF) (exchange at -10 °C, 6 h), $ZnBr_2$ (0.77 mL, 1.5 M in THF, 1.2 mmol), $Pd(dba)_2$ (21 mg, 5 mol %), tfp (18 mg, 10 mol %), and 4-iodo-benzoic acid methyl ester (305 mg, 1.16 mmol). The residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **21b** (115 mg, 57 % yield) as a colorless oil.

IR (KBr): 2977 (m), 1724 (s), 1436 (w), 1280 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H), 7.14-7.10 (m, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.84 (s, 2H), 1.15 (t, J = 7.1 Hz, 3H), 1.11 (s, 6H).

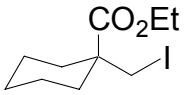
^{13}C-NMR (75 MHz, $CDCl_3$): δ 177.5, 167.5, 143.9, 130.6, 129.6, 128.8, 89.2, 60.9, 52.4, 46.6, 43.9, 25.4, 14.5.

MS (EI) 264 (4), 233 (13), 222 (23), 191 (50), 190 (80), 149 (100), 121 (33), 115 (19), 91 (13).

$C_{15}H_{20}O_4$ HRMS Calcd. 264.1362

Found 264.1359.

Synthesis of 1-iodomethyl-cyclohexanecarboxylic acid ethyl ester (15)[31]



To a solution of lithium diisopropylamide (70.4 mmol) in THF (50 mL) was added ethylcyclohexylcarbocylate (10 g, 64 mmol) in THF (20 mL) at –78 °C under argon and the reaction mixture was stirred for 1 h. Then 17.1g (64 mmol) of CH_2I_2 in THF (20 mL) was added and stirred for 1 h at the same temperature. The reaction mixture was allowed to warm up to rt and strirred for 10 h then quenched with water 100 mL, extracted with Et_2O (3 x 100 mL) and washed with brine. The ethereal phase was dried over $MgSO_4$, filtered and concentrated. The resulting oil was distilled under high vacuum (10^{-3} mbar) affording **15** (15.5 g, 82 % yield) as a colorless oil (Bp = 81 °C).

IR (KBr): 2935 (s), 1734 (s), 1451 (m), 1139 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (q, J = 7.1 Hz, 2H), 3.34 (s, 2H), 2.17-2.09 (m, 2H), 1.64-1.25 (m, 8H), 1.30 (t, J = 7.1 Hz, 3H).

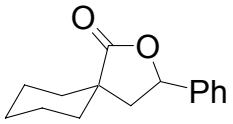
^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.3, 61.2, 47.5, 40.1, 34.6, 25.9, 23.3, 16.2, 14.7.

MS (EI) 296 (18), 223 (15), 169 (100), 141 (10), 123 (38).

$C_{10}H_{17}IO_2$ HRMS Calcd. 296.0273

Found 296.0271.

Synthesis of 3-phenyl-2-oxa-spiro[4.5]decan-1-one (23a)



The reaction was carried out according to TP 1 using **15** (244 mg, 0.82 mmol), *i*-PrMg*n*-Bu (2.46 mL, 1.72 mmol, 0.7 M in THF) (exchange at -30 °C, 3 h), benzaldehyde (183 mg, 1.72 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 4:1) affording **23a** (128 mg, 67 % yield) as a yellow oil.

IR (KBr): 29325 (s), 2857 (m), 1765 (s), 1450 (m), 1328 (m), 1187 (s), 1022 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.52 (m, 5H), 5.34 (dd, J = 6.5 Hz, J = 9.8 Hz, 1H), 2.61 (dd, J = 6.5 Hz, J = 13.1 Hz, 1H), 1.89 (dd, J = 9.8 Hz, J = 13.1 Hz, 1H), 1.82-1.54 (m, 6H), 1.46-1.12 (m, 4H).

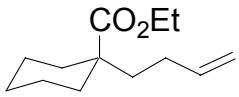
^{13}C-NMR (100 MHz, $CDCl_3$): δ 181.3, 139.8, 128.6, 128.2, 125.2, 77.9, 45.1, 42.1, 34.1, 31.4, 25.2, 22.1.

MS (EI) 231 (19), 185 (19), 129 (16), 126 (24), 104 (100), 91 (14), 81 (11).

$C_{15}H_{18}O_2$ HRMS Calcd. 230.1307

Found 230.1314.

Synthesis of 1-but-3-enyl-cyclohexanecarboxylic acid ethyl ester (23b)



The reaction was carried out according to TP 1 using **15** (205 mg, 0.69 mmol), *i*-PrMg*n*-Bu (2.07 mL, 1.45 mmol, 0.7 M in THF) (exchange at -30 °C, 3 h), CuCN·2LiCl (0.06 mL, 1.0 M in THF, 0.06 mmol), allyl bromide (207 mg, 1.72 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 9:1) affording **23b** (105 mg, 70 % yield) as a colorless oil.

IR (KBr): 2935 (s), 1727 (s), 1453 (m), 1203 (m), 1134 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76-5.62 (m, 1H), 4.94-4.83 (m, 2H), 4.07 (q, J = 7.1 Hz, 2H), 2.04-1.82 (m, 4H), 1.54-1.46 (m, 5H), 1.34-1.05 (m, 5H), 1.18 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 177.0, 139.0, 129.6, 114.7, 60.4, 47.0, 40.1, 34.5, 28.8, 26.3, 23.6, 14.7.

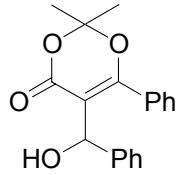
MS (EI) 211 (12), 156 (100), 128 (13), 95 (36), 81 (23), 67 (7).

$C_{13}H_{22}O_2$ HRMS Calcd. 211.1698 $[M+H]^+$

Found 211.1708.

6. Preparation of alkenylmagnesium halides bearing an oxygen functionality at the β-position

Synthesis of 5-(hydroxy-phenyl-methyl)-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (28a)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (118 mg, 0.35 mmol), *i*-PrMgCl (0.24 mL, 0.39 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and benzaldehyde (0.05 mL, 0.5 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 85:15) affording **28a** (90 mg, 81 %) as a white solid.

Mp = 124 °C.

IR (KBr): 3483 (m), 1713 (s), 1621 (m), 1371 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53-7.17 (m, 10H), 5.52 (d, J = 11.5 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H).

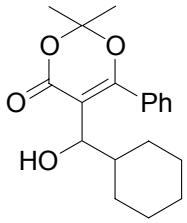
^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.9, 163.1, 143.3, 132.1, 131.5, 129.4, 129.2, 128.7, 127.6, 125.9, 108.2, 106.4, 70.6, 26.6, 24.7.

MS (EI): 310 (1), 252 (41), 223 (69), 207 (21), 147 (26), 105 (100), 77 (68).

$C_{19}H_{18}O_4$ HRMS Calcd. 310.1205

Found 310.1211.

Synthesis of 5-(cyclohexyl-hydroxy-methyl)-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (28b)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (147 mg, 0.44 mmol), *i*-PrMgCl (0.3 mL, 0.49 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and cyclohexanecarbaldehyde (0.09 mL, 0.73 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 2:1) affording **28b** (90 mg, 64 %) as a colorless oil.

IR (KBr): 3501 (m), 2851 (s), 1709 (s), 1621 (m), 1367 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49-7.35 (m, 5H), 3.88 (dd, J = 9.7 Hz, J = 11.3 Hz, 1H), 3.15 (d, J = 11.3 Hz, 1H), 2.08-0.42 (m, 10H), 1.79 (s, 3H), 1.70 (s, 3H).

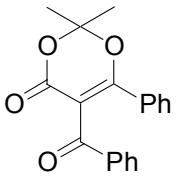
^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.5, 163.1, 132.0, 131.9, 129.4, 128.0, 107.4, 105.9, 74.4, 43.1, 30.5, 30.4, 27.8, 26.6, 26.1, 26.0, 23.7.

MS (EI): 316 (1), 233 (37), 175 (100), 105 (58), 83 (24).

$C_{19}H_{24}O_4$ HRMS Calcd. 316.1675

Found 316.1683.

Synthesis of 5-benzoyl-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (28c)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (129 mg, 0.39 mmol), *i*-PrMgCl (0.26 mL, 0.43 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min), CuCN·2LiCl (0.43 mL, 0.43 mmol, 1 M in THF) and benzoyl chloride (82 mg, 0.58 mmol) to give a crude residue, which was purified

by flash column chromatography on silica gel (pentane/Et_2O 2:1) affording **28c** (100 mg, 83 %) as a yellow solid.

Mp = 62 °C.

IR (KBr): 3413 (w), 2998 (w), 1717 (s), 1667 (m), 1362 (s), 1203 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83-7.79 (m, 2H), 7.46-7.27 (m, 6H), 7.22-7.16 (m, 2H), 1.84 (s, 6H).

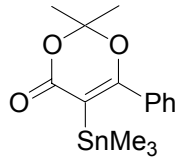
^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.1, 166.4, 160.0, 137.7, 134.0, 132.6, 131.4, 129.9, 129.0, 108.0, 107.2, 25.8.

MS (EI): 223 (100), 147 (39), 105 (61), 77 (45), 51 (14).

$C_{19}H_{16}O_4$ HRMS Calcd. 308.1049

Found 308.1062.

Synthesis of 2,2-dimethyl-6-phenyl-5-trimethylstannanyl-[1,3]dioxin-4-one (28d)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (127 mg, 0.38 mmol), *i*-PrMgCl (0.26 mL, 0.42 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and Me_3SnCl (0.76 mL, 1 M in THF, 0.76 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **28d** (84 mg, 59 %) as a white solid.

Mp = 105 °C.

IR (KBr): 3436 (w), 2995 (m), 1692 (s), 1585 (m), 1323 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46-7.34 (m, 5H), 1.71 (s, 6H), 0.00 (s, 9H).

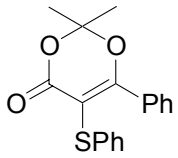
^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 165.4, 135.4, 131.5, 129.0, 128.8, 105.7, 103.3, 25.3, -6.9.

MS (EI): 353 (73), 295 (100), 251 (91), 227 (43), 105 (40), 77 (31).

$C_{15}H_{20}O_3Sn$: Anal.Calcd. C, 49.09 H, 5.49

Found: C, 49.31 H, 5.64.

Synthesis of 2,2-dimethyl-6-phenyl-5-phenylsulfanyl-[1,3]dioxin-4-one (28e)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (119 mg, 0.36 mmol), *i*-PrMgCl (0.24 mL, 0.39 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and PhSSPh (94 mg in 2 mL THF, 0.43 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 3:1) affording **28e** (77 mg, 68 %) as a yellow solid.

Mp = 90 °C.

IR (KBr): 3447 (w), 1734 (s), 1558 (m), 1338 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66-7.02 (m, 10H), 1.74 (d, J = 11.0 Hz, 6H).

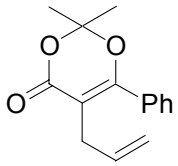
^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 165.4, 162.2, 161.1, 136.9, 135.4, 132.3, 129.8, 129.5, 129.2, 128.5, 127.8, 126.7, 126.6, 106.6, 99.0, 91.7, 25.7.

MS (EI): 312 (2), 302 (3), 254 (10), 210 (6), 110 (18), 105 (100).

$C_{18}H_{16}O_3S$ HRMS Calcd. 312.0820

Found 312.0828.

Synthesis of 5-allyl-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (28f)



The reaction was carried out according to TP 1 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (104 mg, 0.31 mmol), *i*-PrMgCl (0.21 mL, 0.34 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min), CuCN·2LiCl (0.06 mL, 0.06 mmol, 1 M in THF) and allyl bromide (56 mg, 0.47 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 3:1) affording **28f** (63 mg, 81 %) as a colorless oil.

IR (KBr): 2998 (m), 1723 (s), 1626 (m), 1367 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.35 (m, 5H), 5.97-5.84 (m, 1H), 5.05-4.95 (m, 2H), 3.04 (td, J = 1.7 Hz, J = 5.7 Hz, 2H), 1.71 (s, 6H).

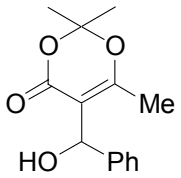
^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.7, 161.3, 135.0, 131.3, 129.8, 127.4, 124.1, 114.7, 104.3, 103.1, 29.0, 24.1.

MS (EI): 244 (10), 186 (91), 158 (42), 105 (100), 77 (36).

$C_{15}H_{16}O_3$ HRMS Calcd. 244.1099

Found 244.1105.

Synthesis of 5-(hydroxy-phenyl-methyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (28g)



The reaction was carried out according to TP 1 using 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one **27b** (99 mg, 0.36 mmol), *i*-PrMgCl (0.24 mL, 0.39 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and benzaldehyde (0.05 mL, 0.54 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 3:1) affording **28g** (68 mg, 76 %) as a colorless oil.

IR (KBr): 3487 (m), 1689 (s), 1633 (m), 1398 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.17 (m, 5H), 5.55 (s, 1H), 4.05 (s, 1H), 2.00 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H).

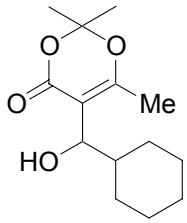
^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.5, 161.1, 141.9, 127.4, 126.2, 124.3, 106.6, 104.7, 68.4, 24.5, 23.8, 16.6.

MS (EI): 248 (3), 190 (75), 161 (75), 147 (100), 43 (47).

$C_{14}H_{16}O_4$ HRMS Calcd. 248.1049

Found 248.1063.

Synthesis of 5-(cyclohexyl-hydroxy-methyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (28h)



The reaction was carried out according to TP 1 using 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one **27b** (297 mg, 1.1 mmol), *i*-PrMgCl (0.75 mL, 1.29 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) and cyclohexanecarbaldehyde (0.2 mL, 1.66 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 2:1) affording **28h** (161 mg, 57 %) as a colorless oil.

IR (KBr): 3469 (m), 2852 (s), 1714 (s), 1634 (s), 1449 (m), 1378 (s), 1270 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (d, J = 9.0 Hz, 1H), 3.36 (s, 1H), 2.15-2.05 (m, 1H), 1.95 (s, 3H), 1.80-0.7 (m, 10H), 1.60 (s, 6H).

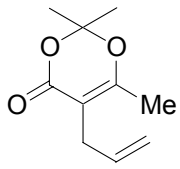
^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 162.5, 106.6, 105.6, 104.4, 74.1, 43.8, 30.4, 30.3, 26.7, 26.3, 26.1, 24.8, 17.9.

MS (EI): 151 (60), 136 (20), 108 (62), 93 (71), 78 (66), 67 (100), 55 (39).

$C_{14}H_{22}O_4$ HRMS Calcd. 254.1518

Found 254.1534.

Synthesis of 5-allyl-2,2,6-trimethyl-[1,3]dioxin-4-one (28i)



The reaction was carried out according to TP 1 using 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one **27b** (228 mg, 0.85 mmol), *i*-PrMgCl (0.55 mL, 0.89 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min) CuCN·2LiCl (0.17 mL, 0.17 mmol, 1 M in THF) and allyl bromide (153 mg, 1.27 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording **28i** (120 mg, 77 %) as a colorless oil.

IR (KBr): 3432 (w), 3000 (w), 1724 (s), 1646 (m), 1397 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.91-5.77 (m, 1H), 5.10-5.02 (m, 2H), 3.04 (d, J = 6.0 Hz, 2H), 1.99 (s, 3H), 1.68 (s, 6H).

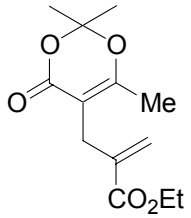
^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 162.4, 135.5, 115.5, 105.4, 103.4, 29.4, 25.5, 17.7.

MS (EI): 182 (7), 124 (60), 109 (22), 96 (28), 81 (35), 43 (100).

$C_{10}H_{14}O_3$ HRMS Calcd. 182.0943

Found 182.0925.

Synthesis of 2-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-ylmethyl)-acrylic acid ethyl ester (28j)



The reaction was carried out according to TP 1 using 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one **27b** (348 mg, 1.29 mmol), *i*-PrMgCl (0.83 mL, 1.35 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min), CuCN·2LiCl (0.11 mL, 0.11 mmol, 1 M in THF) and ethyl 2-(bromomethyl) acrylate (139 mg, 0.72 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 3:1) affording **28j** (120 mg, 65 %) as a colorless oil.

IR (KBr): 3424 (w), 2995 (m), 1722 (s), 1645 (s), 1393 (m), 1152 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.16 (s, 1H), 5.54 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.21 (s, 2H), 1.94 (s, 3H), 1.58 (s, 6H), 1.21 (t, J = 7.1 Hz, 3H).

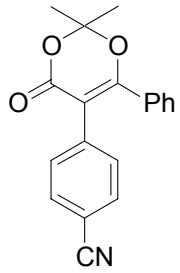
^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 165.6, 162.1, 137.8, 126.1, 105.3, 102.6, 61.2, 27.8, 25.5, 18.0, 14.6.

MS (EI): 254 (1), 197 (100), 168 (15), 151 (41), 125 (20), 99 (14).

$C_{13}H_{18}O_5$ HRMS Calcd. 254.1154

Found 254.1163.

Synthesis of 4-(2,2-dimethyl-4-oxo-6-phenyl-4H-[1,3]dioxin-5-yl)-benzonitrile (30a)



The reaction was carried out according to TP 3 using 5-iodo-1,3-dioxin-4-one **27a** (113 mg, 0.34 mmol), *i*-PrMgCl (0.23 mL, 0.37 mmol, 1.6 M in THF) (exchange at -30 °C, 30 min), $ZnBr_2$ (0.34 mL, 1.2 M in THF, 0.41 mmol), $Pd(dba)_2$ (8.1 mg, 5 mol %), tfp (6.6 mg, 10 mol %) and 4-iodobenzonitrile (65.2 mg, 0.28 mmol). The residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) to give **30a** (50 mg, 57 %) as a white solid.

Mp = 173 °C.

IR (KBr): 3430 (w), 1711 (s), 1616 (m), 1369 (m), 1275 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.10 (m, 9H), 1.83 (s, 6H).

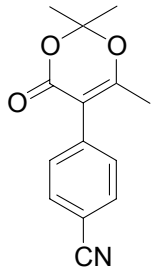
^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.0, 161.6, 138.2, 132.4, 132.3, 131.2, 130.2, 128.8, 119.1, 111.5, 106.4, 25.6.

MS (EI): 305 (3), 247 (10), 203 (14), 105 (100).

$C_{19}H_{15}NO_3$ HRMS Calcd. 305.3273

Found 305.3290.

Synthesis of 4-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-yl)- benzonitrile (30b)



The reaction was carried out according to TP 3 using 5-iodo-2,2,6-trimethyl-[1,3]dioxin-4-one **27b** (294 mg, 1.09 mmol), *i*-PrMgCl (0.71 mL, 1.15 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min), $ZnBr_2$ solution (1.09 mL, 1.31 mmol, 1.2 M in

THF), $Pd(dba)_2$ (20 mg, 0.03 mmol), tfp (16 mg, 0.07 mmol) and 4-iodobenzonitrile (165 mg, 0.72 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/EtOAc 85:15) affording **30b** (95 mg, 54 %) as a yellow solid.

Mp = 95°C.

IR (KBr): 3428 (w), 2229 (m), 1730 (s), 1638 (s), 1397 (m), 1206 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 1.90 (s, 3H), 1.71 (s, 6H).

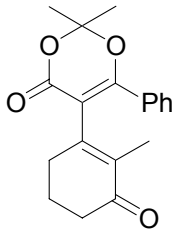
^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 160.8, 137.9, 132.4, 131.9, 119.0, 111.9, 107.5, 106.3, 25.6, 19.2.

MS (EI): 243 (11), 185 (100), 143 (79), 114 (13), 43 (74).

$C_{14}H_{13}NO_3$ HRMS Calcd. 243.0895

Found 243.0904.

Synthesis of 2,2-dimethyl-5-(2-methyl-3-oxo-cyclohex-1-enyl)-6-phenyl-[1,3]dioxin-4-one (30c)



The reaction was carried out according to TP 3 using 5-iodo-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one **27a** (123 mg, 0.37 mmol), *i*-PrMgCl (0.25 mL, 0.41 mmol, 1.6 M in THF), (exchange at -30 °C, 30 min), $ZnBr_2$ solution (0.36 mL, 0.43 mmol, 1.2 M in THF), $Pd(dba)_2$ (9 mg, 0.01 mmol), tfp (7 mg, 0.02 mmol) and 3-iodo-2-methyl-cyclohex-2-enone (72 mg, 0.3 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording **30c** (53 mg, 55 %) as a yellow oil.

IR (KBr): 3407 (m), 2957 (m), 1714 (s), 1603 (s), 1449 (m), 1380 (s), 1251 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44-7.29 (m, 5H), 2.80-2.66 (m, 2H), 2.47-2.29 (m, 2H), 2.15-1.82 (m, 2H), 1.80 (s, 3H), 1.76 (s, 3H), 1.55 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.3, 161.8, 160.2, 148.8, 137.1, 132.1, 129.0, 128.2, 107.4, 106.2, 38.2, 32.0, 26.1, 25.1, 23.1, 13.3.

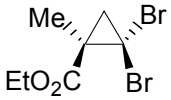
MS (EI): 253 (8), 226 (51), 198 (13), 170 (10), 105 (100), 77 (45).

$C_{19}H_{20}O_4$ HRMS Calcd. 312.1362

Found 312.1389.

7. Preparation of functionalized cyclopropyl carbenoids

Synthesis of 2,2-dibromo-1-methyl-cyclopropanecarboxylic acid ethyl ester (35a)[42]



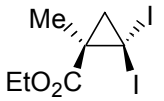
2-Methyl-acrylic acid ethyl ester (5.7 g, 50 mmol), bromoform (25.7 g, 102 mmol) and TBAB (0.5 g) in CH_2Cl_2 (30 mL) were stirred for 12 h at rt with NaOH (8 g) in water (15 mL). Further CH_2Cl_2 (20 mL) was added and the organic layer was washed with 10 % hydrochloric acid (2 x 30 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 15:1) affording **35a** (6.5 g, 46 % yield) as a colorless oil.

IR (KBr): 2982 (w), 1734 (s), 1454 (w), 1314 (w), 1274 (m), 1180 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25-4.10 (m, 2H), 2.34 (d, J = 7.8 Hz, 1H), 1.53 (s, 3H), 1.49 (d, J = 7.8 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.8, 62.3, 35.2, 33.0, 30.4, 21.2, 14.6.

Synthesis of 2,2-diiodo-1-methyl-cyclopropanecarboxylic acid ethyl ester (35b)[42]



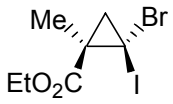
2-Methyl-acrylic acid ethyl ester (3.42 g, 30 mmol), iodoform (13 g, 33 mmol) and TBAB (0.3 g) in CH_2Cl_2 (50 mL) were stirred for 12 h at rt with NaOH (12 g) in water (24 mL). Further CH_2Cl_2 (50 mL) was added and the organic layer was washed with 10 % hydrochloric acid (2 x 30 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 20:1) affording **35b** (3.4 g, 30 % yield) as a red oil.

IR (KBr): 2980 (m), 1732 (s), 1652 (m), 1450 (m), 1310 (s), 1178 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33-4.20 (m, 2H), 2.54 (d, J = 7.8 Hz, 1H), 1.74 (d, J = 7.8 Hz, 1H), 1.52 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.1, 60.2, 34.1, 31.0, 23.3, 12.6, 0.00.

Synthesis of 2-bromo-2-iodo-1-methyl-cyclopropanecarboxylic acid ethyl ester (37a)



The reaction was carried out according to TP 2 using **35a** (345 mg, 1.20 mmol), *i*-PrMgCl (0.66 mL, 1.32 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min), iodine (367 mg, 1.44 mmol in 3 mL Et_2O). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (10 mL) and extracted with Et_2O. The combined organic layers were washed successively with $Na_2S_2O_3$, then with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) affording **37a** (345 mg, 85 % yield) as a colorless oil.

IR (KBr): 3319 (w), 2980 (m), 1731 (s), 1307 (m), 1178 (m), 1026 (m) cm^{-1}.

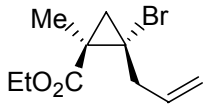
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.25-4.12 (m, 2H), 2.26 (d, J = 7.8 Hz, 1H), 1.58 (d, J = 7.8 Hz, 1H), 1.50 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 62.4, 34.8, 34.5, 20.6, 15.7, 14.7.

MS (EI) 333 (10), 259 (11), 179 (100), 149 (46).

$C_7H_{10}O_2IBr$	HRMS	Calcd.	331.8909
		Found	331.8965.
$C_7H_{10}O_2IBr$	Calcd.	C 25.25	H 3.03
	Found	C 25.34	H 2.97.

Synthesis of 2-allyl-2-bromo-1-methyl-cyclopropanecarboxylic acid ethyl ester (37b)



The reaction was carried out according to TP 2 using **35a** (316 mg, 1.10 mmol), *i*-PrMgCl (0.58 mL, 1.16 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min), CuCN·2LiCl (0.11 mL, 1.0 M in THF, 0.11 mmol), allyl bromide (198 mg, 1.65 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 6:1) affording **37b** (174 mg, 64 % yield) as a colorless oil.

IR (KBr): 3429 (w), 2981 (m), 1724 (s), 1290 (m), 1178 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.83-5.70 (m, 1H), 5.07-4.97 (m, 2H), 4.07 (dq, J = 1.1 Hz, J = 7.1 Hz, 2H), 2.71-2.53 (m, 2H), 1.73 (d, J = 6.5 Hz, 1H), 1.51 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.4 Hz, 1H).

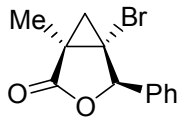
^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 134.9, 117.8, 61.6, 47.3, 42.6, 30.2, 28.7, 22.0, 14.6.

MS (EI): 247 (2), 173 (21), 139 (29), 93 (100), 77 (21).

$C_{10}H_{15}O_2Br$ HRMS Calcd. 246.0255

Found 246.0234.

Synthesis of 5-bromo-1-methyl-4-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (37c)



The reaction was carried out according to TP 2 using **35a** (280 mg, 0.97 mmol), *i*-PrMgCl (0.53 mL, 1.07 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min), benzaldehyde (155 mg, 1.46 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **37c** (157 mg, 60 % yield) as a colorless crystals.

Mp = 100 °C.

IR (KBr): 3523 (w), 2937 (w), 1790 (s), 1294 (m), 1126 (m), 1019 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.31 (m, 5H), 5.69 (s, 1H), 1.48 (d, J = 6.2 Hz, 1H), 1.47 (s, 3H), 1.19 (d, J = 6.1 Hz, 1H).

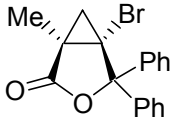
^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.9, 135.2, 129.3, 129.1, 126.1, 84.1, 41.7, 30.3, 24.9, 13.6.

MS (EI) 266 (12), 187 (16), 159 (100), 128 (46), 115 (25), 105 (28).

$C_{12}H_{11}O_2Br$	HRMS	Calcd. 265.9942		
		Found 265.9926.		
$C_{12}H_{11}O_2Br$	Calcd.	C 53.96	H 4.15	Br 29.91
	Found	C 54.11	H 4.12	Br 29.71.

X-ray analysis: Crystallographic data (excluding structure factors) for the structure reported in this thesis have been deposited at the Cambridge Crystallographic Data Centre (no. CCDC-171734). Copies of the data can be obtained free of charge on application to CCDC,12 Union Road, Cambridge CB21EZ, UK (Fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

Synthesis of 5-bromo-1-methyl-4,4-diphenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (37d)



The reaction was carried out according to TP 2 using **35a** (317 mg, 1.10 mmol), *i*-PrMgCl (0.60 mL, 1.21 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min) and bezophenone (242 mg, 1.32 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 10:1) affording **37d** (233 mg, 61 % yield) as a colorless oil.

IR (KBr): 3436 (m), 2930 (w), 1771 (s), 1448 (m), 1123 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61-6.90 (m, 10H), 1.53 (s, 3H), 1.50 (d, J = 6.4 Hz, 1H), 0.80 (d, J = 6.7 Hz, 1H).

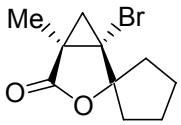
^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 141.0, 137.8, 127.6, 127.4, 127.0, 126.4, 124.6, 90.3, 45.4, 29.8, 27.6, 12.5.

MS (EI) 342 (3), 263 (20), 235 (100), 202 (13), 160 (11).

$C_{18}H_{15}O_2Br$ HRMS Calcd. 342.0255

Found 342.0271.

Synthesis of 5-bromo-1-methyl-4-cyclopentyl-3-oxa-bicyclo[3.1.0]hexan-2-one (37e)



The reaction was carried out according to TP 2 using **35a** (276 mg, 0.96 mmol), *i*-PrMgCl (0.53 mL, 1.06 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min) and cyclopentanone (97 mg, 1.15 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) affording **37e** (145 mg, 61 % yield) as a colorless oil.

IR (KBr): 3530 (w), 2968 (m), 1777 (s), 1341 (m), 1114 (m), 960 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27-1.66 (m, 8H), 1.51 (d, J = 5.7 Hz, 1H), 1.43 (s, 3H), 1.27 (d, J = 5.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 96.5, 44.7, 38.9, 34.5, 30.3, 28.0, 25.1, 24.1, 13.3.

MS (EI) 245 (1), 137 (100), 108 (8).

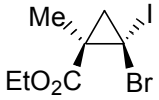
$C_{10}H_{13}O_2Br$ HRMS Calcd. 244.0099

Found 244.0181.

$C_{10}H_{13}O_2Br$ Calcd. C 49.00 H 5.35 Br 32.60

Found C 48.95 H 5.07 Br 32.58.

Synthesis of 2-bromo-2-iodo-cyclopropanecarboxylic acid ethyl ester (38a)



The reaction was carried out according to TP 2 using **35b** (427 mg, 1.12 mmol), *i*-PrMgCl (0.61 mL, 1.23 mmol, 2 M in Et_2O) (exchange at -50 °C, 10 min) and 1,2-dibromo-1,1,2,2-tetrachloro-ethane (512 mg, 1.57 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 9:1) affording **38a** (301 mg, 80 % yield) as a colorless oil.

IR (KBr): 3318 (w), 2980 (m), 1731 (s), 1452 (m), 1270 (m), 1178 (m), 1028 (m) cm^{-1}.

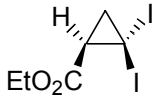
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.25-4.09 (m, 2H), 2.48 (d, J = 7.8 Hz, 1H), 1.48 (d, J = 7.9 Hz, 1H), 1.46 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 62.3, 34.8, 34.2, 26.0, 14.7.

MS (EI) 332 (4), 289 (13), 259 (12), 177(93), 151 (52).

$C_7H_{10}O_2IBr$	HRMS	Calcd.	331.8909
		Found	331.9001.
$C_7H_{10}O_2IBr$	Calcd.	C 25.25	H 3.03
	Found	C 25.43	H 2.98.

Synthesis of 2,2-diiodo-cyclopropanecarboxylic acid ethyl ester (39)[42]



Ethyl acrylate (5 g, 50 mmol), iodoform (19.7 g, 50 mmol) and TBAB (0.5 g) in CH_2Cl_2 (150 mL) were stirred for 12 h at rt with NaOH (20 g) in water (40 mL). Further CH_2Cl_2 (100 mL) was added and the organic layer was washed with 10 % hydrochloric acid (2 x 60 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 9:1) affording **39** (5.1 g, 27 % yield) as a red oil.

IR (KBr): 2980 (m), 1730 (s), 1376 (m), 1181 (s) cm^{-1}.

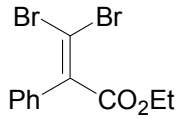
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.32-4.20 (m, 2H), 2.48 (dd, J = 7.1 Hz, J = 9.1 Hz, 1H), 2.23-2.12 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 62.3, 34.2, 31.5, 14.8.

MS (EI) 366 (4), 321 (15), 293 (30), 239 (25), 211 (100), 194 (34), 183 (22), 112 (87), 84 (37), 55 (15).

8. Preparation of alkenyl carbenoids

Synthesis of 3,3-dibromo-2-phenylacrylic acid ethyl ester (41a)[44]



A solution of carbon tetrabromide (13.3 g, 40 mmol) in CH_2Cl_2 (15 mL) was added to a solution of triphenylphosphine (21.0 g, 80 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 30 min at 0 °C, a solution of ethyl phenylglyoxylate **43a** (3.56 g, 20 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was warmed to 25 °C and stirred for 12 h, then added to pentane (70 mL), stirred for 30 min, filtered and concentrated. The crude residue was purified by flash chromatography (pentane/Et_2O 3:1), yielding the product **41a** (3.94 g, 58 % yield) as a yellow oil.

IR (KBr): 2982 (w), 1727 (s), 1204 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 5H), 4.29 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

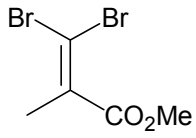
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 142.0, 136.2, 129.4, 129.0, 128.5, 95.7, 62.6, 14.3.

MS (EI) 336 (6), 334 (12), 332 (5), 291 (5), 289 (12), 287 (5), 261 (15), 255 (33), 227 (21), 225 (23), 182 (49), 180 (51), 145 (100), 101 (54).

$C_{11}H_{10}Br_2O_2$ HRMS Calcd. 331.9048

Found 331.9076.

Synthesis of 3,3-dibromo-2-methylacrylic acid methyl ester (41b)[44]



A solution of carbon tetrabromide (6.7 g, 20.1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of triphenylphosphine (10.5 g, 40.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 30 min at 0 °C, a solution of methyl pyruvate **43b** (1.02 g, 10 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was allowed to warm to rt and stirred for 12 h, added to pentane (70 mL), stirred for 30 min, filtered and concentrated. The crude residue was purified by flash chromatography (pentane/Et_2O 3:1), yielding product **41b** (1.78 g, 69 % yield) as a colorless oil.

IR (KBr): 2952 (w), 1732 (s), 1434 (m), 1285 (m), 1132 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 2.07 (s, 3H).

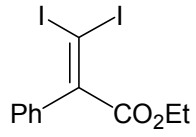
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 134.9, 94.7, 51.9, 21.0.

MS (EI) 260 (19), 258 (44), 255 (22), 229 (39), 227 (91), 225 (42), 201 (16), 199 (32), 197 (17), 179 (100), 177 (100), 119 (24), 117 (24).

$C_5H_6Br_2O_2$ HRMS Calcd. 255.8735

Found 255.8752.

Synthesis of 3,3-diiodo-2-phenylacrylic acid ethyl ester (42)[45]



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (9.1 mL, 44 mmol) in THF (20 mL) under argon. The reaction mixture was cooled to – 10 °C and *n*-BuLi (29.3 mL, 44 mmol, 1.5 M in hexane) was added. The solution was stirred 30 min at – 10 °C and then cooled to – 70 °C. A solution of iodine (5.58 g, 22 mmol) in THF (20 mL) was added and then after 10 min, a solution of diethyl iodomethylphosphonate (6.11 g,

22 mmol) in THF (10 mL) was added. After 90 min at – 70 °C, ethyl phenylglyoxylate **43a** (3.56 g, 20 mmol) in THF (5 mL) was added. The mixture was stirred 10 min at –70 °C then warmed up to rt. After 2 h, water (80 mL) was added and the aqueous solution was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (pentane/Et_2O 9:1), yielding the product **42** (5.9 g, 70 % yield) as a red oil.

IR (KBr): 3435 (w), 2924 (m), 1727 (s), 1442 (m), 1260 (s), 1196 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.17 (m, 5H), 4.11 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H).

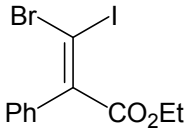
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 153.4, 140.3, 129.4, 129.1, 128.2, 62.7, 20.0, 14.4.

MS (EI) 427 (30), 354 (10), 332 (100), 272 (48), 227 (62), 145 (80), 102 (61), 75 (40), 51 (44).

$C_{11}H_{10}I_2O_2$ HRMS Calcd. 427.8770

Found 427.8818.

Synthesis of 3-bromo-3-iodo-2-phenylacrylic acid ethyl ester (45a)



The reaction was carried out according to TP 2 using **41a** (256 mg, 0.77 mmol), *i*-PrMgCl (0.42 mL, 0.84 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min) and iodine (246 mg, 0.96 mmol). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (10 mL) and extracted with Et_2O. The organic layer was washed successively with $Na_2S_2O_3$, then with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O, 3:1), yielding the product **45a** (261 mg, 89 % yield) as a yellow oil.

IR (KBr): 2981 (w), 1723 (s), 1443 (m), 1200 (s), 1036 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 5H), 4.19 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H).

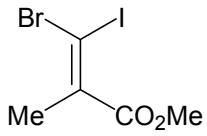
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 147.9, 136.8, 129.3, 129.0, 128.4, 62.7, 57.9, 14.4.

MS (EI) 382 (13), 380 (13), 255 (16), 227 (19), 225 (19), 182 (30), 180 (29), 145 (100), 101 (53).

$C_{11}H_{10}BrIO_2$ HRMS Calcd. 379.8909

Found 379.8910.

Synthesis of 3-bromo-3-iodo-2-methylacrylic acid methyl ester (45b)



The reaction was carried out according to TP 2 using **41b** (252 mg, 0.98 mmol), *i*-PrMgCl (0.53 mL, 1.07 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min), iodine (357 mg, 1.07 mmol). After 4 h, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (10 mL) and extracted with Et_2O. The organic layer was washed successively with $Na_2S_2O_3$, then with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O 3:1), yielding the product **45b** (268 mg, 89 % yield) as a yellow oil.

IR (KBr): 2950 (w), 1728 (s), 1433 (m), 1252 (m), 1128 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 141.7, 57.2, 53.0, 22.2.

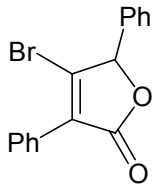
MS (EI) 306 (45), 304 (48), 275 (19), 273 (19), 179 (93), 177 (100), 127 (11).

$C_5H_6BrIO_2$ HRMS Calcd. 303.8596

Found 303.8604.

$C_5H_6BrIO_2$	Calcd.	C 19.70	H 1.98	
	Found	C 19.92	H 2.00.	

Synthesis of 4-bromo-3,5-diphenyl-5H-furan-2-one (46a)



The reaction was carried out according to TP 2 using **41a** (304 mg, 0.91 mmol), *i*-PrMgCl (0.5 mL, 1 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min) and benzaldehyde (0.1 mL, 1.1 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) yielding the product **46a** (158 mg, 55 % yield) as colorless crystals.

Mp = 140 °C.

IR (KBr): 3487 (w), 1752 (s), 1634 (m), 1492 (m), 1294 (s), 1159 (m) cm^{-1}.

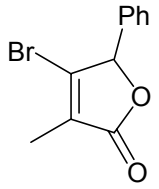
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.85 (m, 2H), 7.55–7.35 (m, 8H), 5.92 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 143.8, 133.7, 130.3, 129.9, 129.5, 129.1, 128.9, 127.9, 85.5.

MS (EI) 314 (4), 235 (100), 191 (23), 189 (22), 179 (33), 129 (13), 105 (100).

$C_{16}H_{11}BrO_2$	HRMS	Calcd. 313.9942			
		Found 313.9922.			
$C_{16}H_{11}BrO_2$	Calcd.	C 60.98	H, 3.52	Br 25.35	
	Found	C 60.87	H 3.51	Br 25.78.	

Synthesis of 4-bromo-3-methyl-5-phenyl-5H-furan-2-one (46b)



The reaction was carried out according to TP 2 using **41b** (283 mg, 1.10 mmol), *i*-PrMgCl (0.6 mL, 1.2 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min) and benzaldehyde (0.16 mL, 1.6 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) yielding the product **46b** (157 mg, 56 % yield) as a colorless oil.

IR (KBr): 3034 (w), 1766 (s), 1660 (m), 1456 (m), 1271 (m), 1088 (m) cm^{-1}.

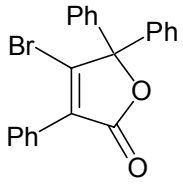
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.30 (m, 3H), 7.21–7.16 (m, 2H), 5.68 (s, 1H), 1.91 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 144.6, 133.6, 130.2, 129.3, 127.7, 85.6, 10.7.

MS (EI) 254 (20), 252 (21), 173 (100), 145 (10), 128 (22), 117 (14), 105 (48).

$C_{11}H_9BrO_2$	HRMS	Calcd.	251.9786
		Found	251.9806.
$C_{11}H_9BrO_2$	Calcd.	C 52.20	H 3.58
	Found	C 52.57	H, 3.62.

Synthesis of 4-bromo-3,5,5-triphenyl-5H-furan-2-one (47)



The reaction was carried out according to TP 2 using **41a** (238 mg, 0.71 mmol), *i*-PrMgCl (0.4 mL, 0.78 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min) and benzophenone (184 mg, 1.1 mmol) to give a crude residue, which was purified by flash

column chromatography on silica gel (pentane/Et_2O 9:1) yielding the product **47** (222 mg, 79 % yield) as a colorless oil.

IR (KBr): 3436 (m), 1762 (s), 1446 (m), 1171 (m) cm^{-1}.

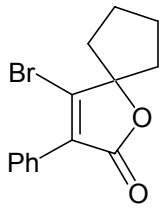
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.72 (m, 2H), 7.45–7.30 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 146.6, 136.7, 129.5, 128.8, 128.2, 127.4, 127.2, 91.1.

MS (EI) 392 (2), 312 (100), 265 (51), 178 (21), 165 (34), 129 (12), 106 (16).

$C_{22}H_{15}BrO_2$	HRMS	Calcd. 390.0255	
		Found 390.0258.	
$C_{22}H_{15}BrO_2$	Calcd.	C 67.53	H 3.86
	Found	C 67.48	H 4.23.

Synthesis of 4-bromo-3-phenyl-1-oxa-spiro[4.4]non-3-en-2-one (48)



The reaction was carried out according to TP 2 using **41a** (312 mg, 0.93 mmol), *i*-PrMgCl (0.51 mL, 1.03 mmol, 2 M in Et_2O) (exchange at -50 °C, 15 min) and cyclopentanone (0.1 mL, 1.12 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 5:1) yielding the product **48** (195 mg, 71 % yield) as a white solid.

Mp = 138 ^{o}C.

IR (KBr): 3470 (w), 1739 (s), 1643 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.70 (m, 2H), 7.51–7.42 (m, 3H), 2.31–2.20 (m, 2H), 2.11–1.90 (m, 6H).

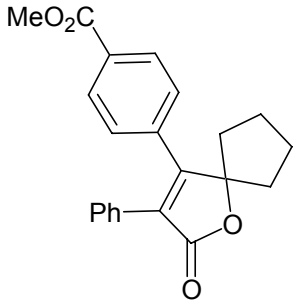
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 145.9, 127.9, 127.1, 126.8, 94.8, 35.6, 23.6.

MS (EI) 294 (1), 292 (1), 213 (100), 186 (9), 157 (28), 129 (43), 115 (19).

$C_{14}H_{13}BrO_2$ HRMS Calcd. 292.0099

Found 292.0084.

Synthesis of 4-(2-oxo-3-phenyl-1-oxa-spiro[4.4]non-3-en-4-yl)-benzoic acid methyl ester (51)



The reaction was carried out according to TP 3 using 4-iodo-benzoic acid methyl ester **50** (200 mg, 0.76 mmol), *i*-PrMgCl (0.52 mL, 0.84 mmol, 1.6 M in THF) (exchange at - 20 °C, 30 min), $ZnBr_2$ (0.56 mL, 1.5 M in THF, 0.84 mmol), $Pd(dba)_2$ (14 mg, 5 mol %), tfp (11 mg, 10 mol %) and bromolactone **48** (150 mg, 0.51 mmol). The residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) to give the spirolactone **51** (135 mg, 76 % yield) as a white solid.

Mp = 135 °C.

IR (KBr): 3480 (w), 2948 (w), 1752 (s), 1728 (s), 1435 (w), 1273 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02–7.98 (m, 2H), 7.36–7.12 (m, 7H), 3.86 (s, 3H), 2.05–1.60 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 166.7, 162.2, 137.7, 131.1, 130.5, 130.4, 130.1, 129.7, 129.4, 129.2, 129.0, 128.8, 128.6, 128.5, 96.3, 52.7, 36.7, 24.8.

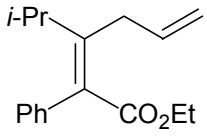
MS (EI) 348 (46), 319 (11), 291 (11), 261 (14), 243 (14), 203 (35), 185 (100), 157 (20).

$C_{22}H_{20}O_4$ HRMS Calcd. 348.1362

Found 348.1356.

9. Preparation of alkenyl Grignard reagents from alkenyl carbenoids

Synthesis of 3-isopropyl-2-phenyl-hexa-2,5-dienoic acid ethyl ester (61a)



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromoester **41a** (230 mg, 0.68 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to –78 °C and a solution of *i*-PrMgCl (0.72 mL, 1.44 mmol, 2 M in Et_2O) was added dropwise. After 15 min of stirring at –78 °C, then 3 h at 0 °C, a solution of CuCN·2LiCl (0.01 mL, 0.01 mmol, 1 M in THF) was slowly added. After 5 min at 0 °C, allyl bromide (0.07 mL, 0.82 mmol) was added and the reaction mixture was allowed to stirr at 0 °C overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O 4:1), yielding the product **61a** (133 mg, 75 % yield) as a colorless oil.

IR (KBr): 3417 (w), 2966 (m), 1715 (s), 1443 (m), 1236 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 5.91–5.76 (m, 1H), 5.08–4.92 (m, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.12 (dt, J = 6.3 Hz, J = 1.7 Hz, 2H), 2.60–2.49 (m, 1H), 1.10 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.8 Hz, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 151.9, 137.5, 129.2, 128.2, 127.1, 115.4, 60.5, 32.3, 20.8, 14.1.

MS (EI) 258 (8), 217 (22), 189 (13), 185 (82), 169 (25), 143 (100), 128 (54), 115 (38), 91 (34).

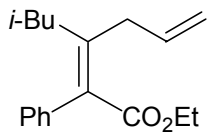
$C_{17}H_{22}O_2$ HRMS Calcd. 258.1620

Found 258.1604.

Compound **61a** prepared in THF according to Scheme 31.

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the diiodoester **41b** (191 mg, 0.44 mmol) in THF (4 mL) under argon. The reaction mixture was cooled to – 78 °C and a solution of *i*-PrMgCl (0.55 mL, 0.93 mmol, 1.7 M in THF) was added dropwise. After 5 min of stirring at – 78 °C, then 2 h at – 10 °C, a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 1 M in THF) was slowly added. After 5 min at – 10 °C, allyl bromide (0.04 mL, 0.5 mmol) was added and the reaction mixture was allowed to stirr at – 10 °C overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O 4:1), yielding a mixture of isomers (determined by GC, GC-MS and NMR, *E:Z*-**61a** = 1:9) (89 mg, 78 % yield) as a colorless oil.

Synthesis of 3-isobutyl-2-phenyl-hexa-2,5-dienoic acid ethyl ester (61b)



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromoester **41a** (216 mg, 0.65 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to – 78 °C and a solution of *i*-BuMgCl (0.68 mL, 1.35 mmol, 2 M in Et_2O) was added dropwise. After 15 min of stirring at – 78 °C, then 4 h at 0 °C, a solution of CuCN·2LiCl (0.06 mL, 0.06 mmol, 1 M in THF) was slowly added. After 5 min at 0 °C, allyl bromide (0.06 mL, 0.77 mmol) was added and the reaction mixture was allowed to stirr at 0 °C overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O, 50:3), yielding the product **61b** (128 mg, 73 % yield) as a colorless oil.

IR (KBr): 3412 (w), 2957 (m), 1715 (s), 1464 (m), 1236 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 3H), 7.21–7.17 (m, 2H), 5.96–5.85 (m, 1H), 5.16–5.06 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.18 (d, J = 6.7 Hz, 2H), 1.91 (d, J = 7.0 Hz, 2H), 1.88–1.76 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.75 (d, J = 6.4 Hz, 6H).

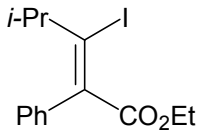
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 146.3, 137.7, 136.0, 132.6, 129.7, 128.0, 127.0, 116.2, 60.5, 41.2, 37.3, 26.4, 22.5, 14.1.

MS (EI) 272 (4), 227 (10), 211 (18), 199 (87), 169 (26), 155 (63), 143 (100), 129 (42), 115 (53), 91 (17).

$C_{18}H_{24}O_2$ HRMS Calcd. 272.1776

Found 272.1765.

Synthesis of 3-iodo-4-methyl-2-phenyl-pent-2-enoic acid ethyl ester (62)



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromoester **41a** (205 mg, 0.61 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to – 78 ^{o}C and a solution of *i*-PrMgCl (0.72 mL, 1.44 mmol, 2 M in Et_2O) was added dropwise. After 15 min of stirring at – 78 ^{o}C, then 3 h at 0 °C, a solution of iodine (342 mg, 1.34 mmol) in Et_2O (4 mL) was added and the reaction mixture was allowed to warm up to rt overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with sat. solution of $Na_2S_2O_3$ and then brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O 5:1), yielding the product **62** (172 mg, 82 % yield) as a colorless oil.

IR (KBr): 3432 (w), 2966 (s), 1727 (s), 1614 (m), 1443 (m), 1266 (s), 1201 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.19 (m, 5H), 4.16 (q, J = 7.1 Hz, 2H), 2.12–2.02 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.4 Hz, 6H).

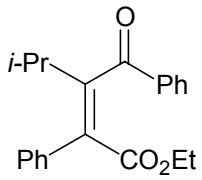
^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.0, 141.3, 136.5, 129.1, 128.6, 128.5, 121.9, 89.1, 62.0, 34.7, 23.9, 14.4.

MS (EI) 344 (3), 217 (44), 189 (24), 171 (31), 143 (100), 128 (80), 115 (14), 77 (13).

$C_{14}H_{17}IO_2$ HRMS Calcd. 344.0273

Found 344.0241.

Synthesis of 3-benzoyl-4-methyl-2-phenyl-pent-2-enoic acid ethyl ester (63)



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromoester **41a** (210 mg, 0.63 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to – 78 °C and a solution of *i*-PrMgCl (0.66 mL, 1.32 mmol, 2 M in Et_2O) was added dropwise. After 15 min of stirring at –78 °C, then 3 h at 0 °C, a solution of CuCN·2LiCl (0.66 mL, 0.66 mmol, 1 M in THF) was slowly added. After 5 min at 0 °C, benzoyl chloride (0.1 mL, 0.75 mmol) was added and the reaction mixture was allowed to stirr at 0 °C overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O 3:1), yielding the product **63** (124 mg, 61 % yield) as a colorless oil.

IR (KBr): 2972 (m), 1712 (s), 1670 (s), 1596 (m), 1448 (m), 1290 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97–7.92 (m, 2H), 7.53–7.25 (m, 8H), 3.78 (q, J = 7.1 Hz, 2H), 2.78–2.64 (m, 1H), 0.90 (d, J = 7.1 Hz, 6H), 0.80 (t, J = 7.1 Hz, 3H).

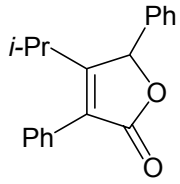
^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 166.5, 157.4, 137.8, 135.9, 133.4, 132.2, 129.7, 129.0, 128.9, 128.7, 128.2, 61.6, 32.1, 21.6, 13.9.

MS (EI) 322 (4), 276 (100), 217 (15), 143 (20), 105 (90), 77 (50).

$C_{21}H_{22}O_3$ HRMS Calcd. 322.1569

Found 322.1581.

Synthesis of 4-isopropyl-3,5-diphenyl-5H-furan-2-one (64)



A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromoester **41a** (214 mg, 0.64 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to – 78 ^oC and a solution of *i*-PrMgCl (0.67 mL, 1.34 mmol, 2 M in Et_2O) was added dropwise. After 15 min of stirring at –78 ^oC, then 3 h at 0 °C, benzaldehyde (0.08 mL, 0.77 mmol) was added and the reaction mixture was allowed to warm up to rt overnight. The reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/Et_2O, 3:1), yielding the product **64** (100 mg, 56 % yield) as a colorless oil.

IR (KBr): 3491 (w), 2970 (m), 1755 (s), 1445 (m), 1132 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.32 (m, 8H), 7.27–7.19 (m, 2H), 5.83 (s, 1H), 2.99–2.96 (m, 1H), 1.03 (d, J = 7.1 Hz, 3H), 0.67 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.5, 169.3, 135.8, 130.7, 129.9, 129.7, 129.3, 129.0, 128.9, 128.0, 127.0, 83.4, 28.5, 22.1, 21.3.

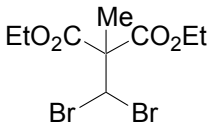
MS (EI) 278 (2), 235 (100), 179 (10), 129 (8), 105 (30), 77 (5).

$C_{19}H_{18}O_2$ HRMS Calcd. 278.1307

Found 278.1300.

10. Preparation of functionalized alkyl carbenoids.

Synthesis of 2-dibromomethyl-2-methyl-malonic acid diethyl ester (66)[50]



Diethylmethylmalonate (5 g, 28.7 mmol) was slowly added to sodium hydride (55 % in mineral oil: 1.4 g, 31.5 mmol) in dry Et_2O (40 mL) during 1 h under argon with vigorous stirring and the resulting thick mixture was refluxed for a further 5 h. Bromoform (8.7 g, 34.4 mmol) was added slowly and the mixture was refluxed for 15 h under argon. After being cooled to 0 ^oC, 10 % aqueous HCl (50 mL) was added and the mixture stirred for 10 min. The organic phase was decanted, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **66** (3.6 g, 37 % yield) as a colorless oil.

IR (KBr): 2983 (w), 1742 (s), 1239 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (s, 1H), 4.30–4.20 (m, 2H), 1.80 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

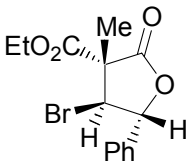
^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.1, 63.0, 46.7, 16.5, 14.3.

MS (EI) 347 (22), 301 (31), 273 (42), 195 (95), 193 (100), 167 (83), 165 (88), 149 (43), 147 (44), 113 (36).

$C_9H_{14}O_4Br_2$ HRMS Calcd. 343.9259

Found 343.9230.

Synthesis of 4-bromo-3-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (67)



The reaction was carried out according to TP 2 using **66** (247 mg, 0.71 mmol), *i*-PrMgCl (0.39 mL, 0.78 mmol, 2 M in Et_2O) (exchange at -78 °C, 20 min) and benzaldehyde (83 mg, 0.78 mmol) to give a crude residue, which was a 6:1 mixture of two diastereoisomers. After purification by flash column chromatography on silica gel (pentane/Et_2O 3:1), the major diastereoisomer of **67** (152 mg, 65 % yield) was obtained as a colorless oil.

Data of the major diastereoisomer

IR (KBr): 2986 (w), 1792 (s), 1747 (s), 1244 (m), 1108 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 5.30 (d, J = 9.1 Hz, 1H), 4.83 (d, J = 9.1 Hz, 1H), 4.23–4.15 (m, 2H), 1.62 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.0, 168.3, 134.7, 130.1, 129.3, 127.0, 84.9, 63.3, 55.8, 55.0, 18.1, 14.3.

MS (EI) 329 (6), 327 (6), 247 (100), 219 (22), 194 (17), 173 (36), 129 (96), 105 (28).

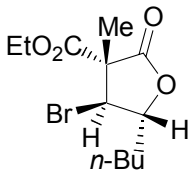
$C_{14}H_{15}O_4Br$ HRMS Calcd. 327.0232 $[M+H]^+$

Found 327.0245.

NMR data of the minor diastereoisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.28 (m, 5H), 5.65 (d, J = 3.6 Hz, 1H), 5.19 (d, J = 3.6 Hz, 1H), 4.33 (dq, J = 7.1 Hz, J = 1.5 Hz, 2H), 1.72 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).

Synthesis of 4-bromo-5-*n*-butyl-3-methyl-2-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (68)



The reaction was carried out according to TP 2 using **66** (233 mg, 0.67 mmol), *i*-PrMgCl (0.37 mL, 0.74 mmol, 2 M in Et_2O) (exchange at -78 °C, 20 min) and *n*-valeraldehyde (69 mg, 0.81 mmol) to give a crude residue, which was a 7:1 mixture of two diastereoisomers. After purification by flash column chromatography on silica gel (pentane/Et_2O 3:1), the major diastereoisomer of **68** (110 mg, 55 % yield) was obtained as a colorless oil.

Data of the major diastereoisomer

IR (KBr): 2960 (w), 1790 (s), 1748 (m), 1457 (w), 1246 (m), 1095 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (d, J = 9.1 Hz, 1H), 4.44–4.38 (m, 1H), 4.28 (q, J = 7.1, 2H), 2.03–1.94 (m, 1H), 1.78–1.62 (m, 1H), 1.60–1.35 (m, 4H), 1.59 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H).

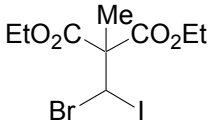
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.7, 168.2, 83.7, 62.7, 55.2, 51.9, 31.6, 27.4, 22.3, 17.5, 14.0.

MS (EI) 307 (2), 249 (2), 183 (25), 155 (10), 137 (8), 109 (100).

$C_{12}H_{19}O_4Br$ HRMS Calcd. 307.0545 $[M+H]^+$

Found 307.0462.

Synthesis of 2-bromo-iodo-methyl-2-methyl-malonic acid diethyl ester (69)



The reaction was carried out according to TP 2 using **66** (279 mg, 0.8 mmol), *i*-PrMgCl (0.44 mL, 0.88 mmol, 2 M in Et_2O) (exchange at -78 °C, 20 min), iodine (245 mg,

0.96 mmol in 3 mL Et_2O). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (10 mL) and extracted with Et_2O. The organic layer was washed successively with $Na_2S_2O_3$, with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **69** (255 mg, 80 % yield) as a colorless oil

IR (KBr): 2982 (w), 1739 (s), 1449 (m), 1233 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (s, 1H), 4.30–4.20 (m, 2H), 1.80 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

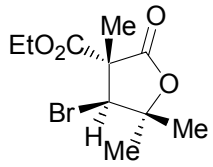
^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.1, 63.0, 46.7, 16.5, 14.3.

MS (EI) 393 (2), 349 (4), 347 (4), 321 (12), 319 (11), 267 (10), 265 (9) 195 (67), 193 (72), 167 (100), 165 (90).

$C_9H_{14}O_4BrI$ HRMS Calcd. 392.9198 $[M+H]^+$

Found 392.9169.

Synthesis of 4-bromo-3,5,5-trimethyl-2-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (70)



The reaction was carried out according to TP 2 using **66** (256 mg, 0.73 mmol), *i*-PrMgCl (0.41 mL, 0.82 mmol, 2 M in Et_2O) (exchange at -78 °C, 20 min) and acetone (51 mg, 0.88 mmol) to give a crude residue. After purification by flash column chromatography on silica gel (pentane/Et_2O 5:1), only one diastereoisomer of **70** (124 mg, 60 % yield) was obtained as a colorless oil.

IR (KBr): 2988 (m), 1782 (s), 1747 (s), 1453 (m), 1381 (m), 1261 (s), 1085 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (s, 2H), 4.20 (dq, J = 7.1 Hz, J = 1.2 Hz, 2H), 1.60 (s, 3H), 1.42 (d, J = 4.0 Hz, 6H), 1.24 (t, J = 7.1 Hz, 3H).

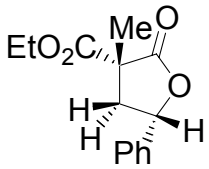
^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.1, 169.3, 85.7, 63.3, 57.7, 56.1, 28.3, 26.7, 20.4, 14.3.

MS (EI) 281 (6), 279 (7), 155 (52), 127 (73), 109 (75), 81 (72), 43 (100).

$C_{10}H_{15}O_4Br$ HRMS Calcd. 279.0232 $[M+H]^+$

Found 279.0205.

Synthesis of ethyl (3R,5S)-3-methyl-2-oxo-5-phenyltetrahydrofuran-3-carboxylate (71a)[51]



To a solution of major diastereomer of **67** (100 mg, 0.3 mmol) and AIBN (5 mg, 0.03 mmol) in dry toluene (2 mL) was added Bu_3SnH (174 mg, 0.6 mmol) and the reaction mixture was stirred for 15 min at rt and then concentrated. The residue was taken up in hexane, treated with aq. KF and extracted with Et_2O (3 x 20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording only one diastereoisomer of **71a** (67 mg, 90 % yield) as a colorless oil.

IR (KBr): 2957 (m), 1783 (s), 1740 (m), 1460 (m), 1381 (w), 1174 (m), 1102 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.44 (dd, J = 6.8 Hz, J = 8.8 Hz 1H), 4.16-4.06 (m, 2H), 2.78 (dd, J = 8.8 Hz, J = 13.1 Hz, 1H), 2.48 (dd, J = 6.8 Hz, J = 13.1 Hz, 1H), 1.56 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H).

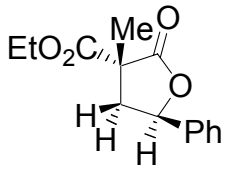
^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.5, 171.1, 146.9, 127.8, 126.9, 124.6, 77.3, 61.3, 41.9, 24.1, 18.8, 12.9.

MS (EI) 248 (7), 220 (43), 174 (85), 131 (48), 115 (74), 105 (100), 91 (36), 41 (26).

$C_{14}H_{16}O_4$ HRMS Calcd. 248.1049

Found 248.1067.

Synthesis of ethyl (3R,5R)-3-methyl-2-oxo-5-phenyltetrahydrofuran-3-carboxylate (71b)[51]

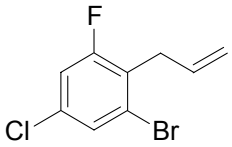


To a solution of minor diastereomer of **67** (20 mg, 0.06 mmol) and AIBN (1 mg, 0.006 mmol) in dry toluene (0.5 mL) was added Bu_3SnH (35 mg, 0.12 mmol) and the reaction mixture was stirred for 15 min at rt and then concentrated. The residue was taken up in hexane, treated with aq. KF and extracted with Et_2O (3 x 5 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording only one diastereoisomer of **71b** (12 mg, 87 % yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.50 (dd, J = 6.1 Hz, J = 10.1 Hz 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.02 (dd, J = 6.1 Hz, J = 13.2 Hz, 1H), 2.04 (dd, J = 10.1 Hz, J = 13.2 Hz, 1H), 1.50 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

11. Selective bromine-magnesium exchange using inductive effect

Synthesis of 2-allyl-1-bromo-5-chloro-3-fluoro-benzene (74)



The reaction was carried out according to TP 2 using 1,2-dibromo-5-chloro-3-fluoro-benzene **72** (260 mg, 0.9 mmol), *i*-PrMgCl (0.45 mL, 0.99 mmol, 2 M in Et_2O), (exchange at rt, 30 min)), CuCN·2LiCl (0.09 mL, 0.09 mmol, 1 M in THF) and allyl bromide (129 mg, 1.08 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 9:1) affording a 94:6 mixture of regioisomers **74** (193 mg, 85 %) as a colorless oil.

NMR data of the major regioisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.34 (m, 1H), 6.97 (dd, J = 9.0 Hz, J =1.9 Hz, 1H), 5.86–5.72 (m, 1H), 5.02–4.92 (m, 2H), 3.46–3.40 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.4, 158.0, 132.3, 127.3, 125.4, 125.2, 124.5, 115.5, 114.7, 114.3, 31.7.

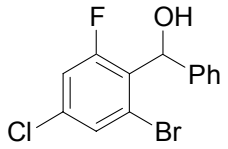
IR (KBr): 3368 (s), 2970 (m), 1561 (s), 1404 (m) cm^{-1}.

MS (EI) 250 (100), 248 (78), 223 (30), 221 (23), 169 (21), 134 (100), 133 (98), 107 (23).

C_9H_7FClBr HRMS Calcd. 247.9404

Found 247.9430.

Synthesis of (2-bromo-4-chloro-6-fluoro-phenyl)-phenyl-methanol (75)



The reaction was carried out according to TP 2 using 1,2-dibromo-5-chloro-3-fluoro-benzene **72** (300 mg, 1 mmol), *i*-PrMgCl (0.52 mL, 1.1 mmol, 2 M in Et_2O), (exchange at rt, 30 min) and benzaldehyde (0.16 mL, 1.56 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 4:1) affording an inseparable 94:6 mixture of regioisomers **75** (204 mg, 62 %) as a colorless oil.

NMR data of the major regioisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.34 (m, 1H), 7.28–7.15 (m, 8H), 6.98 (dd, J = 10.2 Hz, J = 2.2 Hz, 1H), 6.26 (d, J = 8.1 Hz, 1H), 2.9 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.2, 159.9, 146.4, 141.6, 135.4, 129.8, 128.9, 128.1, 127.6, 125.9, 124.3, 117.3, 73.1.

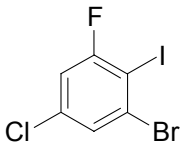
IR (KBr): 3391 (b), 1597 (s), 1404 (s), 1024 (m) cm^{-1}.

MS (EI) 315 (91), 313 (73), 236 (100), 217 (40), 183 (32), 107 (32), 79 (65).

$C_{13}H_9OFClBr$ HRMS Calcd. 313.9509

Found 313.9499.

Synthesis of 1-bromo-5-chloro-3-fluoro-2-iodo-benzene (76)



The reaction was carried out according to TP 2 using 1,2-dibromo-5-chloro-3-fluoro-benzene **72** (290 mg, 1 mmol), *i*-PrMgCl (0.5 mL, 1.1 mmol, 2 M in Et_2O), (exchange at rt, 30 min) and iodide (382 mg, 1.5 mmol, dissolved in 3 mL Et_2O) to give a crude residue, which was purified by flash column chromatography on silica gel

(pentane/Et_2O 9:1) affording an inseparable 94:6 mixture of regioisomers **76** (294 mg, 87 %) as a pink oil.

NMR data of the major regioisomer

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 2.2 Hz, J = 1.5 Hz, 1H), 6.94 (dd, J = 2.1 Hz, J = 7.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 161.1, 136.0, 131.2, 128.3, 115.1, 114.8, 88.6.

^{19}F NMR (375 MHz, $CDCl_3$): δ -79.9.

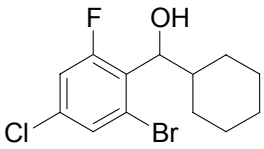
IR (KBr): 1553 (s), 1397 (s), 1093 (w) cm^{-1}.

MS (EI) 335 (100), 333 (93), 208 (22), 128 (25), 93 (6).

$C_6H_2FClBrI$ HRMS Calcd. 333.8057

Found 333.8044.

Synthesis of (2-bromo-4-chloro-6-fluoro-phenyl)-cyclohexyl-methanol (77)



The reaction was carried out according to TP 2 using 1,2-dibromo-5-chloro-3-fluoro-benzene **72** (338 mg, 1.1 mmol), *i*-PrMgCl (0.58 mL, 1.3 mmol, 2 M in Et_2O), (exchange at rt, 30 min) and cyclohexanecarbaldehyde (0.2 mL, 1.64 mmol) to give a crude residue, which was purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording a single regioisomer of **77** (233 mg, 61 %) as a colorless oil.

IR (KBr): 3400 (b), 2852 (s), 1596 (s), 1407 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 1H), 6.98 (dd, J = 10.8 Hz, J = 1.9 Hz, 1H), 4.71 (d, J = 9.2 Hz, 1H), 2.31 (s, 1H), 2.11 (d, J = 11.5 Hz, 1H), 1.89–1.47 (m, 4H), 1.22–0.90 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 163.1, 159.7, 134.5, 129.6, 129.2, 124.5, 117.0, 116.7, 43.7, 30.3, 29.6, 26.6, 26.3, 26.1.

MS (EI) 287 (5), 285 (5), 238 (100), 236 (90), 157 (10), 130 (9), 83 (22), 55 (52).

$C_{13}H_{15}OFClBr$	HRMS	Calcd.	319.9979
		Found	319.9920.

Crystallographic data of compound 37c

Empirical formula	$C_{12}\ H_{11}\ O_2\ Br$	
Formula weight	267.12	
Temperature	293(2) K	
Wavelength	0.71073	
Crystal system	orthorhombic	
Space group	Pna21	
Unit cell dimensions	a = 7.098 (3) Å	alpha = 90 deg.
	b = 24.609 (5) Å	beta = 90 deg.
	c = 6.3907 (14) Å	gamma = 90 deg.
	Volume 1116.3 (5) $Å^3$	
	Z = 4	
Density (calculated)	1.589 g/cm^3	
Absorption coefficient	3.658 mm^{-1}	
F(000)	536	
Crystal size	0.53 x 0.43 x 0.13 mm	
Theta range for data collection	3.29 to 23.98 deg.	
Index ranges	$-8 \leq h \leq 8, -28 \leq k \leq 28, -7 \leq l \leq 7$	
Reflections collected	1914	
Independent reflections	1736 [R(int) = 0.0275]	
Absorption correction	Semi-empirical by psi-scans	
Max. and min. transmission	0.9987 and 0.6397	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	1736 / 1 / 137	
Goodness-of-fit on F2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR^2 = 0.1035	
R indices (all data)	R1 = 0.0819, wR^2 = 0.1356	
Absolute structure parameter	-0.04(3)	
Largest diff. peak and hole	0.786 and -0.770 [$e/Å^3$]	

Crystallographic data of compound 46a

Empirical formula	$C_{16}H_{11}O_2Br$
Formula weight	315.16
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C2/c
Unit cell dimensions	a = 20.885 (2) Å alpha = 90 deg.
	b = 9.2513 (6) Å beta = 122.258 (7) deg.
	c = 15.882 (13) Å gamma = 90 deg.
	Volume 2595.0 (4) $Å^3$
	Z = 8
Density (calculated)	1.613 g/cm^3
Absorption coefficient	3.162 mm^{-1}
F(000)	1264
Crystal size	0.43 x 0.33 x 0.13 mm
Theta range for data collection	2.49 to 23.97 deg.
Index ranges	$0 \leq h \leq 23$, $-10 \leq k \leq 0$, $-18 \leq l \leq 15$
Reflections collected	2028
Independent reflections	1576 [R(int) = 0.0098]
Absorption correction	Semi-empirical by psi-scans
Max. and min. transmission	0.9988 and 0.7116
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2028 / 0 / 172
Goodness-of-fit on F2	1.146

Final R indices [I>2sigma(I)]	R1 = 0.0302, wR^2 = 0.0660
R indices (all data)	R1 = 0.0468, wR^2 = 0.0746

Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	azo*iso*-butyronitrile
aq.	aqueos
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bp	boiling point
br	broad
Bu	butyl
c	concentration
Calcd.	calculated
cat.	Catalytic
conc.	concentrated
cont.	continued
d	doublet
dba	dibenzylideneacetone
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
equiv	equivalent
EI	electron ionisation
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethylether
FG	functional group
GC	gas chromatography
h	hour
HMBC	heteronuclear multiple bond coherence
HRMS	high resolution mass spectroscopy
i-Pr	isopropyl
i-Bu	isobutyl
IR	infra-red
J	coupling constant

M	molar
Me	methyl
min	minute
Mp	melting point
MS	mass spectroscopy
NOESY	nuclear overhauser effect spectroscopy
NMP	*N*-methyl-pyrrolidone
NMR	nuclear magnetig resonance
Ph	phenyl
Piv	pivaloyl
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
sec	seconds
t	triplet
TBAB	tetra-*n*-butylammonium bromide
TEA	triethyl amine
TFA	trifluoroacetic acid
TLC	thin layer chromatography
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TP	typical procedure
UV	ultra-violet

CURRICULUM VITAE

1. Personal data

Name:	Viet Anh
Family name:	Vu
Date of birth:	16 July, 1974
Place of birth:	Hanoi, Vietnam
Sex:	Male
Marital status:	Single
Nationality:	Vietnamese

2. Education background

1991-1996	HoChiMinh City Medicine and Pharmacy University, Faculty of Pharmacy, HoChiMinh City, Vietnam Field of study: Pharmaceutical Science
1998-2000	Vrije Universiteit Brussel, Brussel, Belgium MSc in Medical and Pharmaceutical Research (taught in English) Subject of thesis: "Development of a fast separation strategy for chiral substances using normal phase liquid chromatography"
2000 – 2003	LMU, Chemistry Department, München, Germany PhD in the group of Prof. P. Knochel Subject of thesis: “Preparation of new functional organomagnesium reagents using a halogen-magnesium exchange”

3. Language skills

Vietnamese: mother tongue

English: fluently (written and spoken)

4. Publications

1. Vu, V. A.; Bérillon, L.; Knochel, P. "New Functionalized Alkenylmagnesium Reagents Bearing an Oxygen Function in the beta-Position. Preparation and Reaction of 5-Magnesiated-1,3-Dioxin-4-one Derivatives", *Tetrahedron Lett*. **2001**, *42*, 6847.

2. Knochel, P.; Hupe, E.; Dohle, W.; Lindsay, D. M.; Bonnet, V.; Boudier, A.; Kopp, F.; Demay, S.; Seidel, N.; Calaza, I.; Vu, V. A.; Monguchi, Y.; Sapountzis, I.; Wendicke, S.; Bunlaksananusorn, T. "Functionalized Main Group Organometallics for Organic Synthesis" *Pure Appl. Chem*. **2002**, *47*, 11.

3. Thibonnet, J.; Vu, Viet Anh; Berillon, L.; Knochel. P. "Alkenylmagnesium Reagents *via* a Halide-Magnesium Exchange" *Tetrahedron* **2002**, *58*, 4787.

4. Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. „Practical Synthetic Procedures: Preparation and Reactions of Functionalized Arylmagnesium Reagents" *Synthesis* **2002**, *4*, 565.

5. Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P."Preparation of new functionalized cyclopropylmagnesium reagents" *Angew. Chem.* **2002**, *114,* 361; *Angew. Chem. Int. Ed*. **2002**, *41*, 351.

6. Perrin, C.; Vu, V. A.; Matthijs, N.; Maftouh, M.; Massart, D. L.; Vander Heyden, Y. "Screening approach for chiral separation of pharmaceuticals. Part I. Normal-phase liquid chromatography". *Journal of Chromatography. A*, **2002,** *947(1)*, 69.

7. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. "Highly Functionalized Magnesium Organometallics Prepared *via* a Halogen-Metal Exchange" *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed*. **2003,** *42***,** 4302.

8. Vu, V.A; Marek, I.; Knochel, P. "Stereoselective Preparation of Functionalized Unsaturated Lactones and Esters *via* Functionalized Magnesium Carbenoids" *Synthesis* **2003**, 1797.

5. Poster presentations

1) "Experimental design approach for the chiral separation of Beta Blockers by Normal Phase Liquid Chromatography", ChemoAc meeting Brussels - Belgium, **20 - 21 October 1999**.

2) "Advances in the Knowledge Based System in chiral separation : NPLC and CE", ChemoAC Meeting, Brussels - Belgium, **11-12 April 2000**.

3) "Experimental design approach for the chiral separation of beta-blockers and benzodiazepines using Normal Phase Liquid chromatography", 11th International symposium on Pharmaceutical and Biomedical Analysis Basel - Switzerland, **14-18 May 2000**.

4) "Prepation of functionalized cyclopropylmagensium reagents and functionalized alkenyl carbenoids *via* a halide-magnesium exchange", B.O.S.S-9, Namur (Belgium), **8-12 July, 2002**.