Arylation Reactions

DOI: 10.1002/anie.201103074

Lewis Acid Promoted Benzylic Cross-Couplings of Pyridines with Aryl Bromides**

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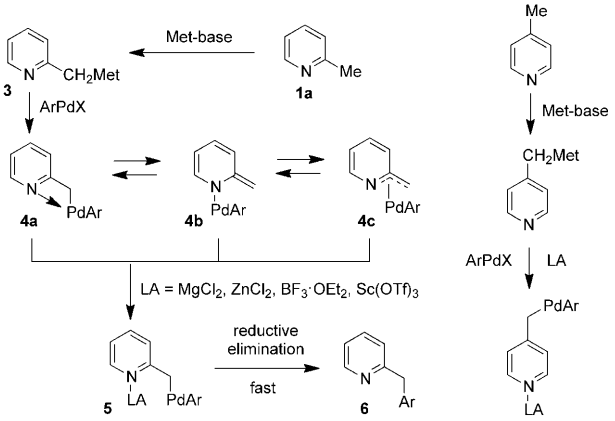
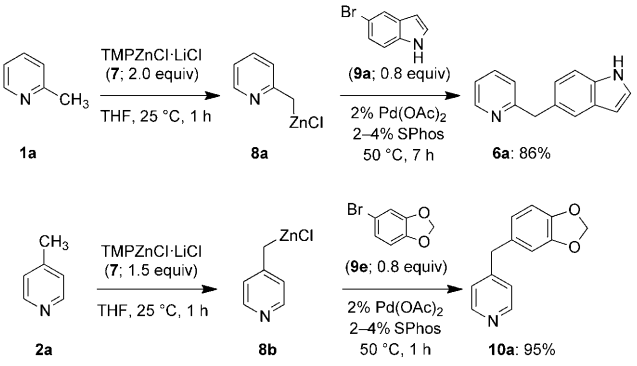
The functionalization of pyridines and related heterocycles is very important because of their biological properties and relevance to material science.[1] The benzylic arylation of pyridines, in particular, is a challenging synthetic problem. Palladium-catalyzed arylations of 2-picoline involving direct C–H activation[2] have no generality, and only few examples have been reported. Thus, azaarenes bearing electron-withdrawing groups may be arylated at 100 °C with a Pd catalyst.[3] Several alternative procedures involving the fragmentation of a 2-(2-pyridyl)ethanol,[4] the arylation of *N*-oxides,[5] and *N*-iminopyridinium ylides[6] have been described. These methods, although displaying generality, require modified N-heterocyclic precursors.[4–6] In addition, whereas 2-picoline (**1a**) can be functionalized in this way, the arylation of 4-picoline (**2a**) has not been described. The difficulty in forming a new carbon–carbon bond with metalated 2-picoline (**3**; or 4-picoline) may be due to the nature of the palladium complexes[7] (**4a–c**) resulting from the reaction with ArPdX (Scheme 1). We anticipate that all of these possible structures are reluctant to undergo a reductive elimination because of the chelation of the heterocyclic nitrogen with the Pd center. Hartwig and co-workers have already shown that palladium-catalyzed aminations are accelerated by a Lewis acid (BEt_3).[8] Nolan and co-workers have also reported that reductive eliminations of Pd complexes are accelerated by $AlCl_3$.[9]

We envisioned that the presence of an appropriate Lewis acid (LA) complexing the nitrogen atom of the heterocycle may lead to a new Pd intermediate such as **5**, which would then undergo fast reductive elimination leading to the cross-coupling product **6**. Similar behavior may be expected for the arylation of 4-picoline (Scheme 1). The beneficial effect of Lewis acids in the additions of 2-picoline to imines and enones has already been demonstrated.[10,11] Thus, we directed our attention toward the use of bases (Met-base) bearing a Lewis acidic metal center for the metalation. Recently, we have reported a kinetically highly active LiCl-solubilized TMP base (TMP = 2,2,6,6-tetramethylpiperidyl): TMPZnCl·LiCl (**7**) displays high chemoselectivity in various directed zincations of arenes and heterocycles.[12,13] Besides, **7** proved to be an excellent base for the generation of nitrile and ester enolates.[13,14] We have also demonstrated that **7** is compatible with additional strong Lewis acids ($MgCl_2$, $BF_3{\cdot}OEt_2$) and forms frustrated Lewis pairs.[15] Herein, we report that Lewis acids such as $ZnCl_2$, $MgCl_2$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ in combination with TMPZnCl·LiCl promote efficiently the Negishi cross-coupling[16] of various methyl-substituted N-heterocycles.



Scheme 1. Lewis acid (LA) promoted benzylic cross-coupling.

Thus, the zincation of 2-picoline (**1a**) with **7** (2.0 equiv)[17] gives the zincated picoline **8a**. Its cross-coupling with 5-bromoindole (**9a**, 0.8 equiv) in the presence of 2 mol% $Pd(OAc)_2$ and 2–4 mol% SPhos[18] affords the desired pyridine **6a** in 86% yield (in Scheme 2). Such cross-coupling reactions can be extended to various substituted aryl bromides (**9b–d**) leading to products **6b–d** in 66 to 95% yield (Table 1, entries 1–3). Also, 2-substituted pyridines such as **1b**,**c** are metalated with **7** under the same conditions and react



Scheme 2. Palladium-catalyzed direct cross-coupling of picolines **1a** and **2a**.

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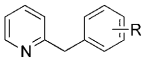
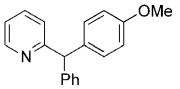
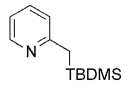
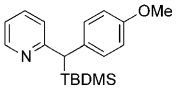
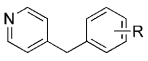
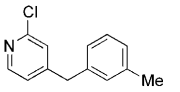
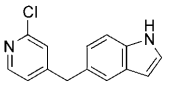
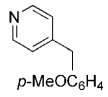
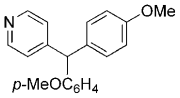
[**] We thank the Fonds der Chemischen Industrie, the European Research Council (ERC), and the Deutsche Forschungsgemeinschaft (DFG) for financial support. We also thank BASF AG (Ludwigshafen), Chemetall GmbH (Frankfurt), and Heraeas (Hanau) for generous gifts of chemicals.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103074.

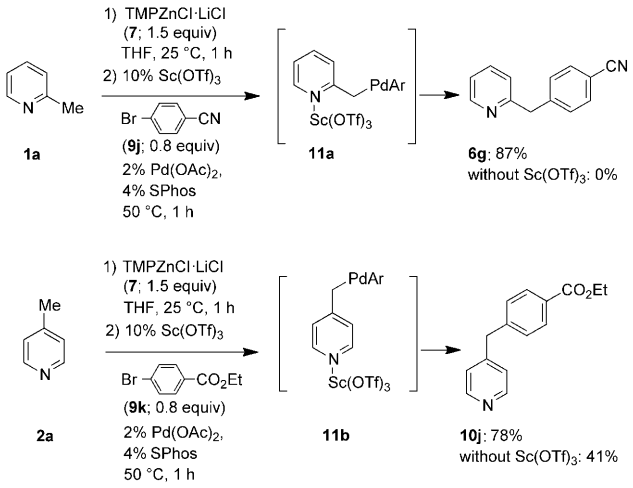
Table 1: Direct benzylic cross-coupling of 2- and 4-picoline derivatives.

Entry	Picoline[a]	Aryl–Br	Product	Yield [%][b]
				
1	**1a** (3)	**9b**: R = 4-OMe	**6b**: R = 4-OMe	95
2	**1a** (6)	**9c**: R = 4-F	**6c**: R = 4-F	78
3	**1a** (6)	**9d**: R = 3-Cl	**6d**: R = 3-Cl	66
				
4	**1b** (20)	**9b**	**6e**	99
				
5[e]	**1c** (11)	**9b**	**6f**	92
				
6	**2a** (1)	**9b**	**10b**: R = 4-OMe	98[c]
7	**2a** (1)	**9f**: R = 3-Me	**10c**: R = 3-Me	82
8	**2a** (1)	**9g**: R = 4-NMe_2	**10d**: R = 4-NMe_2	70
9	**2a** (1)	**9h**: R = 4-OH	**10e**: R = 4-OH	84[c]
10	**2a** (1)	**9i**: R = 4-OPiv	**10f**: R = 4-OPiv	81[c]
				
11	**2b** (1)	**9f**	**10g**	69[d]
				
12	**2b** (1)	**9a**	**10h**	69
				
13	**10b** (3)	**9b**	**10i**	93

[a] Reaction time (h) for the arylation in brackets. [b] Yield of isolated analytically pure product. [c] $Pd(OCOCF_3)_2$ was used as the Pd source. [d] 2 mol% $Pd(OAc)_2$, 4 mol% PCy_3 was used. [e] TBDMS = *tert*-butyldimethylsilyl.

with 4-bromoanisole (**9b**) to provide the desired products (**6e**,**f**) in very high yields (92–99%, Table 1, entries 4 and 5).

To our knowledge, no arylation of 4-picoline (**2a**) has been reported in the literature. However, the smooth zincation of **2a** with **7** (1.5 equiv) proceeds readily, and the palladium-catalyzed cross-coupling of **8b** with various aryl bromides (**9b**, **9e–i**) furnishes the 4-substituted pyridines **10a–f** in 70 to 98% yield (Scheme 2 and Table 1, entries 6–10). 2-Chloro-4-methylpyridine (**2b**) similarly reacts and produces the arylated products **10g** and **10h** in 69% yield (Table 1, entries 11 and 12). Cross-coupling of the 4-substituted pyridine (**10b**) with 4-bromoanisole (**9b**) leads to the desired product (**10i**) in high yield (entry 13). These smooth cross-couplings may be explained by the role that $ZnCl_2$ plays as a Lewis acid. Interestingly, the use of TMPZnCl·$MgCl_2$·2 LiCl (prepared from TMPMgCl·LiCl[19] and $ZnCl_2$) leads to even faster cross-couplings (at least six times faster). However, the reaction is complicated by increased amounts of diarylation[20] making the general use of this Lewis acid unattractive. A further hint showing the importance of Lewis acids for the tentative Pd intermediate of type **5** (Scheme 1) is found in the cross-coupling reaction of picolines (**1a** or **2a**) with electron-deficient aryl bromides. Substrates like 4-bromobenzonitrile (**9j**) and ethyl 4-bromobenzoate (**9k**) gave disappointing results in the presence of either $ZnCl_2$ or $MgCl_2$ as Lewis acids. Therefore, we screened[21] other powerful alternative Lewis acids[22] such as $ScCl_3$, $Sc(OTf)_3$,[23] $Yb(OTf)_3$,[24] and $Y(OTf)_3$.[22a] Thus, the direct cross-coupling of zincated 2-picoline (**8a**) with 4-bromobenzonitrile (**9j**) gave no product (even after additional ligands for the Pd catalyst were screened).[25] However, in the presence of 10 mol% $Sc(OTf)_3$, an efficient palladium-catalyzed cross-coupling took place and afforded the coupling product **6g** in 87% yield (Scheme 3). Similarly, 4-picoline (**2a**) gave the cross-



Scheme 3. $Sc(OTf)_3$-catalyzed cross-coupling of 2-picoline (**1a**) and 4-picoline (**2a**) with electron-poor aryl bromides **9j** and **k**.

coupling product **10j** only in 41% yield without $Sc(OTf)_3$, but the addition of 10 mol% $Sc(OTf)_3$ increased the cross-coupling yield to 78% (Scheme 3). The effect of $Sc(OTf)_3$ may be best explained by an acceleration of the reductive-elimination step in the cross-coupling as a result of the complexation of $Sc(OTf)_3$ to the heterocyclic nitrogen (see **11a**,**b**, Scheme 3). It is anticipated that electron-withdrawing substituents lead to Pd intermediates of type **4** (Scheme 1) which are especially reluctant to undergo reductive elimination. We expect the effect of a Lewis acid to be crucial in these cases. Thus, the cross-couplings of picolines **1a** and **2a** with various electron-deficient aryl bromides (**9j–l**) are dramatically improved by the presence of 10 mol% $Sc(OTf)_3$ and the cross-coupling products **6h** and **10k–l** are obtained in 75–85% yield. In the absence of $Sc(OTf)_3$, the yields of the cross-coupling are between 0 and 51% (Table 2, entries 1–3).

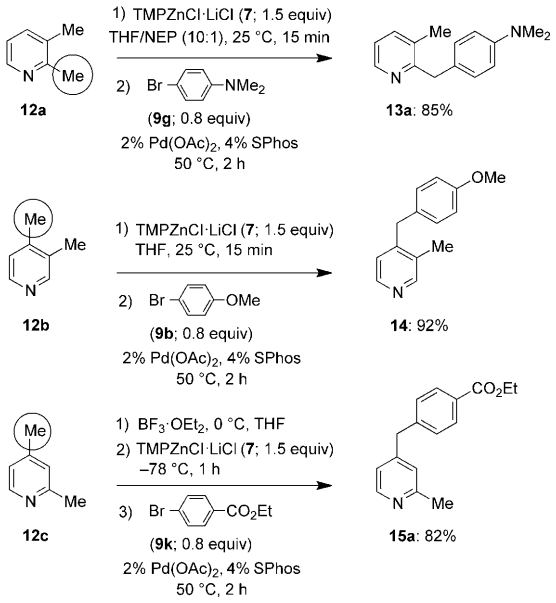
Following the mild zincation of picolines and efficient subsequent cross-coupling, we were set to tackle regioselectivity issues in the arylation of dimethylpyridines. Thus, we

Table 2: Effect of $Sc(OTf)_3$ on the benzylic cross-coupling of 2- and 4-picoline with electron-deficient electrophiles.

Entry	Picoline[a]	Aryl–Br	Product[b]
1	**1a**	**9k**	**6h**: 85% (31)[c]
2	**2a**	**9j**	**10k**: 75% (0)[c]
3	**2a**	**9l**	**10l**: 78% (51)[c]

[a] Conditions: 50 °C, 1 h. [b] Yield of isolated analytically pure product. [c] Yield of isolated product when the reaction was performed without $Sc(OTf)_3$.

examined the arylation of 2,3-, 3,4-, and 2,4-lutidines (**12a–c**). With 2,3-lutidine (**12a**), zincation with **7** occurs exclusively at position 2, leading after palladium-catalyzed arylation with 4-bromo-*N*,*N*-dimethylaniline (**9g**) to the disubstituted pyridine (**13a**) in 85% yield (Scheme 4). Further arylations are



Scheme 4. Selective cross-couplings of lutidines **12a–12c**.[28]

described in Table 3, entries 1–3. In the case of 3,4-lutidine (**12b**), completely regioselective metalation occurs at position 4 leading after a cross-coupling with 4-bromoanisole (**9b**) to the disubstituted pyridine **14** in 92% yield (Scheme 4). The regioselective arylation of 2,4-lutidine (**12c**) is more challenging since the direct zincation with **7** produces a 2:1 mixture of regioisomers. However, the addition of $BF_3{\cdot}OEt_2$[15a,26] prior to **7** directs the zincation only at position 4 since the complexation of **12c** with $BF_3{\cdot}OEt_2$ at the heterocyclic nitrogen hampers the metalation by **7** at position 2 for steric factors. Thus the zincation occurs at position 4 leading after

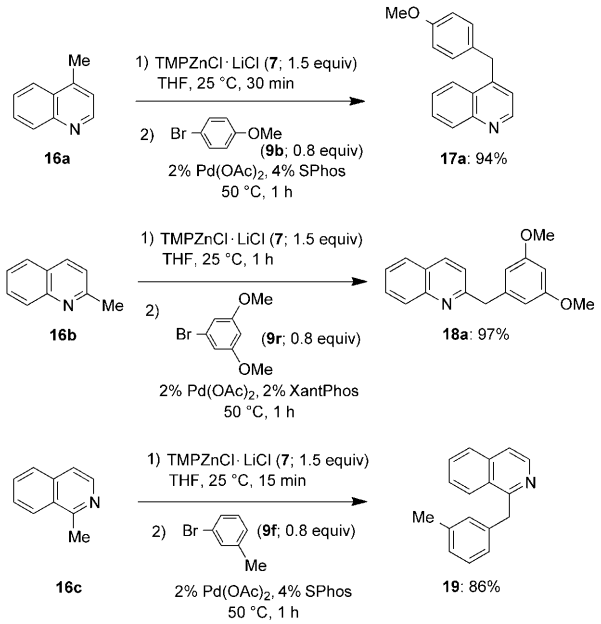
Table 3: Selective benzylic cross-couplings of lutidines with various aryl bromides, chlorides, and a triflate.

Entry	Lutidine	Aryl–X	Product	Yield [%][a]
1	**12a**	**9b**	**13b**: R = 4-OMe	90
2	**12a**	**9f**	**13c**: R = 3-Me	91
3	**12a**	**9m**: R = 4-CF_3	**13d**: R = 4-CF_3	88
4	**12c**	**9b**	**15b**: R = 4-OMe	92[b]
5	**12c**	**9i**	**15c**: R = 4-OPiv	82[b]
6	**12c**	**9j**	**15d**: R = 4-CN	77[b]
7	**12c**	**9n**: X = OTf, R = 4-OMe	**15b**: R = 4-OMe	98[b]
8	**12c**	**9o**: X = Br, R = 2-OMe	**15e**: R = 2-OMe	92[b]
9	**12c**	**9p**: X = Cl, R = 3-OMe	**15f**: R = 3-OMe	86[b]
10	**12c**	**9q**: X = Cl, R = 4-CF_3	**15g**: R = 4-CF_3	88[b]

[a] Yield of isolated analytically pure product. [b] $BF_3{\cdot}OEt_2$ was added prior to TMPZnCl·LiCl.

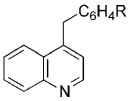
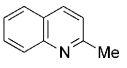
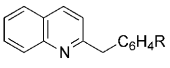
cross-coupling with ethyl 4-bromobenzoate (**9k**) to the pyridine (**15a**) in 82% yield. This reactivity is general and several typical aryl bromides, chlorides, and a triflate (**9b**,**i**,**j**,**n–q**) undergo regioselective arylations at position 4 to provide products **15b–g** in 77–98% yield (Table 3, entries 4–10).[27]

Finally, we briefly examined the arylation of methyl-substituted quinolines (**16a**,**b**) and isoquinoline (**16c**). With **7** zincation is rapid, and the subsequent palladium-catalyzed arylation proceeds well with various aryl bromides (Scheme 5 and Table 4, entries 1–8). In the case of Negishi cross-couplings with aryl bromides bearing an acidic proton, the use of $Pd(OCOCF_3)_2$ introduced by Oshima and Yorimitsu[4]



Scheme 5. Cross-coupling of quinolines **16a–c** with aryl bromides.

Table 4: Cross-couplings of quinolines with various aryl bromides.

Entry	Quinoline[a]	Aryl–X	Product	Yield [%][b]
				
1	**16a** (1)	**9g**	**17b**: R = 4-NMe_2	93
2	**16a** (1)	**9j**	**17c**: R = 4-CN	66
3	**16a** (1)	**9l**	**17d**: R = 3-CF_3	72
4	**16a** (2)	**9h**	**17e**: R = 4-OH	76[c]
5	**16a** (2)	**9s**: R = 4-NH_2	**17f**: R = 4-NH_2	74[c]
				
6	**16b** (1)	**9f**	**18b**: R = 3-Me	96
7	**16b** (1)	**9m**	**18c**: R = 4-CF_3	86
8	**16b** (1)	**9t**: R = 3-F	**18d**: R = 3-F	95

[a] Reaction time (h) for the arylation in brackets. [b] Yield of the isolated analytically pure product. [c] 2 equiv TMPZnCl·LiCl, 2 mol% Pd-$(OCOCF_3)_2$, and 4 mol% SPhos were used.

was advantageous and ensured high yields and fast cross-couplings (Table 4, entries 4 and 5). The arylation of 2-methylquinoline (**16b**) is best performed with the Xantphos[29] ligand since the formation of diarylation by-products can be avoided (Table 4, entries 6–8).

In summary, we have reported the direct palladium-catalyzed arylation of methyl-substituted N-heterocycles (pyridines, quinolines, and isoquinoline) promoted by $ZnCl_2$, $Sc(OTf)_3$, or $BF_3{\cdot}OEt_2$. The action of these Lewis acids may be, in each case, complexation with the heterocyclic nitrogen which facilitates the reductive elimination of the Pd intermediate ($ZnCl_2$, $Sc(OTf)_3$). The addition of a Lewis acid such as $BF_3{\cdot}OEt_2$ can also trigger the regioselectivity of the 2,4-lutidine metalation. The possibility of improving related Pd cross-couplings by the addition of Lewis acids is currently under investigation in our laboratory.

Received: May 4, 2011
Published online: June 30, 2011

Keywords: cross-coupling · metalation · pyridine · zinc

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