Arylation Reactions

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

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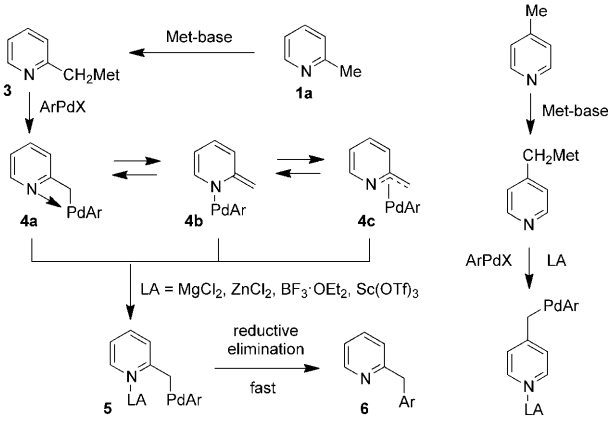
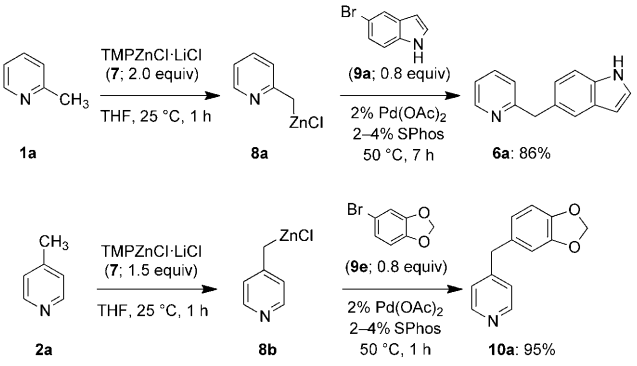
The functionalization of pyridines and related heterocycles is very important because of their biological properties and relevance to material science.[1] The benzylic arylation of pyridines, in particular, is a challenging synthetic problem. Palladium-catalyzed arylations of 2-picoline involving direct 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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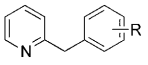
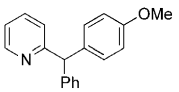
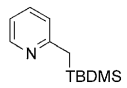
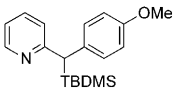
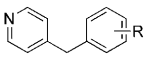
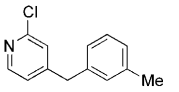
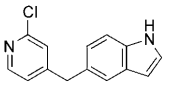
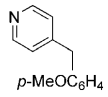
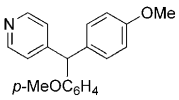
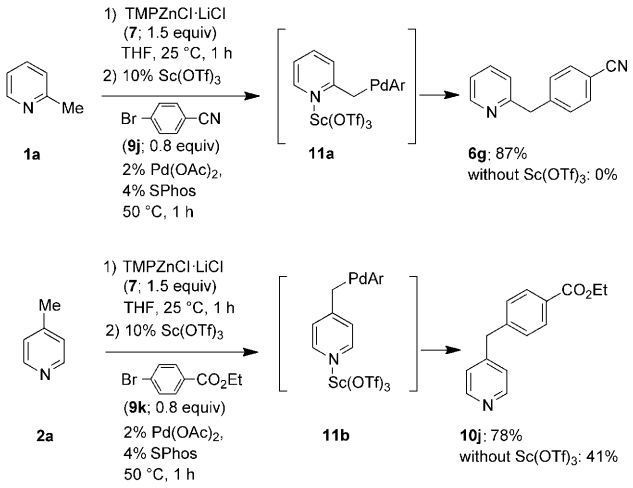
***Table 1:*** Direct benzylic cross-coupling of 2- and 4-picoline derivatives.

| 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

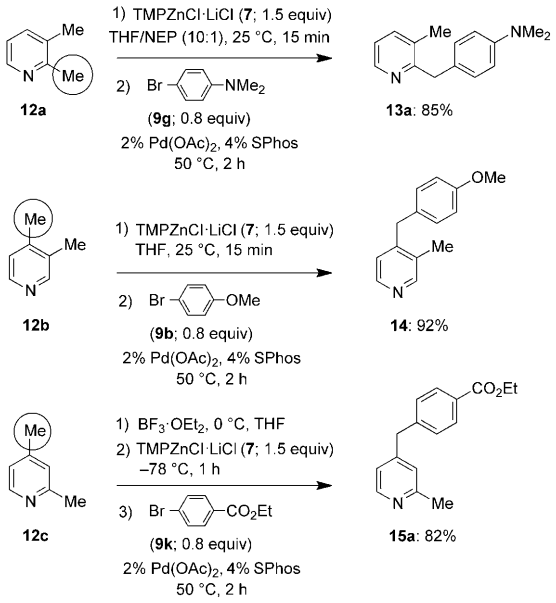
  

***Table 2:*** Effect of $Sc(OTf)_3$ on the benzylic cross-coupling of 2- and 4-picoline with electron-deficient electrophiles.

| 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

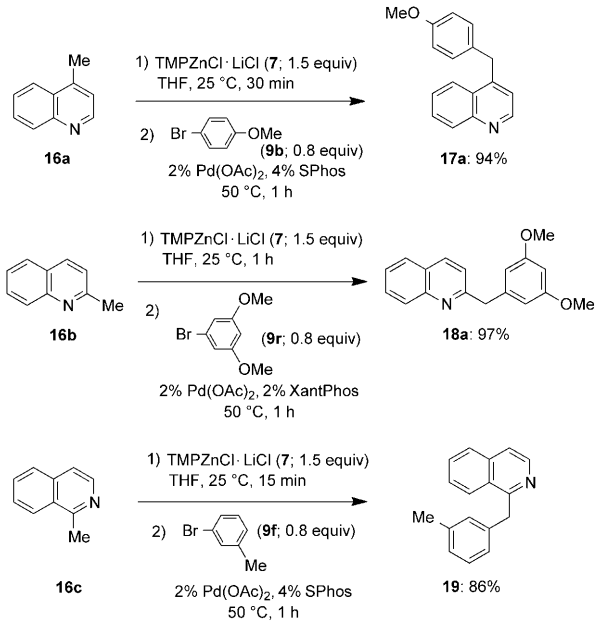
***Table 3:*** Selective benzylic cross-couplings of lutidines with various aryl bromides, chlorides, and a triflate.

| 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]

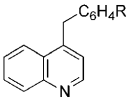
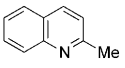
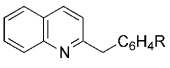
Finally, we briefly examined the arylation of methyl-substituted quinolines (**16a**,**b**) and isoquinoline (**16c**). With **7** zincation is rapid, and the subsequent palladium-catalyzed arylation proceeds well with various aryl bromides (Scheme 5 and Table 4, entries 1–8). In the case of Negishi 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.

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