BF_3-Mediated Coupling

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Transition-Metal-Free BF_3-Mediated Oxidative and Non-Oxidative Cross-Coupling of Pyridines**

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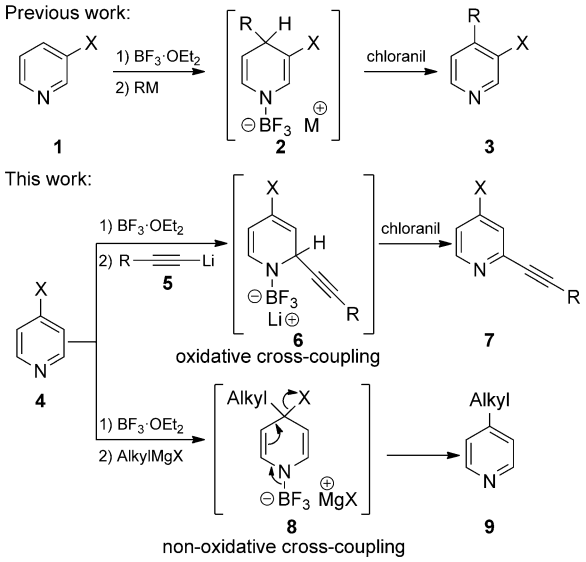
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *We report a BF_3-mediated direct alkynylation of pyridines at C(2) by using a variety of alkynyllithium reagents (oxidative cross-coupling). Moreover, we have developed a novel transition-metal-free cross-coupling method between alkylmagnesium reagents and 4-substituted pyridines, such as isonicotinonitrile and 4-chloropyridine, by employing $BF_3{\cdot}OEt_2$ as a promoter. The combination of these methods enabled us to efficiently prepare a range of di-, tri-, and tetrasubstituted pyridines.*

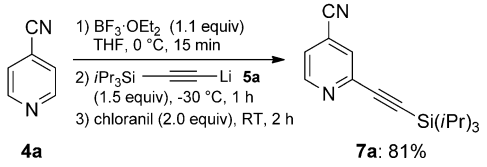
Functionalization of the pyridine scaffold is an important synthetic task, since polyfunctional pyridines are widely used for pharmaceutical and biological applications.[1] Transition-metal-catalyzed cross-coupling methods have been used extensively to functionalize the pyridine skeleton.[2,3] However, the use of Pd or Ni catalysts has some drawbacks, such as the toxicity or price of the metal and the need for ligands. Recently, we reported that 3-substituted pyridines of type **1** undergo BF_3-mediated[4] oxidative cross-coupling reactions[5,6] at position 4 with various alkyl- and arylmagnesium or -zinc reagents to give 3,4-disubstituted pyridines of type **3** via a tentative intermediate of type **2** (Scheme 1).[7] These reactions are remarkably regioselective and proceed almost only at position 4. We wondered which reaction course would be observed if position 4 of the pyridine ring was occupied by a substituent. Herein, we report 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 atom with BF_3 makes positions 2, 4, and 6 of the pyridine ring especially electrophilic, thus favoring the formation of new carbon–carbon bonds 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 doesn't require either an oxidative step or a transition-metal catalyst but proceeds through an addition-elimination step mediated by $BF_3{\cdot}OEt_2$. This method allows the direct substitution of X (X = CN, Cl) in pyridines of type **4** with various alkyl groups from Grignard reagents via the tentative intermediate **8** to afford products of type **9**.[8] We will demonstrate that these new reactions allow a convenient functionalization of the pyridine scaffold to obtain various di-, tri-, and tetrasubstituted pyridines.[9]



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

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



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

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Under these conditions, a variety of 4-substituted pyridines (**4**; X = CN, Cl, Br, Ar, or R) react with various alkynyllithium compounds[10] bearing an alkyl (**5b** and **5c**), aryl (**5e** and **5g**), silyl (**5d**), or alkenyl substituent (**5f**) to afford the expected functionalized pyridines **7b–k** in yields of 53–89% (Table 1, entries 1–10). No coupling product **7b** was detected in the absence of $BF_3{\cdot}OEt_2$ (Table 1, entry 1). Notably, the presence of an electron-withdrawing substituent at position 4 is not required, and an aryl or a *tert*-butyl substituent at position 4 lead to the expected products **7i–k** in yields of 53–63% (Table 1, entries 8–10). In the case of **4e**, the addition occurs at position 6 (rather than at position 2) as a result of the steric hindrance of the carbethoxy group. In the absence of a substituent at position 4, we still observed a reaction at positions 2 or 6. Thus, 2-cyanopyridine (**10a**) reacts with the alkynyllithium compound **5h** at position 6 to furnish the 2,6-disubstituted pyridine **11** in 66% yield. When electron-withdrawing substituents are present at position 3, a smooth alkynylation occurs at position 2 to give the 2,3-disubstituted pyridines **12a–c** in yields of 69–82% (Table 1, entries 12–14).[11] The coupling reaction also proceeds well when electron-rich 3-picoline (**1d**) is used as the substrate, yet surprisingly it takes place at the more crowded C(2)-position and a 2,3-disubstituted product (**12d**) is obtained (Table 1, entry 15). Even pyridine itself (**13**) undergoes the coupling reaction with the lithium reagent **5f** and gives 2-substituted product **14** in 66% yield (Table 1, entry 16).

A double functionalization at positions 2 and 6 can also be readily achieved. Thus, isonicotinonitrile (**4a**) is alkynylated at position 2 by our standard procedure, which results in the formation of **7l** and **7m** in yields of 65 and 76%, respectively. The addition of a second alkynyllithium reagent in the presence of $BF_3{\cdot}OEt_2$ followed by oxidative rearomatization furnishes

Table 1: Direct alkynylation of pyridine derivatives using various alkynyllithium compounds.

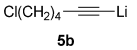
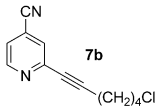
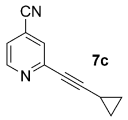
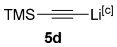
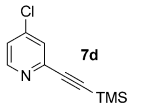
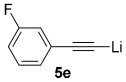
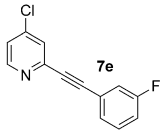
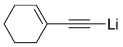
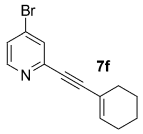
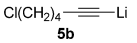
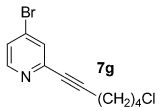
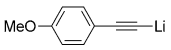
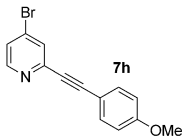
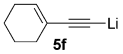
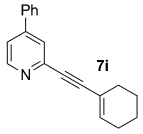
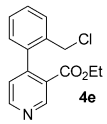
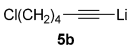
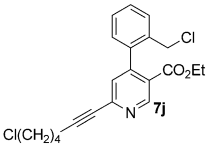
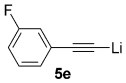
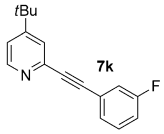
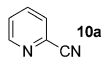
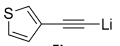
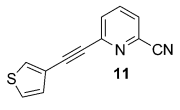
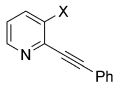
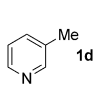
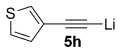
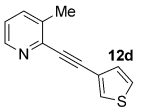
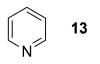
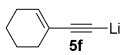
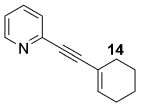
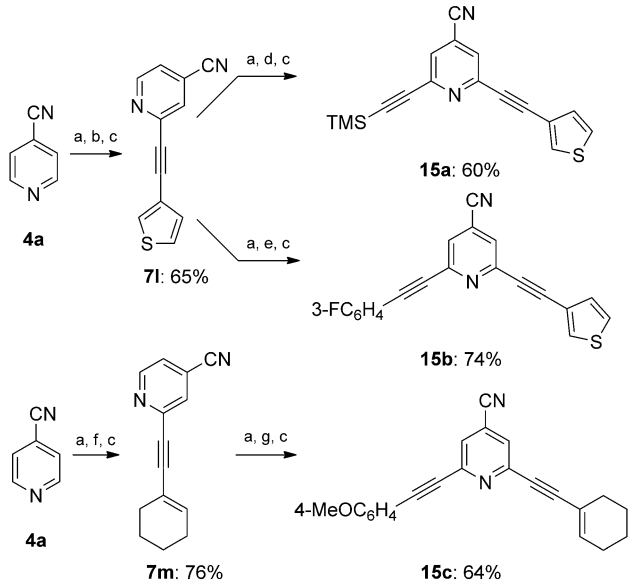
Entry	Substrate	Alkinyllithium reagent	Product	Yield [%][a]
1	 **4a**	 **5b**	 **7b**	89 (0)[b]
2	 **4a**	 **5c**	 **7c**	71
3	 **4b**	 **5d**	 **7d**	89[c]
4	 **4b**	 **5e**	 **7e**	71
5	 **4c**	 **5f**	 **7f**	77
6	 **4c**	 **5b**	 **7g**	82
7	 **4c**	 **5g**	 **7h**	75
8	 **4d**	 **5f**	 **7i**	63
9	 **4e**	 **5b**	 **7j**	53
10	 **4f**	 **5e**	 **7k**	61
11	 **10a**	 **5h**	 **11**	66
12 13 14	 **1a**: X = Cl **1b**: X = Br **1c**: X = I	 **5i**	 **12a**: X = Cl **12b**: X = Br **12c**: X = I	74 82 69

Table 1: (Continued)

Entry	Substrate	Alkinyllithium reagent	Product	Yield [%][a]
15	 **1d**	 **5h**	 **12d**	64
16	 **13**	 **5f**	 **14**	66

[a] Yields of isolated, analytically pure products. [b] Reaction performed in the absence of $BF_3{\cdot}OEt_2$. [c] TMS = trimethylsilyl.



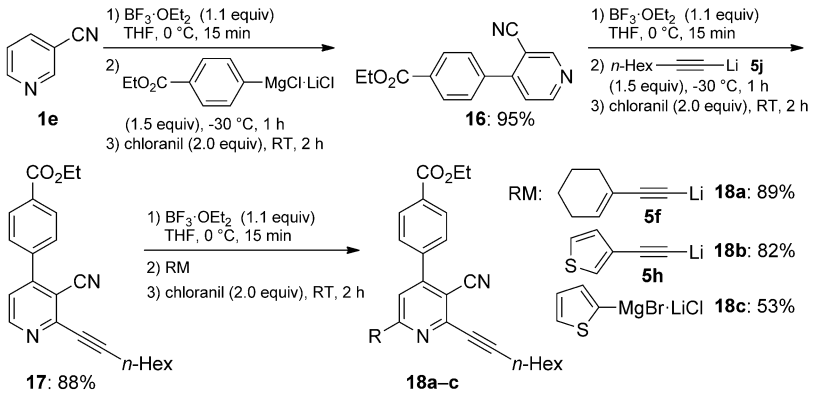
Scheme 3. BF_3-mediated direct alkynylation leading to the preparation of 2,4,6-trisubstituted pyridines. Reaction conditions: a) $BF_3{\cdot}OEt_2$ (1.1 equiv, THF, 0 °C, 15 min); b) **5h** (1.5 equiv, −30 °C, 1 h); c) chloranil (2.0 equiv, 25 °C, 2 h); d) **5d** (1.5 equiv, −30 °C, 1 h); e) **5e**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

the 2,4,6-trisubstituted pyridines (**15a–c**) in yields of 60–74% (Scheme 3).

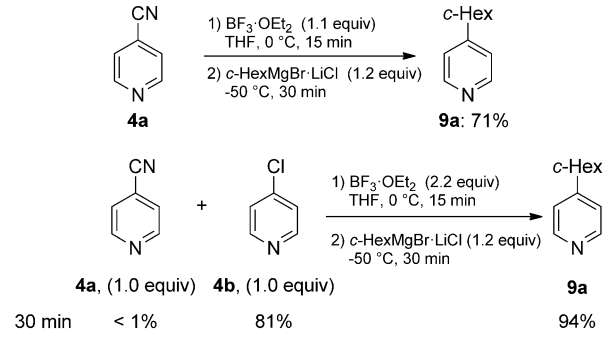
Moreover, highly functionalized tetrasubstituted pyridines were obtained from nicotinonitrile (**1e**) by a sequence of several oxidative cross-coupling reactions. The first carbon–carbon bond formation occurs at position 4 as expected,[7] which leads to the disubstituted pyridine **16** in 95% yield. Positions 2 and 6 of **16** can be readily differentiated since the cyano group strongly activates position 2. Therefore, the addition of the alkynyllithium reagent **5j** in the presence of $BF_3{\cdot}OEt_2$ produces only the 2,3,4-trisubstituted pyridine **17** in 88% yield after treatment with chloranil. Finally, a range of organometallic reagents such as alkynyllithium compounds **5f** and **5h** or 2-thienylmagnesium halide undergo an oxidative cross-coupling at position 6 to afford the tetrasubstituted pyridines **18a–c** in yields of 53–89% (Scheme 4).

Treating isonicotinonitrile (**4a**) in the presence of $BF_3{\cdot}OEt_2$ with an alkylmagnesium reagent complexed with lithium chloride instead of an alkynyllithium resulted in 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) to afford the 4-substituted pyridine **9a** in 71% yield (Scheme 5).

The BF_3-mediated cross-coupling can be extended to various primary and secondary organomagnesium reagents to afford the 4-substituted pyridines **9b–e** in 46–89% yield (Table 2). The substitution does not occur without the assistance of $BF_3{\cdot}OEt_2$ (Table 2, entry 1). Interestingly, 2-chloro-4-cyanopyridine (**19**), 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 to give chloropyridine **9e** as the only detectable product in 46% yield (Table 2, entry 4). To evaluate the difference in reactivity between a chloro and a cyano substituent in such BF_3-mediated cross-coupling reactions, 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, and leads 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 5). 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]

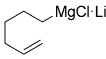
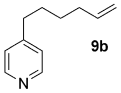
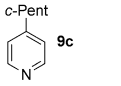
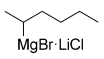
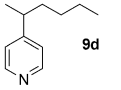
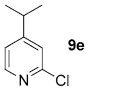


Scheme 4. BF_3-mediated polyfunctionalization of nicotinonitrile (**1e**) for the preparation of 2,3,4,6-tetrasubstituted pyridines.



Scheme 5. 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.

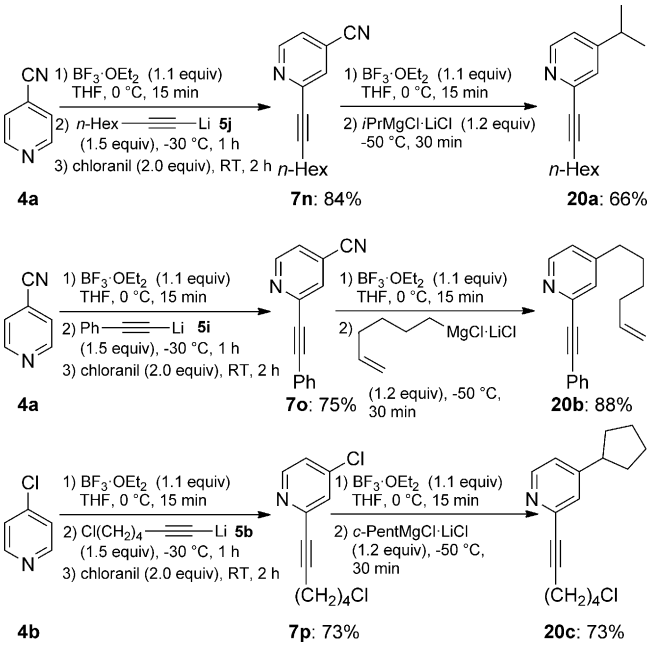
Table 2: Non-oxidative cross-coupling of isonicotinonitrile (**4a**) or 4-chloropyridine (**4b**) using Grignard reagents.

Entry	Substrate	Grignard reagent	Product	Yield [%][a]
1	 **4a**		 **9b**	89(0)[b]
2	 **4a**	*c*-PentMgCl·LiCl	 **9c**	63
3	 **4a**		 **9d**	72(76)[c]
4	 **19**	*i*PrMgCl·LiCl	 **9e**	46

[a] Yields of isolated, analytically pure products. [b] Reaction performed in the absence of BF_3·OEt_2. [c] 4-Chloropyridine (**4b**) was used as the substrate.

To demonstrate the versatility of our methods we have combined the two new functionalization procedures of pyridines (oxidative and non-oxidative cross-coupling reactions) to produce various 2,4-disubstituted pyridines of type **20**. Thus, isonicotinonitrile (**4a**) and 4-chloropyridine (**4b**) were treated with the alkynyllithium reagents **5b**,**j**,**i** in the presence of BF_3·OEt_2, which led after oxidative workup with chloranil to the 2-alkynylated pyridines **7n–p** in yields of 73–84%. After these oxidative cross-coupling reactions, we performed a BF_3-mediated cross-coupling with various alkylmagnesium reagents, which afforded the 2,4-disubstituted pyridines **20a–c** in yields of 66–88% by substitution of the chloro or cyano substituent (Scheme 6). Interestingly, the 2,6-dialkynylisonicotinonitriles **15a–c** (Scheme 3) do not undergo these cross-coupling reactions and only starting materials are recovered, thus indicating that the complexation of BF_3 at the pyridine nitrogen atom (and not at the cyano nitrogen atom) is crucial for the success of this substitution reaction.

In summary, we have developed two new functionalization procedures for pyridines. The oxidative cross-coupling



Scheme 6. Consecutive BF_3-mediated alkynylation and substitution for the preparation of 2,4-disubstituted pyridines.

proceeds with alkynyllithium reagents and affords 2- or 6-substituted pyridines after oxidative rearomatization. On another 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. Extension to other N-heterocycles and applications to the synthesis of natural products is currently underway.

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[10] The alkynyllithium compounds were prepared by the reaction of the corresponding alkynes with *n*BuLi; for more details, see the Supporting Information.

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

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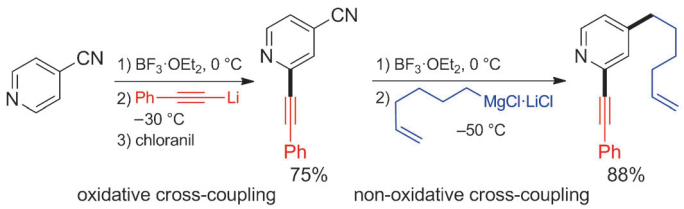
Communications

BF_3-Mediated Coupling

Q. Chen, T. León,
P. Knochel* _____ ■■■■–■■■■

Transition-Metal-Free BF_3-Mediated Oxidative and Non-Oxidative Cross-Coupling of Pyridines



Oxidative or non-oxidative—That is the question! Pyridines bearing a substituent at position 4 readily undergo a BF_3-mediated oxidative coupling at position 2 with a wide range of alkynyllithium compounds. In contrast, 4-cyano- or 4-chloropyridines undergo a novel BF_3-mediated cross-coupling at position 4 with alkylmagnesium reagents. The combination of the two transition-metal-free procedures allows the preparation of a broad range of pyridines.