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BF_3-Mediated Direct Functionalizations of Pyridines

von

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aus

Shanghai, China

2014

Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

München, am 14 Feburary 2014

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Quan Chen

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1. Gutachter: Prof. Dr. Paul Knochel
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To

Xiaohui & Yinmiao

In memory of my mother-in-law

天若有情天亦老，人间正道是沧桑。

Mao Zedong

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Chapter 1. Introduction

1.1 Overview

Over the past 100 years, organic chemistry has been greatly developed in all the subfields such as synthetic methodologies, mechanism studies and analytical methods. A large variety of natural products, medicines, and functional materials can be prepared artificially nowadays. However, a synthetic route always requires multiple steps and expensive reagents, catalysts or solvents, resulting in high cost and a huge amount of waste. To resolving these problems, one of the main challenges of modern synthetic organic chemistry is preparing highly applicable target compounds selectively, efficiently and economically under mild conditions. Meanwhile, the loading of expensive or toxic reagents should be avoided, and the amount of wastes should be reduced.[1]

On the other hand, after decades of improvement, the organometallic chemistry has well matured, enabling the preparations of versatile functional organometallic reagents [2] for further transformations such as transition-metal-catalyzed cross-couplings.[3] Although many transition-metal-catalysts have been well known for their good activity and selectivity, the high price and difficulties in recovery hamper their applications in large scale transformations in industry. To explain these problems in details, three randomly picked examples of famous transition-metal-catalysts are shown in Figure 1: the Grubbs second generation catalyst for olefin- metathesis,[4] the PEPPSI-IPr for cross-coupling reactions [5] and the Hayashi catalyst for enantioselective 1,4-additions.[6] Notably, all of these catalysts are very expensive not only because of the employment of expensive transition-metals as catalytic centers, but also owing to the requirements of complex ligands to sustain the catalysts' activity and control the chemo-, regio- and stereoselectivity. Also, the transition-metal-catalyzed procedures are frequently accompanied by side reactions such as homo-coupling and β-hydride elimination. Besides, the toxicity of most transition-metals and the difficulties in removal of the harmful metal contamination in products make these procedures unattractive especially for pharmaceutical industry.[7]

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[1] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) R. Noyori, *Green Chem.* **2003**, *5*, G37; c) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259; d) R. Noyori, *Chem. Commun.* **2005**, 1807; e) R. H. Crabtree, *Organometallics* **2011**, *30*, 17.

[2] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

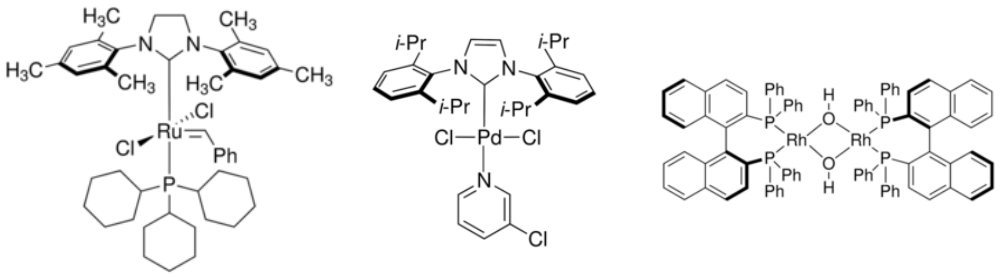
[3] *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[4] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.

[5] C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, 4343.

[6] T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829.

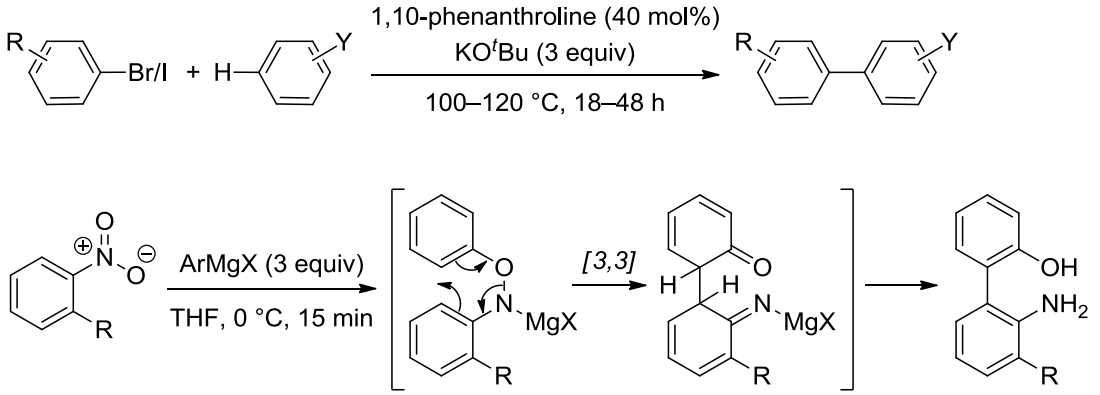
[7] a) C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889; b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang, *Org. Process Res. Dev.* **2005**, *9*, 198.



Grubbs II: 83 €/100 mg **PEPPSI-IPr**: 110 €/1 g **Hayashi Catalyst**: 354 €/1 g

Figure 1. Transition-metal-catalysts and their prices (data from Sigma-Aldrich ®).

As a better choice, the transition-metal-free cross-couplings or other similar procedures are really appreciated especially in industry because they get rid of all the drawbacks of transition-metals. Although such procedures are still rare, recently several elegant methods have been developed. In 2010, the Shi group reported a cross-coupling between arylbromides or iodides and simple arenes with the assistance of potassium butoxide, affording a series of biaryls. The reaction is proposed to undergo a radical pathway and a catalytic amount of phenanthroline type compounds is believed to facilitate the radical generation.[8] In 2013, the Kurti group reported a novel biaryl formation from ortho-substituted nitrobenzenes and arylmagnesium species. The *N*,*O*-biarylhydroxylamine is believed to form firstly, followed by a [3,3]-sigmatropic rearrangement to produce the 2-amino-2'-hydroxy-1,1'-biaryl as a highly functionalized product (Scheme 1).[9] The advantages of these processes are quite apparent, not only since there is no need of transition-metals, but also because they give products which are not easily accessible by transition-metal-catalyzed reactions.



Scheme 1. Transition-metal-free cross-couplings.

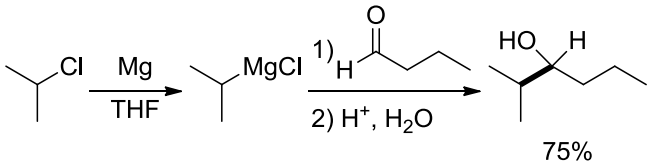
1.2 Preparation of Functionalized Organomagnesium Reagents

In 1912, Victor Grignard (1871–1935), a French organic chemist, was awarded that

[8] C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nature Chem.* **2010**, *2*, 1044.

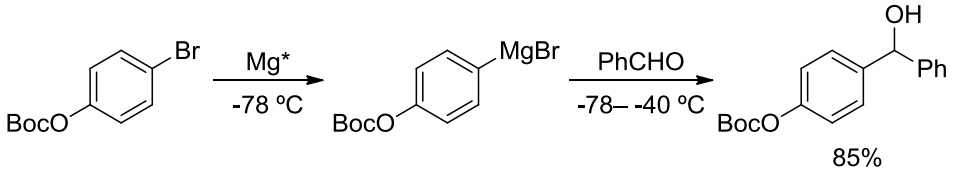
[9] H. Gao, D. H. Ess, M. Yousufuddin, L. Kurti, *J. Am. Chem. Soc.* **2013**, *135*, 7086.

year's Nobel Prize for chemistry for his contribution to the preparation of a series of organometallic reagents through a convenient direct insertion of magnesium metal into a carbon–halogen bond.[10] The insertion reaction proceeds smoothly in a solvent such as diethyl ether or THF. The produced organomagnesium species, which are called Grignard reagents now, are highly nucleophilic and react with a variety of electrophiles such as ketone, aldehyde, epoxide and organic halides to form a new carbon–carbon bond. These methods have been proven very useful and efficient in organic synthesis (Scheme 2).[11]



Scheme 2. Preparation of a Grignard reagent for the C–C bond formation

However, considering that the Grignard reagents are quite reactive at room temperature, the direct insertion method always requires a high reaction temperature (usually the boiling point of the solvent) and therefore is not compatible with many functional groups. To resolve this problem, *Rieke et al.* developed an elegant method to use in-situ reduced magnesium (also other metals including Ca, Zn, In and Cu), which is highly reactive owing to its big surface area and less coverage of surface oxides, for the preparation of functionalized Grignard reagents at low temperature (Scheme 3).[12]



Scheme 3. Preparation of functionalized Grignard reagent using active Rieke Mg.

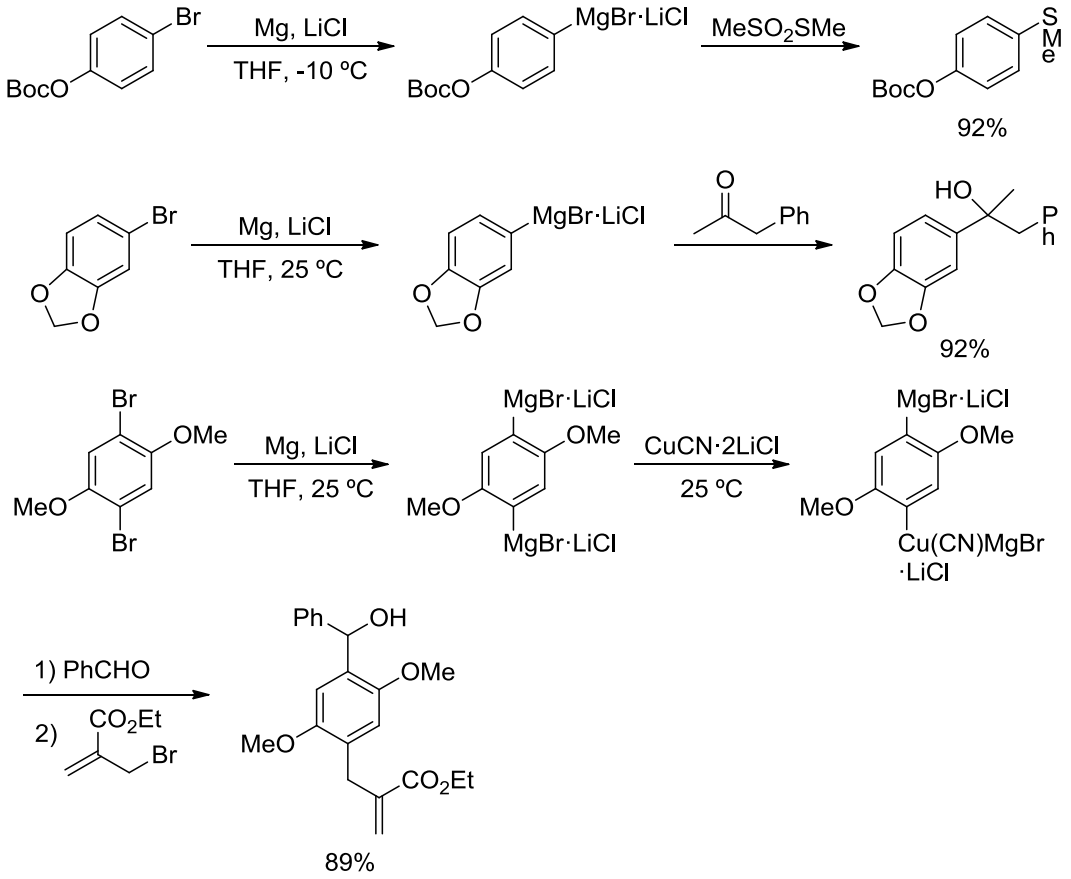
As a further improvement of the direct insertion method, *Knochel et al.* reported a LiCl-promoted preparation of Grignard reagent using commercial magnesium turnings or powder. In this procedure, LiCl is believed to solubilize the generated organomagnesium species and thus remove their clusters accumulating on the surface of metals, leading to more vacant sites for the following insertion reactions. As a

[10] V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.

[11] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **2000**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey Jr.), Wiley-VCH, New York, **2000**; c) J. Wiss, M. Länzlinger, M. Wermuth, *Org. Proc. Res. Dev.* **2005**, *9*, 365.

[12] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; c) J. Lee, R. Verlade-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

result, the insertion step is highly accelerated and the reaction can even occur at low temperature (≤ 0 °C). Thus, a variety of functionalized aryl and heteroaryl magnesium species can be prepared from the corresponding iodides, bromides and even chlorides (Scheme 4).[13]



Scheme 5. LiCl-promoted insertion of magnesium into functionalized aryl bromides.

As an alternative method, the halogen-metal exchange can easily furnish the Grignard reagent under mild conditions, avoiding the high temptation for reaction initiation in the insertion method. Therefore, a series of functional groups can be tolerated during these procedures. Despite the early examples,[14] *Knochel et al.* developed an iodine-magnesium exchange method employing ^{i}PrMgBr, $^{i}Pr_2Mg$ or PhMgCl and used it to prepare functionalized Grignard reagents (Scheme 5).[15]

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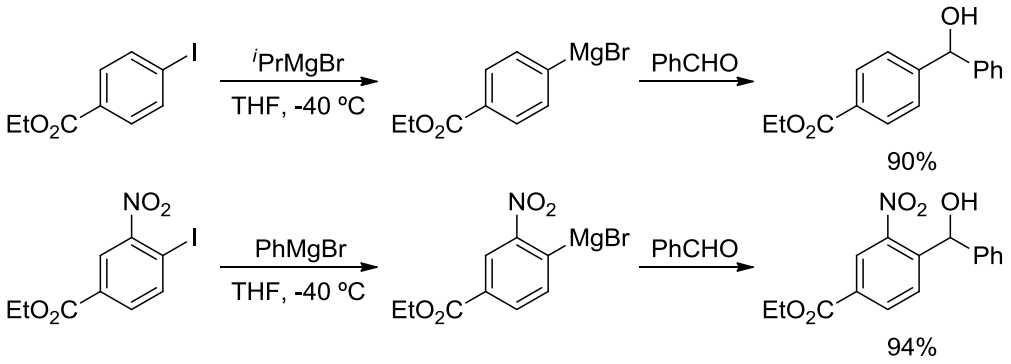
[13] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

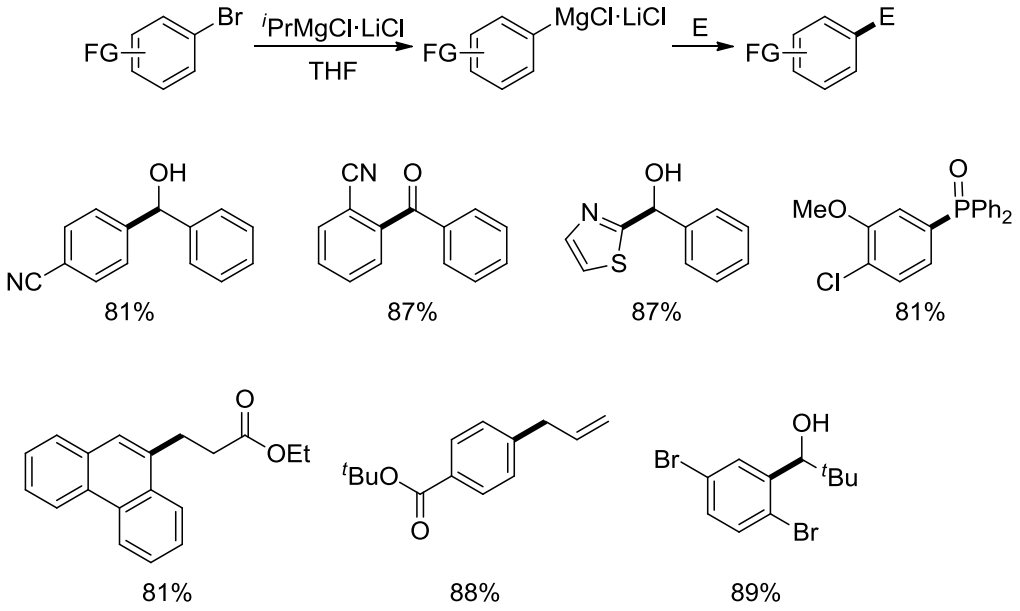
[14] a) C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372; b) J. Villiéras, *Bull. Chem. Soc. Fr.* **1967**, *5*, 1520; c) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr.* **1986**, *24*, 470.

[15] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.



Scheme 5. Preparation of functionalized arylmagnesium species through iodine-magnesium exchange.

Although the iodine-magnesium exchange proceeds smoothly under mild conditions, the similar bromo-magnesium exchange is ofen sluggish at low temperature, being in competition with other side reactions. Interestingly, in the presence of a stoichimetric amount of LiCl, this exchange is dramatically accelerated and a variety of functionalized Grignard reagents can be prepared and used for further synthesis (Scheme 6).[16]



Scheme 6. Preparation of functionalized Grignard reagents from aromatic or heteroaromatic bromide using ^{i}PrMgCl·LiCl.

1.3 Preparation of Functionalized Organozinc Reagents

Organozinc reagents are another big family of organometallic reagents and have been applied in versatile organic synthetic methodologies such as Negishi coupling.[17] Because of the high covalent character of the carbon–zinc bond, many kinds of

[16] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

[17] A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683.

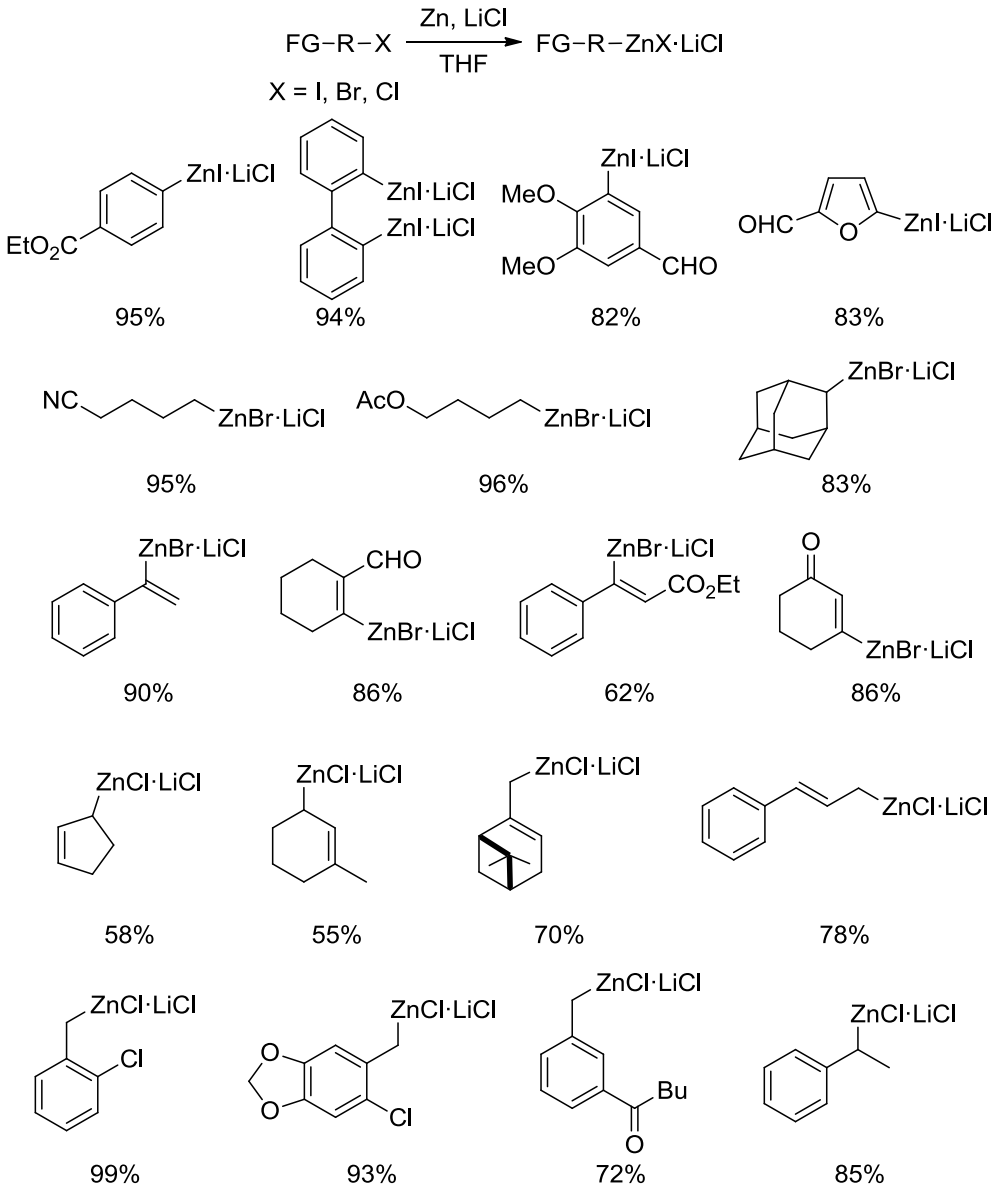
functional groups can be introduced to the organozinc reagents. However, there are several drawbacks of organozinc reagents such as its lower reactivity in comparison with Grignard reagents and the difficulties in preparations, limiting their applications. For the purpose of preparation simplicity and atom economy, the direct insertion of zinc powder into carbon–halogen bonds has been proved to be the most attractive method. Nevertheless, owing to the inertness of zinc powder, the direct insertion procedure usually requires very harsh conditions and only can proceed smoothly at some activated organohalides, narrowing the substrate scope.

As a similar method for the preparation of Grignard reagent (vide supra), *Rieke et al.* also employed highly active Zn*, which is prepared by in-situ reduction of $ZnCl_2$, for the preparation of functionalized organozinc reagents using less active arylbromides.[18] Considering the difficulties for the preparation of active Zn, this method is still less convenient.

Recently, *Knochel et al.* developed a LiCl-mediated zinc insertion in THF for the preparation of functionalized organozinc reagents. The effect of LiCl is believed to be the same as its effect for the preparation of Grignard reagent (vide supra). With the aid of LiCl, the insertion step is highly accelerated and previously unavailable organozinc reagents can be obtained using this method. Thus, a variety of functionalized aryl, alkyl, alkenyl, allyl and benzyl organozinc reagents can be easily prepared within a single step (Scheme 7).[19]

[18] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, 56, 1445; b) R. D. Rieke, *Aldrichim. Acta* **2000**, *52*, 52; c) S. H. Kim, R. D. Rieke, *Tetrahedron* **2010**, *66*, 3135.

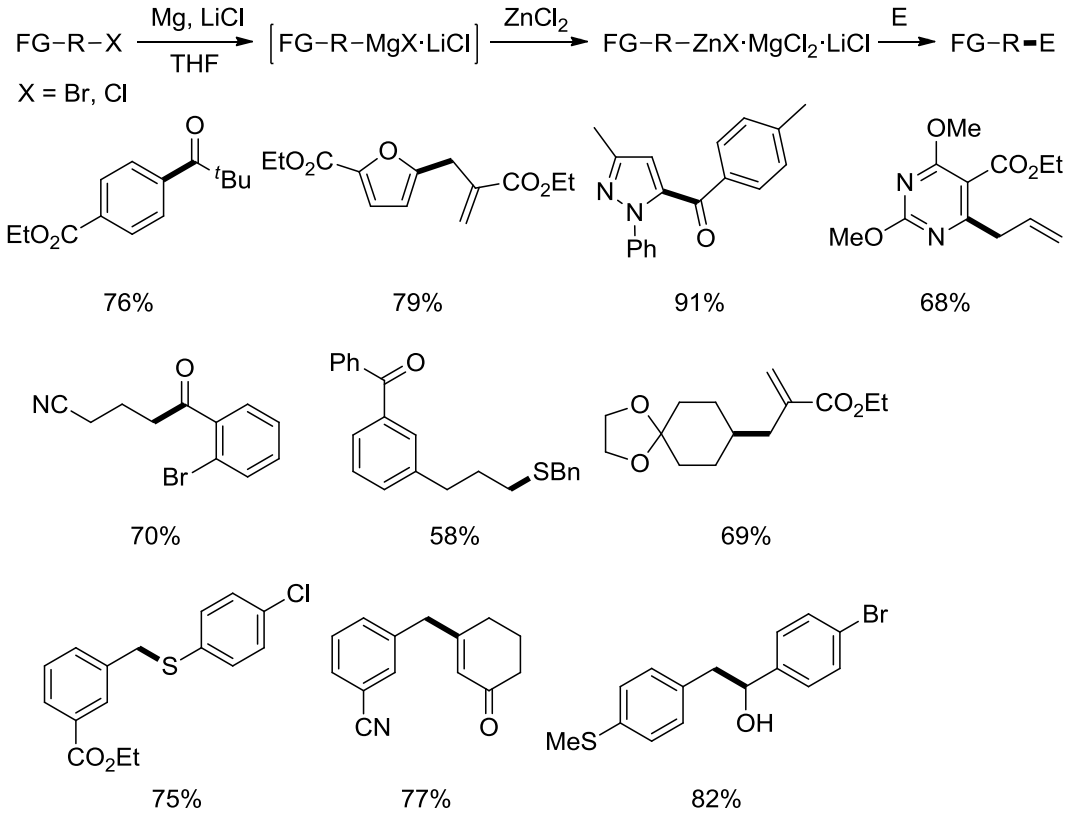
[19] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) H. Ren, G. Dunet, P. Mayer, P. Knochel *J. Am. Chem. Soc.* **2007**, *129*, 5376; c) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; d) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; e) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678; f) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, **2008**, *73*, 7380; g) C. Samann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.



Scheme 7. LiCl-promoted zinc insertion for the preparation of functionalized organozinc reagents.

For the preparation of more challenging arylzinc reagents, usually the active yet expensive aryl iodides or highly activated aryl bromides are still needed. The direct insertion of zinc powder into less active arylbromides or aryliodides bearing electron-donating groups is always very sluggish, even in the presence of LiCl and under harsh conditions. Then an elegant method was developed in the same group. To combine the advantages of the good activity of magnesium turnings and the stability of zinc reagents, *Knochel et al.* reported the preparation of arylzinc reagents using non-activated arylbromides and magnesium turnings in the presence of LiCl and $ZnCl_2$. The functionalized arylbromides can undergo the magnesium insertion quickly under mild conditions and the formed arylmagnesium species will transmetalate to $ZnCl_2$ immediately, leading to the more stable arylzincs, which can react with the following added electrophiles such as ketone, aldehyde, acidchloride and allylhalide.

Moreover, this method can be extended to other organohalides such as alkylhalide and benzylhalide. With the complexation of $MgCl_2$, the reactivity of the produced organozinc reagents is dramatically increased (Scheme 8).[13a,20]

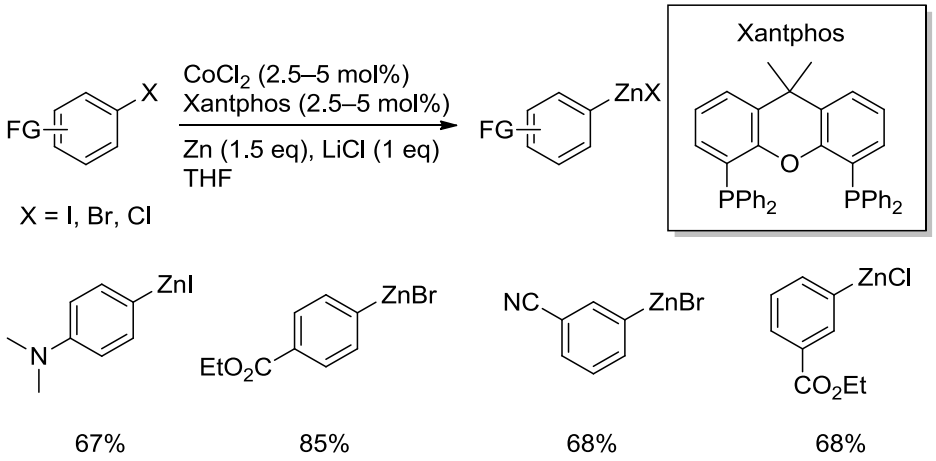


Scheme 8. Preparation of organozinc reagents using Mg turnings and $ZnCl_2$.

Although a wide scope of organozinc reagents can be readily prepared using this method, the formed organozinc species are unstable owing to its high activity and thus cannot be stored for a long time even at low temperature. An alternative method for the preparation of organozinc reagents from electron-rich aryliodides and bromides is using a transition-metal-catalyst for accelerating the insertion step. Recently, *Yoshikai et al.* reported a Cobalt/Xantphos-catalyzed preparation of arylzinc reagents from aryl iodides, bromides, and even chlorides. In these reactions, the LiCl is still necessary (Scheme 9).[21]

[20] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel *Chem. Eur. J.* **2009**, *15*, 7192; c) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082; d) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665; e) M. A. Schade, G. Manolikakes, P. Knochel *Org. Lett.* **2010**, *12*, 3648.

[21] M.-Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972.



Scheme 9. $CoCl_2$/Xantphos-catalyzed zinc insertion to aryl halides.

1.4 Direct Functionalization of Pyridines

Pyridine derivatives (including quinolines, acridines and other similar compounds) are a large family of *N*-heterocycles which may display biological activity. Many bioactive compounds such as nature products, medicines, and agrochemicals bear the pyridine scaffold (Figure 2).[22]

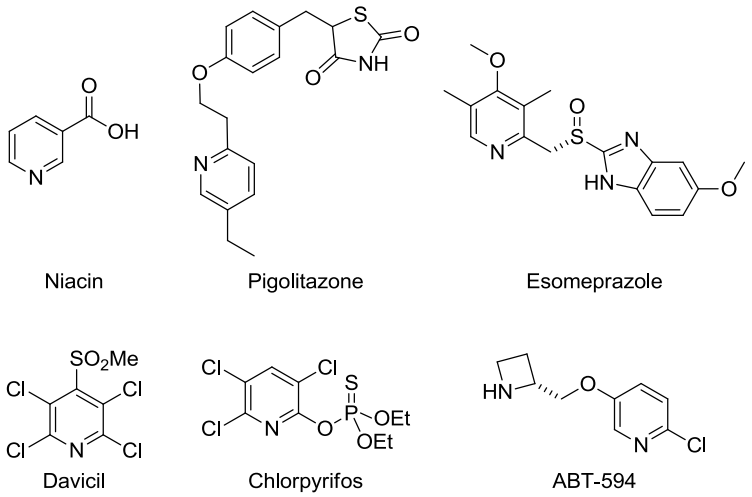


Figure 2. Selected examples of bioactive pyridine derivatives.

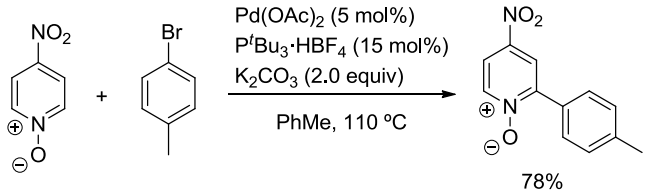
During the past decades, numerous methods have been developed for the preparation of pyridine derivatives, including the transition-metal-catalyzed cross-couplings[23]

[22] a) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; b) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627; d) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459; e) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052; f) A. R. Hardin Narayan, R. Sarpong, *Org. Biomol. Chem.* **2012**, *10*, 70.

[23] a) N. Miyaura, *Cross-Coupling Reactions. A Practical Guide*, Springer, Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**; c) *Organotransition Metal Chemistry* (Ed.: J.

and ring-closure reactions. [24] In comparison with these classical methods, the advantages of direct pyridine functionalization are quite apparent. For example, there is no need of a pre-installation of halogens on the pyridine core, and the scope of substrate is much wider. Also, a highly functionalized pyridine can be synthesized by a shortened route using direct functionalization pathways. On the other hand, the directed metalation of pyridine scaffolds has been studied for a long time.[25] However, because of the multiple vacant positions on pyridine core and the strong electrophilicity of pyridine itself, the bulky and expensive bases such as LIC-KOR mixture (LIC =butyllithium, plus KOR = potassium *tert*-butoxide) and TMP bases are always employed to control the regioselectivity and suppress the side reactions. Nevertheless, the formed 2-pyridyl organometallics are unstable and incompatible in most cross-coupling reactions.

As a typical example of direct pyridine functionalization, the recently well developed transition-metal-catalyzed C–H bond activation has been widely applied in the synthesis of polyfunctional pyridine derivatives. Although the electron-rich heterocycles can easily undergo such a transformation through an electrophilic aromatic substitution (S_EAr) pathway, the electron-deficiency of pyridines makes their direct functionalization a challenging goal. In 2005, *Fagnou et al.* reported firstly a palladium-catalyzed direct arylation reaction, using pyridine *N*-oxides as activated substrates instead of naked pyridines and arylbromides as the reaction partners (Scheme 10). The enhanced reactivity of such a kind of substrates is attributed to the electron-deficient nitrogen; hence the acidity of the two ortho-protons of the pyridine ring is dramatically increased. The arylated pyridine *N*-oxides can be readily reduced employing Pd/C and ammonium formate.[26]



Scheme 10. Palladium-catalyzed direct ortho-arylation of pyridine *N*-oxides.

Later, *Charette et al.* developed a similar palladium-catalyzed arylation of *N*-iminopyridinium ylides. It is believed that except activating the pyridine ring, the amide functionality of substrates performs as a stronger Lewis base for the

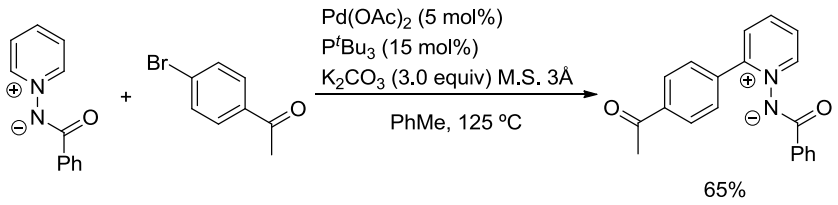
F. Hartwig), University Science Books, Sausalito, California, **2010**.

[24] a) J. Barluenga, M. Ferrero, F. Palacios, *Tetrahedron* **1997**, *53*, 4521; b) J. Barluenga, M. A. Fernandez-Rodriguez, P. Garcia-Garcia, E. Aguilar, *J. Am. Chem. Soc.* **2008**, *130*, 2764; c) C. Lau, G. C. Tsui, M. Lautens, *Synthesis* **2011**, 3908; d) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204.

[25] a) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem., Int. Ed.* **2011**, *50*, 9794.

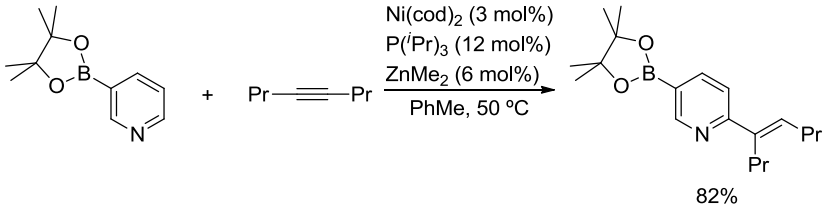
[26] L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020.

complexation of the palladium center, directing the following C–H bond insertion (Scheme 11).[27]



Scheme 11. Palladium-catalyzed direct ortho-arylation of *N*-iminopyridinium ylides.

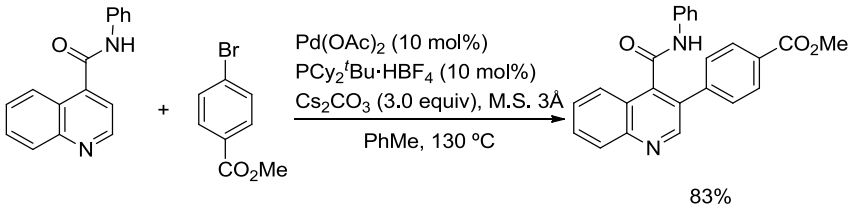
However, these methods require a pre-installation of an auxiliary group and final removing of it, introducing several extra steps and narrowing the substrate scope. To get rid of such an auxiliary group, *Nakao et al.* proposed a strategy of generating an active pyridine species *in-situ* by coordinating it to a mild Lewis acid. Thus, in the presence of a catalytic amount of Lewis acids such as $ZnMe_2$, $ZnPh_2$, and $AlMe_3$, the pyridine derivatives react smoothly with internal alkynes, leading to the ortho-alkenylated pyridines in good yields (Scheme 12).[28]



Scheme 12. Nickel/Lewis acid catalyzed direct ortho-alkenylation of pyridines.

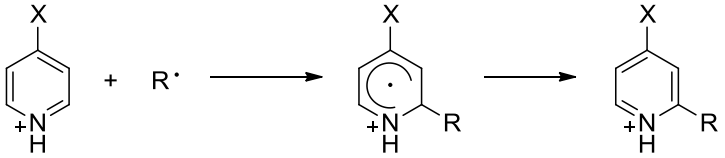
On another hand, the direct functionalization of pyridines at other positions is rare owing to the charge distribution of the pyridine ring. *Yu et al.* used readily available nicotinamide and isonicotinamide derivatives as substrates for the palladium(0)/PR_3-catalyzed direct arylation. In these cases, the functionalization occurs specifically at the meta or para positions of the pyridine ring. The amide functionality is used as a directing group for giving this unique regioselecivity (Scheme 13).[29]

[27] A. Lariv ée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52.
[28] Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666.
[29] M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 1275.



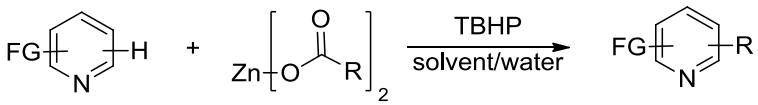
Scheme 13. Palladium catalyzed direct arylation of isonicotinamides.

Besides, the pyridine derivatives can easily react with certain alkyl and acyl radicals, which are formed from precursors such as carboxylic acids, halides and boronic acids.[30] Because of the nature of the pyridyl radical intermediate, this reaction proceeds similar to Friedel-Crafts reactions yet with higher activity and opposite regioselectivity (Scheme 14).



Scheme 14. The pathway of Minisci reaction.

Recently, *Baran et al.* developed an interesting strategy using zinc sulphinate as a radical precursor for the pyridine functionalization.[31] A series of alkyls and fluoroalkyls can be introduced to substrates using this method. Amazingly, the reaction proceeds well even in open flasks with the presence of water (Scheme 15).



Scheme 15. Rapid pyridine functionalization using zinc sulphinate and TBHP.

Although the transition-metal-catalyzed C–H activation and radical reaction have been proved to be very efficient methods for direct pyridine functionalization, they still have some drawbacks such as the necessity of transition metals and the limited scope of substrate and functionality. Meanwhile, with the rapid development of the preparation methods of organometallic reagents, the oxidative Chichibabin-type two step strategies (nucleophilic addition followed by oxidative rearomatization) represent one of the most expedient methods for the direct functionalization of pyridine derivatives.[32] In most cases, a pre-activation of the pyridine ring such as *N*-oxidation,

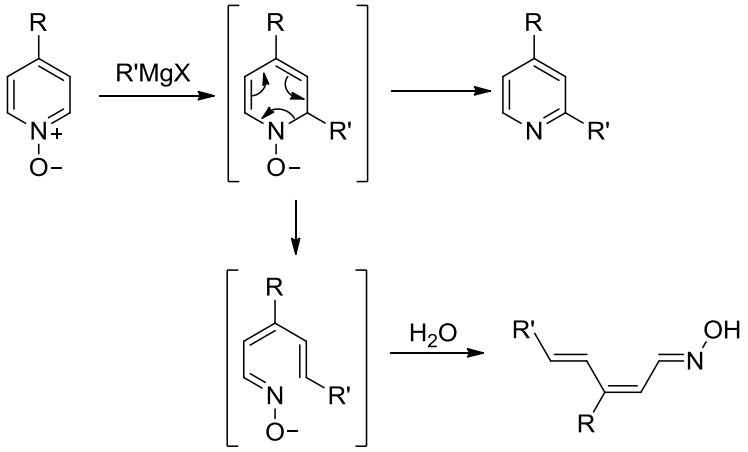
[30] F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489.

[31] Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95.

[32] a) D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223; b) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141; c) H. Andersson, R. Olsson, F. Almqvist, *Org.*

N-acylation or *N*-alkylation is required.

During the early stage of systematic studying of Grignard reagent's activity, people had already started to apply it for the pyridine functionalization through a nucleophilic addition. Rather than the inert pyridine itself, the more active pyridine *N*-oxide had been proved to be a better substrate attributing to its higher electrophilicity. However, in the preliminary examples the desired pyridine products were isolated in very low yields. The following studies indicated that a ring-opened byproduct, the 2,4-dienal oxime, was formed (Scheme 16).[33] The poor chemo-selectivity hampered the further application of this method.



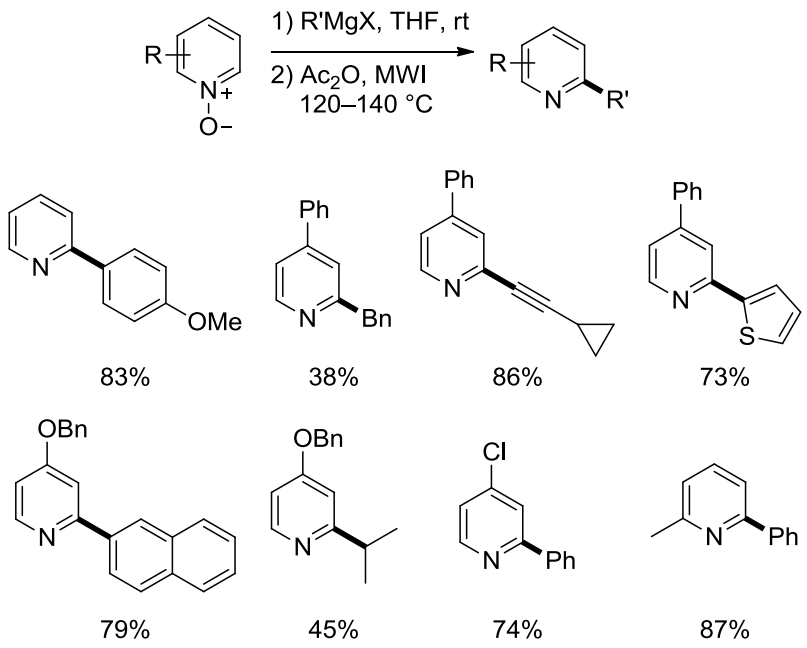
Scheme 16. Nucleophilic addition of Grignard reagent to pyridine *N*-oxide.

Recently, *Almqvist et al.* revisited this field and modified the conditions to achieve high chemo-selectivity towards pyridine products. The key of success is using acetic anhydride and high temperature for work up to suppress the undesired ring-opening. Under this condition, the addition specifically occurs at C(2) and affords mono- or disubstituted pyridines from pyridine *N*-oxides and a variety of aryl, alkyl, benzyl and alkynylmagnesium reagents (Scheme 17).[34]

Biomol. Chem. **2011**, *9,* 337; d) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642; e) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400.

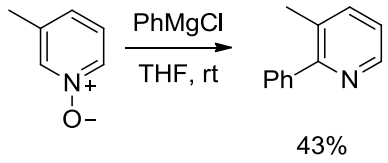
[33] a) T. Kato, H. Yamanaka, *J. Org. Chem.* **1965**, *30,* 910; b) R. M. Kellogg, T. J. Van Bergen, *J. Org. Chem.* **1971**, *36,* 1705; c) P. Schiess, P. Ringele, *Tetrahedron Lett.* **1972**, *13,* 311.

[34] H. Andersson, F. Almqvist, R. Olsson, *Org. Lett.* **2007**, *9,* 1335.



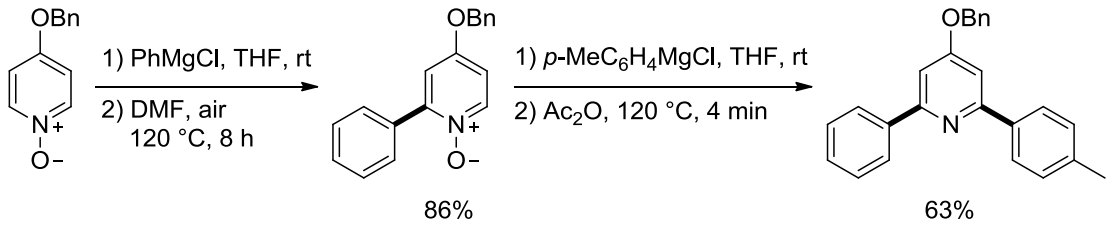
Scheme 17. Direct functionalization of pyridine *N*-oxides using Grignard reagents.

Interestingly, in the reaction of 3-substituted pyridine *N*-oxide such as 3-picoline *N*-oxide, the dienal oxime is not formed and the direct arylation occurs at the more crowded C(2) position, affording the 2,3-disubstituted pyridine in 43% yield (Scheme 18).



Scheme 18. Synthesis of 2,3-disubstituted pyridine.

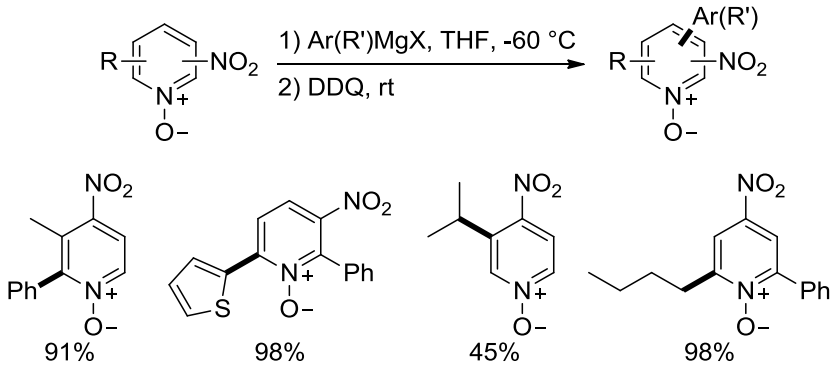
It is noteworthy that a set of consecutive direct arylations of a 4-substituted pyridine *N*-oxide has also been screened. After the first addition of PhMgCl, heating of the intermediate under air gave the 1,4-disubstituted pyridine *N*-oxide in 86% yield. Then, a second arylation can be easily performed and finally a 2,4,6-trisubstituted pyridine was obtained (Scheme 19).



Scheme 19. Consecutive direct arylations of pyridine *N*-oxide.

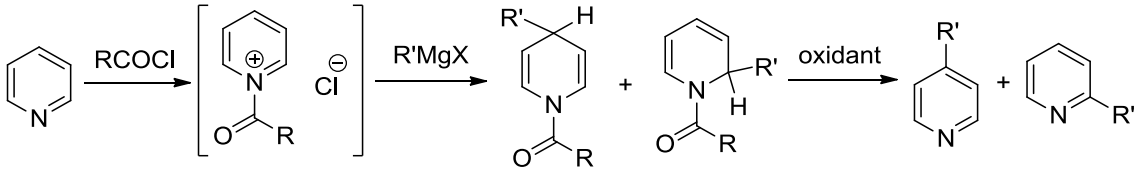
Although the reaction activity, the chemoselectivity and regioselectivity have been

increased greatly under the modified conditions, the functional group tolerance is still unsatisfying because the addition reaction is operated at room temperature, at which most of the functional groups cannot survive in the presence of a Grignard reagent. However, at a much lower reaction temperature (-60 ℃), it is found that the addition reaction of nitropyridine *N*-oxides still proceeds smoothly and the Grignard reagents specifically adds to the pyridine ring, instead of the more reactive nitro group (Scheme 20). [35] Notably, for the reaction of 4-nitropyridine *N*-oxide, the isopropylmagnesium species adds selectively at the position 3, the ortho position of nitro group, instead of the position 2.



Scheme 20. Direct functionalization of pyridine-*N*-oxides with a nitro substituent.

The pyridine derivatives can also be activated by acyl chloride to form an *N*-acylpyridinium salt. Then, a Grignard reagent easily adds to this in-situ prepared intermediate, leading to *N*-acyldihydropyridine derivatives, which can undergo a oxidative rearomatization to form substituted pyridines. However, in those early reported cases, a mixture of 1,2-addition and 1,4-addition products were obtained (Scheme 21).[36]



Scheme 21. One-step synthesis of substituted pyridine derivatives from *N*-acylpyridinium.

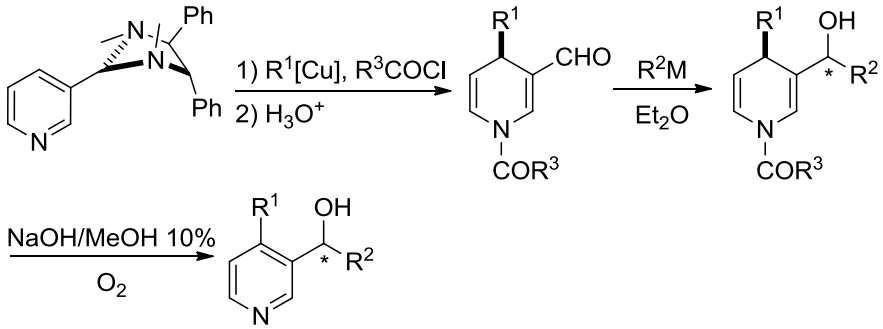
Meanwhile, inspired by the HSAB theory, people found that while using a series of soft nucleophiles such as organocopper or organozinc reagents instead of Grignard reagents or organolithium reagents, the para position of the pyridine ring was preferentially attacked whereas the ortho position was leaved untouched, leading to

[35] F. Zhang, X.-F. Duan, *Org. Lett.* **2011**, *13*, 6102.

[36] a) G. Fraenkel, J. W. Cooper, C. M. Fink, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 523; b) R. E. Lyle, J. L. Marshall, D. L.Comins, *Tetrahedron Lett.* **1977**, 1015; c) R. E. Lyle, D. L. Comins, *J. Org. Chem.* **1976**, *41*, 3250.

the 1,4-adddition products predominantly (Table 1)[37]. *Comins et al.* reported the regioselectivity of the addition of Grignard reagents to the pyridinium salts were dramatically changed in the presence of a catalytic amount of CuI. The produced dihydropyridine were readily rearomatized by alkaline S_8 treatment under heating (entries 1–3).[37a] Nearly at the same time, *Akiba et al.* proved that the organocopper reagent itself such as RCu·BF_3 also added selectively at the position 4 of pyridine and both alkyl and aryl group was introduced with good functional group tolerance. The oxidation was operated by flowing oxygen to the neat dihydropyridine species (entries 4 and 5).[37b] Later, the benzylic copper reagents (entries 6 and 7)[37c] or benzylic zinc reagents (entries 8 and 9)[37d] were also screened for the pyridine functionalization, and the 4-substituted products were selectively afforded.

To control the stereoselectivity of the addition step, *Mangeney et al.* prepared a chiral aminal, obtained from nicotinaldehyde and chiral diamines with *C2* symmetry. This aminal undergoes the addition of organocopper reagents at position 4 to form 1,4-dihydropyridine-3-carboxaldehydes in good diastereoselectivity. One more addition of an organometallic reagent furnishes a chiral alcohol, which can be easily rearomatized by alkaline oxidation, affording a chiral pyridyl alcohol (Scheme 22).[38]



Scheme 22. Diastereoselective 1,4-addition to pyridine with a chiral auxiliary.

Some other pyridine activation methods including *N*-alkylation,[39] *N*-triflylation[40] and *N*-pyridinium formation[41] have also been reported for the following direct pyridine functionalizations. These methods have been applied for the synthesis of natural products and other bio-active compounds.

---

[37] a) D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315; b) K. Akiba, Y. Iseki, M. Wada, *Tetrahedron Lett.* **1982**, *23*, 429; c) T.-L. Shing, W.-L. Chia, M.-J. Shiao, T.-Y. Chau, *Synthesis* **1991**, 849; d) A. P. Krapcho, D. J. Waterhouse, A. Hammach, R. Di Domenico, E. Menta, A. Oliva, S. Spinelli, *Synth. Commun.* **1997**, *27*, 781.

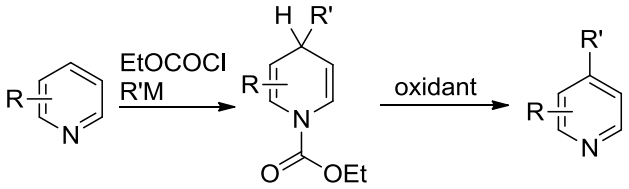
[38] P. Mangeney, R. Gosmini, S. Raussou, M. Commerçon, *Tetrahedron Lett.* **1993**, *34*, 6399.

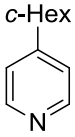
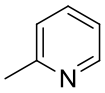
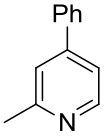
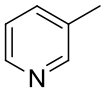
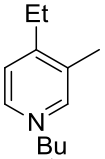
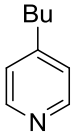
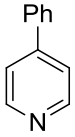
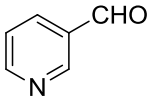
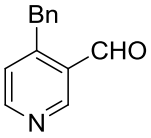
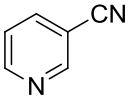
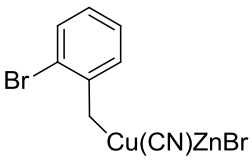
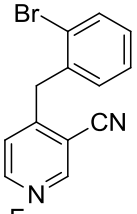
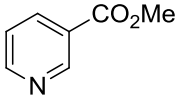
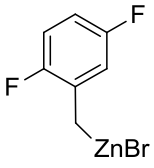
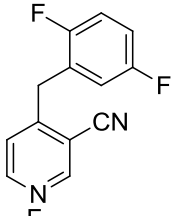
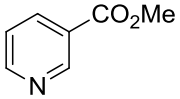
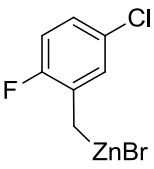
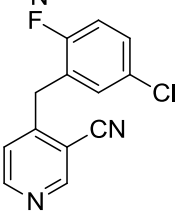
[39] R. Loska, M. Mąkosza, *J. Org. Chem.* **2007**, *72*, 1354.

[40] a) A. R. Katritzky, S. Zhang, T. Kurz, M. Wang, *Org. Lett.* **2001**, *3*, 2807; b) E. J. Corey, Y. Tian, *Org. Lett.* **2005**, *7*, 5535.

[41] A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, *J. Am. Chem. Soc.* **2001**, *123*, 11829.

Table 1. 1,4-addition to pyridines using soft organometallics.



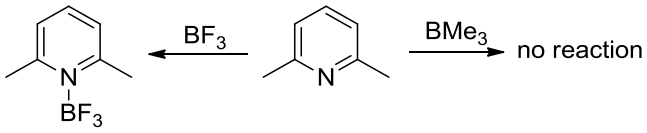
Entry	Substrate	R'M	Product	Oxidant	Yield %	Ref.
1		*c*-HexMgCl/5% CuI		S_8	77	37a
2		PhMgCl/5% CuI		S_8	55	37a
3		EtMgCl/5% CuI		S_8	68[a]	37a
4		$BuCu \cdot BF_3$		O_2/neat	68	37b
5		$PhCu \cdot BF_3$		O_2/neat	59	37b
6		BnCu(CN)ZnBr		S_8	25	37c
7				S_8	66	37c
8[b]				S_8	76	37d
9[b]				S_8	50	37d

[a]A trace amount of regio-isomers were still observed. [b]PhOCOCl was used instead of EtOCOCl for the preparation of pyridinium salt.

1.5 Frustrated Lewis Pairs

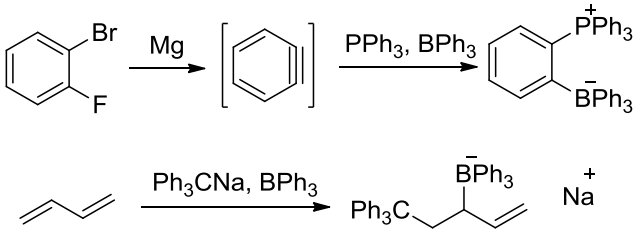
In 1923, Gilbert N. Lewis defined a molecule with an empty molecular orbital to accept an electron-pair as acid, and a molecule which can donate an electron-pair as base.[42] Since then, the concept of Lewis acid/base has been used widely to rationalize many chemical processes and guide the development of new synthetic methodologies. As a common understanding now, mixing a Lewis acid and a Lewis base results in a neutralization and the formation of a Lewis acid/base adduct.

However, during the study of coordination between pyridines and boranes, *Brown et al.* found that the 2,6-lutidine formed a stable adduct with BF_3 but there was no reaction between 2,6-lutidine and BMe_3 at low temperature (Scheme 23).[43] It was explained by the steric conflict between the two bulky species.



Scheme 23. Treatment of 2,6-lutidine with BF_3 and BMe_3.

Later, some similar phenomenons were observed, that instead of forming a stable adduct, the mixed Lewis acid and base afforded a weakly interacted pair and still expressed their Lewis acidity and basicity in the following transformations. For example, as a classical Lewis acid and base, triphenylphosphine and triphenylborane were mixed and preferably underwent a benzyne insertion, instead of quenching each other. Similarly, while mixing tritylsodium and triphenylborane, the two species were still active enough to produce a trapping product with 1,3-butadiene (Scheme 24).[44]

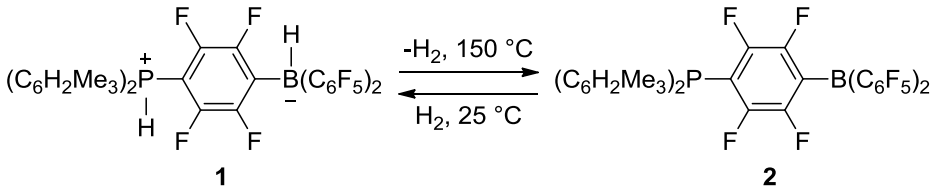


Scheme 24. Early examples of Frustrated Lewis Pair.

To generalize this concept, in 2006 the Stephan group prepared a zwitterionic species (**1**) which undergoes a thermal liberation of H_2 at a temperature above 100 ℃, leading to a phosphino-borane (**2**). In solution, **2** proved to be monomeric because of the

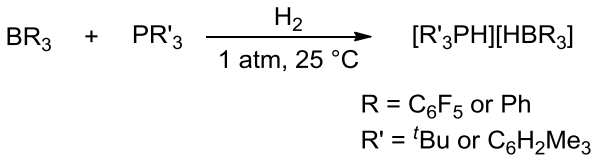
[42] G, N, Lewis, *Valence and the Structure of Atoms and Molecules*, Chemical Catalogue Company, New York, **1923**.
[43] H. C. Brown, H. I. Schlesinger, S. Z. Cardon, *J. Am. Chem. Soc.* **1942**, *64*, 325.
[44] a) G. Wittig, E. Benz, *Chem. Ber.* **1959**, *92*, 1999; b) W. Tochtermann, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 351.

bulky groups surrounding the B and P atoms, hampering dimerization or higher aggregation. Thus, it is called a sterically "frustrated Lewis pair" (FLP). By treating **2** with H_2 at 25 ℃, the rapid regeneration of **1** was observed (Scheme 25).[45] Mechanism studies indicated that during this reaction, the complexation of H_2 to Lewis acidic B firstly occurred. With the assistance of the Lewis basic P, the H–H bond heterolytic cleaved followed by an intramolecular H^+ migration to P.



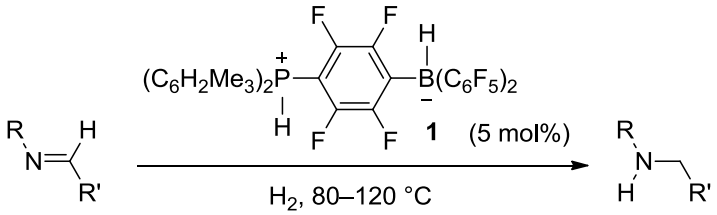
Scheme 25. H_2 storage and releasing using **1** and **2**.

Inspired by this strategy and related mechanism information, later an intermolecular H–H bond cleavage using sterically demanding phosphines and boranes was reported by the same group. A series of phosphonium borates were obtained as products of these transformations (Scheme 26).[46]



Scheme 26. Heterolytic cleavage of H_2 by phosphines and boranes.

The hydrogen uptake/releasing cycle by **1**/**2** can be applied in catalytic transformations such as imines hydrogenation. Treating the imine substrates in the presence of a catalytic amount of **1**, the hydrogenation proceeds smoothly under heating and 1–5 atm of H_2, providing a transition-metal-free strategy of catalytic hydrogenation (Scheme 27).[47]



Scheme 27. Catalytic hydrogenation of imines using **1** as a catalyst.

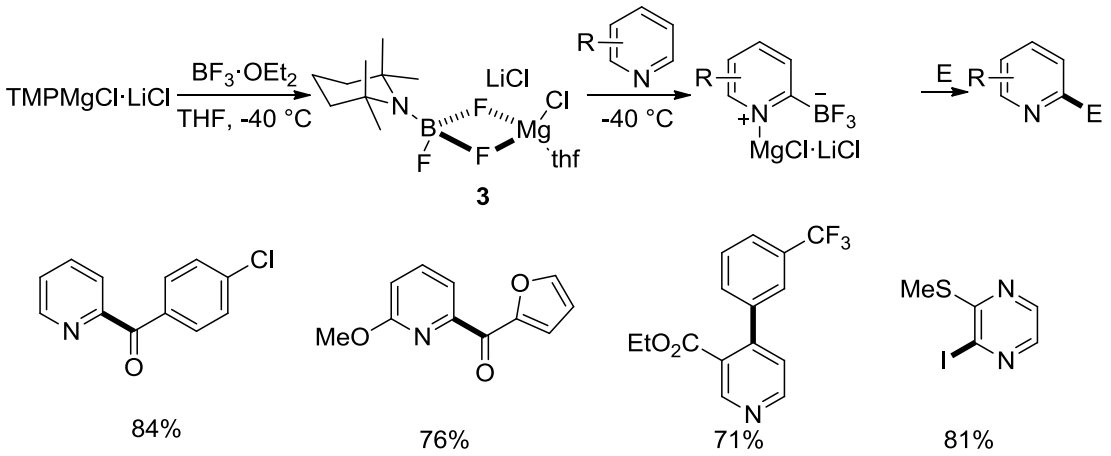
Recently, the Knochel group reported a novel Lewis pair **3**, which was easily prepared

[45] a) G. C. Welch, R. R. S. Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124; b) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.

[46] G. C. Welch, D. W. Stephan, *J. Am. Chem. Soc.* **2007**, *129*, 1880.

[47] P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 8050.

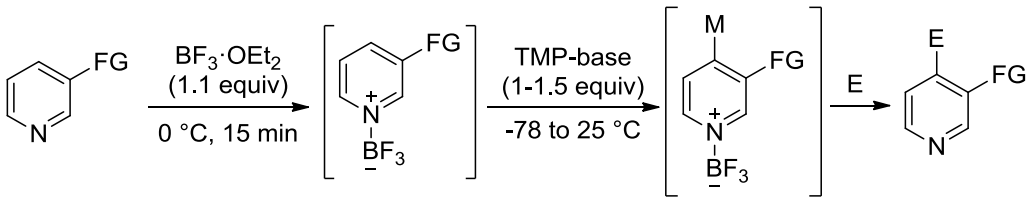
by mixing the TMP base and $BF_3 \cdot OEt_2$ at low temperature. It can regioselectively deprotonate pyridine derivatives, affording a variety of pyridylmagnesium species for further synthetic reactions (Scheme 28).[48]



Scheme 28. Regioselective metalation of pyridines mediated by FLP **3**.

1.6 Objectives

The direct functionalization of simple and commercial available pyridines into more complex pyridine derivatives for applications in biology and material science is a challenging task for organic synthetic chemists. Our group has developed a BF_3-triggered direct metalation of pyridines. The formed pyridylmetallic species can be trapped by electrophiles with or without transition-metal-catalysts, affording a variety of polyfunctional pyridine derivatives (Scheme 29).[48,49]



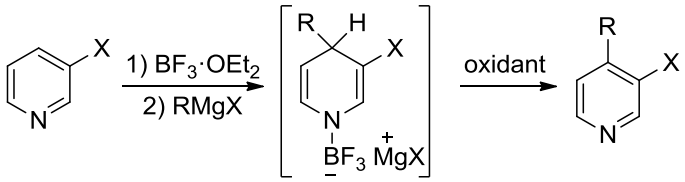
Scheme 29. Regioselective functionalization of pyridines using $BF_3 \cdot OEt_2$ and TMP-bases.

As a variant of this method, we designed a pyridine functionalization method using BF_3-activated pyridines as substrates for a following Chichibabin-type nucleophilic addition by alkyl- and arylmagnesium reagents. The regioselectivity of the addition should be controlled by the complexed BF_3, which shields the C(2) and C(6) position of the pyridine ring by steric hindrance. Thus the C(4) position should be preferred. An oxidative work up is necessary to rearomatize the 1,4-dihydropyridine

[48] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

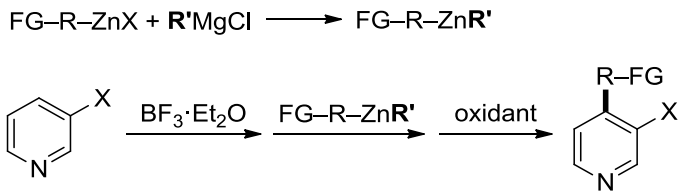
[49] a) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306; b) S. M. Manolikakes, M. Jaric, K. Karaghiosoff, P. Knochel, *Chem. Commun.* **2013**, *49*, 2124.

intermediate to obtain the pyridine product (Scheme 30).



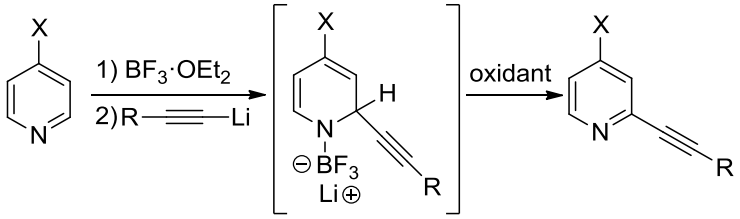
Scheme 30. BF_3-mediated Chichibabin-type reaction.

As an attempt to introduce more functionalities into the substrates, a variety of functional organozinc reagents would be screened under a similar condition. Nevertheless, the organozinc reagents are less reactive than Grignard reagents and therefore the addition of an organozinc reagent to the pyridine rings might be sluggish. Considering the diorganozinc species were more reactive than the corresponding monoorganozinc species, we planned to convert the functional organozinc reagents to diorganozinc species with a non-transferrable ligand and use them in-situ for the following pyridine functionalization (Scheme 31).



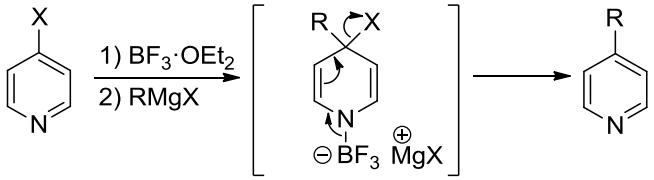
Scheme 31. BF_3-mediated pyridine functionalization using functional organozinc reagents.

Besides, based on the HSAB theory, we hypothesized that in comparison with organomagnesium or zinc species, a smaller and harder nucleophile such as alkynyllithium can undergo a 1,2-addition, instead of the 1,4-addition, to selectively functionalize the C(2) position of pyridines (Scheme 32).



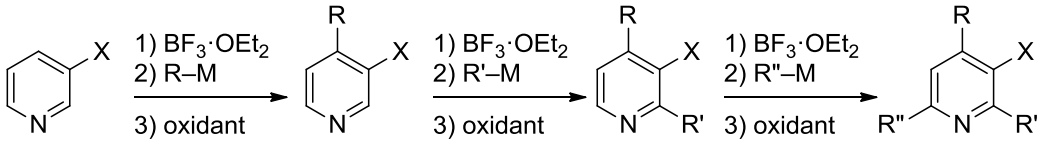
Scheme 32. BF_3-mediated pyridine functionalization at C(2) using alkynyllithiums.

Also, if the C(4) position of pyridine ring has already been substituted by a suitable leaving group (X), then after the treatment with BF_3·OEt_2 and Grignard reagents, the 4,4-disubstituted-1,4-dihydropyridine intermediate should be formed and after the cleavage of C–X bond, a cross-coupling product will be observed (Scheme 33).

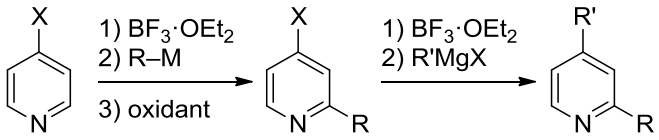


Scheme 33. BF_3-mediated cross-coupling of 4-substituted pyridines.

With a combination of above methods, a successive functionalization of pyridines was proposed, affording di-, tri- and tetra-substituted pyridine products within several simple steps (Scheme 34 and 35).

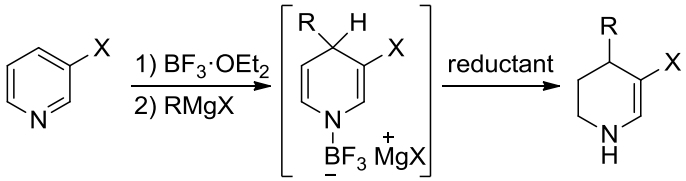


Scheme 34. BF_3-mediated polyfunctionalization of pyridines through oxidative cross-couplings.



Scheme 35. BF_3-mediated polyfunctionalization of pyridines through oxidative and non-oxidative cross-couplings.

Finally, the addition/oxidation strategy would be modified and an addition/reduction method would be used for the synthesis of piperidine derivatives. A suitable reduction condition is crucial for the final step (Scheme 36).



Scheme 36. Addition/reduction method for the synthesis of piperidines.

Chapter 2. BF_3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines

2.1 Introduction

Pyridines are an important class of *N*-heterocycles including many bioactive compounds [1] and functional materials. [2] The direct functionalization of these heterocyclic scaffolds has been achieved by numerous methods, including C–H activation, [3] radical reaction, [4] and directed metalation. [5] Nevertheless, these approaches always require the addition of catalytic or stoichiometric amounts of transition-metals, most of which are expensive and non-environmentally benign. Besides, such transition-metal catalyzed procedures are frequently accompanied by side reactions such as homo-coupling and *β*-hydride elimination. Moreover, especially

[1] a) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; b) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627; d) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459; e) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052; f) A. R. Hardin Narayan, R. Sarpong, *Org. Biomol. Chem.* **2012**, *10*, 70.

[2] a) A. Yokoyama, I. Nishiyama, A. Yoshizawa, *Ferroelectrics* **1993**, *148*, 139; b) Y. G. Skrypink, T. F. Doroshenko, *Mater. Sci.* **1996**, *32*, 537; c) H. Tsutsumi, K. Okada, T. Oishi, *Electrochim. Acta* **1996**, *41*, 2657; d) C. G. Bangcuyo, M. E. Rampey-Vaughn, L. T. Quan, S. M. Angel, M. D. Smith, U. H. F. Bunz, *Macromolecules* **2002**, *35*, 1563; e) M. Vetrichelvan, S. Valiyaveettil, *Chem. Eur. J.* **2005**, *11*, 5889.

[3] a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020; b) A. Lariv ée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52; c) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448; d) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070; e) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666; f) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 1275; g) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616.

[4] a) F. Minisci, C. Giordano, E. Vismara, S. Levi, V. Tortelli, *J. Am. Chem. Soc.* **1984**, *106*, 7146; b) F. Minisci, F. Fontana, E. Vismara, *J. Heterocycl. Chem.* **1990**, *27*, 79; c) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194; d) G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852; e) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95; f) F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122.

[5] a) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

for the pharmaceutical industry, the removal of harmful transition-metal contamination is often costly and difficult.[6]

To avoid using transition-metals, oxidative Chichibabin-type two step strategies (nucleophilic addition followed by oxidative aromatization) represent one of the most expedient methods for the direct functionalization of pyridine derivatives.[7] However, a pre-activation of the pyridine ring such as *N*-oxidation, *N*-acylation or *N*-alkylation is usually required.[8] Especially for hard nucleophiles such as organolithium, Grignard and organozinc reagents, the nucleophiles add mostly to the C(2)-position of the pyridine ring. The formation of a small but not negligible amount of a 4-substituted product is often observed, lowering somewhat the synthetic value of these methods.[9]

[6] a) C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889; b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang, *Org. Process Res. Dev.* **2005**, *9*, 198.

[7] a) D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223; (b) R. J. Lavilla, *Chem. Soc., Perkin Trans. 1* **2002**, 1141; c) H. Andersson, R. Olsson, F. Almqvist, *Org. Biomol. Chem.* **2011**, *9*, 337; d) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642; e) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400.

[8] *N*-Oxidation: a) T. Kato, H. Yamanaka, *J. Org. Chem.* **1965**, *30*, 910; b) R. M. Kellogg, T. J. Van Bergen, *J. Org. Chem.* **1971**, *36*, 1705; c) P. Schiess, P. Ringele, *Tetrahedron Lett.* **1972**, *13*, 311; d) H. Andersson, F. Almqvist, R. Olsson, *Org. Lett.* **2007**, *9*, 1335; e) H. Andersson, M. Gustafsson, D. Boström, R. Olsson, F. Almqvist, *Angew. Chem. Int. Ed.* **2009**, *48*, 3288; f) H. Andersson, T. Sainte-Luce Banchelin, S. Das, R. Olsson, F. Almqvist, *Chem. Commun.* **2010**, *46*, 3384; g) F. Zhang, X.-F. Duan, *Org. Lett.* **2011**, *13*, 6102; h) M. Hussain, T. Sainte-Luce Banchelin, H. Andersson, R. Olsson, F. Almqvist, *Org. Lett.* **2013**, *15*, 54; *N*-Acylation: i) D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315; j) K. Akiba, Y. Iseki, M. Wada, *Tetrahedron Lett.* **1982**, *23*, 429; k) D. L. Comins, *Tetrahedron Lett.* **1983**, *24*, 2807; l) T.-L. Shing, W.-L. Chia, M.-J. Shiao, T.-Y. Chau, *Synthesis* **1991**, 849. m) W.-L. Chia, M.-J. Shiao, *Tetrahedron Lett.* **1991**, *32*, 2033; n) P. Mangeney, R. Gosmini, S. Raussou, M. Commerçon, *Tetrahedron Lett.* **1993**, *34*, 6399; o) A. P. Krapcho, D. J. Waterhouse, A. Hammach, R. Di Domenico, E. Menta, A. Oliva, S. Spinelli, *Synth. Commun.* **1997**, *27*, 781; p) D. L. Comins, L. S. King, E. D. Smith, F. C. Février, *Org. Lett.* **2005**, *7*, 5059; *N*-Alkylation: q) R. Loska, M. Mąkosza, *J. Org. Chem.* **2007**, *72*, 1354; Others: r) A. R. Katritzky, S. Zhang, T. Kurz, M. Wang, *Org. Lett.* **2001**, *3*, 2807; s) E. J. Corey, Y. Tian, *Org. Lett.* **2005**, *7*, 5535.

[9] a) A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, *J. Am. Chem. Soc.* **2001**, *123*, 11829; b) C. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2003**, *125*, 6360.

2.2 Results and Discussion

2.2.1 BF_3-Mediated Direct Alkylation of Pyridines using Grignard Reagents

During the primary studies, we found a novel *transition-metal-free* $BF_3 \cdot OEt_2$[10] mediated regioselective synthesis of 4-substituted pyridine derivatives using LiCl activated Grignard[11] or organozinc reagents.[12] Thus, the treatment of 3-chloropyridine (**1a**) with $BF_3 \cdot OEt_2$ (1.1 equiv, THF, 0 °C, 15 min) affords the Lewis pair (**2**). Subsequent addition of ^{i}PrMgCl·LiCl (1.2 equiv, -50 °C, 0.5 h) leads to the tentative intermediate (**3**), which was conveniently aromatized by chloranil[13] (2.0 equiv, 25 °C, 2 h) affording the 3-chloro-4-isopropylpyridine (**4a**) in 89% isolated yield. The regioisomeric 2-substitution product is not observed (Scheme 1). BF_3 facilitates considerably this addition reaction and without this Lewis acid, no reaction occurs.

The presence of LiCl has a beneficial effect since the addition of EtMgCl·LiCl provides the product (**4b**) in 94% NMR yield (NMR-determination with internal standard calibration). In the absence of LiCl, EtMgCl furnishes the desired product (**4b**) in only 67% NMR yield (Table 1, entry 1).

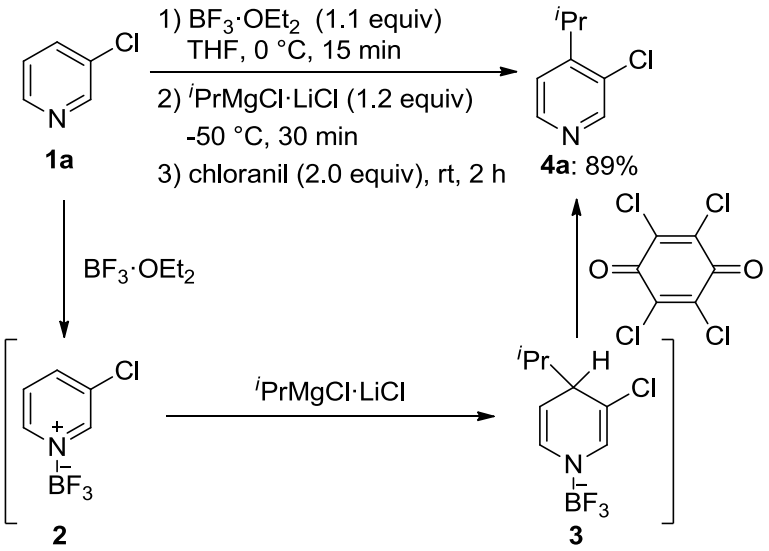
---

[10] a) K. Maruyama, Y. Yamamoto, *J. Am. Chem. Soc.* **1977**, *99*, 8068; b) K. B. Aubrecht, M. D. Winemiller, D. B. Collum, *J. Am. Chem. Soc.* **2000**, *122*, 11084; b) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275; c) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46; d) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; e) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306.

[11] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; c) F. M. Piller, A. Metzger, M. A. Schade, B. A. Hagg, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

[12] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; c) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082; d) A.Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

[13] a) A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 5010; b) V. del Amo, S. R. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.



Scheme 1. Selective addition of a Grignard reagent to 3-chloropyridine.

A range of primary and secondary alkylmagnesium derivatives add in the presence of LiCl to 3-chloropyridine (**1a**) to furnish regiospecifically the 4-substituted products (**4c–f**) in 70–94% yield (entries 2–5). Notably, even a tertiary alkyl group such as a *tert*-butyl group can be introduced to nicotinonitrile (**1b**) in 70% yield (entry 6). In order to exclude a radical pathway, we used hex-5-en-1-ylmagnesium chloride as a radical clock, but did not observe any cyclized product and only the linear substituted pyridine (**4h**) was obtained in 76% NMR yield (entry 7). Several other 3-substituted pyridines such as 3-bromopyridine (**1c**), ethyl nicotinate (**1d**), 3-phenylpyridine (**1e**) and 3-vinylpyridine (**1f**) add ^{i}PrMgCl·LiCl, leading to the desired 4-substituted pyridines (**4i–l**) in 47–79% yield (entries 8–11).

Also, 2-chloropyridine (**1g**) adds ^{i}PrMgCl·LiCl in C(4)-position to afford the corresponding disubstituted pyridine (**4m**) in 76% NMR yield. Interestingly, the 2-chloro substituent is inert under these conditions (entry 12). Similarly, a 1,2,3-trisubstituted pyridine (**4n**) can be readily prepared in 93% isolated yield (entry 13).

In the case of quinolines (**1i–k**), the addition of ^{i}PrMgCl·LiCl occurs with good regioselectivity to afford the 4-substituted quinolines (**4o–q**) in 78–86% isolated yield (entries 14–16). However, <10% of the corresponding 2-substituted quinolines[14] have also been isolated.[15]

[14] See Experimental Section.

[15] For other substrates such as pyridine, 3-picoline and 2-methoxypyridine, the addition is very slow and only affords trace amount of the desired products. A 4-substituted substrate such as ethyl isonicotinate does not give any addition product. See Table 2.

Table 1. Direct alkylation of pyridine derivatives using Grignard reagents

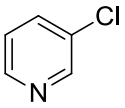
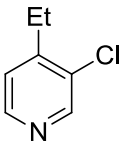
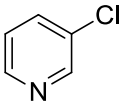
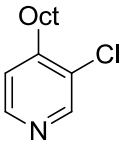
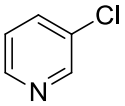
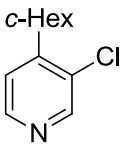
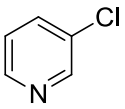
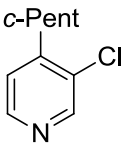
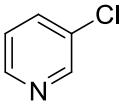
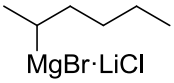
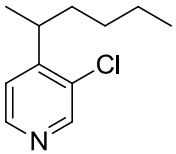
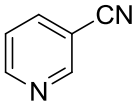
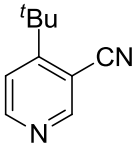
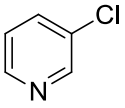
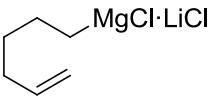
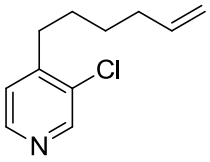
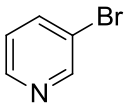
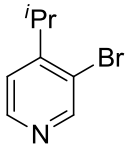
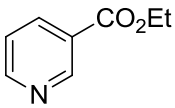
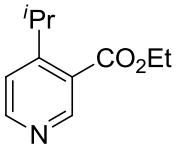
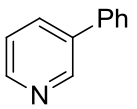
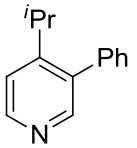
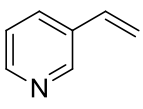
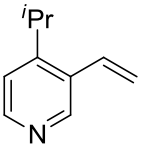
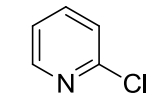
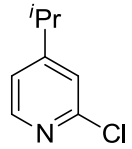
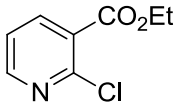
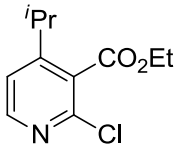
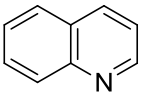
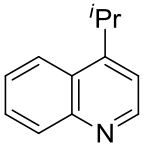
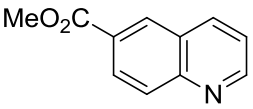
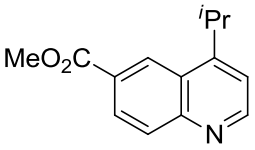
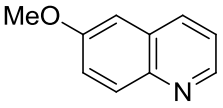
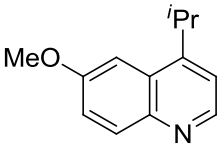
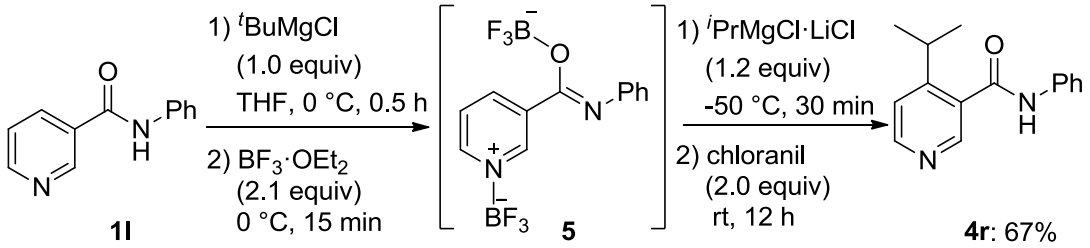
Entry	Substrate		Grignard Reagent	Product		Yield %[a]
1		**1a**	EtMgCl·LiCl		**4b**	(94, 67[b])
2		**1a**	OctMgBr·LiCl		**4c**	94
3		**1a**	*c*-HexMgBr·LiCl		**4d**	70
4		**1a**	*c*-PentMgCl·LiCl		**4e**	89
5		**1a**			**4f**	91
6		**1b**	^{t}BuMgCl·LiCl		**4g**	70
7		**1a**			**4h**	44[c] (76)
8		**1c**	^{i}PrMgCl·LiCl		**4i**	67
9		**1d**	^{i}PrMgCl·LiCl		**4j**	79
10		**1e**	^{i}PrMgCl·LiCl		**4k**	72
11		**1f**	^{i}PrMgCl·LiCl		**4l**	47

Table 1. Continued.

12		**1g**	^{i}PrMgCl·LiCl		**4m**	53[c] (76)
13		**1h**	^{i}PrMgCl·LiCl		**4n**	93
14		**1i**	^{i}PrMgCl·LiCl		**4o**	80
15		**1j**	^{i}PrMgCl·LiCl		**4p**	86
16		**1k**	^{i}PrMgCl·LiCl		**4q**	78

[a]Isolated yields of analytically pure products. NMR yields are given in parenthesis. [b]The reaction is performed with EtMgCl. [c]The low isolated yield is caused by a difficult chromatographical separation.

Also, nicotinamides are widely used as building blocks for many pharmaceuticals. However, the direct functionalization of nicotinamides always relies on transition-metal catalyzed procedures.[3f,16] Here, an equivalent of ^{t}BuMgCl is used to deprotonate the amide nitrogen of the nicotinamde (**1l**) and two equivalents of BF_3 OEt_2 are added, leading to the tentative intermediate **5**. The isopropylmagnesium reagent reacts smoothly with **5** and the desired product (**4r**) is obtained in 67% isolated yield (Scheme 2).



Scheme 2. Direct alkylation of nicotinamide (**1l**).

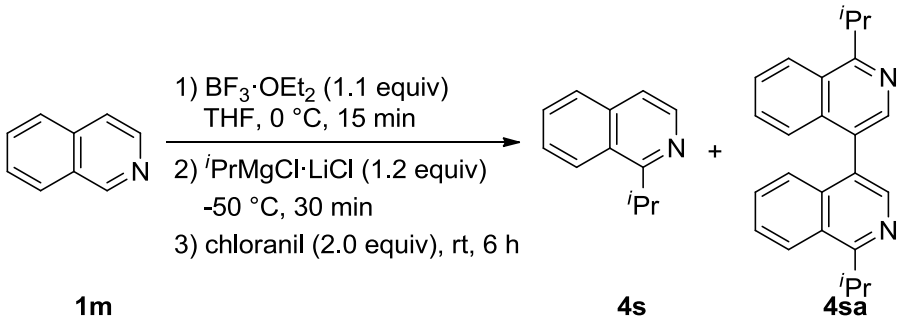
To get more information of the potential and scope of this reaction, some other

[16] Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428.

substrates have also been screened, in the reactions with different Grignard reagents (Table 2). A naked pyridine and pyridines with electron-donating groups such as 3-picoline and 2-methoxypyridine only give trace amounts of the addition products (**4aa**–**ac**). More electron-rich substrates such as DMAP cannot afford any detectable product. Also, when using 2-substituted pyridine derivatives, the reactions proceed quite sluggishly and usually result in very low yields of the addition products, or even no reaction (**4ad**–**ag**). One possible explanation is that because of the bulky ortho-substituents of these pyridine derivatives, the corresponding BF_3-adducts are not stable even at low temperature (See Chapter 1, Ref. 43). A 4-substituted pyridine derivative, ethyl isonicotinate also fails to give the product (**4ah**). In this case the attached BF_3 shields the ortho-positions and thus an alkyl Grignard reagent cannot add to the C(2) position. With a mild electron-withdrawing group, the 3-fluoropyridine can be converted to the corresponding products (**4ai**–**aj**) in moderate yields. In the reaction between 3-iodopyridine and ^{i}PrMgCl·LiCl, the exchange occurs much faster than the addition and the product (**4ak**) is not formed. If a bulky Grignard reagent such as ^{t}BuMgCl is employed for the reaction of 3-chloropyridine, only 14% of the product (**4al**) are obtained. For pyridines with functional groups such as nitro and amide, the desired products (**4am** and **4an**) are formed in low yields. Other functionalized pyridines such as 3-acetylpyridine, 3-phenylcarbonylpyridine, 2-phenylcarbonylpyridine and 2-vinylpyridine afford more complex mixtures after the reaction.

For other heterocycles such as pyrazine and pyrimidine, the addition products (**4ao** and **4ap**) are produced in 12% and 38% yields. Also, benzo[*f*]quinoline gives the product **4aq** in 18% yield together with other isomers. Quinazoline or pyridazine also produces a mixture of regio-isomers. And benzoxazole or 2,2'-bipyridine just decomposes during the reaction. Imidazo[1,2-*a*]pyridine is inert toward the addition of Grignard reagents under these conditions.

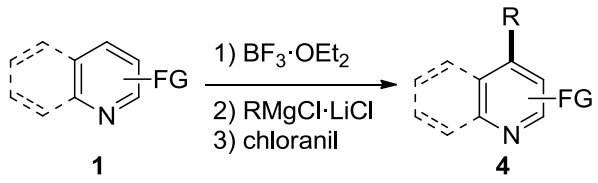
While using isoquinoline (**1m**) to react with ^{i}PrMgCl·LiCl, in addition to the desired product **4s**, a dimerized product **4sa** was also detected (Scheme 3).[17]

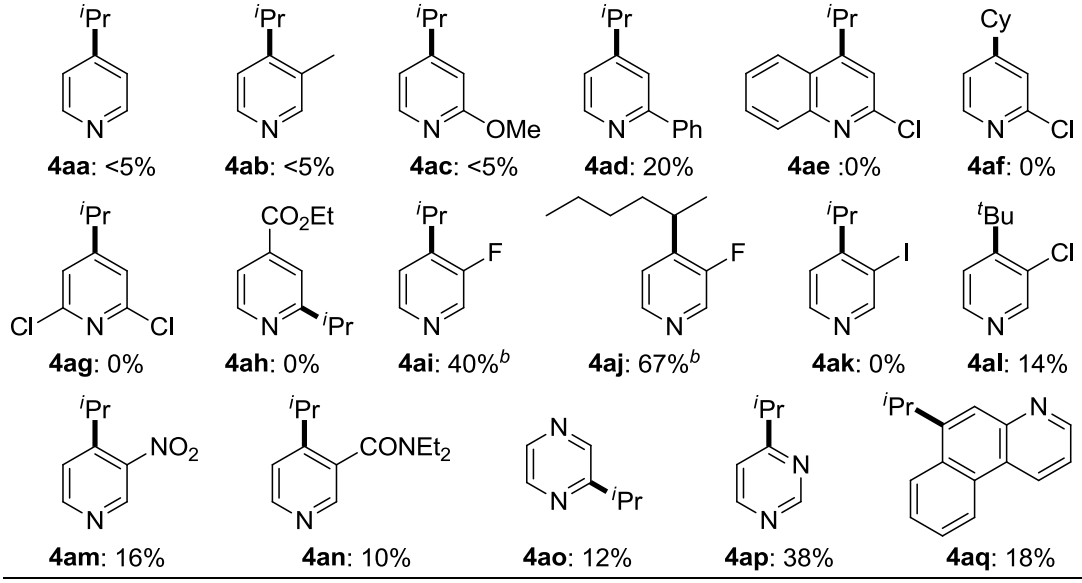


Scheme 3. Reaction of isoquinoline.

[17] T. Louerat, Y. Fort, V. Mamane, *Tetrahedron Lett.* **2009**, *50*, 5716.

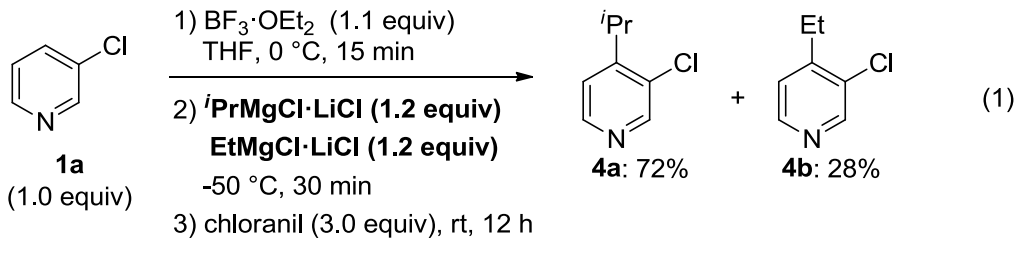
Table 2. Other examples of direct alkylation of pyridine derivatives using Grignard reagents.[a]

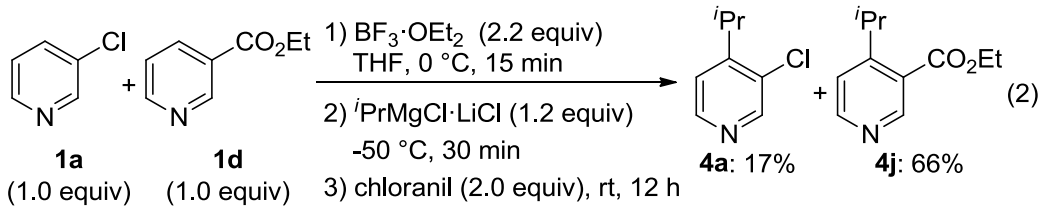




[a]Yields determined by GC or NMR. [b]Owing to the volatility of these compounds, some part of these products was lost during the workup.

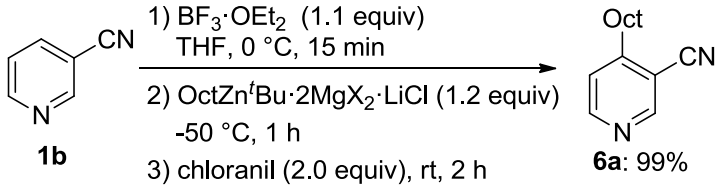
To explore some mechanistic details of this reaction, 3-chloropyridine (**1a**) was reacted with $BF_3 OEt_2$ and pre-mixed ^{i}PrMgCl ŁLiCl and EtMgCl ŁLiCl in equal amounts. Interestingly, the bulkier isopropyl adduct (**4a**) is mainly formed (eq 1). It indicates that rather than steric effects, the nucleophilicity and aggregation of the Grignard reagents play a more important role in these additions to pyridines. Besides, more electro-deficient ethyl nicotinate (**1d**) undergoes the addition of the Grignard reagent more readily (ca. 4 times) than 3-chloropyridine (**1a**); (eq 2).





2.2.2 BF_3-Mediated Direct Alkylation of Pyridines using Organozinc Reagents

To expand the scope of this reaction, we have investigated the use of alkylzinc reagents[12c] for the nucleophilic addition. The addition of OctZnBr·$MgCl_2$·LiCl to nicotinonitrile (**1b**) led to an unsatisfactory reaction with uncompleted conversion. However, by forming the mixed diorganozinc reagent OctZn^tBu, readily prepared by adding ^{t}BuMgCl to OctZnBr·$MgCl_2$·LiCl, we obtained a fast and quantitative addition to nicotinonitrile (**1b**) at -50 °C. After oxidative treatment with chloranil, the desired 4-substituted pyridine (**6a**) was obtained in 99% yield (Scheme 4). The *tert*-butyl group plays in all these reactions the role of a non-transferable ligand. [18] It should be noticed that although the *tert*-butyl group bears 9 *β*-hydrogens, no significant *β*-hydride elimination is observed in these reactions, since no transition-metal is present. This enables us to avoid using more expensive non-transferable ligands such as neopentyl, neophyl[18b] or trimethylsilylmethyl,[18 a,c] which bear no *β*-hydrogen.



Scheme 4. Selective addition of an organozinc reagent to nicotinonitrile

Thus, a variety of functionalized zinc reagents react under these conditions and highly functionalized products were obtained in 60–93% yield (Table 3). Remarkably, functionalized mixed diorganozinc reagents bearing an acetoxy, a carbethoxy[19] or a cyano group can be prepared and used without problems. In the case of 3-cyanopyridine, some part of the substrate is destroyed by the active dialkylzinc reagent so the yield of the desired product is low, although almost all the substrate has been consumed when the reaction finishes (entry 3). Surprisingly, the reaction using a bulky cyanoalkylzinc reagent (entry 8) works much better than the reaction using a similar yet less bulkier zinc reagent (entry 9). One possible reason is that the coordinative cyano group can deactivate the BF_3 and remove it from the substrate. While employing the 6-chlorohexylzinc reagent, the dechloronated product **6ka** is obtained together with the desired product **6k** (entry 10). To be noticed, an 8 mmol reaction using a functionalized zinc reagent also works well and gives the corresponding alkyl pyridine **6m** in 63% yield (entry 12). A functionalized secondary alkylzinc reagent also adds to the substrate (**1a**) but because of the severe *β*-hydride elimination during the in situ preparation of the zinc reagent, the yield of the product **6o** is less than 20% (entry 14).

[18] a) S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley, C. K. Reddy, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1496; b) C. Lutz, P. Jones, P. Knochel, *Synthesis* **1999**, 312; c) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, *11*, 1794.

[19] E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 3368.

Table 3. Direct alkylation of pyridine derivatives using alkylzinc reagents

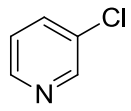
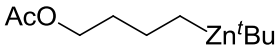
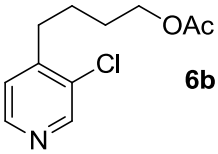
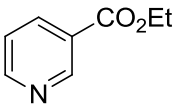
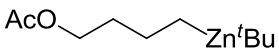
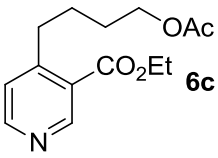
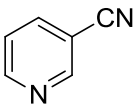
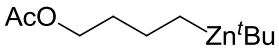
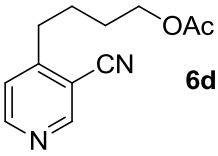
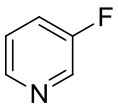
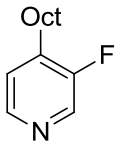
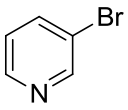
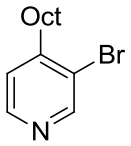
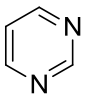
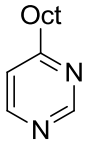
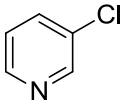
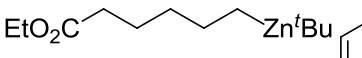
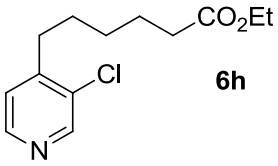
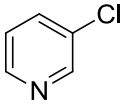
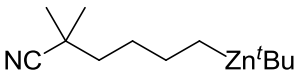
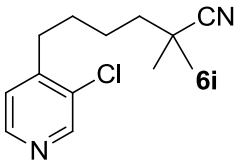
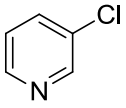
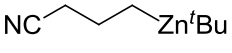
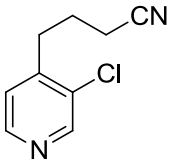
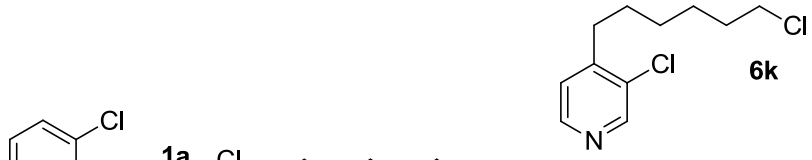
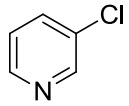
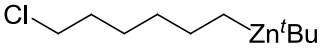
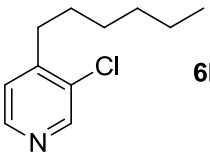
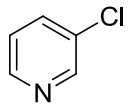
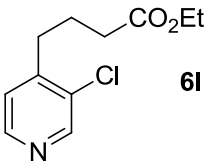
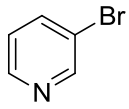
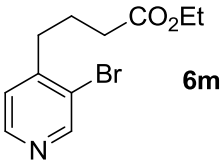
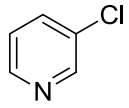
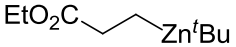
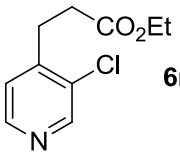
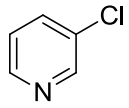
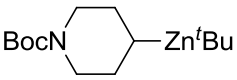
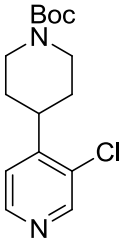
Entry	Substrate		Zinc Reagent[a]	Product		Yield %[b]
1		**1a**			**6b**	93
2		**1d**			**6c**	79
3		**1b**			**6d**	(35)
4		**1n**	OctZn^{t}Bu		**6e**	(44)
5		**1c**	OctZn^{t}Bu		**6f**	(78)
6		**1o**	OctZn^{t}Bu		**6g**	(34)
7		**1a**			**6h**	68
8		**1a**			**6i**	60
9		**1a**			**6j**	(<5)

Table 3. Continued.

				**6k**	-
10		**1a**		 **6ka**	-
11		**1a**		 **6l**	85
12[c]		**1c**		 **6m**	63
13		**1a**		 **6n**	86
14		**1a**		 **6o**	(<20)

[a]2MgX$_2$·LiCl is omitted for clarity. [b]Isolated yields of analytically pure products. NMR yields are given in parenthesis. [c]The reaction was carried in a 8 mmol scale.

2.2.3 BF_3-Mediated Direct Arylation of Pyridines using Grignard Reagents

Next, we have examined the arylation of functionalized pyridines (Table 4). Here, arylmagnesium reagents proved to give the best results and a smooth addition is obtained with a variety of Grignard reagents leading to polyfunctional 4-arylated pyridines (**7a–n**; 42–99%). Remarkably, a number of functional groups are tolerated in the starting pyridines such as an ester (entries 1–4), an amide (entry 5), a ketone (entry 6), a nitro[8g] (entry 7) and a cyano group (entries 8–14). In a large scale (8 mmol) reaction, 2-chloromethylphenylmagnesium bromide[20] adds to ethyl nicotinate (**1d**) and leads to the pyridine (**7d**) in 83% isolated (entry 4). Both Grignard reagents with electron-withdrawing (entry 9) or electron-donating groups (entry 10) afford 4-arylated pyridines (**7i** and **7j**) in high yields. Even a bulky Grignard reagent such as

[20] B. Haag, Z. Peng, P. Knochel, *Org. Lett.* **2009**, *11*, 4270.

mesitylmagnesium bromide reacts efficiently with nicotinonitrile (**1b**) and furnishes the 4-mesitylnicotinonitrile (**7k**) in 98% isolated yield (entry 11). For a 4-subsituted starting pyridine such as isonicotinonitrile (**1s**), the addition of a Grignard reagent cannot occur at C(4) but proceeds at C(2) and furnishes the corresponding product in acceptable yields (entries 12 and 13). Finally, 2-chloronicotinonitrile (**1t**) is converted to the 1,2,3-trisubstituted pyridine (**7n**) in 57% isolated yield (entry 14).

Table 4. Direct arylation of pyridine derivatives using Grignard reagents.

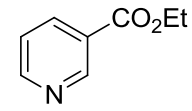
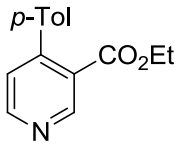
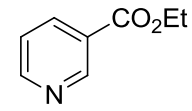
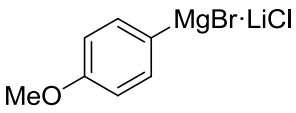
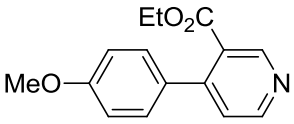
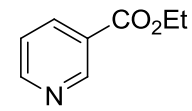
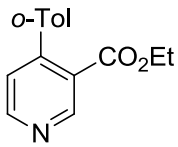
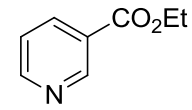
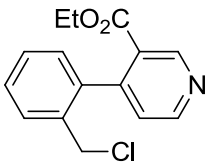
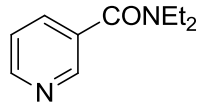
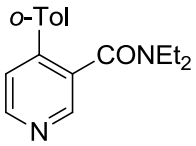
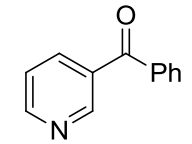
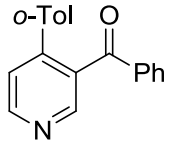
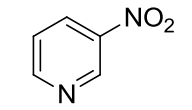
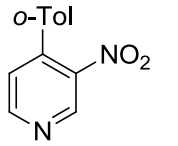
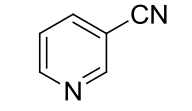
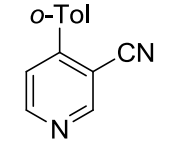
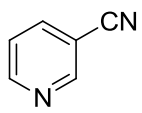
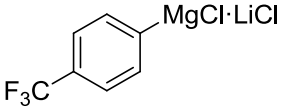
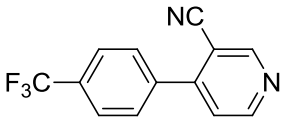
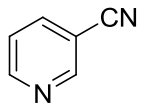
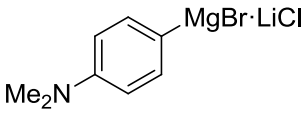
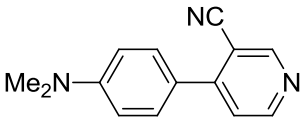
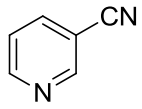
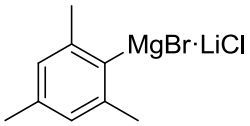
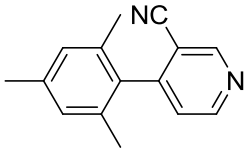
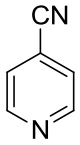
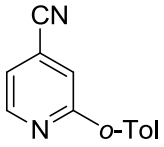
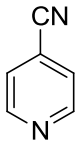
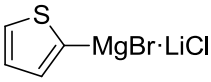
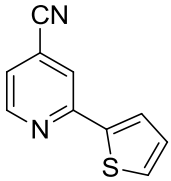
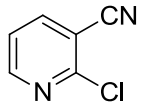
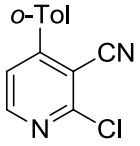
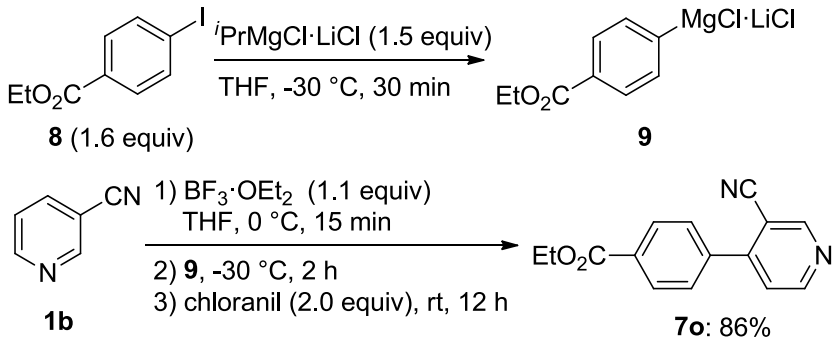
Entry	Substrate		Grignard Reagent	Product		Yield %[a]
1		**1d**	*p*-TolMgBr·LiCl		**7a**	80
2		**1d**			**7b**	81
3		**1d**	*o*-TolMgBr·LiCl		**7c**	83
4[b]		**1d**			**7d**	83
5		**1p**	*o*-TolMgBr·LiCl		**7e**	87
6		**1q**	*o*-TolMgBr·LiCl		**7f**	68
7		**1r**	*o*-TolMgBr·LiCl		**7g**	58
8		**1b**	*o*-TolMgBr·LiCl		**7h**	97

Table 4. Continued.

9		**1b**			**7i** 89
10		**1b**			**7j** 99
11		**1b**			**7k** 98
12		**1s**	*o*-TolMgBr·LiCl		**7l** 45
13		**1s**			**7m** 42
14		**1t**	*o*-TolMgBr·LiCl		**7n** 57

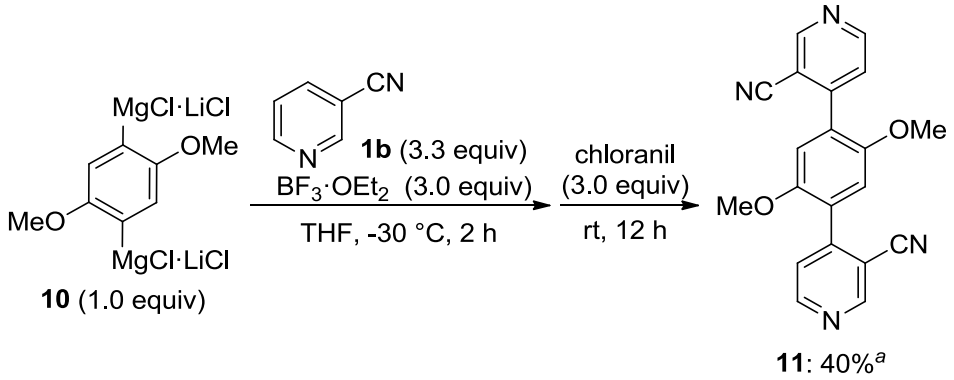
[a]Isolated yields of analytically pure products. [b]The reaction was carried in a 8 mmol scale.

To introduce a more functionalized aryl group, *p*-EtO_2C-$C_6H_4MgCl \cdot LiCl$ (**9**) was prepared *in situ* via iodine/magnesium exchange.[11a] In a reversed addition procedure, a mixture of nicotinonitrile (**1b**) and $BF_3 \cdot OEt_2$ was added to the Grignard reagent **9** to furnish a dual-functionalized pyridine (**7o**) in 86% isolated yield (Scheme 5).



Scheme 5. Selective addition of a functionalized Grignard reagent to nicotinonitrile.

Nicotinonitrile oligomers are usually used as functional materials, but their synthesis is always complex.[21] Surprisingly, with the aid of BF_3 OEt_2, a dimagnesiated species (**10**)[11b] reacts with two equivalents of nicotinonitrile and affords a fluorescent compound (**11**) in one step (Scheme 6).



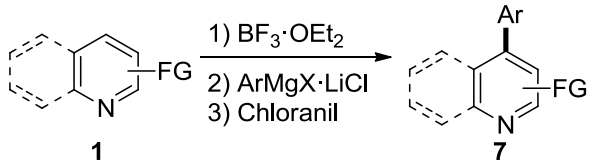
[a]Yield based on Grignard reagent.

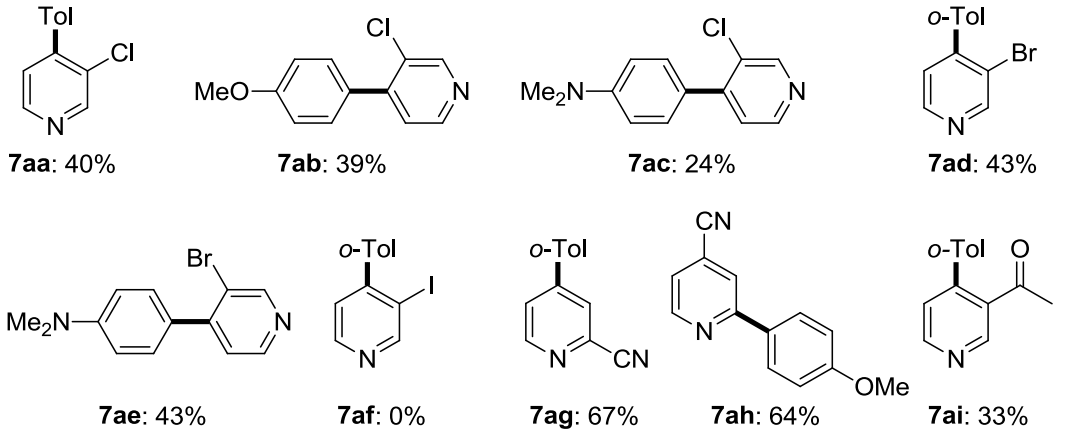
Scheme 6. Double addition to nicotinonitriles using a 1,4-dimagnesiated aromatic reagent.

For other substrates without a strong electron-withdrawing group such as 3-chloropyridine and 3-bromopyridine, the additions proceed sluggishly even using an electron-rich Grignard reagent, affording products (Table 5, **7aa–ae**) in moderate yields. Still, while applying 3-iodopyridine as the substrate, instead of addition the exchange reaction proceeds exclusively without the detection of the desired product **7af**. *o*-TolMgCl·LiCl adds to 2-Cyanopyridine and gives the product **7ag** in 67% yield. For isonicotinonitrile, the addition of 4-$MeOC_6H_4MgCl$·LiCl occurs selectively at the position 2 and affords the product **7ah** in 64% yield. Meanwhile, some trace amount of substitution product can also be detected (see Chapter 3). 3-Acetylpyridine affords the product (**7ai**) in low yield and only a trace amount of the product **7aj** is formed in the reaction between *o*-TolMgCl·LiCl and pyrimidine. A series of more complex Grignard reagents with functional groups such as carbetoxy, nitro and trifluoromethyl also react with substrates and afford highly functionalized products (**7ak–an**) in moderate to good yields. However, the reaction employing 3-pyridylmagnesium chloride-lithium chloride is very sluggish and only trace amount of the desired coupling product (**7ao**) is observed. The addition of 2-thiophenylmagnesium chloride-lithium chloride toward 2-chloronicotinonitrile affords the desired product (**7ap**) in less than 5% yield.

[21] a) N. Li, P. Wang, S.-L. Lai, W. Liu, C.-S. Lee, S.-T. Lee, Z. Liu, *Adv. Mater.* **2010**, *22*, 527; b) J. You, M.-F. Lo, W. Liu, T.-W. Ng, S.-L. Lai, P. Wang, C.-S. Lee, *J. Mater. Chem.* **2012**, *22*, 5107.

Table 5. Other examples of direct arylation of pyridine derivatives using Grignard reagents.[a]





7aa: 40% **7ab**: 39% **7ac**: 24% **7ad**: 43%

7ae: 43% **7af**: 0% **7ag**: 67% **7ah**: 64% **7ai**: 33%

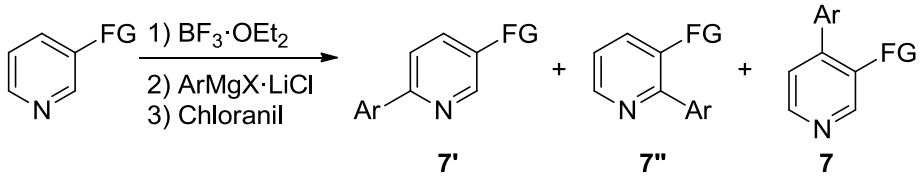
7aj: <5% **7ak**: 74% **7al**: 62% **7am**: 60%

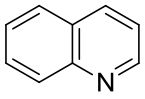
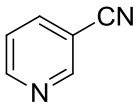
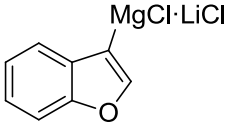
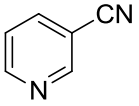
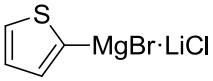
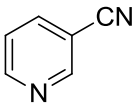
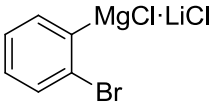
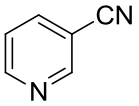
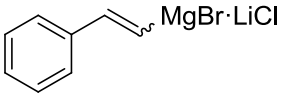
7an: 33% **7ao**: <5% **7ap**: <5%

[a]Yields determined by GC or NMR.

Meanwhile, in some examples a mixture of regioisomers is obtained (Table 6). Quinoline (**1i**) affords a mixture of 2- and 4-adducts in nearly 1:1 ratio (entry 1). Interestingly, some heteroaryl Grignard reagents such as 3-benzofurylmagnesium chloride-lithium chloride and 2-thiophenylmagnesium chloride-lithium chloride always lead to poor regioselectivity (entries 2 and 3), perhaps owing to the change of aggregation and related bulkiness of the active organometallic species. The blocking of position 2 of substrates forces the additions proceed in position 4, but in very low yields (vide supra). Also, 2-bromophenyl and 2-phenylethenyl Grignard reagents add to isonicotinonitrile (**1d**) nonspecifically, affording a mixture of regioisomers (entries 4 and 5).

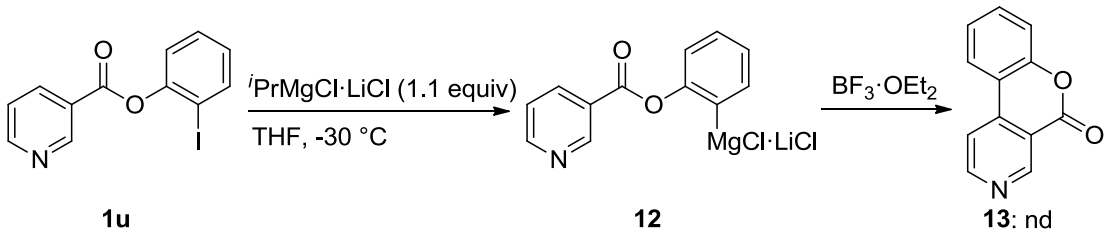
Table 6. Direct arylation of pyridine derivatives giving a mixture of regioisomers.



Entry	Substrate		Grignard Reagent	Yield %[a] 7'	7"	7
1		**1i**	*p*-TolMgBr·LiCl	-	30	31
2		**1b**		-	29	55
3		**1b**		35	40	26
4		**1b**		28	14	58
5		**1b**		6	30	63

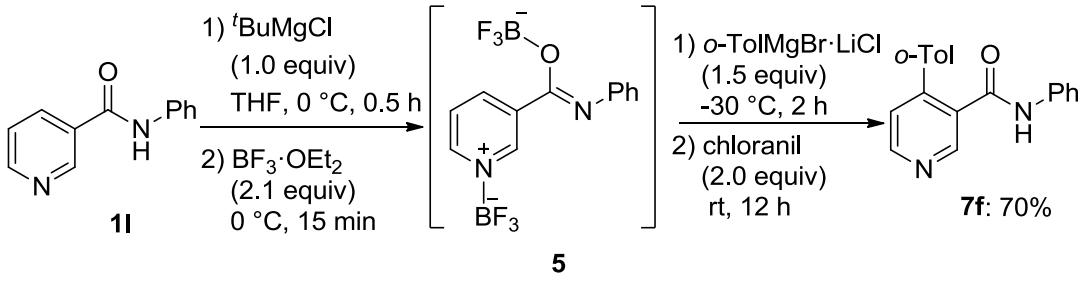
[a]Yields dertermined by GC or NMR.

An intramolecular cyclization through the BF_3-mediated cross-coupling was also screened. Thus, the I/Mg exchange was firstly performed of **1u** at -30 ℃ to obtain the arylmagnesium species **12**. But after the treatment of BF_3 OEt_2, the desired cyclized product **13** was not detected (Scheme 7).



Scheme 7. BF_3-mediated cyclization.

Similarly to alkylation, the arylation of nicotinamide (**1l**) also proceeds using 2 equivalents of BF_3 OEt_2 and *o*-TolMgX. The arylated product **7f** was obtained in 70% isolated yield (Scheme 8).



Scheme 8. Direct arylation of nicotinamide (**1l**).

2.3 Summary

In summary, a transition-metal-free BF_3 OEt_2 mediated functionalization of pyridines with functionalized alkyl and aryl groups has been developed. An excellent C(4)-regioselectivity makes this method a complement to previously reported ones. A large variety of functionalized coupling products can be obtained in good yields using this method. Besides, this reaction is practical and can be performed at a larger scale with no yield decrease.

2.4 Experimental Section

2.4.1 General Considerations

All reactions are carried out under argon atmosphere in flame-dried glassware. Syringes which are used to transfer anhydrous solvents or reagents are purged with argon prior to use. THF is continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be pure as determined by ^{1}H-NMR (25 ℃) and capillary GC. Column chromatographical purifications are performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM from Merck). Mass spectra and high resolution mass spectra (HRMS) are recorded using electron ionization (EI) or electrospray ionization (ESI). Grignard reagents and organozinc reagents are prepared according to the literature.[11,12] BF_3 OEt_2 is purchased from Aldrich and distilled before use.

2.4.2 Typical Procedures

Typical Procedure for the BF_3-mediated direct alkylation of pyridine derivatives using alkyl Grignard reagents (TP1)

A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**1**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. BF_3 OEt_2 (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 50 ℃ followed by dropwise addition of a THF solution of an alkyl Grignard reagent (1.2 mmol), and stirring the reaction mixture at the same temperature for 30 min. Then chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room

temperature and continuously stirred for 2 h. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with Et_2O several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**4**).

Typical Procedure for the BF_3-mediated direct alkylation of pyridine derivatives using organozinc reagents (TP2)

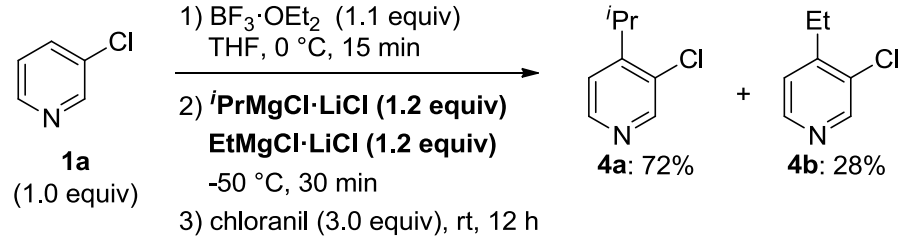
According to the literature,[12c] a functionlized organozinc reagent is prepared using Mg-turnings (109 mg, 4.5 mmol), LiCl (95 mg, 2.25 mmol), $ZnCl_2$ (1M solution in THF, 2.0 mL, 2.0 mmol) and alkyl bromide (1.8 mmol). The reaction is carried out at 25 ˚C and monitored by GC until all the alkyl bromide has been consumed.

A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**1**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. BF_3 OEt_2 (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. Then the reaction mixture is cooled to -50 ℃. The produced alkylzinc reagent is transferred to this flask followed by dropwise addition of a THF solution of ^{t}BuMgCl (1.5 mmol), and stirring the reaction mixture at the same temperature for 1 h. Then chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with Et_2O several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**6**).

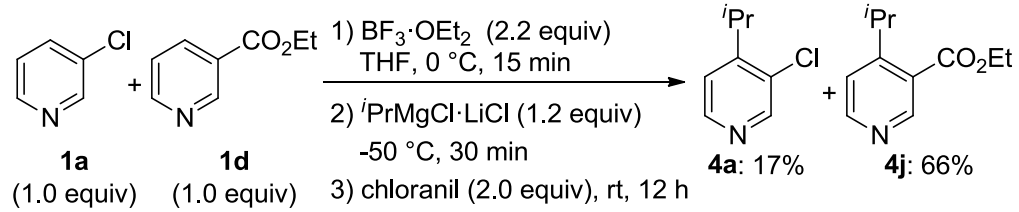
Typical Procedure for the BF_3-mediated direct arylation of pyridine derivatives using aryl Grignard reagents (TP3)

A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**1**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. BF_3 OEt_2 (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 30 ℃ followed by dropwise addition of a THF solution of an aryl Grignard reagent (1.5 mmol), and stirring the reaction mixture at the same temperature for 2 h. Then chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**7**).

2.4.3 Competition Experiments

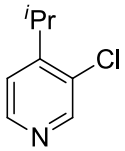


According to **TP1**, 3-chloropyridine (**1a**; 1.0 mmol) reacts with a THF solution of pre-mixed ^{i}PrMgCl·LiCl (1.2 mmol) and EtMgCl·LiCl (1.2 mmol). After filtration, the crude products are measured by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard, giving the corresponding NMR yields of each product.



According to **TP1**, a mixture of 3-chloropyridine (**1a**; 1.0 mmol) and ethyl nicotinate (**1d**; 1.0 mmol) reacts with ^{i}PrMgCl·LiCl (1.2 mmol) in the presence of 2.2 mmol $BF_3 \cdot OEt_2$. After filtration, the crude products are measured by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard, giving the corresponding NMR yields of each product.

2.4.4 Product Synthesis and Analytical Data



4a

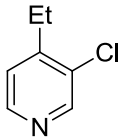
3-chloro-4-isopropylpyridine (4a): To a solution of 3-chloropyridine (**1a**; 115 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.2 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.94 mL, 1.27 M in THF, 1.1 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4a** (140 mg, 89%) as a brown oil.

^{1}H NMR (599 MHz, $CDCl_3$) δ ppm 8.52 (s, 1 H), 8.43 (d, *J*=5.2 Hz, 1 H), 7.25 (d, *J*=5.2 Hz, 1 H), 3.44 - 3.31 (m, *J*=13.7, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.27 (d, *J*=6.9 Hz, 6 H).

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 155.22, 148.62, 147.29, 131.74, 121.61, 30.00, 21.72 (2 C).

MS (70 eV, EI) *m/z* (%): 155 (79), 140 (100), 104 (96), 77 (34).

HRMS for $C_8H_{10}ClN$: calcd. 155.0502; found 155.0479 (M^+).



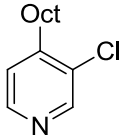
4b

3-chloro-4-ethylpyridine (4b): To a solution of 3-chloropyridine (**1a**; 115 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with EtMgCl·LiCl (1.6 mL, 1.25 M in THF, 2.0 mmol) or EtMgCl (0.82 ml, 2.44 M in THF, 2.0 mmol). After filtration, an NMR yield of 94% or 67% is given using mesitylene as an internal standard. The crude product of the reaction using EtMgCl·LiCl is diluted in EtOAc and washed with 2M HCl for 3 three times. The aqueous layers are combined and neutralized with a NaOH solution. Then it is washed with EtOAc 3 times and the organic layers are combined and dried by K_2CO_3. After evaporating the extra solvents, the mixture is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4b** (56 mg, 39%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (s, 1 H), 8.39 (d, *J*=5.0 Hz, 1 H), 7.17 (d, *J*=5.0 Hz, 1 H), 2.77 (q, *J*=7.6 Hz, 2 H), 1.26 (t, *J*=7.6 Hz, 3 H); in accordance with the literature.[22]

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.29, 149.05, 147.69, 132.00, 123.98, 25.95, 12.83.

MS (70 eV, EI) *m/z* (%): 141 (100), 126 (49), 106 (63), 77 (24).



4c

3-chloro-4-octylpyridine (4c): To a solution of 3-chloropyridine (**1a**; 114 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with OctMgBr·LiCl (2.8 mL, 0.72 M in THF, 2.0 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4c** (212 mg, 94%) as a brown oil.

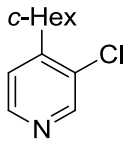
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (s, 1 H), 8.35 (d, *J*=5.0 Hz, 1 H), 7.15 (d, *J*=5.0 Hz, 1 H), 2.72 (t, 2 H), 1.71 - 1.52 (m, 2 H), 1.40 - 1.21 (m, 10 H), 0.88 (t, *J*=6.1 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.53, 148.90, 147.18, 132.18, 124.83, 32.80, 31.79, 29.26 (2 C), 29.13, 28.69, 22.61, 14.05.

MS (70 eV, EI) *m/z* (%): 224 (20), 188 (15), 174 (26), 161 (100).

HRMS for $C_{13}H_{20}ClN$: calcd.225.1284; found 225.1315 (M^+).

[22] S. Hayashi, N. Ueno, A. Murase, Y. Nakagawa, Takada, *J. Eur. J. Med. Chem.* **2012**, *50*, 179.



4d

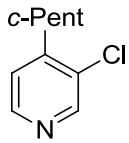
3-chloro-4-cyclohexylpyridine (4d): To a solution of 3-chloropyridine (**1a**; 111 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with *c*-HexylMgBr·LiCl (2.0 mL, 0.59 M in THF, 1.2 mmol) for 1 h. The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4d** (134 mg, 70%) as a reddish brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (s, 1 H), 8.37 (d, *J*=5.0 Hz, 1 H), 7.14 (d, *J*=5.0 Hz, 1 H), 3.05 – 2.84 (m, 1 H), 1.93 - 1.69 (m, 5 H), 1.53 - 1.14 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.11, 149.21, 147.83, 131.49, 121.81, 40.03, 32.07 (2 C), 26.39 (2 C), 25.89.

MS (70 eV, EI) *m/z* (%): 195 (100), 160 (37), 139 (90), 127 (41).

HRMS for $C_{11}H_{14}ClN$: calcd. 195.0815; found 195.0811 (M^+).



4e

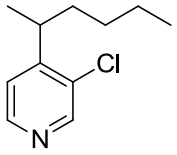
3-chloro-4-cyclopentylpyridine (4e): To a solution of 3-chloropyridine (**1a**; 112 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with *c*-PentMgCl·LiCl (1.2 mL, 1.01 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4e** (158 mg, 89%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (br. s., 1 H), 8.36 (br. s., 1 H), 7.18 (d, *J*=5.0 Hz, 1 H), 3.46 - 3.26 (m, 1 H), 2.19 – 1.95 (m, 2 H), 1.91 - 1.63 (m, 4 H), 1.63 - 1.42 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 152.64, 149.03, 147.62, 132.13, 121.74, 41.52, 32.54 (2 C), 25.41 (2 C).

MS (70 eV, EI) *m/z* (%): 181 (100), 152 (40), 146 (60), 139 (99), 104 (35).

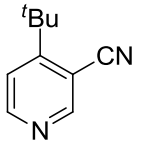
HRMS for $C_{10}H_{12}ClN$: calcd. 181.0658; found 181.0643 (M^+).



4f

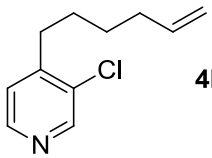
3-chloro-4-(hexan-2-yl)pyridine (4f): To a solution of 3-chloropyridine (**1a**; 111 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with 2-HexylMgCl·LiCl (1.7 mL, 0.72 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4f** (177

mg, 91%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (s, 1 H), 8.38 (d, *J*=5.3 Hz, 1 H), 7.14 (d, *J*=5.3 Hz, 1 H), 3.32 - 3.09 (m, 1 H), 1.69 - 1.42 (m, 2 H), 1.35 - 1.09 (m, 7 H), 0.84 (t, *J*=6.9 Hz, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.68, 149.25, 147.70, 131.81, 121.87, 36.06, 34.89, 29.37, 22.53, 20.09, 13.85.
MS (70 eV, EI) *m/z* (%): 197 (46), 141 (100), 104 (39), 77 (23).
HRMS for $C_{11}H_{16}ClN$: calcd. 197.0971; found 197.0974 (M^+).



4g

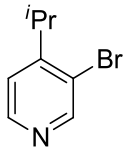
4-(*tert*-butyl)nicotinonitrile (4g): To a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (1 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{t}BuMgCl·LiCl (3.3 mL, 0.60 M in THF, 2.0 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2) furnishing the compound **4g** (112 mg, 70%) as a red oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.82 (s, 1 H), 8.68 (d, *J*=5.5 Hz, 1 H), 7.40 (d, *J*=5.5 Hz, 1 H), 1.52 (s, 9 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.44, 154.92, 152.88, 120.85, 118.00, 108.56, 35.83, 29.31 (3 C).
MS (70 eV, EI) *m/z* (%): 160 (29), 145 (100), 118 (24).
HRMS for $C_{10}H_{12}N_2$: calcd. 160.1001; found 160.0987 (M^+).



4h

3-chloro-4-(hex-5-en-1-yl)pyridine (4h): To a solution of 3-chloropyridine (**1a**; 114 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with hex-5-en-1-ylMgCl·LiCl (1.2 mL, 1.02 M in THF, 1.2 mmol). After filtration, an NMR yield of 76% is given using mesitylene as an internal standard. The product is partially separated from the unconverted substrate by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4h** (87 mg, 44%) as a reddish brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (s, 1 H), 8.37 (d, *J*=5.0 Hz, 1 H), 7.14 (d, *J*=4.9 Hz, 1 H), 5.91 - 5.68 (m, *J*=17.0, 10.3, 6.6, 6.6 Hz, 1 H), 5.09 - 4.90 (m, 2 H), 2.73 (t, *J*=7.5 Hz, 2 H), 2.11 (q, *J*=7.0 Hz, 2 H), 1.73 - 1.57 (m, 2 H), 1.57 - 1.40 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.23, 148.91, 147.53, 138.32, 132.07, 124.75, 114.77, 33.38, 32.59, 28.44, 28.14.
MS (70 eV, EI) *m/z* (%): 195 (34), 160 (52), 152 (60), 139 (100), 127 (73), 117 (38).

HRMS for $C_{11}H_{14}ClN$: calcd. 195.0815; found 195.0804 (M^+).



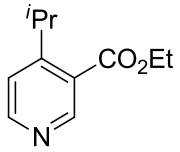
4i

3-bromo-4-isopropylpyridine (4i): To a solution of 3-bromopyridine (**1c**; 160 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.27 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4i** (135 mg, 67%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.67 (s, 1 H), 8.46 (d, *J*=5.1 Hz, 1 H), 7.25 (d, *J*=5.5 Hz, 1 H), 3.23 - 3.44 (m, *J*=13.7, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 1.27 (d, *J*=7.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.19, 150.99, 147.59, 122.95, 122.05, 32.70, 21.86.

MS (70 eV, EI) *m/z* (%): 199 (81), 184 (98), 104 (100), 77 (28).



4j

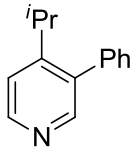
ethyl 4-isopropylnicotinate (4j): To a solution of ethyl nicotinate (**1d**; 153 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.28 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2) furnishing the compound **4j** (155 mg, 79%) as a pink oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.94 (s, 1 H), 8.62 (d, *J*=5.3 Hz, 1 H), 7.32 (d, *J*=5.3 Hz, 1 H), 4.40 (q, *J*=7.2 Hz, 2 H), 3.89 - 3.69 (m, *J*=13.8, 6.8, 6.8, 6.8, 6.6 Hz, 1 H), 1.41 (t, *J*=7.0 Hz, 3 H), 1.27 (d, *J*=6.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.53, 158.83, 152.12, 150.90, 126.03, 120.99, 61.32, 29.25, 23.09 (2 C), 14.21.

MS (70 eV, EI) *m/z* (%): 193 (89), 146 (100), 132 (59), 117 (24).

HRMS for $C_{11}H_{15}NO_2$: calcd. 193.1103; found 193.1100 (M^+).



4k

4-isopropyl-3-phenylpyridine (4k): To a solution of 3-phenylpyridine (**1e**; 155 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.00 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with

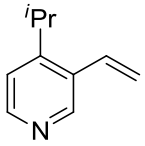
^{i}PrMgCl·LiCl (1.6 mL, 1.28 M in THF, 2.0 mmol) for 1 h. The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:2) furnishing the compound **4k** (142 mg, 72%) as a reddish brown oil.

^{1}H NMR (400 MHz, BENZENE-d_6) δ ppm 8.61 (s, 1 H), 8.58 (d, *J*=5.3 Hz, 1 H), 7.18 - 7.04 (m, 5 H), 6.88 (d, *J*=5.1 Hz, 1 H), 2.97 (spt, *J*=6.8 Hz, 1 H), 0.91 (d, *J*=6.8 Hz, 6 H).

^{13}C NMR (101 MHz, BENZENE-d_6) δ ppm 154.78, 151.33, 149.95, 139.06, 137.33, 130.09 (2 C), 128.91 (2 C), 127.95, 120.76, 29.61, 23.69 (2 C).

MS (70 eV, EI) *m/z* (%): 197 (87), 182 (100), 167 (96).

HRMS for $C_{14}H_{15}N$: calcd. 197.1205; found 197.1194 (M^+).



4l

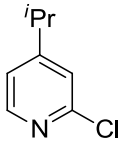
4-isopropyl-3-vinylpyridine (4l): To a solution of 3-vinylpyridine (**1f**; 107 mg, 1.0 mmol) in THF (2 ml) is added BF_3·OEt_2 (156 mg, 1.00 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.93 mL, 1.29 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4l** (71 mg, 47%) as a pink oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.59 (s, 1 H), 8.44 (d, *J*=5.2 Hz, 1 H), 7.16 (d, *J*=5.2 Hz, 1 H), 6.96 (dd, *J*=17.4, 11.0 Hz, 1 H), 5.67 (dd, *J*=17.4, 1.1 Hz, 1 H), 5.41 (dd, *J*=11.0, 1.1 Hz, 1 H), 3.29 - 3.07 (m, *J*=13.7, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.24 (d, *J*=6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.21, 148.83, 147.38, 132.23, 131.80, 119.64, 117.91, 28.94, 22.42 (2 C).

MS (70 eV, EI) *m/z* (%): 147 (70), 132 (98), 117 (100).

HRMS for $C_{10}H_{13}N$: calcd. 147.1048; found 147.1028 (M^+).

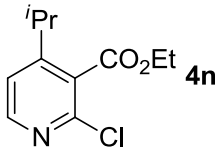


4m

2-chloro-4-isopropylpyridine (4m): To a solution of 2-chloropyridine (**1g**; 111 mg, 1.0 mmol) in THF (2 ml) is added BF_3·OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.28 M in THF, 1.2 mmol). After filtration, an NMR yield of 76% is given using mesitylene as an internal standard. The product is partially separated from the unconverted substrate by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:19) furnishing the compound **4m** (80 mg, 53%) as a brown oil.

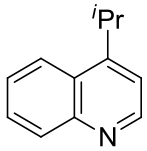
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.27 (d, *J*=5.0 Hz, 1 H), 7.18 (br. s., 1 H), 7.07 (dd, *J*=5.3, 1.1 Hz, 1 H), 2.98 - 2.79 (m, *J*=13.8, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.26 (d, *J*=6.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 160.97, 151.64, 149.51, 122.33, 120.87, 33.49, 22.90 (2 C).
MS (70 eV, EI) *m/z* (%): 155 (83), 140 (100), 120 (35), 104 (69), 77 (31).
HRMS for $C_8H_{10}ClN$: calcd. 155.0502; found 155.0487 (M^+).



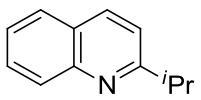
4n

ethyl 2-chloro-4-isopropylnicotinate (4n): To a solution of ethyl 2-chloronicotinate (**1h**; 186 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.00 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.28 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4) furnishing the compound **4n** (212 mg, 93%) as a pink oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.30 (d, *J*=5.3 Hz, 1 H), 7.17 (d, *J*=5.3 Hz, 1 H), 4.41 (q, *J*=7.0 Hz, 2 H), 2.99 - 2.78 (m, *J*=13.6, 6.9, 6.8, 6.8, 6.8 Hz, 1 H), 1.37 (t, *J*=7.0 Hz, 3 H), 1.22 (d, *J*=6.9 Hz, 6 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.86, 157.62, 149.82, 147.15, 129.45, 119.48, 62.02, 31.42, 22.87 (2 C), 13.92.
MS (70 eV, EI) *m/z* (%): 227 (88), 199 (43), 182 (100), 162 (51), 148 (49), 117 (41), 91 (29).
HRMS for $C_{11}H_{14}ClNO_2$: calcd. 227.0713; found 227.0710 (M^+).



4o

4-isopropylquinoline (4o): To a solution of quinoline (**1i**; 128 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.27 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:2) furnishing the compound **4o** (136 mg, 80%) as a reddish oil and **4oa** (11 mg, 6%) as a pink oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.85 (d, *J*=4.7 Hz, 1 H), 8.12 (t, *J*=9.5 Hz, 2 H), 7.69 (td, *J*=7.6, 1.1 Hz, 1 H), 7.62 - 7.49 (m, 1 H), 7.30 (d, *J*=4.4 Hz, 1 H), 3.66 - 3.83 (m, *J*=13.7, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 1.40 (d, *J*=6.6 Hz, 6 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.46, 150.28, 148.20, 130.24, 128.79, 126.87, 126.17, 123.03, 116.86, 28.26, 22.86 (2 C).
MS (70 eV, EI) *m/z* (%): 171 (60), 156 (100), 143 (5), 128 (15).
HRMS for $C_{12}H_{13}N$: calcd. 171.1048; found 171.1025 (M^+).

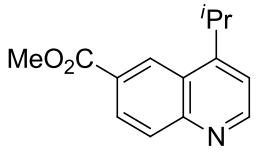


4oa

2-isopropylquinoline (4oa)

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.08 (t, *J*=8.0 Hz, 2 H), 8.08 - 7.64 (m, 2 H), 7.52 - 7.38 (m, 1 H), 7.30 (d, *J*=14 Hz, 1 H), 3.35 - 3.20 (m, 1 H), 1.40 (d, *J*=7.0 Hz, 6 H); in accordance with the literature.[23]

MS (70 eV, EI) *m/z* (%): 171 (29), 156 (100), 143 (25), 128 (29).



4p

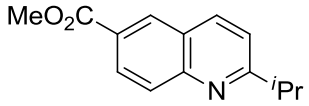
methyl 4-isopropylquinoline-6-carboxylate (4p): To a solution of methyl quinoline-6-carboxylate (**1j**; 186 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.27 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:1) furnishing the compound **4p** (197 mg, 86%) and **4pa** (24 mg, 10%) as brown oils.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.86 (d, *J*=4.7 Hz, 1 H), 8.83 (s, 1 H), 8.27 - 8.16 (m, 1 H), 8.15 - 8.03 (m, 1 H), 7.30 (d, *J*=4.3 Hz, 1 H), 3.94 (s, 3 H), 3.87 - 3.65 (m, 1 H), 1.36 (d, *J*=6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.66, 155.94, 152.28, 150.08, 130.47, 128.15, 127.50, 126.22, 125.98, 117.56, 52.23, 28.20, 22.92 (2 C).

MS (70 eV, EI) *m/z* (%): 229 (100), 214 (67), 198 (73), 170 (44), 154 (61).

HRMS for $C_{14}H_{15}NO_2$: calcd. 229.1103; found 229.1094 (M^+).



4pa

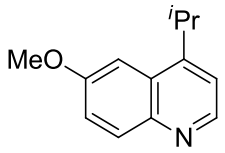
methyl 2-isopropylquinoline-6-carboxylate (4pa)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.54 (d, *J*=1.8 Hz, 1 H), 8.27 (dd, *J*=8.8, 1.9 Hz, 1 H), 8.18 (d, *J*=8.6 Hz, 1 H), 8.08 (d, *J*=8.8 Hz, 1 H), 7.41 (d, *J*=8.6 Hz, 1 H), 3.99 (s, 3 H), 3.35 - 3.22 (m, *J*=13.8, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.41 (d, *J*=7.0 Hz, 6 H); in accordance with the literature.[24]

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.12, 166.79, 149.63, 137.54, 130.63, 129.21, 128.79, 127.15, 126.00, 120.11, 52.31, 37.41, 22.35 (2 C).

MS (70 eV, EI) *m/z* (%): 229 (29), 214 (100), 201 (20).

HRMS for $C_{14}H_{15}NO_2$: calcd. 229.1103; found 229.1097 (M^+).



4q

[23] T. Kobayashi, M. Arisawa, S. Shuto, *Org. Biomol. Chem.* **2011**, *9*, 1219.

[24] PFIZER INC.; RENOVIS, INC. US2012/88746 A1, **2012**.

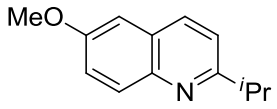
4-isopropyl-6-methoxyquinoline (4q): To a solution of 6-methoxyquinoline (**1k**; 156 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with ^{i}PrMgCl ŀLiCl (0.95 mL, 1.27 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:1) furnishing the compound **4q** (154 mg, 78%) and **4qa** (<4%) as brown oils.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.68 (d, *J*=4.5 Hz, 1 H), 8.01 (d, *J*=9.1 Hz, 1 H), 7.27 - 7.38 (m, 2 H), 7.22 (d, *J*=4.3 Hz, 1 H), 3.91 (s, 3 H), 3.49 - 3.70 (m, 1 H), 1.37 (d, *J*=6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.47, 152.74, 147.77, 144.17, 131.55, 127.65, 120.91, 116.99, 101.37, 55.34, 28.32, 22.54 (2 C).

MS (70 eV, EI) *m/z* (%): 201 (100), 186 (95), 143 (33).

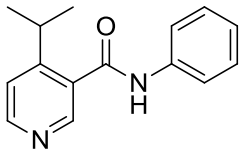
HRMS for $C_{13}H_{15}NO$: calcd. 201.1154; found 201.1141 (M^+).



4qa

2-isopropyl-6-methoxyquinoline (4qa)

MS (70 eV, EI) *m/z* (%): 201 (38), 186 (100), 173 (32), 143 (27).



4r

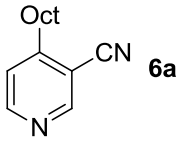
4-isopropyl-*N*-phenylnicotinamide (4r): A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of *N*-phenylnicotinamide (**1l**; 197 mg, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. ^{t}BuMgCl (0.78 ml, 1.28 M in THF, 1.0 mmol) is dropped in and the mixture is stirred for 30 min. Then BF_3 OEt_2 (298 mg, 2.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 50 ℃ followed by dropwise addition of a THF solution of ^{i}PrMgCl ŀLiCl (0.93 ml, 1.29 M in THF, 1.2 mmol), and stirring the reaction mixture at the same temperature for 30 min. Then chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:1) furnishes compound **4r** (159 mg, 67%) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.55 (s, 1 H), 8.60 (d, *J*=5.3 Hz, 1 H), 8.57 (s, 1 H), 7.73 (d, *J*=7.6 Hz, 2 H), 7.48 (d, *J*=5.3 Hz, 1 H), 7.35 (t, *J*=7.8 Hz, 2 H), 7.12 (t, *J*=7.3 Hz, 1 H), 3.29 - 3.18 (m, 1 H), 1.23 (d, *J*=6.8 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 165.86, 154.74, 150.59, 147.25, 138.93, 132.63, 128.75 (2 C), 123.88, 121.00, 119.68 (2 C), 29.46, 22.88 (2 C).

MS (70 eV, EI) *m/z* (%): 240 (31), 148 (100), 130 (47), 92 (17).

HRMS for $C_{15}H_{16}N_2O$: calcd. 240.1263; found 240.1261 (M^+).



6a

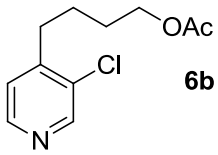
4-octylnicotinonitrile (6a): To a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with OctZnBr·$MgCl_2$·LiCl (1.8 mL, 0.68 M in THF, 1.2 mmol) and ^{t}BuMgCl (0.94 ml, 1.28 M in THF, 1.2 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:2) furnishing the compound **6a** (214 mg, 99%) as a reddish brown oil.

^{1}H NMR (400 MHz, BENZENE-d_6) δ ppm 8.43 (s, 1 H), 8.21 (d, *J*=5.3 Hz, 1 H), 6.33 (d, *J*=5.3 Hz, 1 H), 2.33 (d, *J*=7.8 Hz, 2 H), 1.38 - 1.00 (m, 12 H), 0.92 (t, *J*=7.0 Hz, 3 H).

^{13}C NMR (101 MHz, BENZENE-d_6) δ ppm 155.03, 153.44, 152.78, 123.79, 116.46, 111.12, 34.27, 32.53, 30.21, 29.89, 29.84, 29.68, 23.42, 14.71.

MS (70 eV, EI) *m/z* (%): 215 (5), 187 (21), 173 (29), 159 (32), 145 (100), 131 (55), 118 (37).

HRMS for $C_{14}H_{19}N_2$: calcd.215.1543; found 215.1520 [$(M-H)^+$].



6b

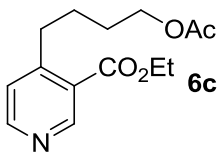
4-(3-chloropyridin-4-yl)butyl acetate (6b): To a solution of 3-chloropyridine (**1a**; 111 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 4-acetoxybutylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2 to 1:1) furnishing the compound **6b** (208 mg, 93%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.45 (s, 1 H), 8.31 (d, *J*=5.0 Hz, 1 H), 7.09 (d, *J*=5.0 Hz, 1 H), 4.04 (br. s., 2 H), 2.70 (br. s., 2 H), 1.98 (s, 3 H), 1.65 (br. s., 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 170.82, 149.09, 148.14, 147.46, 131.84, 124.55, 63.69, 32.09, 28.00, 24.97, 20.73.

MS (70 eV, EI) *m/z* (%): 227 (6), 192 (38), 166 (26), 140 (100), 127 (27).

HRMS for $C_{11}H_{14}ClNO_2$: calcd. 227.0713; found 227.0708 (M^+).



6c

ethyl 4-(4-acetoxybutyl)nicotinate (6c): To a solution of ethyl nicotinate (**1d**; 148 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at

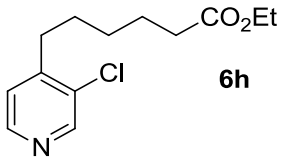
0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 4-acetoxybutylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:4 to 1:2) furnishing the compound **6c** (205 mg, 79%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.06 (s, 1 H), 8.59 (d, *J*=5.1 Hz, 1 H), 7.19 (d, *J*=5.1 Hz, 1 H), 4.40 (q, *J*=7.1 Hz, 2 H), 4.10 (t, *J*=6.0 Hz, 2 H), 3.01 (t, *J*=7.3 Hz, 2 H), 2.05 (s, 3 H), 1.80 - 1.59 (m, 4 H), 1.42 (t, *J*=7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 171.12, 165.95, 152.95, 152.03, 151.66, 125.76, 125.29, 64.04, 61.24, 33.27, 28.48, 27.07, 20.94, 14.21.

MS (70 eV, EI) *m/z* (%): 265 (5), 192 (38), 178 (100), 149 (29).

HRMS for $C_{14}H_{20}NO_4$: calcd. 266.1387; found 266.1388 ($M+H^+$).



6h

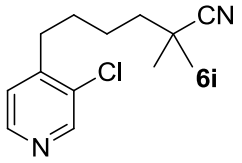
ethyl 6-(3-chloropyridin-4-yl)hexanoate (6h): To a solution of 3-chloropyridine (**1a**; 115 mg, 1.0 mmol) in THF (2 ml) is added BF_3·OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 6-ethoxy-6-oxohexylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2 to 1:1) furnishing the compound **6h** (176 mg, 68%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45 (br. s., 1 H), 8.31 (d, *J*=3.7 Hz, 1 H), 7.11 (d, *J*=4.7 Hz, 1 H), 4.08 (q, *J*=7.1 Hz, 2 H), 2.69 (t, *J*=7.6 Hz, 2 H), 2.27 (t, *J*=7.3 Hz, 2 H), 1.53 - 1.71 (m, 4 H), 1.30 - 1.44 (m, 2 H), 1.21 (t, *J*=7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 173.45, 148.96, 148.83, 147.17, 132.00, 124.73, 60.14, 33.97, 32.45, 28.56, 28.21, 24.48, 14.12.

MS (70 eV, EI) *m/z* (%): 255 (3), 220 (17), 210 (15), 140 (100), 127 (33).

HRMS for $C_{13}H_{18}ClNO_2$: calcd. 255.1026; found 255.1012 (M^+).

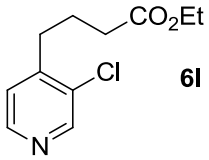


6i

6-(3-chloropyridin-4-yl)-2,2-dimethylhexanenitrile (6i): To a solution of 3-chloropyridine (**1a**; 114 mg, 1.0 mmol) in THF (2 ml) is added BF_3·OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 5-cyano-5-methylhexylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2 to 1:1) furnishing the compound **6i** (142 mg, 60%) as a pale brown oil.

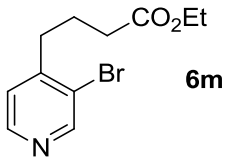
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (s, 1 H), 8.35 (d, *J*=5.0 Hz, 1 H), 7.12 (d, *J*=5.0 Hz, 1 H), 2.73 (t, *J*=7.1 Hz, 2 H), 1.70 - 1.50 (m, 6 H), 1.31 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.11, 148.35, 147.50, 131.87, 124.84, 124.64, 40.59, 32.47, 32.20, 28.56, 26.53 (2 C), 24.93.
MS (70 eV, EI) *m/z* (%): 236 (3), 221 (5), 201 (18), 140 (100), 127 (17).
HRMS for $C_{13}H_{17}ClN_2$: calcd.236.1080; found 236.1071 (M^+).



6l

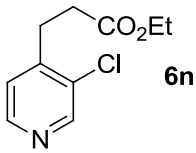
ethyl 4-(3-chloropyridin-4-yl)butanoate (6l): To a solution of 3-chloropyridine (**1a**; 114 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 4-ethoxy-4-oxobutylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2 to 1:1) furnishing the compound **6l** (194 mg, 85%) as a pink oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (s, 1 H), 8.35 (d, *J*=5.0 Hz, 1 H), 7.13 (d, *J*=5.0 Hz, 1 H), 4.10 (q, *J*=7.1 Hz, 2 H), 2.75 (t, *J*=7.5 Hz, 2 H), 2.33 (t, *J*=7.3 Hz, 2 H), 1.94 (quin, *J*=7.5 Hz, 2 H), 1.23 (t, *J*=7.0 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.72, 149.25, 147.68, 147.60, 131.97, 124.72, 60.34, 33.35, 31.82, 23.76, 14.12.
MS (70 eV, EI) *m/z* (%): 227 (7), 192 (10), 182 (20), 140 (100), 126 (18), 88 (18).
HRMS for $C_{11}H_{14}ClNO_2$: calcd. 227.0713; found 227.0703 (M^+).



6m

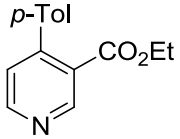
ethyl 4-(3-bromopyridin-4-yl)butanoate (6m): According to literature,[12c] 4-ethoxy-4-oxobutylZnBr·$MgCl_2$·LiCl is prepared using Mg-turnings (875 mg, 36 mmol), LiCl (763 mg, 18 mmol), $ZnCl_2$ (1M solution in THF, 16 mL, 16 mmol) and ethyl 4-bromobutanoate (2.81 g, 14 mmol). The reaction is carried out at 20 ˚C for 6 h until most of the alkylbromide has converted. Then to a solution of 3-bromopyridine (**1c**; 1.26 g, 8.0 mmol) in THF (16 ml) is added $BF_3 \cdot OEt_2$ (1.25 g, 8.8 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP2** and reacted with the freshly prepared alkylzinc reagent and ^{t}BuMgCl (9.4 ml, 1.28 M in THF, 12 mmol) under - 50 ˚C for 1h. Then chloranil (3.93 g, 16 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 5 mL saturated ammonia water solution and extracted with EtOAc several times. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9 to 1:7 to 1:4) furnishing the compound **6m** (1.37 g, 63%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.66 (s, 1 H), 8.42 (d, *J*=5.0 Hz, 1 H), 7.18 (d, *J*=4.7 Hz, 1 H), 4.15 (q, *J*=7.0 Hz, 2 H), 2.79 (t, *J*=7.7 Hz, 2 H), 2.38 (t, *J*=7.3 Hz, 2 H), 1.97 (quin, *J*=7.5 Hz, 2 H), 1.27 (t, *J*=7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.84, 151.79, 149.74, 148.09, 125.13, 123.09, 60.48, 34.49, 33.44, 23.97, 14.22.
MS (70 eV, EI) *m/z* (%): 270 (1), 228 (20), 192 (100), 184 (79), 88 (17).
HRMS for $C_{11}H_{15}BrNO_2$: calcd. 272.0281; found 272.0279 ($M+H^+$).



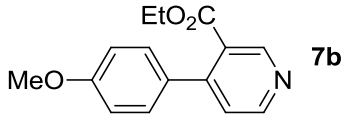
6n

ethyl 3-(3-chloropyridin-4-yl)propanoate (6n): To a solution of 3-chloropyridine (**1a**; 112 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with freshly prepared 3-ethoxy-3-oxopropylZnBr·$MgCl_2$·LiCl and ^{t}BuMgCl (1.2 ml, 1.28 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, Et_2O/*i*-hexane 1:2 to 1:1) furnishing the compound **6n** (182 mg, 86%) as a pale pink oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.53 (s, 1 H), 8.39 (d, *J*=5.0 Hz, 1 H), 7.20 (d, *J*=4.7 Hz, 1 H), 4.14 (q, *J*=7.2 Hz, 2 H), 3.07 (t, *J*=7.6 Hz, 2 H), 2.67 (t, *J*=7.6 Hz, 2 H), 1.24 (t, *J*=7.2 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.90, 149.33, 147.73, 146.80, 132.00, 124.77, 60.69, 32.68, 27.93, 14.11.
MS (70 eV, EI) *m/z* (%): 212 (2), 178 (98), 150 (100), 140 (29), 104 (35), 77 (18).
HRMS for $C_{10}H_{11}ClNO_2$: calcd. 212.0473; found 212.0469 [$(M-H)^+$].



7a

ethyl 4-(*p*-tolyl)nicotinate (7a): To a solution of ethyl nicotinate (**1d**; 149 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *p*-TolMgBr·LiCl (1.5 mL, 1.05 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7a** (190 mg, 80%) as a reddish brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.99 (s, 1 H), 8.69 (d, *J*=5.0 Hz, 1 H), 7.30 (d, *J*=5.0 Hz, 1 H), 7.23 (s, 4 H), 4.19 (q, *J*=7.2 Hz, 2 H), 2.40 (s, 3 H), 1.11 (t, *J*=7.0 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.80, 151.37, 150.38, 150.12, 138.44, 135.40, 128.95 (2 C), 127.88 (2 C), 126.80, 124.78, 61.28, 21.15, 13.68.
MS (70 eV, EI) *m/z* (%): 241 (63), 196 (100), 167 (31), 115 (22).
HRMS for $C_{15}H_{15}NO_2$: calcd. 241.1103; found 241.1092 (M^+).



7b

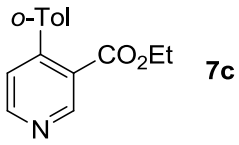
ethyl 4-(4-methoxyphenyl)nicotinate (7b): To a solution of ethyl nicotinate (**1d**; 148 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *p*-$MeOC_6H_4MgBr$·LiCl (1.3 mL, 1.13 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4 to 1:2) furnishing the compound **7b** (203 mg, 81%) as a reddish brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.97 (s, 1 H), 8.67 (d, *J*=5.2 Hz, 1 H), 7.34 - 7.21 (m, 3 H), 6.96 (d, *J*=8.6 Hz, 2 H), 4.20 (q, *J*=7.0 Hz, 2 H), 3.85 (s, 3 H), 1.14 (t, *J*=7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.07, 159.97, 151.57, 150.60, 149.44, 130.59, 129.36 (s, 2 C), 126.72, 124.65, 113.77 (s, 2 C), 61.27, 55.24, 13.78.

MS (70 eV, EI) *m/z* (%): 257 (100), 212 (96), 169 (24).

HRMS for $C_{15}H_{15}NO_3$: calcd. 257.1052; found 257.1044 (M^+).



7c

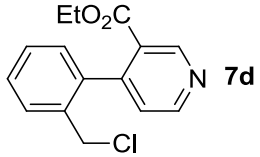
ethyl 4-(*o*-tolyl)nicotinate (7c): To a solution of ethyl nicotinate (**1d**; 151 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr·LiCl (1.4 mL, 1.12 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7c** (201 mg, 83%) as a reddish brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.16 (s, 1 H), 8.74 (d, *J*=4.7 Hz, 1 H), 7.37 - 7.14 (m, 4 H), 7.04 (d, *J*=7.4 Hz, 1 H), 4.10 (q, *J*=7.0 Hz, 2 H), 2.08 (s, 3 H), 1.00 (t, *J*=7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 165.67, 151.56, 150.77 (2 C), 138.62, 134.52, 129.55, 127.99, 127.62, 126.58, 125.34, 125.27, 61.01, 19.68, 13.43.

MS (70 eV, EI) *m/z* (%): 241 (32), 196 (100), 167 (97), 139 (32), 115 (25).

HRMS for $C_{15}H_{15}NO_2$: calcd. 241.1103; found 241.1092 (M^+).



7d

ethyl 4-(2-(chloromethyl)phenyl)nicotinate (7d): To a solution of 2-iodobenzyl chloride (3.23 g, 13 mmol) in THF (9.4 mL) is added dropwise a solution of ^{i}PrMgCl·LiCl (9.4 ml, 1.28 M in THF, 12 mmol) at -20 °C. The reaction mixture is stirred for 30 min to furnish the 2-(chloromethyl)phenylMgCl·LiCl.[25] Then to a

[25] B. Haag, Z. Peng, P. Knochel, *Org. Lett.* **2009**, *11*, 4270.

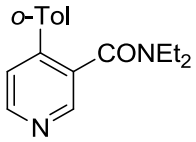
solution of ethyl nicotinate (**1d**; 1.21 g, 8.0 mmol) in THF (16 ml) is added BF_3 OEt_2 (1.25 g, 8.8 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP3** and reacted with the freshly prepared Grignard reagent under -30 ℃ for 2 h. Then chloranil (3.93 g, 16 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 5 mL saturated ammonia water solution and extracted with EtOAc several times. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7d** (1.84 g, 83%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.21 (s, 1 H), 8.78 (d, *J*=5.0 Hz, 1 H), 7.60 - 7.29 (m, 4 H), 7.09 (d, *J*=7.5 Hz, 1 H), 4.39 (d, *J*=11.6 Hz, 1 H), 4.28 (d, *J*=11.9 Hz, 1 H), 4.10 (q, *J*=6.9 Hz, 2 H), 1.01 (t, *J*=7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.44, 151.87, 151.31, 148.85, 138.81, 134.34, 129.82, 128.74, 128.55, 128.18, 126.37, 125.62, 61.26, 43.90, 13.62.

MS (70 eV, EI) *m/z* (%): 275 (32), 225 (49), 194 (55), 182 (34), 166 (100), 139 (55).

HRMS for $C_{15}H_{15}ClNO_2$: calcd. 276.0786; found 276.0785 ($M+H^+$).



7e

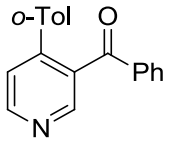
***N,N*-diethyl-4-(*o*-tolyl)nicotinamide (7e):** To a solution of *N,N*-diethylnicotinamide (**1p**; 177 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr ŁiCl (1.3 mL, 1.12 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:1 to 2:1) furnishing the compound **7e** (232 mg, 87%) as a reddish brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.71 - 8.53 (m, 2 H), 7.39 - 7.09 (m, 5 H), 2.94 (br. s., 4 H), 2.23 (s, 3 H), 0.92 (t, *J*=6.5 Hz, 3 H), 0.77 (t, *J*=7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.26, 148.92, 147.15, 146.55, 136.35, 135.27, 132.98, 130.36, 128.83, 128.61, 125.42, 124.77, 42.41, 38.18, 19.95, 13.68, 11.74.

MS (70 eV, EI) *m/z* (%): 267 (14), 196 (100), 167 (38), 139 (11), 115 (13).

HRMS for $C_{17}H_{19}N_2O$: calcd. 267.1492; found 267.1487 [$(M-H)^+$].

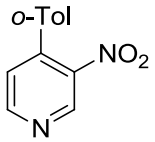


7f

phenyl(4-(*o*-tolyl)pyridin-3-yl)methanone (7f): To a solution of phenyl(pyridin-3-yl)methanone (**1q**; 183 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr ŁiCl (1.3 mL, 1.12 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4 to 1:2) furnishing the compound **7f** (187 mg, 68%) as a reddish brown oil.

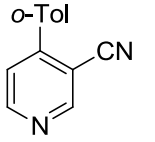
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.77 (br. s., 2 H), 7.61 (d, *J*=7.5 Hz, 2 H), 7.46 (t,

J=7.3 Hz, 1 H), 7.38 - 7.23 (m, 3 H), 7.17 – 6.93 (m, 4 H), 2.14 (s, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.65, 150.48, 149.29, 149.01, 136.97, 136.90, 134.89, 134.85, 133.20, 130.16, 129.45 (s, 2 C), 129.07, 128.42, 128.16 (s, 2 C), 125.48, 125.29, 19.96.
MS (70 eV, EI) *m/z* (%): 273 (24), 258 (43), 196 (100), 167 (24), 105 (27), 77 (39).
HRMS for $C_{19}H_{15}NO$: calcd. 273.1154; found 273.1147 (M^+).



7g

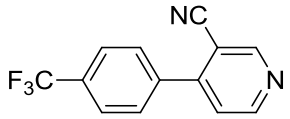
3-nitro-4-(*o*-tolyl)pyridine (7g): To a solution of 3-nitropyridine (**1r**; 125 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr·LiCl (1.3 mL, 1.16 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **7g** (126 mg, 58%) as a yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.23 (s, 1 H), 8.84 (d, *J*=4.9 Hz, 1 H), 7.42 - 7.22 (m, 4 H), 7.09 (d, *J*=7.1 Hz, 1 H), 2.12 (s, 3 H); in accordance with the literature.[26]
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 152.80, 145.43, 145.35, 144.66, 134.94, 134.59, 130.29, 129.13, 127.59, 126.34, 126.03, 19.70; in accordance with the literature.[26]
MS (70 eV, EI) *m/z* (%): 214 (21), 197 (44), 184 (70), 167 (100), 139 (56), 115 (40).
HRMS for $C_{12}H_{10}N_2O_2$: calcd. 214.0742; found 214.0731 (M^+).



7h

4-(*o*-tolyl)nicotinonitrile (7h): To a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (2 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr·LiCl (1.4 mL, 1.12 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7h** (188 mg, 97%) as a pink solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.95 (s, 1 H), 8.81 (d, *J*=5.0 Hz, 1 H), 7.24 - 7.46 (m, 4 H), 7.14 - 7.23 (m, 1 H), 2.22 (s, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.21, 153.02, 152.31, 135.27, 134.99, 130.68, 129.58, 128.71, 126.07, 124.64, 115.91, 110.41, 19.61.
MS (70 eV, EI) *m/z* (%): 194 (100), 167 (26), 139 (18).
HRMS for $C_{13}H_{10}N_2$: calcd. 194.0844; found 194.0836 (M^+).

[26] P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338.



7i

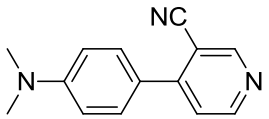
4-(4-(trifluoromethyl)phenyl)nicotinonitrile (7i): To a solution of ^{i}PrMgCl·LiCl (1.2 ml, 1.28 M in THF, 1.5 mmol) 1-iodo-4-(trifluoromethyl)benzene (368 mg, 1.6 mmol) is added at -20 °C. The reaction mixture is stirred for 30 min to furnish the 4-(trifluoromethyl)phenylMgCl·LiCl.[11a] Meanwhile a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with the freshly prepared Grignard reagent. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4 to 1:2) furnishing the compound **7i** (221 mg, 89%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.01 (s, 1 H), 8.88 (d, *J*=5.0 Hz, 1 H), 7.83 (d, *J*=8.3 Hz, 2 H), 7.75 (d, *J*=8.3 Hz, 2 H), 7.50 (d, *J*=5.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.00, 153.10, 150.76, 138.78, 132.20 (q, $^{2}J_{C-F}$=33 Hz), 128.87 (2 C), 126.19 (q, $^{3}J_{C-F}$=3.7 Hz, 2 C), 123.64, 123.63 (q, $^{1}J_{C-F}$=271 Hz), 116.13, 108.58.

MS (70 eV, EI) *m/z* (%): 248 (100), 229 (13), 222 (20), 179 (31).

HRMS for $C_{13}H_7F_3N_2$: calcd. 248.0561; found 248.0539 (M^+).



7j

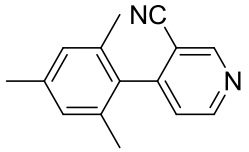
4-(4-(dimethylamino)phenyl)nicotinonitrile (7j): To a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with 4-(dimethylamino)phenylMgBr·LiCl (1.4 mL, 1.09 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:2) furnishing the compound **7j** (220 mg, 99%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.85 (s, 1 H), 8.67 (d, *J*=5.4 Hz, 1 H), 7.64 - 7.55 (m, 2 H), 7.42 (d, *J*=5.3 Hz, 1 H), 6.80 (d, *J*=8.9 Hz, 2 H), 3.05 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.26, 152.25, 152.09, 151.55, 129.45 (2 C), 122.68, 122.03, 117.71, 112.00 (2 C), 107.14, 40.07 (2 C).

MS (70 eV, EI) *m/z* (%): 222 (100), 206 (10), 179 (11).

HRMS for $C_{14}H_{13}N_3$: calcd. 223.1110; found 223.1103 (M^+).



7k

4-mesitylnicotinonitrile (7k): To a solution of nicotinonitrile (**1b**; 104 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with MesMgBr·LiCl (1.5 mL, 1.04 M in THF, 1.5 mmol). The crude product is purified by flash

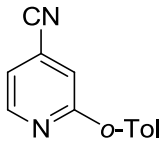
chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7k** (217 mg, 98%) as a red solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.96 (s, 1 H), 8.82 (d, *J*=5.3 Hz, 1 H), 7.26 (d, *J*=5.3 Hz, 1 H), 6.98 (s, 2 H), 2.33 (s, 3 H), 1.99 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.54, 153.16, 152.67, 138.90, 134.64 (2 C), 132.25, 128.65 (2 C), 125.03, 115.60, 111.26, 21.01, 20.01 (2 C).

MS (70 eV, EI) *m/z* (%): 222 (100), 207 (75), 192 (13), 180 (27).

HRMS for $C_{15}H_{14}N_2$: calcd. 222.1157; found 222.1142 (M^+).



7l

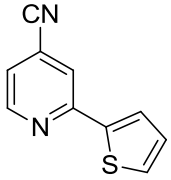
2-(*o*-tolyl)isonicotinonitrile (7l): To a solution of isonicotinonitrile (**1s**; 104 mg, 1.0 mmol) in THF (1 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr·LiCl (1.3 mL, 1.16 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **7l** (87 mg, 45%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.86 (d, *J*=5.0 Hz, 1 H), 7.63 (s, 1 H), 7.46 (dd, *J*=5.0, 1.4 Hz, 1 H), 7.22 - 7.42 (m, 4 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.33, 150.05, 138.25, 135.78, 131.03, 129.51, 129.17, 126.12, 125.45, 122.80, 120.55, 116.53, 20.16.

MS (70 eV, EI) *m/z* (%): 193 (100), 166 (7).

HRMS for $C_{13}H_9N_2$: calcd. 193.0760; found 193.0758 [$(M-H)^+$].



7m

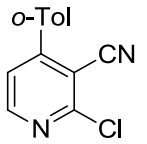
2-(thiophen-2-yl)isonicotinonitrile (7m): To a solution of isonicotinonitrile (**1s**; 104 mg, 1.0 mmol) in THF (1 ml) is added BF_3 OEt_2 (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with thiophen-2-ylMgBr·LiCl (1.2 mL, 1.26 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7m** (78 mg, 42%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.71 (d, *J*=5.3 Hz, 1 H), 7.83 (s, 1 H), 7.64 (d, *J*=3.9 Hz, 1 H), 7.49 (d, *J*=5.0 Hz, 1 H), 7.33 (d, *J*=5.0 Hz, 1 H), 7.15 (t, *J*=4.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.78, 150.46, 142.56, 129.41, 128.41, 126.14, 122.61, 121.11, 120.27, 116.44.

MS (70 eV, EI) *m/z* (%): 186 (100), 142 (15).

HRMS for $C_{10}H_6N_2S$: calcd. 186.0252; found 186.0248 (M^+).



7n

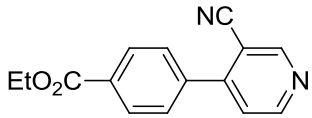
2-chloro-4-(*o*-tolyl)nicotinonitrile (7n): To a solution of 2-chloronicotinonitrile (**1t**; 138 mg, 1.0 mmol) in THF (2 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *o*-TolMgBr·LiCl (1.3 mL, 1.16 M in THF, 1.5 mmol). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **7n** (130 mg, 57%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.58 (d, *J*=5.0 Hz, 1 H), 7.47 - 7.24 (m, 4 H), 7.19 (d, *J*=7.5 Hz, 1 H), 2.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.03, 153.38, 151.55, 134.94, 134.78, 130.81, 129.97, 128.51, 126.20, 123.53, 113.90, 111.00, 19.65.

MS (70 eV, EI) *m/z* (%): 228 (100), 201 (18), 192 (60), 166 (40), 139 (16).

HRMS for $C_{13}H_9ClN_2$: calcd. 228.0454; found 228.0443 (M^+).



7o

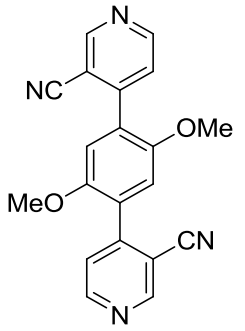
ethyl 4-(3-cyanopyridin-4-yl)benzoate (7o): To a solution of ethyl 4-iodobenzoate (443mg, 1.6 mmol) in THF (1 ml) is added ^{i}PrMgCl·LiCl (1.2 ml, 1.28 M in THF, 1.5 mmol) dropwise at -30 °C. The reaction mixture is stirred for 30 min to furnish the 4-carbethoxyphenylMgCl·LiCl.[11a] Then to a solution of nicotinonitrile (**1b**; 103 mg, 1.0 mmol) in THF (1 ml) is added $BF_3 \cdot OEt_2$ (149 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with the freshly prepared Grignard reagent. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:2) furnishing the compound **7o** (216 mg, 86%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.99 (s, 1 H), 8.86 (d, *J*=5.0 Hz, 1 H), 8.22 (d, *J*=8.1 Hz, 2 H), 7.70 (d, *J*=8.3 Hz, 2 H), 7.52 (d, *J*=5.0 Hz, 1 H), 4.43 (q, *J*=7.2 Hz, 2 H), 1.43 (t, *J*=7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.55, 153.86, 152.86, 151.12, 139.30, 131.93, 130.17 (2 C), 128.34 (2 C), 123.56, 116.14, 108.44, 61.27, 14.18.

MS (70 eV, EI) *m/z* (%): 252 (13), 224 (53), 207 (100), 179 (36), 152 (28), 125 (13).

HRMS for $C_{15}H_{12}N_2O_2$: calcd. 252.0899; found 252.0894 (M^+).



11

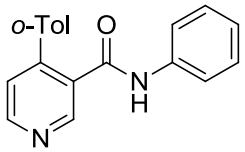
4,4'-(2,5-dimethoxy-1,4-phenylene)dinicotinonitrile (11): To a solution of nicotinonitrile (**1b**; 344 mg, 3.3 mmol) in THF (3 ml) is added $BF_3 \cdot OEt_2$ (426 mg, 3.0 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and the dimagnesiated species (**10**)[11b] (3.0 mL, 0.34 M in THF, 1.0 mmol) is dropped in at -30 °C. The mixture is stirred at the same temperature for 2 h and rearomatized by chloranil (736 mg, 3.0 mmol). The crude product is purified by flash chromatography (SiO_2, THF/*i*-hexane 1:4) furnishing the compound **11** (138 mg, 40%[27]) as a white powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.97 (s, 2 H), 8.86 (d, *J*=5.0 Hz, 2 H), 7.54 (d, *J*=5.3 Hz, 2 H), 6.99 (s, 2 H), 3.86 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 152.94 (2 C), 152.42 (2 C), 150.35 (2 C), 149.20 (2 C), 126.75 (2 C), 125.02 (2 C), 116.39 (2 C), 113.99 (2 C), 110.72 (2 C), 56.20 (2 C).

MS (70 eV, EI) *m/z* (%): 342 (100), 327 (54), 311 (43).

HRMS for $C_{20}H_{14}N_4NaO_2$: calcd. 365.1015; found 365.1012 ($M+Na^+$).



7f

***N*-phenyl-4-(*o*-tolyl)nicotinamide (7f):** A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of *N*-phenylnicotinamide (**1l**; 197 mg, 1.0 mmol) in dry THF (2 mL) and cooled to 0 °C. ^{t}BuMgCl (0.78 ml, 1.28 M in THF, 1.0 mmol) is dropped in and the mixture is stirred for 30 min. Then $BF_3 \cdot OEt_2$ (298 mg, 2.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 30 °C followed by dropwise addition of a THF solution of *o*-TolMgBr·LiCl (1.3 ml, 1.16 M in THF, 1.5 mmol), and stirring the reaction mixture at the same temperature for 2 h. Then chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred overnight. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:1) furnishes compound **7f** (202 mg, 70%) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.36 (s, 1 H), 8.84 (s, 1 H), 8.73 (d, *J*=5.1

[27] Calculated based on Grignard reagent.

Hz, 1 H), 7.49 (d, *J*=7.6 Hz, 2 H), 7.38 (d, *J*=5.1 Hz, 1 H), 7.31 - 7.13 (m, 6 H), 7.04 (t, *J*=7.4 Hz, 1 H), 2.13 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 164.88, 150.02, 147.71, 147.52, 138.71, 137.43, 134.82, 132.95, 129.91, 128.61 (2 C), 128.47, 128.14, 125.42, 125.20, 123.75, 119.60 (2 C), 19.70.

MS (70 eV, EI) *m/z* (%): 288 (5), 196 (100), 167 (38), 93 (28).

HRMS for $C_{19}H_{17}N_2O$: calcd. 289.1335; found 289.1335 ($M+H^+$).

Chapter 3. BF_3-Mediated Direct Alkynylation, Benzylation and Substitution of Functionalized Pyridines

3.1 Introduction

The functionalization of the pyridine scaffold is an important synthetic task since polyfunctional pyridines are widely used for pharmaceutical and biological applications.[1] Transition-metal catalyzed cross-coupling methodology has been extensively used to functionalize the pyridine skeleton.[2,3] However, the use of Pd- or Ni-catalysis has some drawbacks such as the toxicity or price of the metal and the need of ligands. In chapter 2, I described that 3-substituted pyridines of type **1** undergo BF_3-mediated[4] oxidative cross-couplings[5,6] at position 4 with various alkyl-

[1] a) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; b) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627; d) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459; e) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052; f) A. R. Hardin Narayan, R. Sarpong, *Org. Biomol. Chem.* **2012**, *10*, 70.

[2] a) N. Miyaura, *Cross-Coupling Reactions. A Practical Guide*, Springer, Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**; c) *Organotransition Metal Chemistry* (Ed.: J. F. Hartwig), University Science Books, Sausalito, California, **2010**.

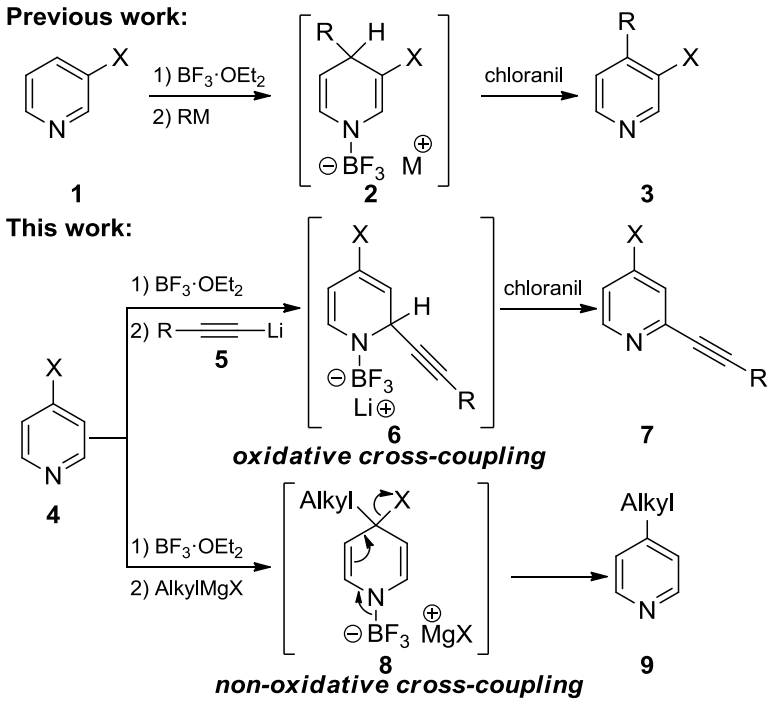
[3] For the transition-metal-catalyzed direct functionalization of pyridines, see: a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020; b) A. Larivée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52; c) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448; d) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070; e) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666; f) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 1275; g) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616.

[4] a) K. Ishihara, N. Hanaki, M. Funahashi, M. Miyata, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721; b) K. B. Aubrecht, M. D. Winemiller, D. B. Collum, *J. Am. Chem. Soc.* **2000**, *122*, 11084; c) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; d) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; e) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306.

[5] For a recent review, see: J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642 and references cited therein. Also, see: J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400.

[6] For a similar type of reactions undergoing a radical pathway, see: a) F. Minisci, C. Giordano, E. Vismara, S. Levi, V. Tortelli, *J. Am. Chem. Soc.* **1984**, *106*, 7146; b) F. Minisci, F. Fontana, E. Vismara, *J. Heterocycl. Chem.* **1990**, *27*, 79; c) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194; d) G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852; e) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95; f) F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122.

and aryl-magnesium or zinc reagents leading via a tentative intermediate of type **2** to 3,4-disubstituted pyridines of type **3** (Scheme 1).[7] These reactions are remarkably regioselective and proceed almost only at position 4.



Scheme 1. BF_3-mediated oxidative and non-oxidative cross-coupling of pyridines.

Then we wondered which reaction course would be observed if the position 4 of the pyridine is occupied by a substituent. Then I found a new BF_3-mediated oxidative cross-coupling of pyridines of type **4** with alkynyllithium derivatives **5** via a tentative intermediate **6** which leads to 2,4-disubstituted pyridines of type **7**. As a guideline for predicting this regioselectivity, it should be noticed that the complexation of the pyridine nitrogen with BF_3 makes the position 2, 4 and 6 of the pyridine ring especially electrophilic, favoring the new carbon–carbon bonds formation at these positions. The overall result may also be governed by steric effects. In the course of this work, we discovered an even more attractive cross-coupling procedure which does require neither an oxidative step nor a transition-metal catalyst but proceeds via an addition-elimination step mediated by $BF_3 \cdot OEt_2$. This method allows a direct substitution of X (X = CN, Cl) in pyridines of type **4** with various alkyl groups from Grignard reagents via the tentative intermediate **8**, affording products of type **9**.[8] I demonstrate that these new reactions allow a convenient functionalization of the pyridine scaffold leading to various polyfunctional di-, tri-, and tetra-substituted pyridines.[9]

[7] Q. Chen, X. Mollat du Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958.

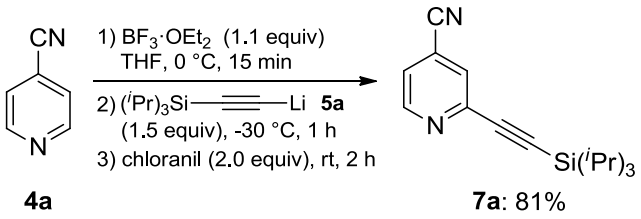
[8] a) Y. Nakao, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2004**, *126*, 13904; b) F. Zhang, S. Zhang, X.-F. Duan, *Org. Lett.* **2012**, *14*, 5618.

[9] a) J. Barluenga, M. Ferrero, F. Palacios, *Tetrahedron* **1997**, *53*, 4521; b) J. Barluenga, M. A. Fernandez-Rodriguez, P. Garcia-Garcia, E. Aguilar, *J. Am. Chem.*

3.2 Results and Discussion

3.2.1 BF_3-Mediated Direct Alkynylation of Pyridines using Alkynyllithiums

As a typical example, a 4-substituted pyridine, isonicotinonitrile (**4a**), was treated with $BF_3 OEt_2$ (1.1 equiv, THF, 0 ℃, 15 min). After subsequent addition of triisopropylsilylethynyllithium (**5a**, 1.5 equiv, -30 ℃, 1 h) and rearomatization with chloranil (2.0 equiv, 25 ℃, 2 h), the 2,4-disubstituted pyridine **7a** was obtained in 81% isolated yield (Scheme 2).



Scheme 2. BF_3-mediated addition of the alkynyllithium (**5a**) to isonicotinonitrile (**4a**).

Under these conditions, a variety of 4-substituted pyridines (**4**; X = CN, Cl, Br, Aryl or Alkyl) react with various alkynyllithiums[10] bearing an alkyl (**5b** and **5c**), aryl (**5e** and **5g**), silyl (**5d**) or alkenyl substituent (**5f**), providing the expected functionalized pyridines **7b**–**k** in 53–89% yield (Table 1, entries 1–10). Notably, the presence of an electron-withdrawing substituent at position 4 is not required and an aryl or a *t*-butyl substituent at position 4 lead to the expected products **7i**–**k** in 53–63% yield (entries 8–10). In the absence of a substituent at position 4, we still observed a reaction at position 2 or 6. Thus, 2-cyanopyridine (**10a**) reacts with the alkynyllithium **5h** at position 6 to furnish the 2,6-disubstituted pyridine **11** in 66% yield. With electron-withdrawing substituents at position 3, a smooth alkynylation occurs at position 2 leading to the 2,3-disubstituted pyridines (**12a**–**c**) in 69–82% yield (entries 12–14).[11] While using electron-rich 3-picoline (**1d**) as a substrate, the coupling reaction also proceeds well, yet surprisingly it takes place at the more crowded C(2)-position and a 2,3-disubstituted product (**12d**) is obtained (entry 15). Even pyridine itself (**13**) undergoes the coupling reaction with the lithium reagent (**5f**) and gives a 2-substituted product (**14**) in 66% yield (entry 16).

Soc. **2008**, *130*, 2764; c) C. Lau, G. C. Tsui, M. Lautens, *Synthesis* **2011**, 3908; d) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204.

[10] The alkynyllithiums were prepared by the reaction of the corresponding alkynes with ^{n}BuLi; see more details in the Experimental Section.

[11] Whereas, as reported before, 3-halopyridines react with alkyl or arylmagnesium reagents at position 4, alkynyllithiums still predominantly react at position 2 leading to 2,4-disubstituted pyridines. However, in each case, 5% of a regioisomer contamine the 2-substituted product.

Table 1. Direct alkynylation of pyridine derivatives using various alkynyllithiums.

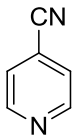
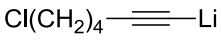
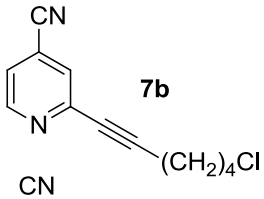
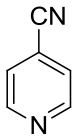
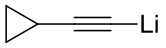
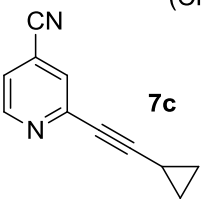
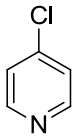
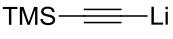
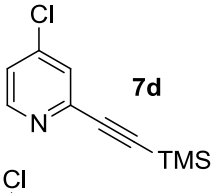
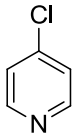
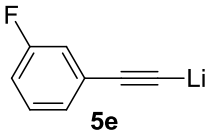
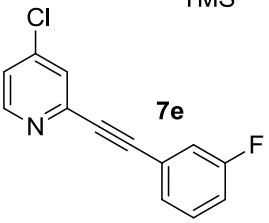
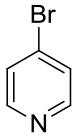
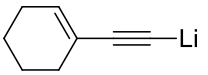
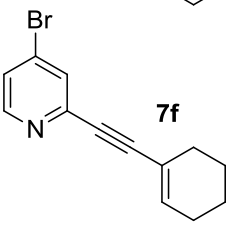
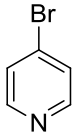
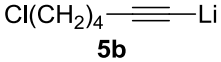
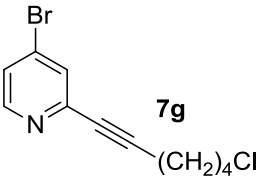
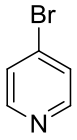
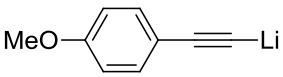
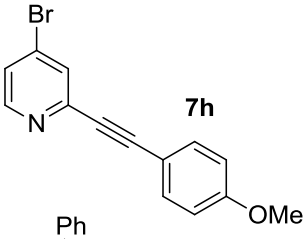
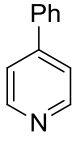
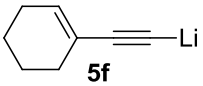
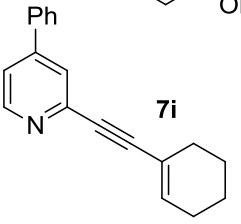
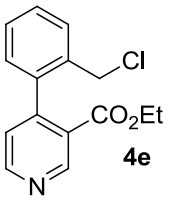
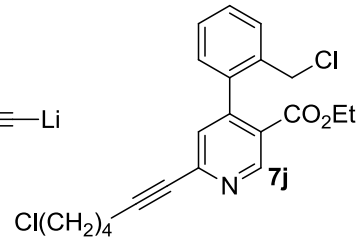
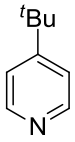
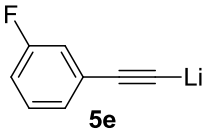
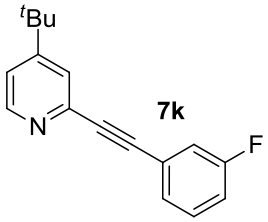
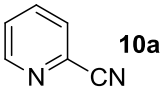
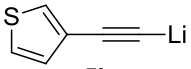
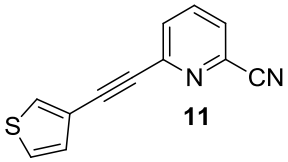
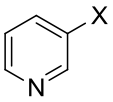
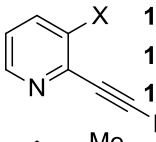
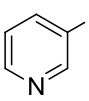
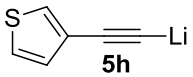
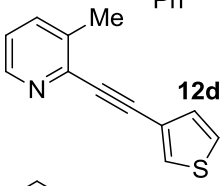
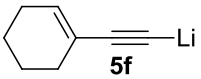
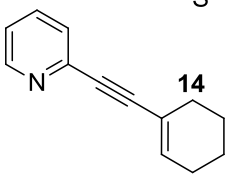
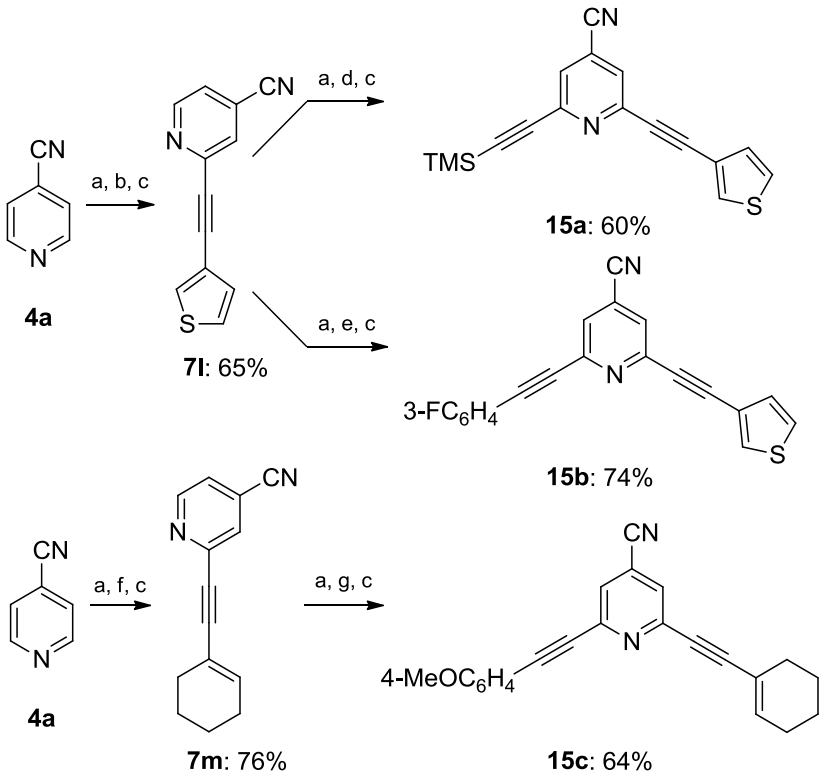
Entry	Substrate	Alkynyllithium Reagent	Product	Yield %[a]
1	 **4a**	 **5b**	 **7b**	89
2	 **4a**	 **5c**	 **7c**	71
3	 **4b**	 **5d**	 **7d**	89
4	 **4b**	 **5e**	 **7e**	71
5	 **4c**	 **5f**	 **7f**	77
6	 **4c**	 **5b**	 **7g**	82
7	 **4c**	 **5g**	 **7h**	75
8	 **4d**	 **5f**	 **7i**	63

Table 1. Continued.

9	 **4e**	$Cl(CH_2)_4$—≡—Li **5b**	 **7j**	53
10	 **4f**	 **5e**	 **7k**	61
11	 **10a**	 **5h**	 **11**	66
12	**1a**: X = Cl		**12a**: X = Cl	74
13	 **1b**: X = Br	Ph—≡—Li **5i**	 **12b**: X = Br	82
14	**1c**: X = I		**12c**: X = I	69
15	 **1d**	 **5h**	 **12d**	64
16	 **13**	 **5f**	 **14**	66

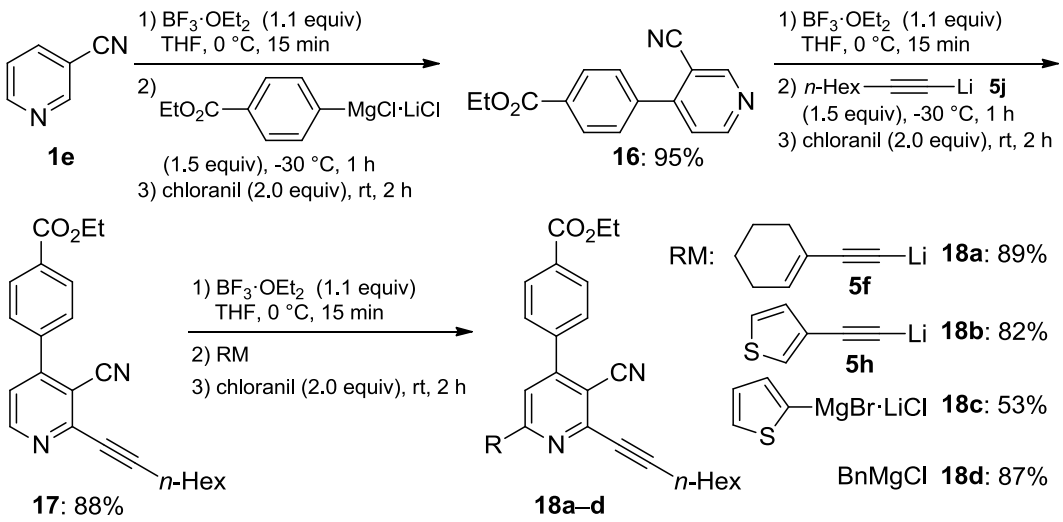
[a]Isolated yields of analytically pure products.

Also, a double functionalization at positions 2 and 6 can be readily achieved. Thus, isonicotinonitrile (**4a**) is alkynylated at position 2 by our standard procedure resulting in the formation of **7l** and **7m** in 65–76% yield. The addition of a second alkynyllithium in the presence of $BF_3 \cdot OEt_2$ followed by oxidative rearomatization furnishes the 2,4,6-trisubstituted pyridines (**15a**–**c**) in 60–74% yield (Scheme 3).



Scheme 3. BF_3-mediated direct alkynylation leading to the preparation of 2,4,6-trisubstituted pyridines. Reaction conditions: a) BF_3 OEt_2 (1.1 equiv, THF, 0 ℃, 15 min); b) **5h** (1.5 equiv, -30 ℃, 1 h); c) chloranil (2.0 equiv, 25 ℃, 2 h); d) **5d** (1.5 equiv, -30 ℃, 1 h); e) **5e** (1.5 equiv, -30 ℃, 1 h); f) **5f** (1.5 equiv, -30 ℃, 1 h); g) **5g** (1.5 equiv, -30 ℃, 1 h).

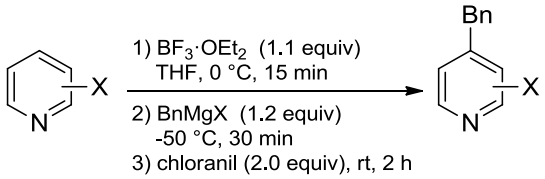
Moreover, highly functionalized tetra-substituted pyridines were obtained from nicotinonitrile (**1e**) via a sequence of several oxidative cross-couplings. The first carbon–carbon bond formation occurs at position 4 as expected, [7] leading to the disubstituted pyridine **16** in 95% yield. The position 2 and 6 of **16** can be readily differentiated since the cyano group activates strongly the position 2. Therefore, the addition of the alkynyllithium (**5j**) in the presence of BF_3 OEt_2 produces only the 2,3,4-trisubstituted pyridine **17** in 88% yield after chloranil treatment. Finally, a range of organometallic reagents such as alkynyllithiums (**5f** and **5h**), 2-thienylmagnesium bromide-lithium chloride or even benzylmagnesium chloride undergo an oxidative cross-coupling at position 6 affording the tetrasubstituted pyridines (**18a**–**d**) in 53–89% yield (Scheme 4).



Scheme 4. BF_3-mediated polyfunctionalization of nicotinonitrile (**1e**) for the preparation of 2,3,4,6-tetrasubstituted pyridines.

3.2.2 BF_3-Mediated Direct Benzylation of Pyridines using Benzylmagnesium Reagents

The unprecedented addition of a benzylic Grignard reagent to **17** led me to examine shortly the BF_3-mediated oxidative coupling of BnMgX (X = Cl or Br) with various halopyridines such as **1a**, **b**, **f** and **10b**. The desired 4-benzylpyridines (**19a**–**d**) were obtained in 72–95% yield (Scheme 5).



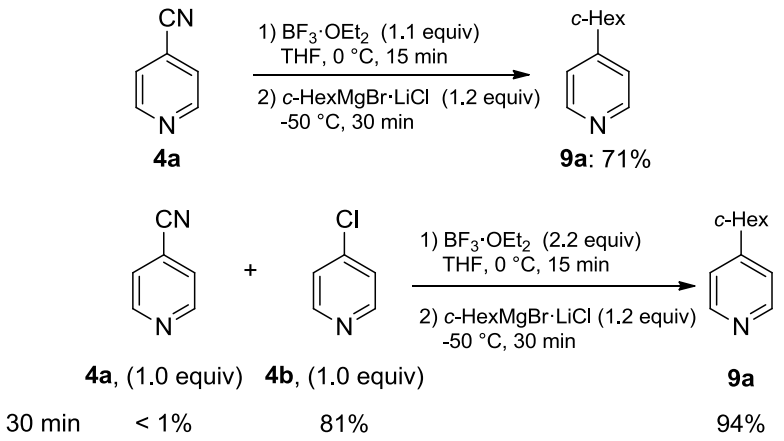
1a: X = 3-Cl
1b: X = 3-Br
1f: X = 3-F
10b: X = 2-Cl

19a: X = 3-Cl, 95%
19b: X = 3-Br, 90%
19c: X = 3-F, 72%
19d: X = 2-Cl, 84%

Scheme 5. Oxidative coupling of BnMgX to pyridines (**1a**, **b**, **f** and **10b**).

3.2.3 BF_3-Mediated Substitution using Grignard Reagents

By treating isonicotinonitrile (**4a**) in the presence of $BF_3{\cdot}OEt_2$ with an alkylmagnesium reagent complexed with lithium chloride instead of an alkynyllithium, we observed the formation of an unexpected 4-substituted product of type **9** (Scheme 1). Thus, the treatment of **4a** with $BF_3{\cdot}OEt_2$ at 0 °C followed by the addition of *c*-HexMgBr·LiCl (1.2 equiv) at -50 °C leads to a very fast cross-coupling reaction (within 30 min) affording the 4-substituted pyridine **9a** in 71% yield (Scheme 6).



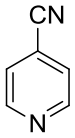
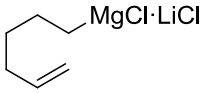
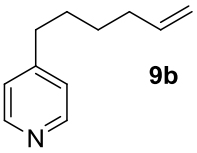
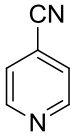
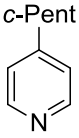
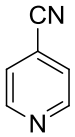
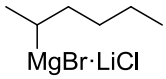
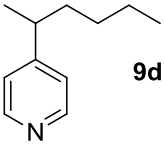
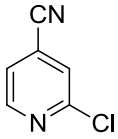
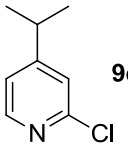
Scheme 6. BF_3-mediated substitution of isonicotinonitrile (**4a**) and 4-chloropyridine (**4b**) by *c*-HexMgBr·LiCl. The yields of the competition experiment were determined by GC using *n*-undecane as an internal standard.

The BF_3-mediated cross-coupling can be extended to various primary and secondary organomagnesium reagents leading to the 4-substituted pyridines (**9b**–**e**) in 46–89% yield (Table 2). Interestingly, the 2-chloro-4-cyanopyridine (**20**) which could in principle undergo a cross-coupling at position 2 (the 2-chloro substituent is a good leaving group)[12] reacts smoothly at position 4 leading to the chloropyridine **9e** as an only detectable product in 46% yield (entry 4). In order to evaluate the difference of reactivity between a chloro- and a cyano-substituent in such BF_3-mediated cross-couplings, we submitted a 1:1 mixture of **4a** and **4b** to a BF_3-mediated cross-coupling with *c*-HexMgBr·LiCl. We found that the cyano group is a better leaving group, leading within 30 min to the full consumption of **4a** and the formation of the desired product **9a** in 94% yield. The chloropyridine **4b** could be recovered in 81% yield (Scheme 6). The higher reactivity of the isonicotinonitrile (**4a**) may be explained by the mesomeric acceptor properties of the cyano group compared to the mesomeric donor properties of the chloro-substituent (acid cyanides are also more electrophilic than acid chlorides).[13]

[12] a) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 4945; b) A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 15346.

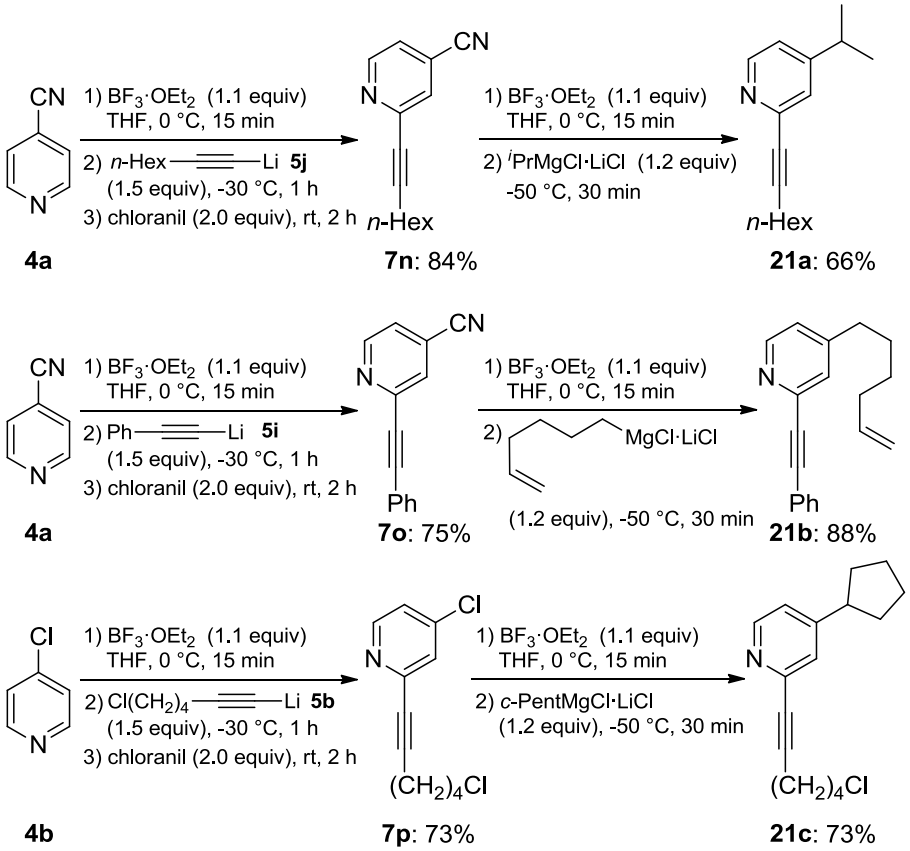
[13] a) S. R. Crabtree, W. L. Alex Chu, L. N. Mander, *Synlett* **1990**, 169; b) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968.

Table 2. Non-oxidative cross-coupling of isonicotinonitrile (**4a**) or 4-chloropyridine (**4b**) using Grignard reagents.

Entry	Substrate	Grignard Reagent	Product	Yield %[a]
1	 **4a**		 **9b**	89
2	 **4a**	*c*-PentMgCl·LiCl	 **9c**	63
3	 **4a**		 **9d**	72 (76)[b]
4	 **20**	^{i}PrMgCl·LiCl	 **9e**	46

[a]Isolated yields of analytically pure products. [b]4-chloropyridine (**4b**) is used as substrate.

In order to demonstrate the versatility of these methodologies, we have combined the two new functionalization procedures of pyridines (oxidative and non-oxidative cross-couplings) for producing various 2,4-disubstituted pyridines of type **21**. Thus, the isonicotinonitrile (**4a**) and 4-chloropyridine (**4b**) were treated with the alkynyllithiums (**5j**,**i**,**b**) in the presence of BF_3 OEt_2 leading after oxidative workup with chloranil to the 2-alkynylated pyridines **7n**–**p** in 73–84% yield. After these oxidative cross-couplings, we have performed a BF_3-mediated cross-coupling with various alkylmagnesium reagents leading by substitution of the chloro- or cyano-substituent to the 2,4-disubstituted pyridines **21a**–**c** in 66–88% yield (Scheme 7). Interestingly, the 2,6-dialkynylisonicotinonitriles (**15a**–**c**; Scheme 3) do not undergo these cross-coupling reactions and only starting materials are recovered, indicating that the BF_3 complexation at the pyridine nitrogen (and not at the cyano nitrogen) is crucial for the success of this substitution reaction.



Scheme 7. Consecutive BF_3-mediated alkynylation and substitution for the preparation of 2,4-disubstituted pyridines.

3.3 Summary

In summary, we have developed two new functionalization procedures of pyridines. The oxidative cross-coupling proceeds with alkynyllithiums and affords 2- or 6-substituted pyridines after oxidative rearomatization. On the hand, the cross-coupling procedure leads to the substitution at position 4 of a chloro- or cyano-substituent by an alkylmagnesium reagent. Neither method requires the use of a transition-metal catalyst.

3.4 Experimental Section

3.4.1 General Considerations

All reactions are carried out under argon atmosphere in flame-dried glassware. Syringes which are used to transfer anhydrous solvents or reagents are purged with argon prior to use. THF is continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be pure as determined by ^{1}H-NMR (25 ℃) and capillary GC. Column chromatographical purifications are performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM from Merck). Mass spectra and high resolution mass spectra (HRMS) are recorded using electron ionization (EI) or electrospray ionization (ESI).

Grignard reagents are prepared according to the literature.[14] Alkynyllithium reagents are prepared according to the literature.[15] The *n*-BuLi is purchased from Rockwood Lithium and titrated before use. Benzylmagnesium chloride (2.0 M in THF) is purchased from Aldrich. $BF_3 \cdot OEt_2$ is purchased from Acros or Aldrich and distilled before use.

3.4.2 Typical Procedures

Typical Procedure for the BF_3-mediated direct alkynylation of pyridine derivatives using alkynyllithium reagents (TP1)

A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**4**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. Then the reaction mixture is cooled to -30 ℃. An alkynyllithium (**5**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of the alkyne in THF at 0 ℃ and stirring for 30 min) is cannulated to the reaction flask and the resulting mixture is stirred at the same temperature for 1 h. Then, chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed to room temperature and continuously stirred for 2 h. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with ethyl acetate several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**7**).

Typical Procedure for the BF_3-mediated direct benzylation of pyridine derivatives using BnMgCl or BnMgBr (TP2)

A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**1**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 ℃. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. Then, the reaction mixture is cooled to -50 ℃. A THF solution of BnMgCl or BnMgBr (1.2 mmol) is added dropwise and the resulting mixture is stirred at the same temperature for 30 min. Then, chloranil (492 mg, 2.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred for 2 h. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with ethyl acetate several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**19**).

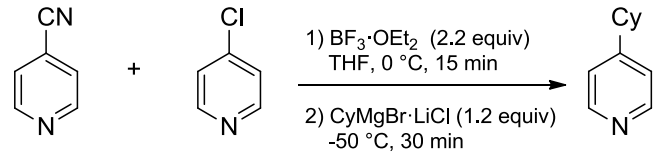
[14] F. M. Piller, A. Metzger, M. A. Schade, B. A. Hagg, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

[15] S. R. Dubbaka, M. Kienle, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 9093.

Typical Procedure for the BF_3-mediated non-oxidative cross-coupling of pyridine derivatives using Grignard reagents (TP3)

A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a pyridine derivative (**4**, 1.0 mmol) in dry THF (2 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. Then, the reaction mixture is cooled to -50 °C. A THF solution of Grignard reagent (1.2 mmol) is added dropwise and the resulting mixture is stirred at the same temperature for 30 min. Finally, it is quenched with 1 mL saturated ammonia water solution and extracted with ethyl acetate several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. Purification by flash chromatography furnishes the desired product (**9**).

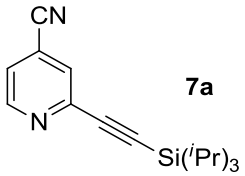
3.4.3 Competition Experiments



	4a, (1.0 equiv)	**4b**, (1.0 equiv)	**9a**
0 min	100%	100%	0%
30 min	< 1%	81%	94%

According to **TP3**, a mixture of isonicotinonitrile (**4a**; 1.0 mmol) and 4-chloropyridine (**4b**; 1.0 mmol) reacts with *c*-HexMgBr·LiCl (2.0 mL, 0.59 M in THF, 1.2 mmol) in the presence of $BF_3 \cdot OEt_2$ (2.2 mmol). After quenching, the crude products are measured by GC using undecane as an internal standard, giving the corresponding GC yields of each product.

3.4.4 Product Synthesis and Analytical Data

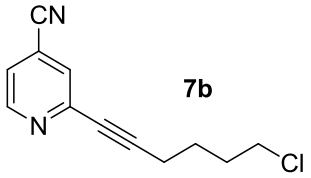


7a

2-[(triisopropylsilyl)ethynyl]isonicotinonitrile (7a): To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with 1-triisopropylsilylethynyllithium (**5a**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of triisopropylsilylacetylene in THF (274 mg, 2 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **7a** (230 mg, 81%) as a light yellow oil.

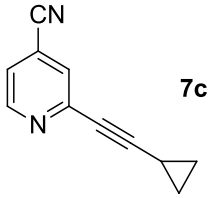
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.76 (d, *J*=5.0 Hz, 1 H), 7.67 (s, 1 H), 7.45 (dd,

J=5.0, 1.4 Hz, 1 H), 1.16 (*br*. s, 21 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.82, 144.49, 128.83, 123.80, 120.72, 115.70, 103.83, 95.49, 18.50 (6 C), 11.07 (3 C).
MS (70 eV, EI) *m/z* (%): 284 (5), 241 (100), 213 (41), 199 (18), 185 (32), 171 (25), 155 (10).
HRMS for $C_{17}H_{24}N_2Si$: calcd. 284.1709; found 284.1697 (M^+).



7b

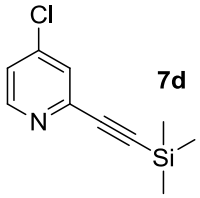
2-(6-chlorohex-1-yn-1-yl)isonicotinonitrile (7b): To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5b**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 6-chlorohex-1-yne in THF (175 mg, 1.5 mmol) at -10 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7b** (195 mg, 89%) as a light reddish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.70 (d, *J*=5.1 Hz, 1 H), 7.56 (d, *J*=1.5 Hz, 1 H), 7.40 (dd, *J*=5.1, 1.5 Hz, 1 H), 3.58 (t, *J*=6.4 Hz, 2 H), 2.51 (t, *J*=6.9 Hz, 2 H), 1.95 (m, 2 H), 1.79 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.79, 145.02, 128.22, 123.45, 120.79, 115.88, 93.32, 79.58, 44.30, 31.53, 25.29, 18.67.
MS (70 eV, EI) *m/z* (%): 218 (5), 181(55), 155(100), 142(15).
HRMS for $C_{12}H_{11}N_2Cl$: calcd. 218.0611; found 218.0612 (M^+).



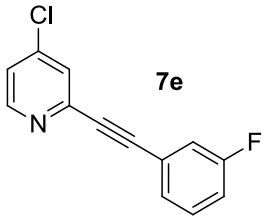
7c

2-(cyclopropylethynyl)isonicotinonitrile (7c): To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5c**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of ethynylcyclopropane in THF (99 mg, 1.5 mmol) at -20 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7c** (120 mg, 71%) as a pink oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.67 (dd, *J*=5.0, 1.0 Hz, 1 H), 7.53 (dd, *J*=1.5, 1.0 Hz, 1 H), 7.37 (dd, *J*=5.0, 1.5 Hz, 1 H), 1.55–1.43 (m, 1 H), 0.97–0.88 (m, 4 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.70, 145.22, 128.11, 123.08, 120.67, 115.97, 97.83, 74.27, 9.03 (2C), 0.09.

MS (70 eV, EI) *m/z* (%): 168 (55), 142 (100).
HRMS for $C_{11}H_8N_2$: calcd. 168.0687; found 168.0682 (M^+).



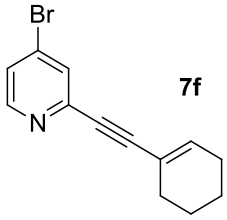
4-chloro-2-((trimethylsilyl)ethynyl)pyridine (7d): [16] To a solution of 4-chloropyridine (**4b**; 113 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5d**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of trimethylsilylacetylene in THF (147 mg, 1.5 mmol) at -40 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7d** (187 mg, 89%) as a colorless oil. Caution: volatile compound.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (dd, *J*=5.4, 0.5 Hz, 1 H), 7.51 (dd, *J*=2.0, 0.5 Hz, 1 H), 7.28 (dd, *J*=5.4, 2.0 Hz, 1 H), 0.27 (s, 9 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.56, 145.08, 144.97, 128.18, 124.23, 103.00, 97.13, -0.40 (3C).
MS (70 eV, EI) *m/z* (%): 209 (25), 194 (100), 166 (5), 140 (5).
HRMS for $C_{10}H_{12}NClSi$: calcd. 209.0428; found 209.0433 (M^+).



4-chloro-2-((3-fluorophenyl)ethynyl)pyridine (7e): To a solution of 4-chloropyridine (**4b**; 113 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5e**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 1-ethynyl-3-fluorobenzene in THF (180 mg, 1.5 mmol) at -40 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7e** (164 mg, 71%) as a pale brownish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (d, *J*=5.4 Hz, 1 H), 7.55–7.52 (m, 1 H), 7.40–7.30 (m, 2 H), 7.30–7.26 (m, 2 H), 7.13–7.05 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.42 (d, *J*=247.1 Hz), 150.96, 144.35, 144.32, 130.23 (d, *J*=8.6 Hz), 128.16 (d, *J*=3.1 Hz), 127.48, 123.74, 123.62, 118.98 (d, *J*=23.1 Hz), 116.87 (d, *J*=21.2 Hz), 89.07 (d, *J*=3.5 Hz), 88.31.

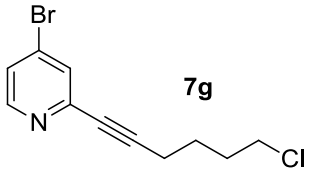
[16] PCT Intl Appl, **2008** WO 2008003665 A1 20080110.

^{19}F NMR (280 MHz, $CDCl_3$) δ ppm -112.5 (m).
MS (70 eV, EI) *m/z* (%): 231 (100), 196 (20), 169 (25), 149 (5).
HRMS for $C_{13}H_7NClF$: calcd. 231.0251; found 231.0250 (M^+).



7f

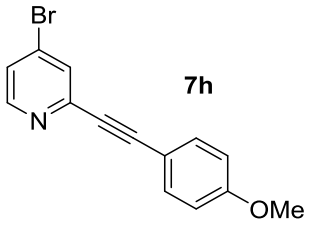
4-bromo-2-(cyclohex-2-en-1-ylethynyl)pyridine (7f): To a solution of 4-bromopyridine (**4c**; 157 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5f**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 3-ethynylcyclohex-1-ene in THF (159 mg, 1.5 mmol) at -10 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7f** (203 mg, 77%) as a light reddish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.36 (d, *J*=5.3 Hz, 1 H), 7.58 (dd, *J*=1.9, 0.5 Hz, 1 H), 7.35 (dd, *J*=5.4, 1.9 Hz, 1 H), 6.34 (m, 1 H), 2.23 (m, 2 H), 2.19–2.11 (m, 2 H), 1.72–1.56 (m, 4 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.30, 145.86, 139.05, 133.27, 130.65, 126.37, 120.58, 93.37, 85.68, 28.89, 26.05, 22.28, 21.46.
MS (70 eV, EI) *m/z* (%): 260 (100), 247 (45), 234 (50), 208 (5).
HRMS for $C_{13}H_{12}N_2Br$: calcd. 261.0153; found 261.0182 (M^+).



7g

4-bromo-2-(6-chlorohex-1-yn-1-yl)pyridine (7g): To a solution of 4-bromopyridine (**4c**; 157 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5b**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 6-chlorohex-1-yne in THF (175 mg, 1.5 mmol) at -10 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7g** (225 mg, 82%) as a reddish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.35 (d, *J*=5.1 Hz, 1 H), 7.55 (d, *J*=1.5 Hz, 1 H), 7.37 (dd, *J*=5.3, 1.5 Hz, 1 H), 3.59 (t, *J*=6.4 Hz, 2 H), 2.49 (t, *J*=6.9 Hz, 2 H), 2.01–1.89 (m, 2 H), 1.84–1.72 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.19, 145.55, 133.44, 130.76, 126.66, 92.22, 80.33, 44.71, 31.72, 25.53, 18.76.
MS (70 eV, EI) *m/z* (%): 272 (10), 236 (100), 208 (90), 195 (15).

HRMS for $C_{11}H_{11}NBrCl$: calcd. 270.9763; found 270.9749 (M^+).



7h

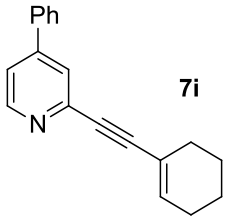
4-bromo-2-((4-methoxyphenyl)ethynyl)pyridine (7h): To a solution of 4-bromopyridine (**4c**; 157 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5g**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 1-ethynyl-4-methoxybenzene in THF (198 mg, 1.5 mmol) at -40 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7h** (216 mg, 75%) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.40 (dd, *J*=5.4, 0.6 Hz, 1 H), 7.68 (dd, *J*=1.9, 0.6 Hz, 1 H), 7.54–7.49 (m, 2 H), 7.39 (dd, *J*=5.4, 1.9 Hz, 1 H), 6.92–6.86 (m, 2 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 160.43, 150.37, 144.76, 143.32, 133.72, 129.91, 125.78, 119.00, 114.11, 91.16, 86.43, 55.33.

MS (70 eV, EI) *m/z* (%): 286 (100), 272 (45), 165 (40).

HRMS for $C_{14}H_{10}ONBr$: calcd. 286.9946; found 286.9954 (M^+).



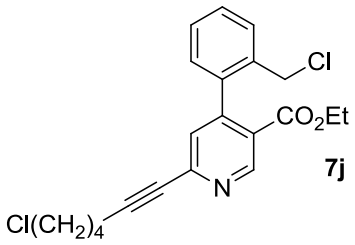
7i

2-(cyclohex-1-en-1-ylethynyl)-4-phenylpyridine (7i): To a solution of 4-phenylpyridine (**4d**; 310 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5f**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 3-ethynylcyclohex-1-ene in THF (319 mg, 1.5 mmol) at -50 °C and stirring for 40 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9 to 1:4) furnishing the compound **7i** (328 mg, 63%) as a brown oil.

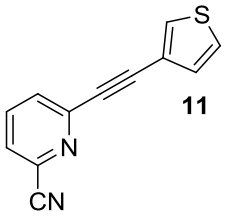
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.58 (d, *J*=5.3 Hz, 1 H), 7.69 - 7.53 (m, 3 H), 7.53 - 7.40 (m, 3 H), 7.38 (dd, *J*=5.3, 1.9 Hz, 1 H), 6.33 (dt, *J*=3.9, 2.0 Hz, 1 H), 2.35 - 2.20 (m, 2 H), 2.20 - 2.06 (m, 2 H), 1.76 - 1.53 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.94, 148.47, 143.98, 137.27 (2 C), 129.11, 128.95 (2 C), 126.76 (2 C), 124.65, 120.13, 119.93, 91.51, 86.13, 28.68, 25.71, 22.05,

21.24.
MS (70 eV, EI) *m/z* (%): 259 (100), 243 (15), 230 (25).
HRMS for $C_{19}H_{17}N$: calcd. 259.1361; found 259.1353 (M^+).

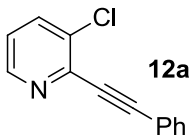


ethyl 6-(6-chlorohex-1-yn-1-yl)-4-(2-(chloromethyl)phenyl)nicotinate (7j): To a solution of ethyl 4-(2-(chloromethyl)phenyl)nicotinate (**4e**; 328 mg, 1.19 mmol) in THF (2 mL) is added BF_3 OEt_2 (186 mg, 1.3 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5b**: 1.8 mmol; prepared by adding ^{n}BuLi (1.8 mmol) to a 0.90 M solution of 6-chlorohex-1-yne in THF (208 mg, 1.8 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **7j** (248 mg, 53%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.14 (s, 1 H), 7.59 - 7.48 (m, 1 H), 7.48 - 7.31 (m, 3 H), 7.08 (d, *J*=7.2 Hz, 1 H), 4.38 (d, *J*=11.6 Hz, 1 H), 4.29 (d, *J*=11.6 Hz, 1 H), 4.09 (q, *J*=7.2 Hz, 2 H), 3.59 (t, *J*=6.4 Hz, 2 H), 2.53 (t, *J*=6.8 Hz, 2 H), 2.04 – 1.89 (m, 2 H), 1.89 - 1.73 (m, 2 H), 1.00 (t, *J*=7.2 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.02, 151.66, 148.92, 146.03, 138.36, 134.17, 129.67, 128.70, 128.39 (2 C), 128.09, 124.46, 93.42, 80.51, 61.19, 44.34, 43.81, 31.45, 25.26, 18.71, 13.54.
HRMS for $C_{21}H_{22}Cl_2NO_2$: calcd. 390.1022; found 390.1023 ($M+H^+$).

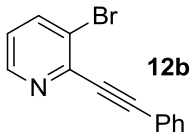


6-(thiophen-3-ylethynyl)picolinonitrile (11): To a solution of 2-cyanopyridine (**10a**; 208 mg, 2.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (312 mg, 2.2 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5h**: 3.0 mmol; prepared by adding ^{n}BuLi (3.0 mmol) to a 1.5 M solution of 3-ethynylthiophene in THF (325 mg, 3.0 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9 to 1:4) furnishing the compound **11** (278 mg, 66%) as a brown solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.83 (t, *J*=7.9 Hz, 1 H), 7.70 (br. s., 1 H), 7.69 (dd, *J*=4.8, 1.0 Hz, 1 H), 7.63 (dd, *J*=7.6, 1.0 Hz, 1 H), 7.34 (dd, *J*=5.1, 2.9 Hz, 1 H), 7.30 - 7.22 (m, 1 H).

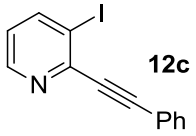
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 145.09, 137.32, 134.13, 131.34, 129.94, 129.85, 127.0, 125.87, 120.38, 116.57, 87.0, 86.67.
MS (70 eV, EI) *m/z* (%): 210 (100), 184 (8).
HRMS for $C_{12}H_6N_2S$: calcd. 210.0252; found 210.0247 (M^+).
Mp: 150–153 ℃.



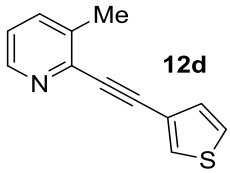
3-chloro-2-(phenylethynyl)pyridine (12a): To a solution of 3-chloropyridine (**1a**; 114 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5i**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of ethynylbenzene in THF (153 mg, 1.5 mmol) at 0 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **12a** (159 mg, 74%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (dd, *J*=4.6, 1.2 Hz, 1 H), 7.72 (dd, *J*=8.2, 1.2 Hz, 1 H), 7.68 - 7.56 (m, 2 H), 7.43 - 7.31 (m, 3 H), 7.18 (dd, *J*=8.0, 4.7 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 147.59, 141.89, 136.59, 134.01, 132.05 (2 C), 129.26, 128.30 (2 C), 123.27, 121.77, 94.70, 85.71.
MS (70 eV, EI) *m/z* (%): 213 (100), 178 (25), 151 (24).
HRMS for $C_{13}H_9ClN$: calcd. 214.0418; found 214.0418 ($M+H^+$).



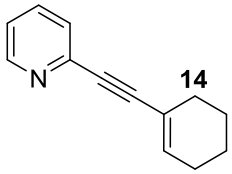
3-bromo-2-(phenylethynyl)pyridine (12b): To a solution of 3-bromopyridine (**1b**; 157 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5i**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of ethynylbenzene in THF (153 mg, 1.5 mmol) at 0 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **12b** (210 mg, 82%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.52 (d, *J*=4.1 Hz, 1 H), 7.89 (d, *J*=8.0 Hz, 1 H), 7.70 - 7.57 (m, 2 H), 7.43 - 7.30 (m, 3 H), 7.09 (dd, *J*=8.0, 4.7 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.03, 143.48, 139.75, 132.00 (2 C), 129.25, 128.29 (2 C), 123.72, 123.43, 121.74, 94.06, 87.28.
MS (70 eV, EI) *m/z* (%): 259 (100), 178 (43), 151 (49).
HRMS for $C_{13}H_9BrN$: calcd. 257.9913; found 257.9911 ($M+H^+$).



3-iodo-2-(phenylethynyl)pyridine (12c): To a solution of 3-iodopyridine (**1c**; 205 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5i**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of ethynylbenzene in THF (153 mg, 1.5 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **12c** (211 mg, 69%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.54 (d, *J*=4.1 Hz, 1 H), 8.11 (d, *J*=7.5 Hz, 1 H), 7.63 (d, *J*=3.0 Hz, 2 H), 7.36 (br. s., 3 H), 7.01 – 6.86 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.49, 147.05, 145.95, 131.91 (2 C), 129.24, 128.25 (2 C), 123.38, 121.63, 98.69, 93.24, 90.11.
MS (70 eV, EI) *m/z* (%): 305 (100), 177 (24), 151 (32).
HRMS for $C_{13}H_9IN$: calcd. 305.9774; found 305.9773 ($M+H^+$).



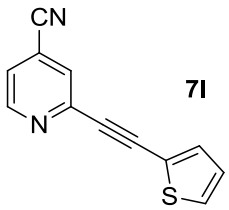
3-methyl-2-(thiophen-3-ylethynyl)pyridine (12d): To a solution of 3-picoline (**1d**; 93 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5h**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 3-ethynylthiophene in THF (162 mg, 1.5 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **12d** (127 mg, 64%) as a yellowish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.44 (d, *J*=3.2 Hz, 1H), 7.62 (m, 1H), 7.55–7.50 (m, 1H), 7.33–7.28 (m, 1H), 7.27–7.22 (m, 1H), 7.17–7.10 (m, 1H), 2.49 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 147.36, 143.11, 136.94, 135.72, 129.95, 129.82, 125.46, 122.60, 121.61, 88.19, 87.11, 19.41.
MS (70 eV, EI) *m/z* (%): 199 (100), 154 (50).
HRMS for $C_{12}H_9NS$: calcd. 199.0456; found 199.0455 (M+).



2-(cyclohex-1-en-1-ylethynyl)pyridine (14):[17] To a solution of pyridine (**13**; 79 mg,

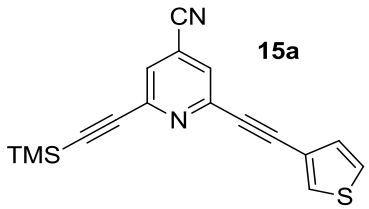
[17] H. Li, G. A. Grasa, T. J. Colacot, *Org. Lett.* **2010**, *12*, 3332.

1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with with the lithium reagent (**5f**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 1-ethynylcyclohex-1-ene in THF (159 mg, 1.5 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **14** (121 mg, 66%) as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.54 (dd, *J* = 4.1, 0.8 Hz, 1 H), 7.64–7.57 (m, 1 H), 7.38 (m, 1 H), 7.20–7.14 (m, 1 H), 6.33–6.26 (m, 1 H), 2.26–2.18 (m, 2 H), 2.18–2.09 (m, 2 H), 1.71–1.54 (m, 4 H).



7l

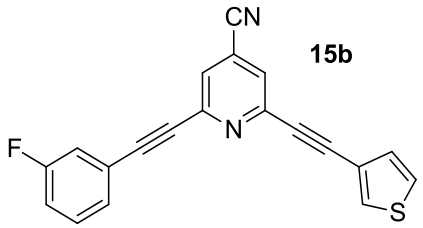
2-(thiophen-2-ylethynyl)isonicotinonitrile (7l): To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5h**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 2-ethynylthiophene in THF (162 mg, 1.5 mmol) at -50 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7l** (137 mg, 65%) as a reddish solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.77 (dd, *J*=5.0, 0.9 Hz, 1 H), 7.69 (m, 2 H), 7.44 (dd, *J*=5.0, 1.5 Hz, 1 H), 7.38 (m, 1 H), 7.25 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.97, 144.86, 131.35, 129.87, 128.25, 125.90, 123.60, 120.92, 120.43, 115.84, 87.54, 86.74.
MS (70 eV, EI) *m/z* (%): 210 (100), 184 (15), 166 (12), 139 (5).
HRMS for $C_{12}H_6N_2S$: calcd. 210.0252; found 210.0247 (M^+).
Mp: 115–117 °C.



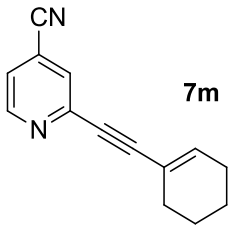
15a

2-(thiophen-3-ylethynyl)-6-((trimethylsilyl)ethynyl)isonicotinonitrile (15a): To a solution of 2-(thiophen-2-ylethynyl)isonicotinonitrile (**7l**; 113 mg, 0.54 mmol) in THF (2 mL) is added BF_3 OEt_2 (84 mg, 0.59 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5d**: 0.81 mmol; prepared by adding ^{n}BuLi (0.81 mmol) to a 0.75 M solution of trimethylsilylacetylene in THF (79 mg, 0.81 mmol) at -40 °C and stirring for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3)

furnishing the compound **15a** (99 mg, 60%) as a yellowish solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (dd, *J*=3.0, 1.2 Hz, 1 H), 7.60 (d, *J*=1.4 Hz, 1 H), 7.56 (d, *J*=1.4 Hz, 1 H), 7.33 (dd, *J*=5.0, 3.0 Hz, 1 H), 7.24 (dd, *J*=5.0, 1.2 Hz, 1 H), 0.27 (s, 9 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 145.06, 144.67, 131.58, 129.88, 127.08, 127.01, 125.91, 121.29, 120.36, 115.35, 101.28, 99.08, 87.85, 86.55, -0.51 (3C).
MS (70 eV, EI) *m/z* (%): 306 (50), 291 (100), 145 (5), 135 (2).
HRMS for $C_{17}H_{14}N_2SSi$: calcd. 306.0647; found 306.0633 (M^+).
Mp: 135–137 ℃.



2-((3-fluorophenyl)ethynyl)-6-(thiophen-3-ylethynyl)isonicotinonitrile (15b): To a solution of 2-(thiophen-2-ylethynyl)isonicotinonitrile (**7l**; 132 mg, 0.63 mmol) in THF (2 mL) is added BF_3 OEt_2 (98 mg, 0.69 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5e**: 0.94 mmol; prepared by adding ^{n}BuLi (0.94 mmol) to a 0.75 M solution of 1-ethynyl-3-fluorobenzene in THF (113 mg, 0.94 mmol) at 0 ℃ and stirring for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **15b** (152 mg, 74%) as a yellowish solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.75–7.71 (m, 1 H), 7.68–7.64 (m, 2 H), 7.45–7.32 (m, 4 H), 7.32–7.26 (m, 1 H), 7.21–7.11 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.56, 162.28 (d, *J*=247.5 Hz), 145.26, 144.70, 140.79, 131.69, 130.24 (d, *J*=8.6 Hz), 129.90, 128.18 (d, *J*=3.2 Hz), 126.97 (d, *J*=14.7 Hz), 125.96, 122.98 (d, *J*=9.5 Hz), 120.88 (d, *J*=87.6 Hz), 118.99 (d, *J*=23.2 Hz), 117.25 (d, *J*=21.2 Hz), 115.35, 90.75 (d, *J*=3.5 Hz), 88.06, 87.34, 86.52.
^{19}F NMR (280 MHz, $CDCl_3$) δ ppm -112.2 (m).
MS (70 eV, EI) *m/z* (%): 328 (100), 302 (2), 283 (2), 164 (2).
HRMS for $C_{20}H_9N2FS$: calcd. 328.0470; found 328.0473 (M^+).
Mp: 155–157 ℃.



2-(cyclohex-2-en-1-ylethynyl)isonicotinonitrile (7m): To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to

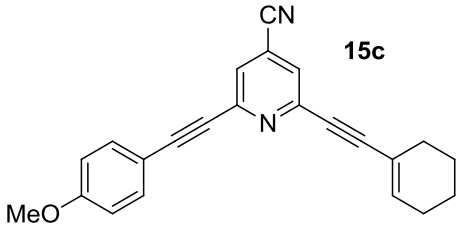
TP1 and reacted with the lithium reagent (**5f**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 3-ethynylcyclohex-1-ene in THF (159 mg, 1.5 mmol) at 0 ℃ and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7m** (158 mg, 76%) as a light yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.71 (dd, *J*=5.0, 0.9 Hz, 1 H), 7.58 (dd, *J*=1.5, 0.9 Hz, 1 H), 7.37 (dd, *J*=5.0, 1.5 Hz, 1 H), 6.38 (m, 1 H), 2.27-2.19 (m, 2 H), 2.18-2.12 (m, 2 H), 1.73-1.56 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.82, 145.31, 139.08, 128.15, 123.11, 120.70, 119.63, 115.94, 94.38, 84.82, 28.60, 25.92, 22.07, 21.25.

MS (70 eV, EI) *m/z* (%): 208 (95), 192 (55), 179 (55), 166 (5).

HRMS for $C_{14}H_{13}N_2$: calcd. 209.1079; found 209.1072 ($M+H^+$).



15c

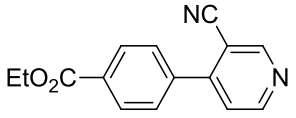
2-(cyclohex-1-en-1-ylethynyl)-6-((4-methoxyphenyl)ethynyl)isonicotinonitrile (15c): To a solution of 2-(cyclohex-2-en-1-ylethynyl)isonicotinonitrile (**7m**; 47 mg, 0.23 mmol) in THF (2 mL) is added $BF_3{\cdot}OEt_2$ (35 mg, 0.25 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5g**: 0.34 mmol; prepared by adding ^{n}BuLi (0.34 mmol) to a 0.75 M solution of 1-ethynyl-4-methoxybenzene in THF (45 mg, 0.34 mmol) at -40 ℃ and stirring for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **15c** (49 mg, 64%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.56–7.54 (m, 2 H), 7.53–7.51 (m, 1 H), 7.48 (d, *J*=1.4 Hz, 1 H), 6.93–6.86 (m, 2 H), 6.44–6.35 (m, 1 H), 3.84 (s, 3 H), 2.31–2.12 (m, 4 H), 1.80–1.58 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.73, 146.41, 146.17, 140.20, 134.75, 127.16, 126.97, 121.81, 120.39, 116.34, 114.91, 113.93, 95.18, 93.31, 86.68, 85.26, 55.71, 28.74, 26.12, 22.22, 21.39.

MS (70 eV, EI) *m/z* (%): 338 (100), 323 (5), 310 (5), 266 (5).

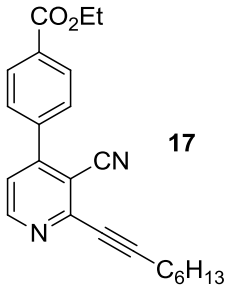
HRMS for $C_{23}H_{18}ON_2$: calcd. 338.1419; found 338.1414 (M^+).



16

ethyl 4-(3-cyanopyridin-4-yl)benzoate (16):[7] To a solution of ethyl 4-iodobenzoate (803mg, 3.2 mmol) in THF (2 mL) is added ^{i}PrMgCl·LiCl (2.3 ml, 1.29 M in THF, 3.0 mmol) dropwise at -30 ℃. The reaction mixture is stirred for 30 min to furnish the 4-carbethoxyphenylmagnesium chloride-lithium chloride. Then to a solution of nicotinonitrile (**1e**; 208 mg, 2.0 mmol) in THF (2 mL) is added $BF_3{\cdot}OEt_2$ (312 mg,

2.2 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min at 0 °C and cannulated to the freshly prepared Grignard reagent at -30 °C and the resulting mixture is stirred at the same temperature for 1 h. Then chloranil (984 mg, 4.0 mmol) is added and the mixture is warmed up to room temperature and continuously stirred for 2 h. Finally, it is quenched with 2 mL saturated ammonia water solution and extracted with ethyl acetate several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:2) furnishing the compound **16** (479 mg, 95%) as a reddish solid.[18]



17

ethyl 4-(3-cyano-2-(oct-1-yn-1-yl)pyridin-4-yl)benzoate (17): To a solution of ethyl 4-(3-cyanopyridin-4-yl)benzoate (**16**; 483 mg, 1.91 mmol) in THF (4 mL) is added BF_3 OEt_2 (299 mg, 2.11 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5j**: 2.87 mmol; prepared by adding ^{n}BuLi (2.87 mmol) to a 1.4 M solution of 1-octyne in THF (317 mg, 2.87 mmol) at 0 °C and stirring for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **17** (605 mg, 88%) as a reddish brown oil.

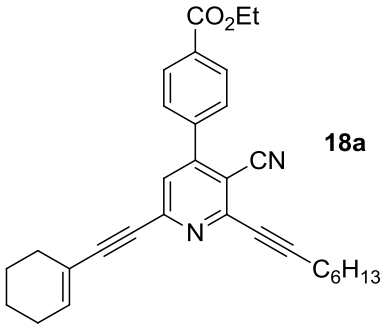
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.73 (d, *J*=5.0 Hz, 1 H), 8.20 (d, *J*=8.0 Hz, 2 H), 7.67 (d, *J*=8.3 Hz, 2 H), 7.35 (d, *J*=5.3 Hz, 1 H), 4.42 (q, *J*=7.2 Hz, 2 H), 2.55 (t, *J*=7.0 Hz, 2 H), 1.85 - 1.60 (m, *J*=7.4, 7.4, 7.3, 7.0 Hz, 2 H), 1.60 - 1.47 (m, 2 H), 1.42 (t, *J*=7.2 Hz, 3 H), 1.38 - 1.21 (m, 4 H), 0.90 (t, *J*=6.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.54, 152.19, 151.90, 147.61, 139.47, 131.88, 130.07 (2 C), 128.36 (2 C), 121.76, 115.59, 110.88, 99.14, 77.96, 61.24, 31.17, 28.48, 27.87, 22.37, 19.48, 14.18, 13.92.

MS (70 eV, EI) *m/z* (%): 359 (100), 345 (12), 331 (99), 315 (38), 303 (62), 287 (84), 275 (30), 244 (25).

HRMS for $C_{23}H_{23}O_2N_2$: calcd. 359.1754; found 359.1752 ($M\text{-}H^+$).

[18] For analytical data, see Chapter 2.



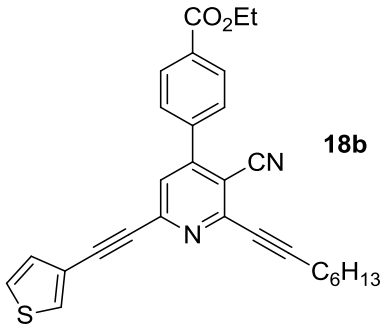
18a

ethyl 4-(3-cyano-6-(cyclohex-1-en-1-ylethynyl)-2-(oct-1-yn-1-yl)pyridin-4-yl)benzoate (18a): To a solution of the substrate (**17**; 72 mg, 0.20 mmol) in THF (0.5 mL) is added 0.22 mL of a 1 M BF_3 OEt_2 solution in THF (0.22 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5f**: 0.30 mmol; prepared by adding ^{n}BuLi (0.30 mmol) to a 0.60 M solution of 1-ethynylcyclohex-1-ene in THF (32 mg, 0.30 mmol) at -50 ℃ and stirring for 40 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:19) furnishing the compound **18a** (83 mg, 89%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (d, *J*=8.2 Hz, 2 H), 7.65 (d, *J*=8.2 Hz, 2 H), 7.39 (s, 1 H), 6.41 (br. s., 1 H), 4.42 (q, *J*=7.1 Hz, 2 H), 2.53 (t, *J*=7.1 Hz, 2 H), 2.21 - 2.28 (m, 2 H), 2.21 - 2.13 (m, 2 H), 1.72 - 1.57 (m, 6 H), 1.49 (dt, *J*=14.6, 7.4 Hz, 2 H), 1.42 (t, *J*=7.1 Hz, 3 H), 1.38 - 1.27 (m, 4 H), 0.90 (t, *J*=6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.72, 151.93, 147.80, 146.70, 139.89, 139.30, 132.01, 130.19 (2 C), 128.41 (2 C), 124.79, 119.74, 115.89, 108.87, 99.27, 96.44, 85.61, 77.86, 61.37, 31.29, 28.63, 28.53, 27.94, 26.01, 22.49, 22.05, 21.21, 19.62, 14.30, 14.04.

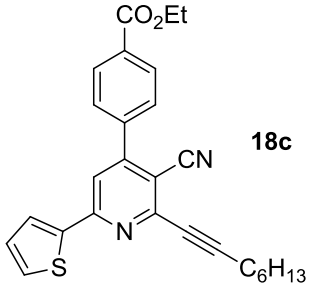
HRMS for $C_{31}H_{33}O_2N_2$: calcd. 465.2537; found 465.2536 ($M+H^+$).



18b

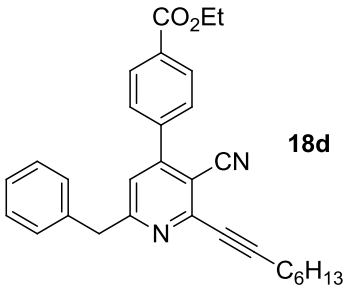
ethyl 4-(3-cyano-2-(oct-1-yn-1-yl)-6-(thiophen-3-ylethynyl)pyridin-4-yl)benzoate (18b): To a solution of the substrate (**17**; 72 mg, 0.20 mmol) in THF (0.5 mL) is added 0.22 mL of a 1 M BF_3 OEt_2 solution in THF (0.22 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5h**: 0.40 mmol; prepared by adding ^{n}BuLi (0.40 mmol) to a 0.60 M solution of 3-ethynylthiophene in THF (43 mg, 0.40 mmol) at -50 ℃ and stirring for 45 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **18b** (77 mg, 82%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.21 (d, *J*=8.2 Hz, 2 H), 7.70 (d, *J*=2.2 Hz, 1 H), 7.68 (d, *J*=8.2 Hz, 2 H), 7.50 (s, 1 H), 7.34 (dd, *J*=4.9, 3.0 Hz, 1 H), 7.25 (d, *J*=4.9 Hz, 1 H), 4.43 (q, *J*=7.1 Hz, 2 H), 2.55 (t, *J*=7.1 Hz, 2 H), 1.74 - 1.64 (m, 2 H), 1.50 (quin, *J*=7.4 Hz, 2 H), 1.43 (t, *J*=7.1 Hz, 3 H), 1.39 - 1.27 (m, 4 H), 0.90 (t, *J*=6.9 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.66, 152.12, 147.88, 146.18, 139.14, 132.08, 131.81, 130.20 (2 C), 129.88, 128.41 (2 C), 125.94, 124.73, 120.39, 115.76, 109.25, 99.54, 89.34, 87.48, 77.80, 61.36, 31.27, 28.60, 27.91, 22.47, 19.60, 14.27, 14.02.
HRMS for $C_{29}H_{27}O_2N_2S$: calcd. 467.1788; found 467.1789 ($M+H^+$).



18c

ethyl 4-(3-cyano-2-(oct-1-yn-1-yl)-6-(thiophen-2-yl)pyridin-4-yl)benzoate (18c): To a solution of the substrate (**17**; 72 mg, 0.20 mmol) in THF (0.5 mL) is added 0.22 mL of a 1 M BF_3 OEt_2 solution in THF (0.22 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min followed by a dropwise addition of of 2-thienylmagnesium bromide-lithium chloride (0.35 mL, 0.40 mmol, 1.14 M in THF) at -30 ℃. The resulting mixture is stirred for 1 h. Then, chloranil (98 mg, 0.40 mmol) is added and the mixture is warmed up to room temperature and continuously stirred for 2 h. Finally, it is quenched with saturated ammonia water solution (2 mL) and extracted with ethyl acetate several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:19) furnishing the compound **18c** (48 mg, 53%) as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.21 (d, *J*=8.2 Hz, 2 H), 7.75 (d, *J*=3.6 Hz, 1 H), 7.69 (d, *J*=8.2 Hz, 2 H), 7.59 (s, 1 H), 7.54 (d, *J*=4.9 Hz, 1 H), 7.16 (t, *J*=4.4 Hz, 1 H), 4.43 (q, *J*=7.1 Hz, 2 H), 2.56 (t, *J*=7.1 Hz, 2 H), 1.71 (qd, *J*=7.5, 7.3 Hz, 2 H), 1.52 (qd, *J*=7.3, 7.1 Hz, 2 H), 1.43 (t, *J*=7.1 Hz, 3 H), 1.38 - 1.29 (m, 4 H), 0.91 (t, *J*=6.7 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.81, 155.01, 152.45, 147.70, 142.39, 139.97, 131.89, 130.63, 130.20 (2 C), 128.53, 128.41 (2 C), 127.66, 116.80, 116.19, 108.52, 99.01, 78.16, 61.38, 31.30, 28.64, 27.99, 22.50, 19.74, 14.30, 14.06.
HRMS for $C_{27}H_{27}O_2N_2S$: calcd. 443.1788; found 443.1788 ($M+H^+$).



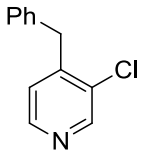
18d

ethyl 4-(6-benzyl-3-cyano-2-(oct-1-yn-1-yl)pyridin-4-yl)benzoate (18d): To a solution of the substrate (**17**; 72 mg, 0.20 mmol) in THF (0.5 mL) is added 0.22 mL of a 1 M $BF_3 \cdot OEt_2$ solution in THF (0.22 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with BnMgCl (0.15 mL, 0.30 mmol, 2.0 M in THF) at -50 °C for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **18d** (79 mg, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.15 (d, *J*=8.2 Hz, 2 H), 7.56 (d, *J*=8.2 Hz, 2 H), 7.35 - 7.30 (m, 2 H), 7.30 - 7.23 (m, 3 H), 7.08 (s, 1 H), 4.40 (q, *J*=7.1 Hz, 2 H), 4.24 (s, 2 H), 2.56 (t, *J*=7.3 Hz, 2 H), 1.70 (qd, *J*=7.5, 7.3 Hz, 2 H), 1.51 (quin, *J*=7.3 Hz, 2 H), 1.40 (t, *J*=7.1 Hz, 3 H), 1.37 - 1.28 (m, 4 H), 0.90 (t, *J*=6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.73, 165.03, 152.31, 147.28, 139.81, 137.57, 131.81, 130.10 (2 C), 129.16 (2 C), 128.89 (2 C), 128.42 (2 C), 127.01, 121.41, 116.00, 108.80, 98.91, 78.15, 61.32, 44.88, 31.29, 28.64, 27.99, 22.50, 19.68, 14.28, 14.04.

HRMS for $C_{30}H_{31}O_2N_2$: calcd. 451.2380; found 451.2380 ($M+H^+$).



19a

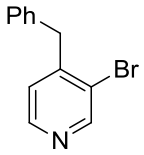
4-benzyl-3-chloropyridine (19a): To a solution of 3-chloropyridine (**1a**; 113 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with BnMgCl (1.4 mL, 1.2 mmol, 0.85 M in THF) at -50 °C for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **19a** (193 mg, 95%) as a reddish oil.

^{1}H NMR[19] (300 MHz, $CDCl_3$) δ ppm 8.54 (s, 1 H), 8.34 (d, *J*=5.0 Hz, 1 H), 7.20 - 7.39 (m, 3 H), 7.17 (d, *J*=6.9 Hz, 2 H), 6.99 (d, *J*=5.0 Hz, 1 H), 4.06 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.18, 147.64, 147.36, 137.15, 132.02, 128.98 (2 C), 128.65 (2 C), 126.75, 125.06, 38.35.

MS (70 eV, EI) *m/z* (%): 203 (85), 168 (100), 139 (27), 91 (25).

HRMS for $C_{12}H_{10}ClN$: calcd. 203.0502; found 203.0510 (M^+).

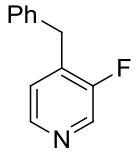


19b

4-benzyl-3-bromopyridine (19b): To a solution of 3-bromopyridine (**1b**; 159 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP2** and reacted with BnMgBr (1.2 mL, 1.2 mmol, 0.98 M in THF) at -50 °C for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **19b** (224 mg, 90%) as a colorless oil.

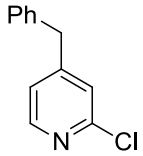
[19] T.-L. Shing, W.-L. Chia, M.-J. Shiao, T.-Y. Chau *Synthesis*, **1991**, 849.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.67 (s, 1 H), 8.34 (d, *J*=5.0 Hz, 1 H), 7.38 - 7.09 (m, 5 H), 6.97 (d, *J*=4.7 Hz, 1 H), 4.04 (s, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.52, 149.19, 147.96, 137.04, 128.96 (2 C), 128.58 (2 C), 126.70, 125.40, 123.15, 40.87.
MS (70 eV, EI) *m/z* (%): 249 (45), 168 (100), 139 (36), 91 (17).
HRMS for $C_{12}H_{11}NBr$: calcd. 248.0069; found 248.0069 ($M+H^+$).



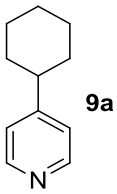
19c

4-benzyl-3-fluoropyridine (19c): To a solution of 3-fluoropyridine (**1f**; 99 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP2** and reacted with BnMgBr (1.2 mL, 1.2 mmol, 0.98 M in THF) at -50 ℃ for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **19c** (138 mg, 72%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.40 (d, *J*=1.7 Hz, 1 H), 8.28 (d, *J*=5.0 Hz, 1 H), 7.39 - 7.12 (m, 5 H), 7.08 (t, *J*=5.7 Hz, 1 H), 4.01 (s, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 158.13 (d, *J*=253.1 Hz), 145.39 (d, *J*=5.0 Hz), 137.51 (d, *J*=24.8 Hz), 137.43, 137.15 (d, *J*=13.4 Hz), 128.90 (2 C), 128.79 (2 C), 126.87, 125.33 (d, *J*=2.0 Hz), 34.09 (d, *J*=2.5 Hz).
^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -131.98 (d, *J*=5.9 Hz).
MS (70 eV, EI) *m/z* (%): 187 (15), 182 (32), 91 (100).
HRMS for $C_{12}H_{11}NF$: calcd. 188.0870; found 188.0896 ($M+H^+$).
Mp: 114–116 ℃.

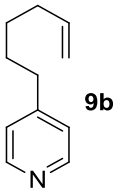


19d

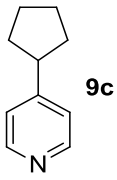
4-benzyl-2-chloropyridine (19d): To a solution of 2-chloropyridine (**10b**; 114 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 ℃. The reaction mixture is stirred for 15 min according to **TP2** and reacted with BnMgCl (0.60 mL, 1.2 mmol, 2.0 M in THF) at -50 ℃ for 30 min. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:19) furnishing the compound **19d** (172 mg, 84%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.24 (d, *J*=5.3 Hz, 1 H), 7.38 - 7.19 (m, 3 H), 7.19 - 7.07 (m, 3 H), 7.01 (d, *J*=5.0 Hz, 1 H), 3.92 (s, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.33, 151.57, 149.39, 137.82, 128.86 (2 C), 128.72 (2 C), 126.81, 124.28, 122.82, 40.74.
MS (70 eV, EI) *m/z* (%): 203 (100), 168 (83), 139 (22), 91 (32).
HRMS for $C_{12}H_{10}NBr$: calcd. 203.0252; found 203.049 (M^+).



4-cyclohexylpyridine (9a): [20] To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *c*-HexMgBr·LiCl (2.0 mL, 0.59 M in THF, 1.2 mmol) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **9a** (115 mg, 71%) as a light yellowish oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (d, *J*=6.0 Hz, 2 H), 7.10 (d, *J*=6.0 Hz, 2 H), 2.54-2.41 (m, 1 H), 1.95-1.76 (m, 4 H), 1.76-1.71 (m, 1 H), 1.47-1.33 (m, 4 H), 1.32-1.16 (m, 1 H).



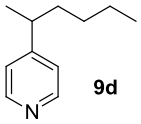
4-(hex-5-en-1-yl)pyridine (9b):[3e] To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with hex-5-en-1-ylmagnesium chloride·lithium chloride (1.2 mL, 1.02 M in THF, 1.2 mmol) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **9b** (143 mg, 89%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (d, *J*=6.0 Hz, 2 H), 7.12 (d, *J*=5.5 Hz, 2 H), 5.80 (ddt, *J*=16.9, 10.0, 6.6 Hz, 1 H), 5.09–4.89 (m, 2 H), 2.60 (t, *J*=7.6 Hz, 2 H), 2.18–1.97 (m, 2 H), 1.77–1.54 (m, 2 H), 1.54–1.30 (m, 2 H).



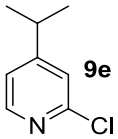
4-cyclopentylpyridine (9c):20 To a solution of isonicotinonitrile (**4a**; 105 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *c*-PentMgBr·LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **9c** (93 mg, 63%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.47 (d, *J*=6.0 Hz, 2 H), 7.13 (d, *J*=6.0 Hz, 2 H),

[20] G. A. Molander , O. A. Argintaru, I. Aron , S. D. Dreher, *Org. Lett.* **2010**, *12*, 5783.

2.97 (quin, *J*=8.5 Hz, 1 H), 2.18 – 1.95 (m, 2 H), 1.92 - 1.48 (m, 6 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.36, 149.42 (2 C), 122.43 (2 C), 44.95, 33.74 (2 C), 25.35 (2 C).
MS (70 eV, EI) *m/z* (%): 147 (100), 118 (70), 105 (75).
HRMS for $C_{10}H_{13}N$: calcd. 147.1048; found 147.1050 (M^+).



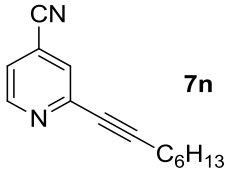
4-(hexan-2-yl)pyridine (9d)[21]
From 4a: To a solution of isonicotinonitrile (**4a**; 105 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *i*-HexMgBr·LiCl (1.7 mL, 1.2 mmol, 0.72 M in THF) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **9d** (118 mg, 72%) as a pale brown oil.
From 4b: To a solution of 4-chloropyridine (**4b**; 113 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with *i*-HexMgBr·LiCl (1.7 mL, 1.2 mmol, 0.72 M in THF) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **9d** (124 mg, 76%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (d, *J*=5.1 Hz, 2 H), 7.09 (d, *J*=5.0 Hz, 2 H), 2.71–2.57 (m, 1 H), 1.61–1.49 (m, 2 H), 1.32–1.10 (m, 7 H), 0.88–0.78 (m, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.84, 150.46, 123.34, 39.66, 37.53, 29.83, 22.78, 21.59, 14.03.
MS (70 eV, EI) *m/z* (%): 163 (51), 106 (100).
HRMS for $C_{11}H_{17}N$: calcd. 163.1361; found 163.1346 (M^+).



2-chloro-4-isopropylpyridine (9e): To a solution of 2-chloroisonicotinonitrile (**20**; 138 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with ^{i}PrMgCl·LiCl (0.95 mL, 1.2 mmol, 1.3 M in THF) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:19) furnishing the compound **9e** (71 mg, 46%) as a brown oil. The ^{1}H NMR data is in accordance with the literature:
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.27 (d, *J*=5.0 Hz, 1 H), 7.18 (br. s., 1 H), 7.07 (dd, *J*=5.3, 1.1 Hz, 1 H), 2.98 - 2.79 (m, *J*=13.8, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.26 (d, *J*=6.9 Hz, 6 H).

[21] Y. Kato, T. Mase, *Tetrahedron Lett.* **1999**, *40*, 8823.

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 160.97, 151.64, 149.51, 122.33, 120.87, 33.49, 22.90 (2 C).**Error! Bookmark not defined.**



7n

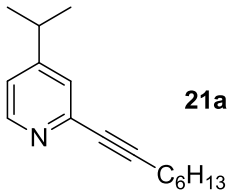
2-(oct-1-yn-1-yl)isonicotinonitrile (7n): To a solution of isonicotinonitrile (**4a**; 105 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with 1-octynyllithium (**5j**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 1-octyne in THF (166 mg, 1.5 mmol) at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **7n** (180 mg, 84%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.71 (d, *J*=4.4 Hz, 1 H), 7.57 (s, 1 H), 7.42 (d, *J*=5.0 Hz, 1 H), 2.45 (t, *J*=7.0 Hz, 2 H), 1.63 (quin, *J*=7.1 Hz, 2 H), 1.54 - 1.39 (m, 2 H), 1.39 - 1.18 (m, 4 H), 0.89 (br. s., 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.51, 145.01, 127.95, 123.06, 120.46, 115.69, 94.31, 78.87, 31.02, 28.36, 27.85, 22.24, 19.09, 13.77.

MS (70 eV, EI) *m/z* (%): 211 (79), 197 (43), 183 (82), 169 (86), 155 (100), 142 (75), 114 (36).

HRMS for $C_{14}H_{15}N_2$: calcd. 211.1230; found 211.1228 ($M\text{-}H^+$).



21a

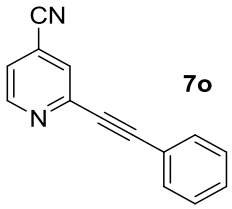
4-isopropyl-2-(oct-1-yn-1-yl)pyridine (21a): To a solution of the substrate (**7n**; 164 mg, 0.77 mmol) in THF (1 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with ^{i}PrMgCl ·LiCl (0.72 mL, 0.93 mmol, 1.3 M in THF) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **21a** (117 mg, 66%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.42 (d, *J*=5.3 Hz, 1 H), 7.24 (s, 1 H), 7.03 (dd, *J*=5.1, 1.5 Hz, 1 H), 2.93 - 2.75 (m, *J*=13.8, 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 2.43 (t, *J*=7.0 Hz, 2 H), 1.70 - 1.55 (m, *J*=7.4, 7.4, 7.3, 7.0 Hz, 2 H), 1.53 - 1.40 (m, 2 H), 1.38 - 1.27 (m, 4 H), 1.24 (d, *J*=6.9 Hz, 6 H), 0.90 (t, *J*=6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.52, 149.60, 143.76, 124.90, 120.66, 90.35, 80.51, 33.31, 31.27, 28.58, 28.32, 22.85 (2 C), 22.43, 19.24, 13.94.

MS (70 eV, EI) *m/z* (%): 228 (54), 214 (41), 200 (97), 186 (70), 172 (100), 159 (73), 144 (32).

HRMS for $C_{16}H_{22}N$: calcd. 228.1747; found 228.1742 ($M\text{-}H^+$).



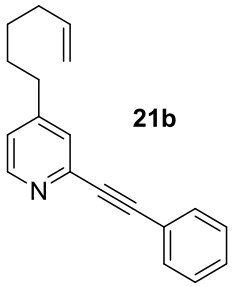
2-(phenylethynyl)isonicotinonitrile (7o): [22] To a solution of isonicotinonitrile (**4a**; 104 mg, 1.0 mmol) in THF (2 mL) is added BF_3 OEt_2 (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with phenylethynyllithium (**5i**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of phenylacetylene (153 mg, 1.5 mmol) in THF at 0 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7o** (126 mg, 62%) as a light reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.79 (dd, *J*=5.1, 1.0 Hz, 1 H), 7.73 (dd, *J*=1.5, 1.0 Hz, 1 H), 7.63-7.59 (m, 2 H), 7.45 (dd, *J*=5.1, 1.5 Hz, 1 H), 7.43-7.35 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.98, 144.86, 132.20, 129.71, 128.53, 123.70, 121.27, 120.92, 119.15, 115.84, 92.19, 86.96.

MS (70 eV, EI) *m/z* (%): 204 (100), 177 (14), 150 (7), 126 (7).

HRMS for $C_{14}H_9N_2$: calcd. 205.0766; found 205.0759 ($M+H^+$).



4-(hex-5-en-1-yl)-2-(phenylethynyl)pyridine (21b): To a solution of 2-(phenylethynyl)isonicotinonitrile (**7o**; 40 mg, 0.20 mmol) in THF (2 mL) is added BF_3 OEt_2 (31 mg, 0.22 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with hex-5-en-1-ylmagnesium chloride-lithium chloride (0.24 mL, 1.02 M in THF, 1.2 mmol) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **21b** (45 mg, 88%) as a colorless oil.

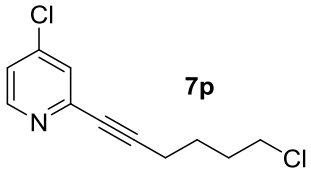
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (dd, *J*=5.1, 0.8 Hz, 1 H), 7.62–7.57 (m, 2 H), 7.39–7.32 (m, 4 H), 7.06 (dd, *J*=5.1, 1.7 Hz, 1 H), 5.79 (ddt, *J*=16.9, 10.2, 6.7 Hz, 1 H), 5.07–4.92 (m, 2 H), 2.65–2.58 (m, 2 H), 2.15–2.05 (m, 2 H), 1.72–1.62 (m, 2 H), 1.51–1.38 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 152.79, 150.79, 144.12, 139.23, 132.83 (2C), 129.65, 129.14 (2C), 128.06, 123.90, 123.12, 115.49, 89.38, 89.29, 35.13, 33.66, 29.77, 28.51.

MS (70 eV, EI) *m/z* (%): 261 (20), 206 (20), 193 (100), 146 (20).

HRMS for $C_{19}H_{19}N$: calcd. 261.1517; found 261.1517 (M^+).

[22] J. Tsuji, K. Mizutani, I. Shimizu, K. Yamamoto, *Chem. Lett.* **1989**, *5*, 773.



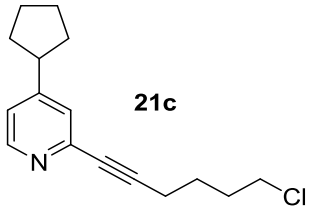
4-chloro-2-(6-chlorohex-1-yn-1-yl)pyridine (7p): To a solution of 4-chloropyridine (**4b**; 113 mg, 1.0 mmol) in THF (2 mL) is added $BF_3 OEt_2$ (156 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP1** and reacted with the lithium reagent (**5b**: 1.5 mmol; prepared by adding ^{n}BuLi (1.5 mmol) to a 0.75 M solution of 6-chlorohex-1-yne in THF (175 mg, 1.5 mmol) at -10 °C and stirring for 30 min). The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **7p** (166 mg, 73%) as a reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.4 Hz, 1 H), 7.38 (dd, *J*=2.0, 0.5 Hz, 1 H), 7.21 (dd, *J*=5.4, 2.0 Hz, 1 H), 3.59 (t, *J*=6.4 Hz, 2 H), 2.50 (t, *J*=6.9 Hz, 2 H), 2.01–1.90 (m, 2 H), 1.84–1.72 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.47, 145.72, 144.91, 127.74, 123.67, 92.00, 80.51, 44.70, 31.73, 25.53, 18.75.

MS (70 eV, EI) *m/z* (%): 227 (5), 192 (90), 164 (100), 151 (25).

HRMS for $C_{11}H_{11}NCl_2$: calcd. 227.0269; found 227.0262 (M^+).



2-(6-chlorohex-1-yn-1-yl)-4-cyclopentylpyridine (21c): To a solution of 4-chloro-2-(6-chlorohex-1-yn-1-yl)pyridine (**7p**; 70 mg, 0.31 mmol) in THF (2 mL) is added $BF_3 OEt_2$ (48 mg, 0.34 mmol) dropwise at 0 °C. The reaction mixture is stirred for 15 min according to **TP3** and reacted with Grignard reagent (0.37 mmol) at -50 °C. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:3) furnishing the compound **21c** (58 mg, 73%) as a palid brownish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.40 (d, *J*=5.1 Hz, 1 H), 7.25 (d, *J*=1.7 Hz, 1 H), 7.05 (dd, *J*=5.2, 1.8 Hz, 1 H), 3.59 (t, *J*=6.5 Hz, 2 H), 3.01–2.87 (m, 1 H), 2.49 (t, *J*=6.9 Hz, 2 H), 2.13–1.92 (m, 4 H), 1.85–1.66 (m, 6 H), 1.65–1.49 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.79, 150.54, 144.26, 126.44, 122.35, 89.66, 81.71, 45.19, 44.83, 34.02 (2C), 31.77, 25.70, 25.66 (2C), 18.74.

MS (70 eV, EI) *m/z* (%): 261 (25), 226 (100), 198 (95), 185 (15).

HRMS for $C_{16}H_{20}NCl$: calcd. 261.1284; found 261.1284 (M^+).

Chapter 4. BF_3-Mediated Direct Functionalization of Pyridines for the Preparation of Piperidine Derivatives

4.1 Introduction

Similar to pyridine, the piperidine derivative is another large family of molecules including thousands of natural products and pharmaceuticals (Figure 1).[1]

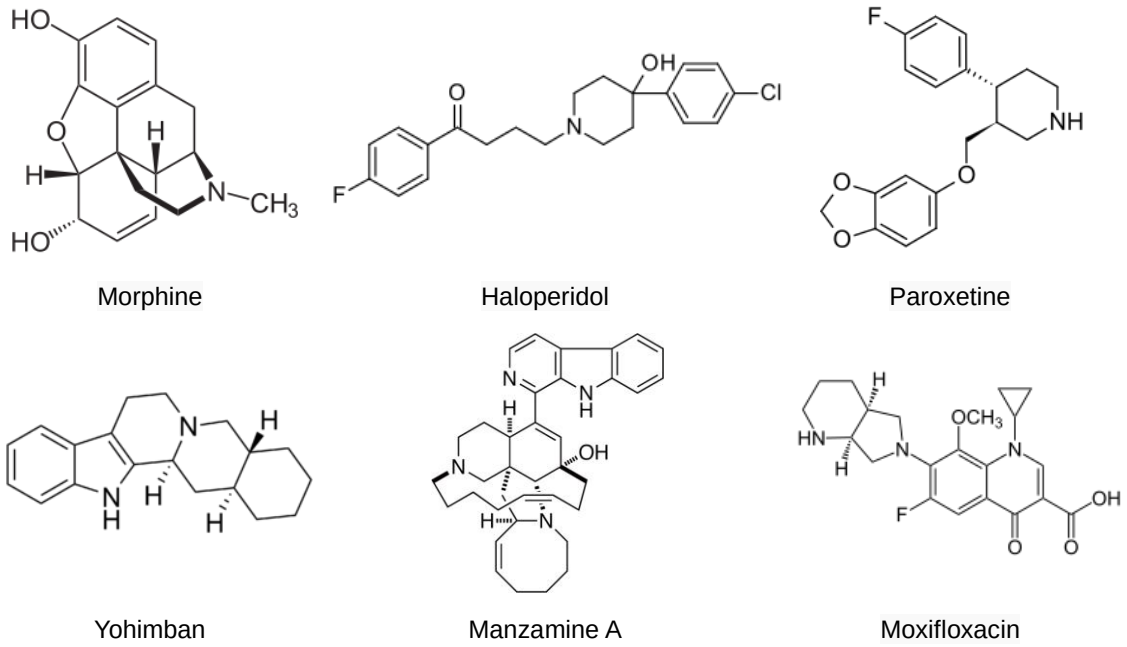


Figure 1. Bio-active piperidine derivatives.

As a saturated version of pyridine, piperidine derivative can be synthesized by pyridine reduction or hydrogenation. However, because of the inertness of the aromatic pyridine ring, usually the direct hydrogenation of pyridines requires harsh conditions (a high pressure of hydrogen) and noble metal catalysts.[2]

Meanwhile, during the studies of the Chichibabin-type nucleophilic addition of pyridines, people realized that the addition intermediate can undergo not only an oxidative rearomatization, but also a reduction to furnish a piperidine-type product.[3] *Charette et al.* reported a method to prepare 1,2,5,6-tetrahydropyridines through a C(2) regioselective addition of Grignard reagents to *N*-benzoyliminopyridinium ylides followed by the reduction with a methanolic solution of $NaBH_4$ (Scheme 1).[4] The

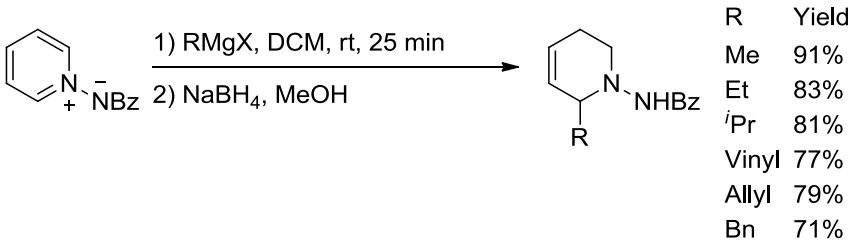
[1] a) T. P. Lebold, J. L. Wood, J. Deitch, M. W. Lodewyk, D. J. Tantillo, R. Sarpong, *Nat. Chem.* **2013**, *5*, 126; b) Z. Lu, Y. Li, J. Deng, A. Li, *Nat. Chem.* **2013**, *5*, 679.

[2] a) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; b) J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35.

[3] J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642.

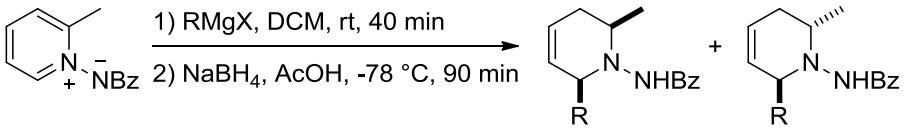
[4] C. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2003**, *125*, 6360.

reaction also occurs at 2-substituted pyridines, favoring the *cis*-isomer as the main product (Scheme 2).



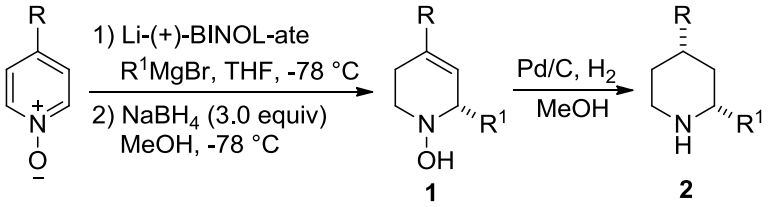
R	Yield
Me	91%
Et	83%
^{i}Pr	81%
Vinyl	77%
Allyl	79%
Bn	71%

Scheme 1. Formation of 1,2,5,6-tetrahydropyridines.



Scheme 2. Formation of 2,6-disubstituted 1,2,5,6-tetrahydropyridines.

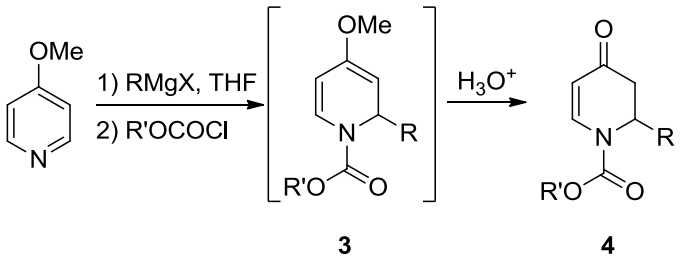
Almqvist et al. reported a similar Grignard reagent addition to pyridine-*N*-oxides at position 2 with the assistance of a chiral lithium binolate. The addition intermediate was reduced by $NaBH_4$, affording the product **1** in good yield and *ee*. Compound **1** can be further reduced by palladium on charcoal and hydrogen gas to afford the piperidine product **2** (Scheme 3).[5]



Scheme 3. Enantioselective synthesis of substituted piperidines.

As another method to work up the addition intermediate, *Comins et al.* employed the 4-methoxypyridine as starting material. After acylation, the presence of the 4-methoxy group forces the Grignard reagents to add at position 2, providing the 1,2-dihydropyridine intermediate **3** which easily undergoes a hydrolysis with a mild acidic workup to furnish 2,3-dihydro-4-pyridone (**4**) as a stable product (Scheme 4).[6] This compound is proved to be a very useful substrate for natural product synthesis.

[5] M. Hussain, T. Sainte-Luce Banchelin, H. Andersson, R. Olsson, F. Almqvist, *Org. Lett.* **2013**, *15*, 54.
[6] D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1986**, *27*, 4549.

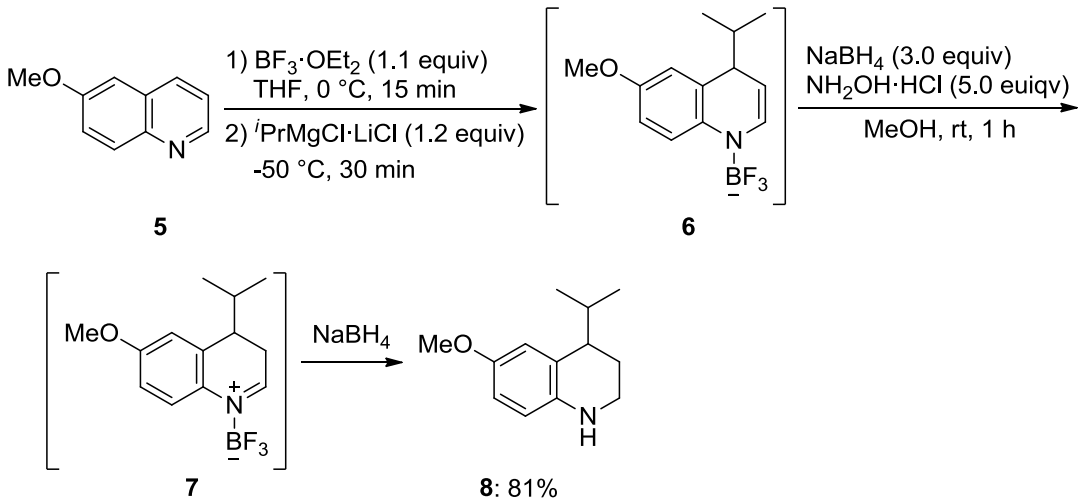


3 **4**

Scheme 4. Synthesis of *N*-acyl-2,3-dihydro-4-pyridones from 4-methoxypyridine.

4.2 Results and Discussion

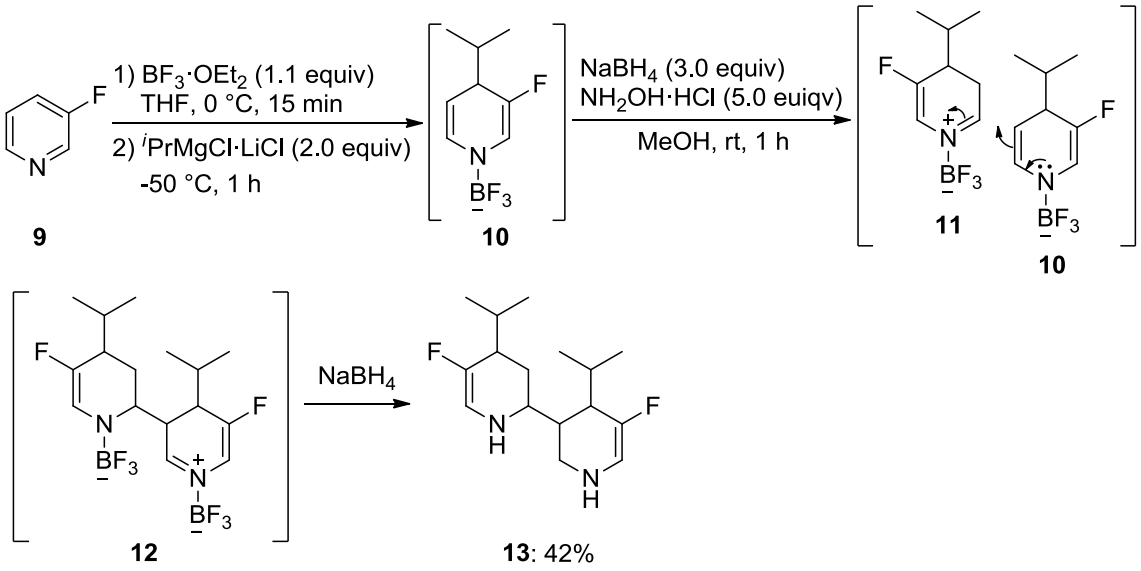
With the assistance of BF_3 OEt_2, the aromatic Π bonds of pyridine rings can be easily opened by organometallic reagents (vide supra). If the produced dihydropyridine intermediate is treated with a reductant, it will be reduced to a piperidine derivative. Thus, the 6-methoxyquinoline (**5**) is readily converted to the intermediate (**6**) through the BF_3-mediated addition of ^{i}PrMgCl ŀLiCl at -50 ℃. However, a solution of $NaBH_4$ in MeOH is not reactive enough to reduce the intermediate (**6**) completely. Further studies indicated that an acid was necessary to accelerate the reduction step by protonating the BF_3-attached nitrogen atom, leading to the iminium **7**, which can be easily reduced by $NaBH_4$ then. After screening of a variety of proton sources, mild acids such as NH_4Cl, NH_2OH ŀHCl, Py ŀHCl, 4-ClPy ŀHCl, and 4-BrPy ŀHCl gave optimum results, while other stronger or weaker acids such as H_2O, $NaHCO_3$, HOAc, KH_2PO_4, $PhNH_2$ ŀHCl, and $PivCO_2H$ led to the reduction product **8** in low yields, accompanied by the formation of side products of decomposition or oligomerization of intermediate **7**. In this case, NH_2OH ŀHCl is the optimum proton source to afford the product **8** in 81% isolated yield after a smooth reduction at room temperature for 1 h (Scheme 5). Other reductive reagents such as $NaBH_3CN$ and $NaBH(OAc)_3$ are not efficient enough. The catalytic hydrogenation using Pd/C and 1 atm H_2 only gave a trace amount of the reduced product.



5 **6** **7** **8**: 81%

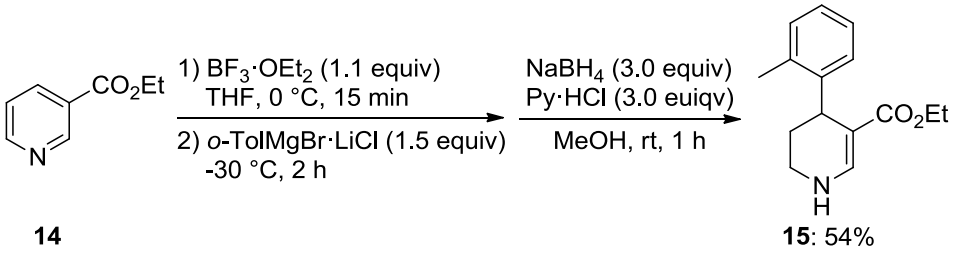
Scheme 5. Preparation of piperidine **8** from 6-methoxyquinoline **5** through addition/reduction.

In the reaction using 3-fluoropyridine (**9**), a dimerization was observed. After addition of the Grignard reagent, the intermediate **10** is protonated by $NH_2OH \cdot HCl$, providing the iminium **11**. This species is attacked by one molecule of remained **10**, leading to the dimerized species **12**, which is finally reduced and converted to the compound **13** as the main product (Scheme 6).



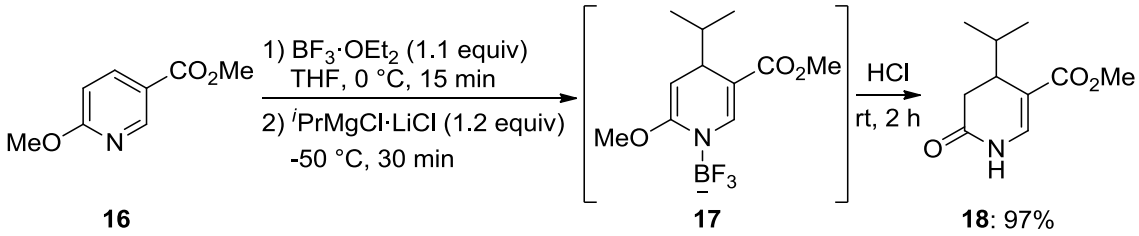
Scheme 6. Preparation of **13** through an addition/dimerization/reduction of 3-fluoropyridine **9**.

The ethyl nicotinate also reacts with $BF_3 \cdot OEt_2$ and *o*-TolMgBr·LiCl easily. After the treatment of $NaBH_4$/Py·HCl, the 1,4-dihydropyridine intermediate is reduced to a 1,4,5,6-tetrahydropyridine derivative **15** in 54% yield (Scheme 7). The double bond conjugated to the ester cannot be easily reduced under this condition.



Scheme 7. Preparation of 1,4,5,6-tetrahydropyridine derivative (**15**) from ethyl nicotinate (**14**).

Also, the acidic hydrolysis method developed by Comins can be applied to the BF_3-mediated addition reaction. The methyl 6-methoxynicotinate (**16**) undergoes the addition of $^{i}PrMgCl \cdot LiCl$ with the assistance of $BF_3 \cdot OEt_2$, leading to the 1,4-dihydropyridine intermediate (**17**). After the workup using an aqueous solution of 2 M hydrochloric acid, the carbonyl group is readily unmasked and a γ-lactam type product **18** is obtained almost quantitively (Scheme 8).



16 **17** **18**: 97%

Scheme 8. Preparation of γ-lactam (**18**) from 6-methoxynicotinate (**16**).

4.3 Summary

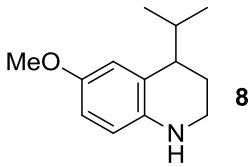
In this chapter, I have described a novel $NaBH_4$-mediated reduction rather than the previously introduced chloranil oxidation for converting the BF_3-attached 1,4-dihydropyridine intermediates to piperidine derivatives. Also, the acidic workup of an addition intermediate bearing a methyl enolate functionality can readily afford a lactam product. Thus, a new category of products can be collected based on these workup methods.

4.4 Experimental Section

4.4.1 General Considerations

All reactions are carried out under argon atmosphere in flame-dried glassware. Syringes which are used to transfer anhydrous solvents or reagents are purged with argon prior to use. THF is continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be pure as determined by ^{1}H-NMR (25 ℃) and capillary GC. Column chromatographical purifications are performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM from Merck). Mass spectra and high resolution mass spectra (HRMS) are recorded using electron ionization (EI) or electrospray ionization (ESI). Grignard reagents are prepared according to the literature.[7] $NaBH_4$ is purchased from Acros. BF_3 OEt_2 is purchased from Acros or Aldrich and distilled before use.

4.4.2 Product Synthesis and Analytical Data



8

4-isopropyl-6-methoxy-1,2,3,4-tetrahydroquinoline (8): A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a 6-methoxyquinoline (**5**, 157 mg, 1.0 mmol) in dry THF (4 mL) and cooled to 0 ℃. BF_3 OEt_2 (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 50 ℃ followed by dropwise addition of a THF solution of ^{i}PrMgCl·LiCl (0.93 mL, 1.29 M, 1.2 mmol),

[7] F. M. Piller, A. Metzger, M. A. Schade, B. A. Hagg, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

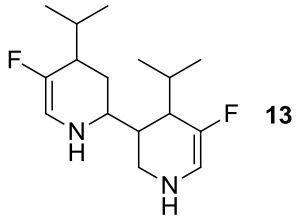
and stirring the reaction mixture at the same temperature for 30 min. A solution of $NaBH_4$ (114 mg, 3.0 mmol in 2 mL MeOH) and a solution of $NH_2OH \cdot HCl$ (348 mg, 5.0 mmol in 2 mL MeOH) are added and the mixture is warmed up to room temperature and continuously stirred for 1 h. Finally, it is quenched with aqueous NaOH solution (1 mL, 1 M) and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:9) furnishing the compound **8** (163 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.65 (d, *J*=2.8 Hz, 1 H), 6.62 - 6.54 (m, 1 H), 6.41 (d, *J*=8.6 Hz, 1 H), 3.71 (s, 3 H), 3.54 (s, 1 H), 3.34 - 3.11 (m, 2 H), 2.57 (q, *J*=6.2 Hz, 1 H), 2.17 - 1.98 (m, *J*=13.3, 6.9, 6.7, 6.7 Hz, 1 H), 1.95 - 1.69 (m, 2 H), 1.00 (d, *J*=6.6 Hz, 3 H), 0.84 (d, *J*=6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.30, 138.98, 125.89, 114.98, 114.79, 112.42, 55.71, 41.94, 40.04, 30.49, 22.88, 21.25, 17.94.

MS (70 eV, EI) *m/z* (%): 205 (34), 162 (100), 147 (14), 131 (15).

HRMS for $C_{13}H_{19}NO$: calcd.205.1467; found 205.1461 (M^+).



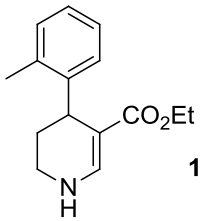
13

5,5'-difluoro-4,4'-diisopropyl-1,1',2,2',3,3',4,4'-octahydro-2,3'-bipyridine (13): A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of a 3-fluoropyridine (**9**, 98 mg, 1.0 mmol) in dry THF (2 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to -50 °C followed by dropwise addition of a THF solution of ^{i}PrMgCl·LiCl (1.55 mL, 1.29 M, 2.0 mmol), and stirring the reaction mixture at the same temperature for 1 h. A solution of $NaBH_4$ (114 mg, 3.0 mmol in 2 mL MeOH) and a solution of $NH_2OH \cdot HCl$ (348 mg, 5.0 mmol in 2 mL MeOH) are added and the mixture is warmed up to room temperature and continuously stirred for 1 h. Finally, it is quenched with aqueous NaOH solution (1 mL, 1 M) and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **13** (60 mg, 42%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.29 - 3.05 (m, 3 H), 2.85 - 2.70 (m, 2 H), 2.49 - 2.12 (m, 3 H), 2.01 (s, 2 H), 1.81 - 1.64 (m, 2 H), 1.50 (dd, *J*=15.5, 10.5 Hz, 2 H), 1.15 - 1.01 (m, 6 H), 0.96 (dd, *J*=8.2, 6.8 Hz, 6 H).

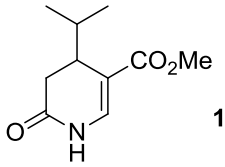
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 99.05, 99.04, 98.92, 98.83, 96.40, 96.38, 96.21, 96.12, 60.77, 60.47, 60.45, 60.15, 56.01, 55.98, 55.78, 55.75, 50.78, 50.76, 47.88, 47.66, 45.18, 45.17, 44.95, 44.94, 43.83, 43.76, 43.52, 43.45, 38.18, 38.14, 38.07, 38.02, 32.49, 32.47, 30.71, 30.60, 27.76, 23.43, 23.39, 23.15, 23.06, 21.98, 21.56.

^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -160.64, -165.83.
MS (70 eV, EI) *m/z* (%): 284 (8), 142 (100), 100 (22).
HRMS for $C_{16}H_{27}N_2F_2$: calcd.285.2137; found 285.2140 ($M+H^+$).



15

ethyl 4-(o-tolyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (15): A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of ethyl nicotinate (**14**, 149 mg, 1.0 mmol) in dry THF (2 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 30 °C followed by dropwise addition of a THF solution of *o*-TolMgBr·LiCl (1.29 mL, 1.16 M, 1.5 mmol), and stirring the reaction mixture at the same temperature for 2 h. A solution of $NaBH_4$ (114 mg, 3.0 mmol in 2 mL MeOH) and a solution of Py·HCl (347 mg, 3.0 mmol in 1 mL MeOH) are added and the mixture is warmed up to room temperature and continuously stirred for 1 h. Finally, it is quenched with aqueous NaOH solution (1 mL, 1 M) and extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:4) furnishing the compound **15** (131 mg, 54%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.74 (d, *J*=6.4 Hz, 1 H), 7.19 - 6.93 (m, 4 H), 4.74 (br. s., 1 H), 4.21 (d, *J*=5.0 Hz, 1 H), 4.00 (q, *J*=7.0 Hz, 2 H), 3.16 - 2.90 (m, 2 H), 2.44 (s, 3 H), 2.00 - 1.81 (m, 1 H), 1.68 (d, *J*=13.0 Hz, 1 H), 1.12 (t, *J*=7.0 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.30, 144.39, 143.53, 134.92, 130.20, 127.59, 125.68, 125.26, 97.31, 58.82, 36.25, 32.39, 26.57, 19.17, 14.37.
MS (70 eV, EI) *m/z* (%): 245 (55), 216 (68), 200 (39), 172 (100), 154 (41).
HRMS for $C_{15}H_{19}NO_2$: calcd.245.1416; found 245.1406 (M^+).



18

methyl 4-isopropyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (18): A dry and argon flushed 10 ml flask, equipped with a magnetic stirring bar and a rubber septum is charged with a solution of methyl 6-methoxynicotinate (**16**, 167 mg, 1.0 mmol) in dry THF (2 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) is added dropwise and stirred for 15 min at the same temperature. The reaction mixture is cooled to - 50 °C followed by dropwise addition of a THF solution of ^{i}PrMgCl·LiCl (0.93 mL, 1.29 M, 1.2 mmol), and stirring the reaction mixture at the same

temperature for 30 min. Then an aqueous HCl solution (1 mL, 2 M) is added and the reaction mixture is warmed up to room temperature, stirring for another 2 h. Finally, it is extracted with EtOAc several times. The organic phases are combined and filtered through a layer of silica gel. The filtrate is concentrated in vacuo. The crude product is purified by flash chromatography (SiO_2, EtOAc/*i*-hexane 1:2) furnishing the compound **18** (192 mg, 97%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.34 (br. s., 1 H), 7.36 (d, *J*=5.5 Hz, 1 H), 3.74 (s, 3 H), 2.86 - 2.72 (m, 1 H), 2.65 - 2.51 (m, 2 H), 1.96 - 1.76 (m, 1 H), 0.93 (d, *J*=6.9 Hz, 3 H), 0.85 (d, *J*=6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.30, 167.02, 135.07, 111.16, 51.49, 36.74, 31.89, 31.12, 19.93, 17.82.

MS (70 eV, EI) *m/z* (%): 198 (12), 155 (100), 123 (40).

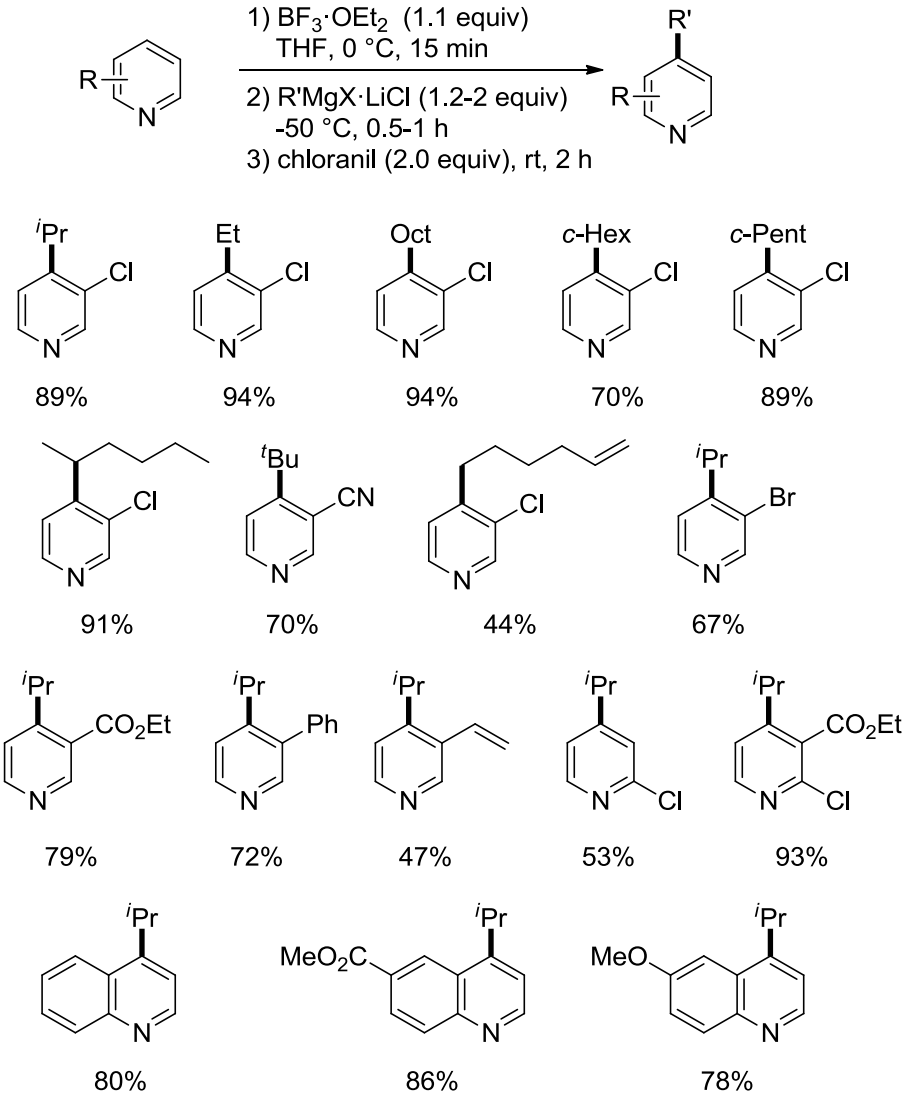
HRMS for $C_{10}H_{15}NO_3$: calcd.197.1052; found 197.1056 (M^+).

Chapter 5. Summary and Outlook

In this thesis, I introduce a series of BF_3-mediated pyridine functionalizations and transformations using organometallic reagents such as Grignard reagents, organozinc and alkynyllithium reagents. The key for the successes of these reactions is the pre-*N*-activation of pyridines by BF_3 OEt_2, which doesn't quench the following added organometallic reagents at low temperature. The main results of this work will be summarized as follows.

5.1 BF_3-Mediated Direct Alkylation of Pyridines using Grignard Reagents

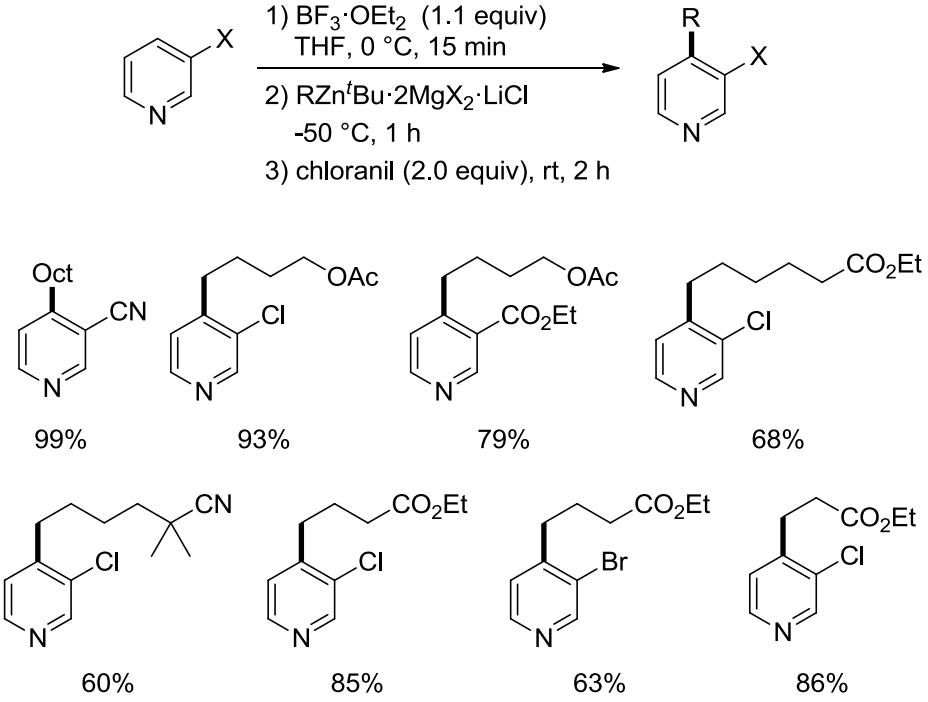
After treatment of BF_3 OEt_2, a variety of alkylmagnesium reagents add regioselectively to the C(4) positions of pyridines and quinolines. Functional groups such as chloro, bromo, vinyl, phenyl, cyano and carbethoxy are tolerated under this condition (Scheme 1).



Scheme 1. BF_3-mediated direct alkylation of pyridines using Grignard reagents.

5.2 BF_3-Mediated Direct Alkylation of Pyridines using Organozinc Reagents

With the assistance of a non-transferable ligand, the in-situ prepared dialkylzinc species react with pyridine derivatives smoothly in the presence of $BF_3 \cdot OEt_2$. After the formal cross-coupling reactions, the alkyl groups with functionalities such as acetoxy, nitro and carbethoxy are introduced to the position 4 of pyridines (Scheme 2).

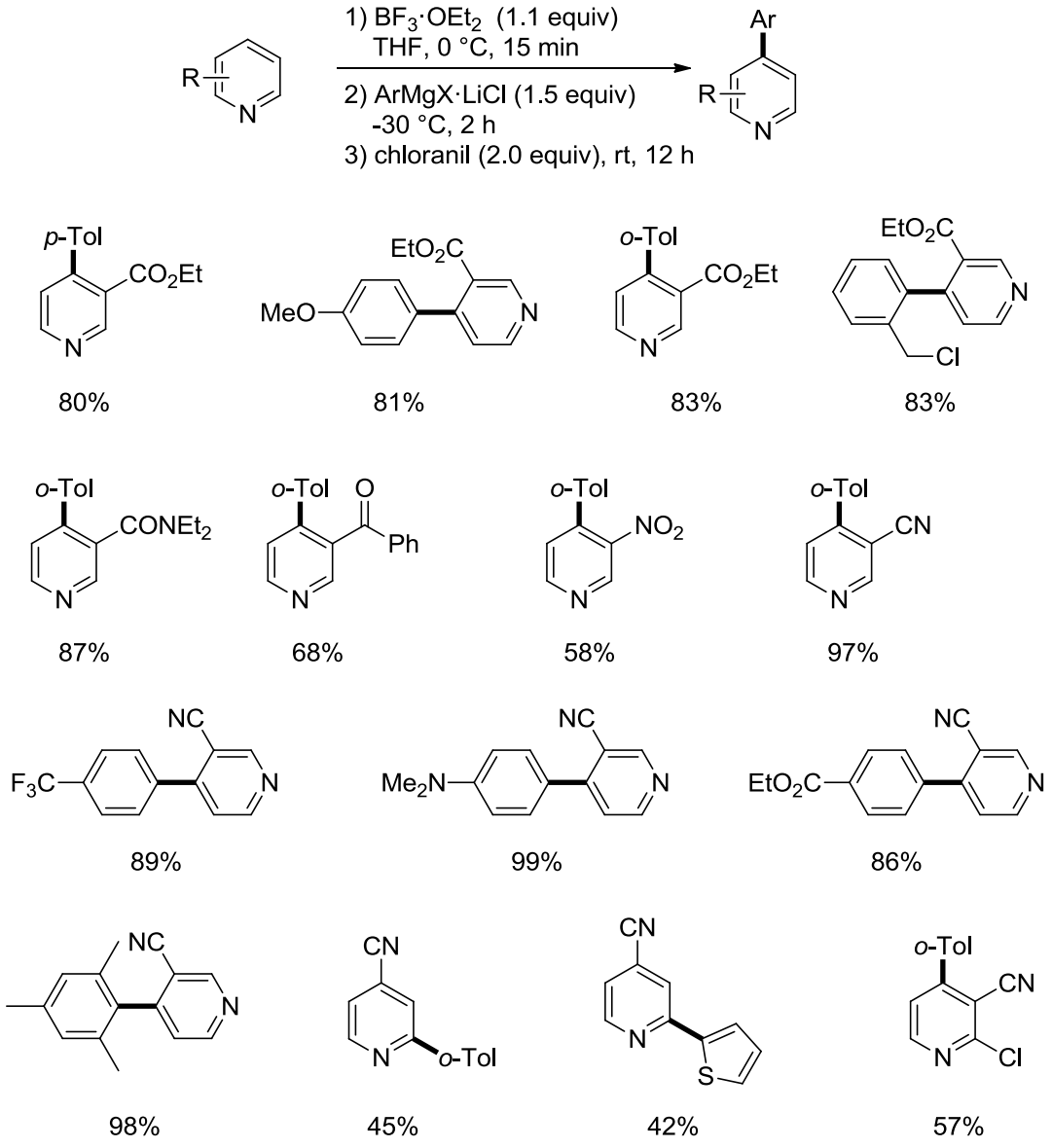


Scheme 2. BF_3-mediated direct alkylation of pyridines using organozinc reagents.

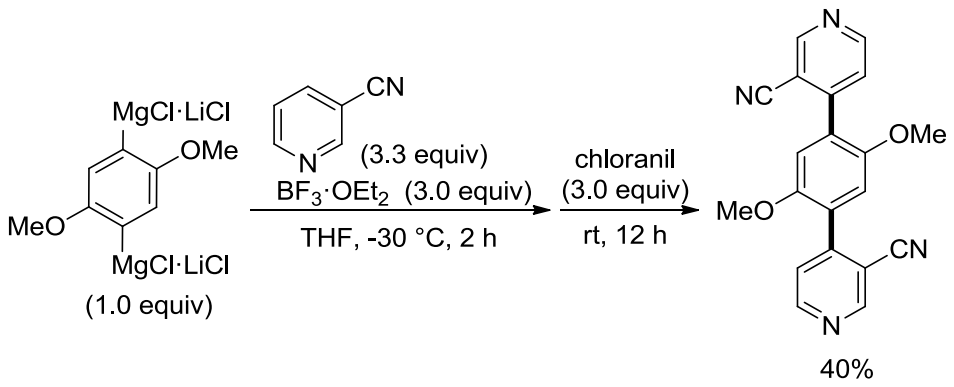
5.3 BF_3-Mediated Direct Arylation of Pyridines using Grignard Reagents

Also, the same strategy can be applied to the cross-coupling between pyridines and arylmagnesium species, which have good functional group tolerance. Thus, the functional pyridine substrates such as nicotinonitrile, nicotinamide and 3-nitropyridine works well with functional aryl or heteroaryl Grignard reagents, affording the cross-coupling products in good yield (Scheme 3).

With the aid of $BF_3 \cdot OEt_2$, a dimagnesiated species reacts with two equivalents of nicotinonitrile and affords a fluorescent compound in one step (Scheme 4).



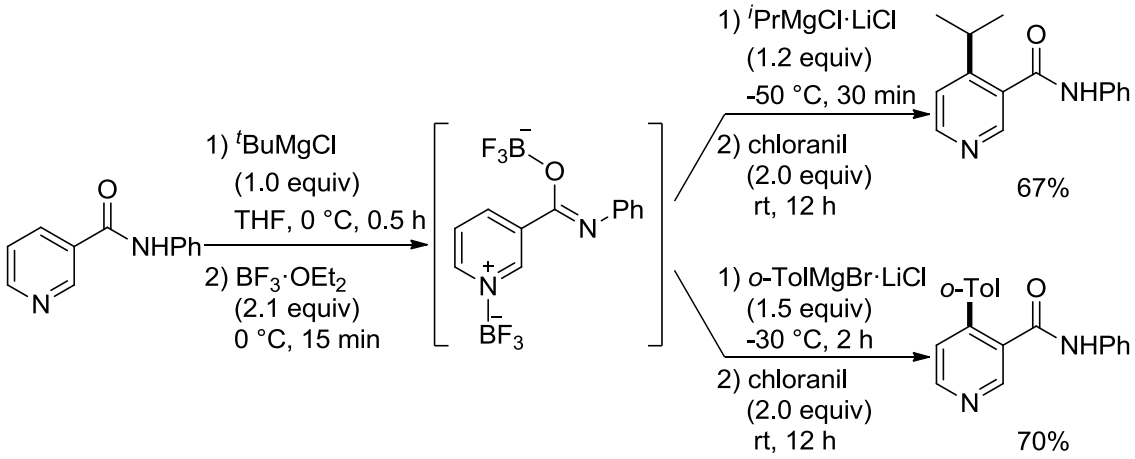
Scheme 3. BF_3-mediated direct arylation of pyridines using Grignard reagents.



Scheme 4. Double addition to nicotinonitriles using a 1,4-dimagnesiated aromatic reagent.

5.4 BF_3-Mediated Direct Alkylation and Arylation of Nicotinamide using Grignard Reagents

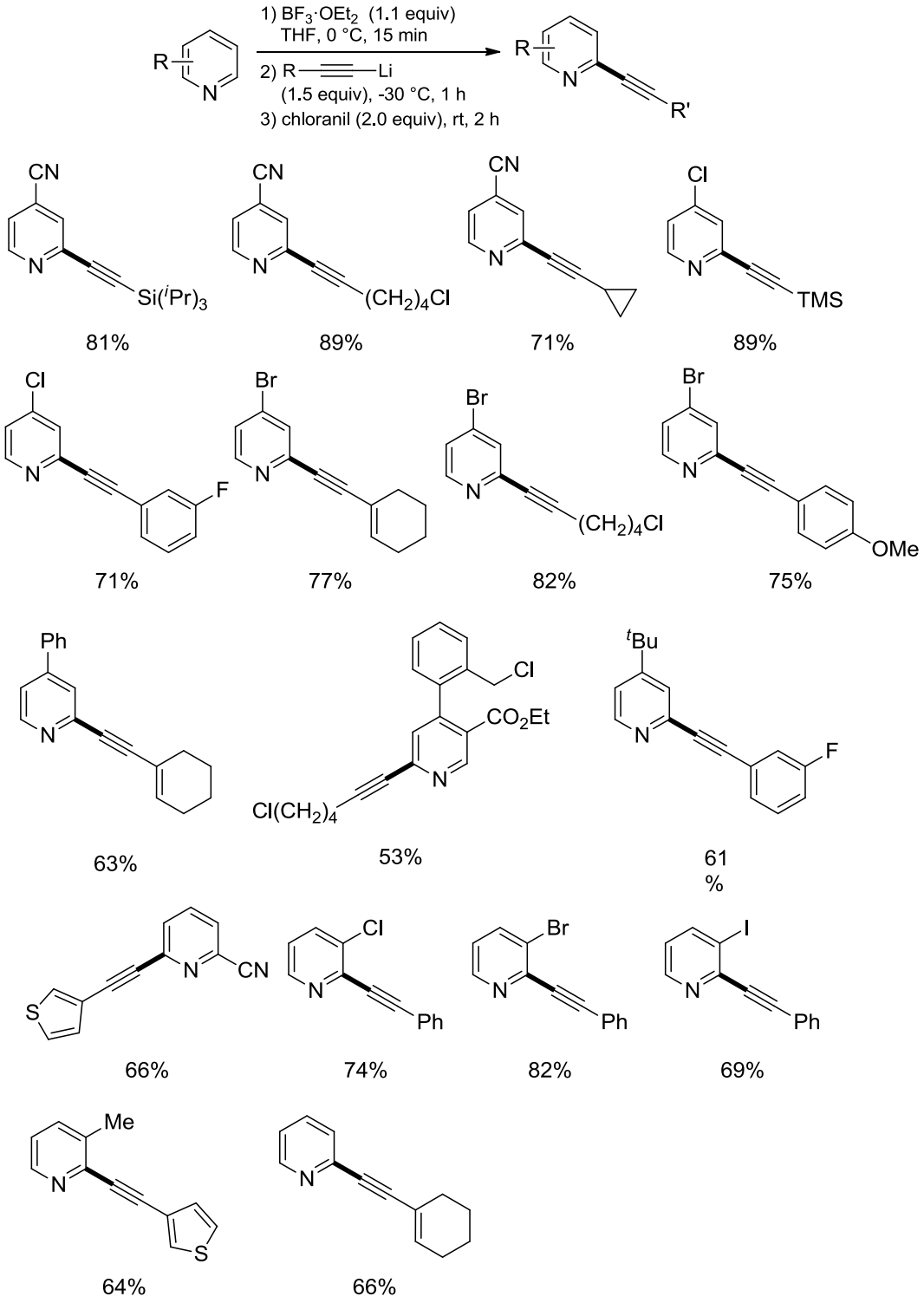
The regioselective direct functionalization of nicotinamides is not easy. After the addition of an equivalent of ^{t}BuMgCl for the deprotonation of the amide nitrogen and two equivalents of $BF_3 \cdot OEt_2$ for activation and protection, a tentative intermediate is produced. Both alkyl and aryl Grignard reagents react readily with it and the desired products are obtained in good yields (Scheme 5).



Scheme 5. BF_3-Mediated direct alkylation and arylation of nicotinamide using Grignard reagents.

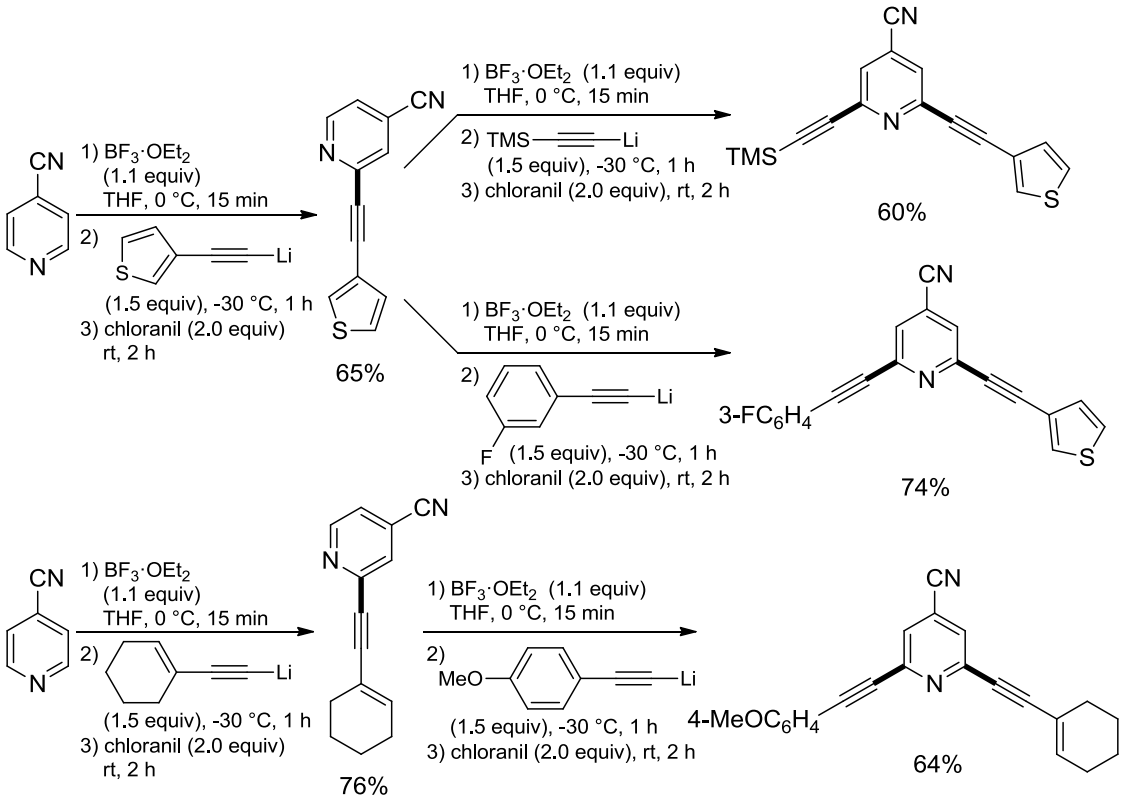
5.5 BF_3-Mediated Direct Alkynylation of Pyridines using Alkynyllithiums

With the assistance of $BF_3 \cdot OEt_2$, the pyridine substrates also react with alkynyllithium reagents which are readily prepared by deprotonation of terminal alkynes using ^{n}BuLi. This time the addition selectively occurs at C(2) of the pyridine ring with a variety of alkynyllithiums bearing an alkyl, aryl, silyl or alkenyl substituent (Scheme 6).



Scheme 6. BF_3-mediated direct alkynylation of pyridines using alkynyllithiums.

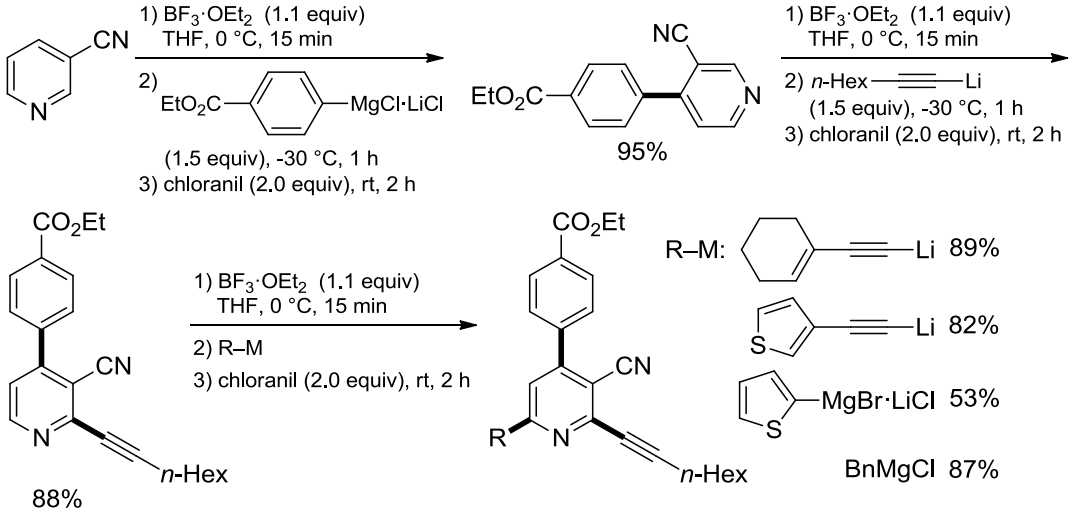
Besides, a double functionalization at positions 2 and 6 of pyridines can be readily achieved by introducing different alkynyl groups one by one (Scheme 7).



Scheme 7. BF_3-mediated direct alkynylation leading to the preparation of 2,4,6-trisubstituted pyridines.

5.6 Successive functionalization of the pyridine core using BF_3-mediated oxidative cross-couplings

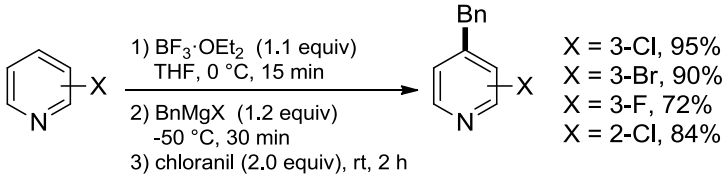
The polyfunctionalization of a pyridine derivative can be achieved through a series of BF_3-mediated oxidative cross-couplings (Scheme 8).



Scheme 8. Successive functionalization of the pyridine core using BF_3-mediated oxidative cross-couplings.

5.7 BF_3-Mediated Direct Benzylation of Pyridines using Benzylmagnesium Reagent

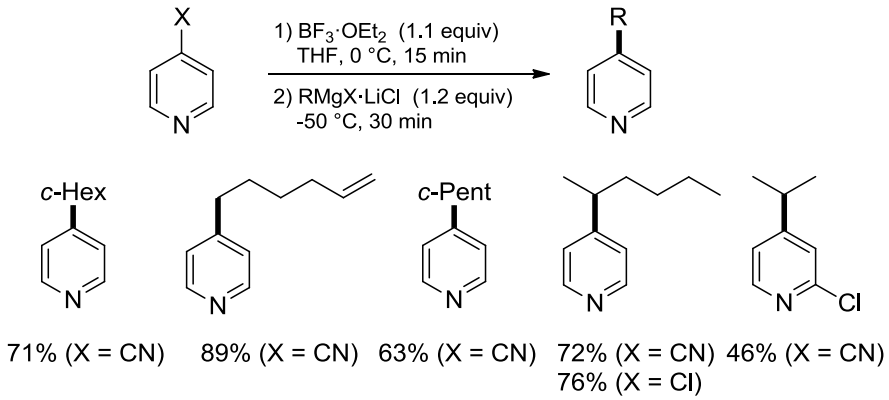
The benzylation works on the BF_3-activated pyridines using benzylmagnesium reagents. The 4-benzylated pyridines were obtained in good yields (Scheme 9).



Scheme 9. BF_3-mediated direct benzylation of pyridines using benzylmagnesium reagents.

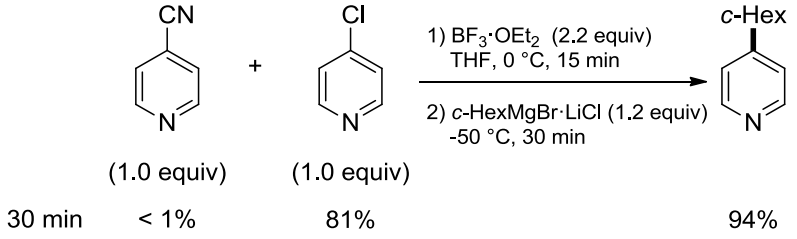
5.8 BF_3-Mediated Cross-Couplings between 4-Substituted Pyridines and Grignard Reagents

Moreover, we developed a novel transition-metal-free cross-coupling between alkylmagnesium reagents and 4-substituted pyridines such as isonicotinonitrile and 4-chloropyridine employing BF_3 OEt_2 as a promoter (Scheme 10).



Scheme 10. BF_3-mediated cross-couplings between 4-substituted pyridines and Grignard reagents.

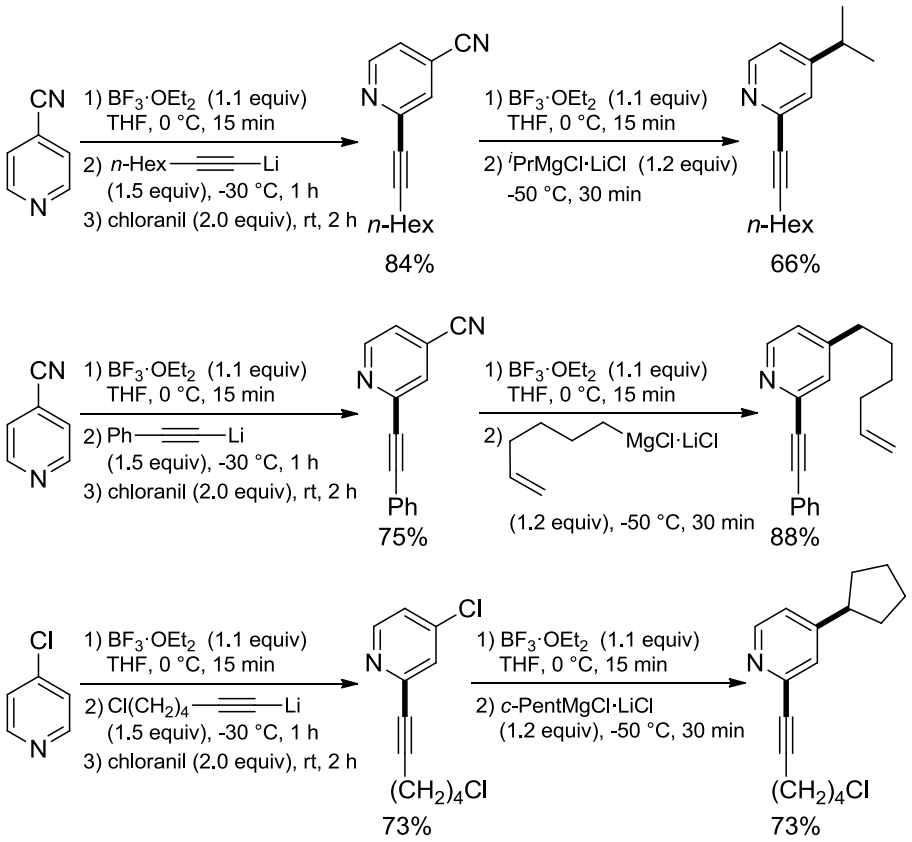
In a competition experiment, it is indicated that the cyano is a better leaving group than chloro under this transition-metal-free condition (Scheme 11).



Scheme 11. BF_3-mediated competition cross-coupling.

5.9 Consecutive BF_3-Mediated Alkynylation and Substitution

The combination of the oxidative and non-oxidative cross-couplings enabled us to efficiently prepare a broad range of 2,4-disubstituted pyridines (Scheme 12).

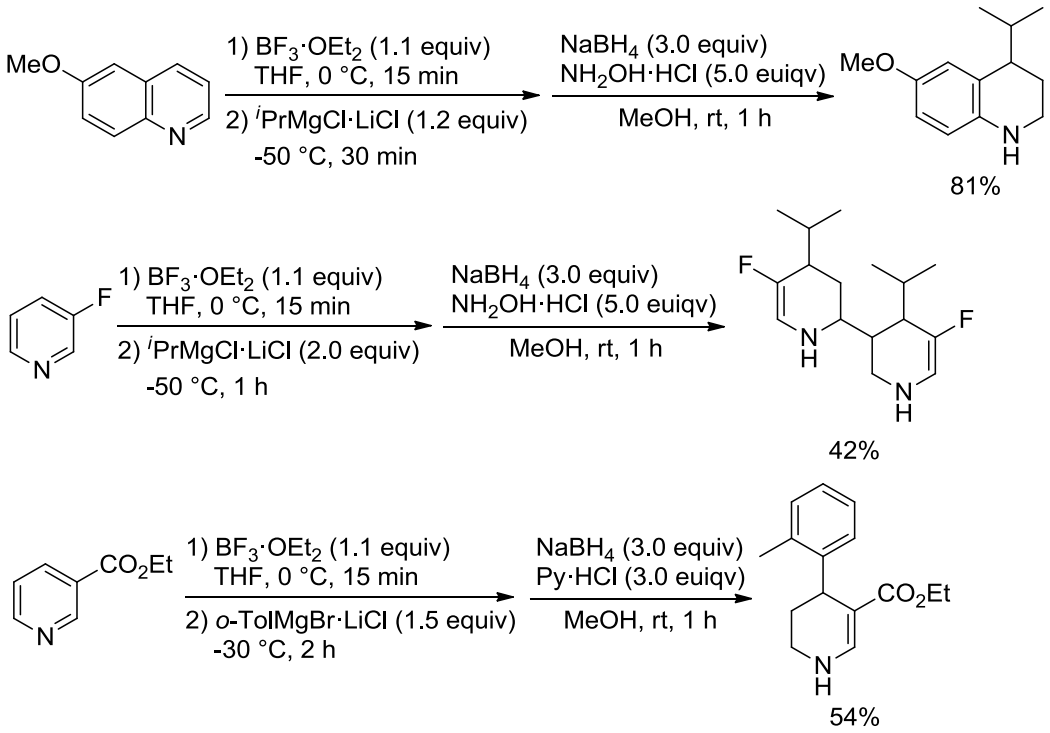


Scheme 12. Consecutive BF_3-mediated alkynylation and substitution for the preparation of 2,4-disubstituted pyridines.

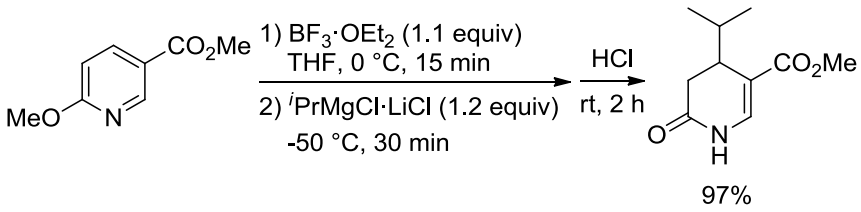
5.10 BF_3-Mediated Addition/Reduction or Hydrolysis for Preparing Piperidines

Under acidic reductive conditions, the intermediates formed by BF_3-mediated additions are converted to piperidine derivatives (Scheme 13).

Besides, if the addition intermediate with a methyl enolate moiety is treated with acid, the hydrolysis will occur, resulting in the formation of a γ-lactam derivative (Scheme 14).



Scheme 13. BF_3-mediated conversion of pyridines to piperidines through a reductive workup.



Scheme 14. BF_3-mediated addition/acidic hydrolysis for preparing γ-lactam.

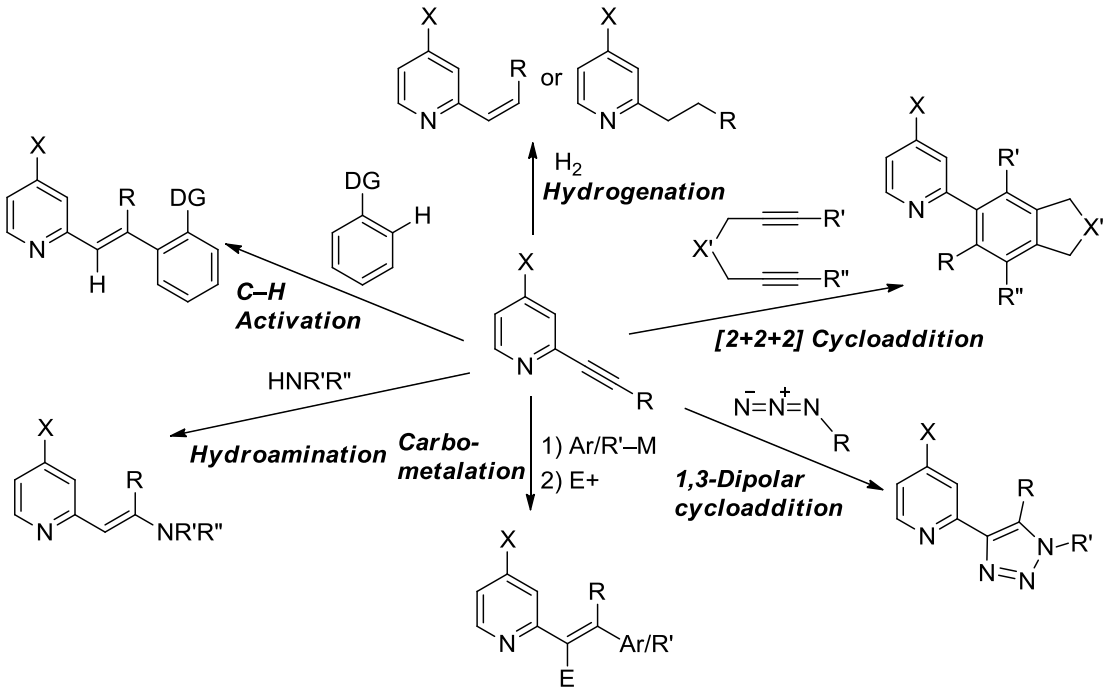
5.11 Outlook

As a main task of the next stage, the oxidation step of BF_3-mediated oxidative cross-couplings should be optimized. During the reported workup procedure, chloranil produces a lot of waste and dirties, leading to the difficulties in product purification. It would be nice to replace chloranil with another mild and clean oxidant, such as oxygen, which is beneficial for a large scale manipulation.

Also, the BF_3-mediated benzylation has just been briefly studied. More efforts are necessary in this area, and it is promising to employ highly functional benzyl organometallic reagents as the coupling partner.

The piperidine synthesis should also be carefully studied in the future. The scope of substrates is still narrow right now. An efficient and transition-metal-free methodology for preparing bio-active piperidines such as natural products and medicines will be very attractive to the pharmaceutical industry.

Finally, because of the already well-developed alkyne chemistry, the easily prepared 2-alkynylpyridines can undergo a variety of reactions such as hydrogenation, cycloaddition, carbometalation, hydroamination and C–H activation to obtain more complex molecules (Scheme 15).



Scheme 15. Further transformations of 2-alkynylpyridines prepared by BF_3-mediated pyridine alkynylation.

List of Abbreviations

Ac	acetyl
Alk	alkyl
aq.	aqueous
Ar	aryl
br	broad (NMR)
Bu	butyl
cal.	calculated
conc.	concentrated
d	doublet (NMR)
dist.	distilled
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
equiv	equivalent
E	electrophile
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
FLP	frustrated Lewis pair
GC	gas chromatography
h	hour
Hal	halogen
Het	hetero
Hex	hexyl
HRMS	high resolution mass spectroscopy
HSAB	hard and soft acids and bases

Hz	Hertz
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
L	ligand
LA	Lewis acid
LB	Lewis base
Py	pyridine
M	mol/L
m	*meta*
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
MHz	Megahertz
^{n}Bu	*n*-butyl
^{n}Pr	*n*-propyl
nd	not detected
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride
Ph	phenyl
ppm	parts per million
Py	pyridyl
R	organic substituent/alkyl
sat.	saturated
^{t}Bu	*tert*-butyl
T	temperature
t	reaction time

TLC	thin layer chromatography
Tf	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl/tetramethylsilane
Tol	tolyl
Ts	4-toluenesulfonyl
TP	typical procedure

Curriculum Vitae

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PERSONAL INFORMATION:

Date of Birth	08.03.1985
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Marital Status	Married since July 2012

LANGUAGES:

Chinese (native), English (fluent), Japanese (intermediate), German (elementary)

EDUCATION:

Ph.D., Chemistry (Prof. Paul Knochel) Since Jun. 2011

Department of Chemistry, Ludwig-Maximilians-Universität, Munich, Germany

M.S., Chemistry (Prof. Eiichi Nakamura) Sep. 2010

Department of Chemistry, School of Science, The University of Tokyo, Tokyo, Japan

Thesis Tile: "Cobalt-Catalyzed Direct Arylation and Alkylation of Aromatic C–H Bond"

B.S., Chemistry (Prof. Liangbing Gan) Jul. 2007

College of Chemistry and Molecular Engineering, Peking University, Beijing, China

Thesis Title: "Synthesis of Aza[60]fullerene"

RESEARCH EXPERIENCE:

2011.6-present ***Knochel Group, Ludwig-Maximilians-Universität***

Group Leader: Prof. Paul Knochel

Developing BF_3-mediated regioselective direct functionalizations of pyridines using organometallic reagents.

2008.10-2011.5 ***Nakamura Group, The University of Tokyo***

Group Leader: Prof. Eiichi Nakamura

Research of iron- and cobalt-catalyzed directed arylation and alkylation reactions between aromatic C–H bonds and alkyl halides, Grignard reagents and olefins, under mild conditions.

2008.4-2008.9 ***ERATO Nakamura Functional Carbon Cluster Project***

Project Leader: Prof. Eiichi Nakamura

Preparation of C_{60} and C_{70} multi adducts which are applied for OPV.

2005.7-2008.3 ***Gan Group, Peking University***

Group Leader: Prof. Liangbing Gan

Preparation of azafullerene derivatives.

SOCIETY ACTIVITY:

5.2010-5.2011 Secretary General of Peking University Alumni Association in Japan

PUBLICATIONS:

Chen, Q.; León, T.; Knochel, P. "Transition-Metal-Free BF_3-Mediated Oxidative and non-Oxidative Cross-Couplings of Pyridines" *Angew. Chem. Int. Ed.*DOI: 10.1002/anie.201400750.

Chen, Q.; Mollat du Jourdin, X.; Knochel, P. "Transition-Metal-Free BF_3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines using Grignard or Organozinc Reagents" *J. Am. Chem. Soc.* **2013**, 135, 4958–4961.

Ilies, L.; Konno, E.; **Chen, Q.**; Nakamura, E. "Iron-Catalyzed *ortho* Monoarylation of Benzamide Derivatives" *Asian J. Org. Chem.* **2012**, *1*, 142–145.

Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. "Cobalt-Catalyzed Coupling of Alkyl Grignard Reagent with Benzamide and 2-Phenylpyridine Derivatives through Directed C–H Bond Activation under Air" *Org. Lett.*, **2011**, *13*, 3232–3234.

Ilies, L.; **Chen, Q.**; Zeng, X.; Nakamura, E. "Cobalt-Catalyzed Chemoselective Insertion of Alkene into the *ortho*-C–H Bond of Benzamide" *J. Am. Chem. Soc.* **2011**, *133*, 5221-5223.

Chen, Q.; Ilies, L.; Nakamura, E. "Cobalt-Catalyzed *ortho*-Alkylation of Secondary Benzamide with Alkyl Chloride through Directed C−H Bond Activation," *J. Am. Chem. Soc.* **2011**, *133*, 428–429.

Zhang, G.; Huang, S.; Xiao, Z.; **Chen, Q.**; Gan, L.; Wang, Z. "Preparation of Azafullerene Derivatives from Fullerene-Mixed Peroxides and Single Crystal X-ray Structures of Azafulleroid and Azafullerene," *J. Am. Chem. Soc.* **2008**, *130*, 12614–12615.

MEETINGS:

Chen, Q.; Yamakawa, K.; Yoshikai, N.; Nakamura, E. "Cobalt-Catalyzed Direct Arylation of 2-Arylpyridine Derivatives," The 89th CSJ Annul Meeting, 2–F2–29, Tokyo, March 2009.

Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. "Cobalt-Catalyzed Direct Alkylation of Benzamide and 2-Arylpyridine Derivatives," The 90th CSJ Annul Meeting, 2–F1–01, Osaka, March 2010.

OMCOS 16:16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Shanghai, July 24–28, 2011.