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# Palladium-Catalyzed (*N*-Oxido-2-pyridinyl)methyl Transfer from 2-(2-Hydroxyalkyl)pyridine *N*-Oxide to Aryl Halides by β-Carbon Elimination

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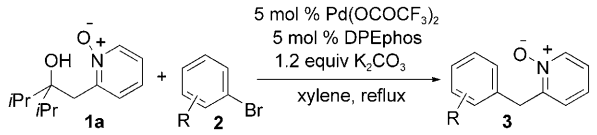
Pyridine *N*-oxides are an important class of compounds found in organic chemistry as oxidants,[1] ligands of transition metals,[2] organocatalysts,[3] and synthetic intermediates for substituted pyridines.[4,5] In addition, pyridine *N*-oxides and related compounds often show biological activity.[6] Development of new methods for the synthesis of pyridine *N*-oxides is hence important. During the course of our recent studies on chelation-assisted carbon–carbon bond cleavage under palladium catalysis,[7] we have discovered the palladium-catalyzed (*N*-oxido-2-pyridinyl)methyl transfer from 2-(2-hydroxylalkyl)pyridine *N*-oxide derivatives to aryl bromides, providing 2-benzylpyridine *N*-oxide derivatives. Recently Fagnou et al. reported the synthesis of 2-benzylpyridine *N*-oxides by palladium-catalyzed direct arylation at the benzylic $sp^3$ carbon atom of 2-methylpyridine *N*-oxide derivatives.[5e] However, the substrate scope was limited because of the strongly basic conditions by using sodium *tert*-butoxide. Moreover, this direct route requires a special apparatus for microwave irradiation. Facile synthetic methods of functionalized pyridine *N*-oxides hence have to be explored.

Treatment of bromobenzene (**2a**) with 2-(2-hydroxyalkyl)-pyridine *N*-oxide **1a** in the presence of potassium carbonate and a palladium catalyst in refluxing xylene provided 2-benzylpyridine *N*-oxide (**3a**) in good yield (Table 1, entry 1). Palladium(II) acetate as well as palladium(II) trifluoroacetate resulted in high efficiency.[8] The choice of the bidentate phosphine ligand was crucial. DPEphos and *rac*-binap[9] acted as effective ligands, while other bidentate ligands or monodentate ligands exhibited poor to moderate activity for this reaction.[10] Although the *N*-oxide may oxidize the phosphine ligand, no significant formation of phosphine oxide was observed. The use of chlorobenzene instead of bromobenzene provided **3a** in 27% yield.

Table 1. Pd-catalyzed (*N*-oxido-2-pyridinyl)methyl transfer to aryl halides **2** from alcohol **1a**.[a]




| Entry | 2 | R | *t* [h] | 3 | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | **2a** | H | 3 | **3a** | 80 |
| 2 | **2b** | 4-Me | 5 | **3b** | 68 |
| 3 | **2c** | 4-OMe | 11 | **3c** | 68[c] |
| 4 | **2d** | 4-F | 4 | **3d** | 84[c] |
| 5 | **2e** | 4-Cl | 3 | **3e** | 74[c] |
| 6 | **2f** | 4-$CF_3$ | 7 | **3f** | 78[c] |
| 7 | **2g** | 4-$COCH_3$ | 11 | **3g** | 71 |
| 8 | **2h** | 4-$CO_2Et$ | 3 | **3h** | 75 |
| 9 | **2i** | 4-CHO | 5 | **3i** | 72 |
| 10 | **2j** | 4-CN | 8 | **3j** | 78 |
| 11 | **2k** | 2-Me | 3 | **3k** | 100 |
| 12 | **2l** | 2,6-$Me_2$ | 11 | **3l** | 98 |
| 13 | **2m** | (1-naphthyl ($^1$Np)) | 2 | **3m** | 81 |
| 14 | **2n** | 2-COPh | 11 | **3n** | 74 |

[a] A mixture of **1a** (1.0 mmol), **2** (1.2 mmol), $Pd(OCOCF_3)_2$ (0.05 mmol), DPEphos (0.05 mmol), and $K_2CO_3$ (1.2 mmol) was boiled in xylene (4.0 mL). [b] Yield of isolated product. [c] *rac*-binap (0.05 mmol) was used as a ligand.

A wide range of *p*-substituted aryl bromides including electron-deficient as well as electron-rich ones could be employed (Table 1, entries 2–10). In some cases, using *rac*-binap as a ligand was more effective for the reaction (entries 3–6). It is worth noting that aryl bromides bearing a variety of carbonyl groups such as a formyl group were tolerated (entries 7–9). Synthesis of these products should be difficult by Fagnou's method.[5e] The conventional oxidation of the parent pyridine would not be applicable to the synthesis of **3i**.[11] Sterically demanding aryl bromides also participated in the reaction (entries 11–14). Unfortunately, the reactions of alkenyl halides failed to yield the corresponding

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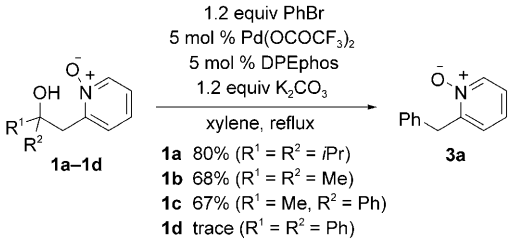
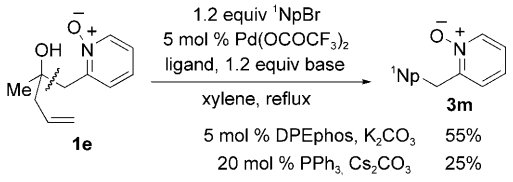
products. The reaction of iodobenzene afforded a complex mixture, and **3a** was obtained in 27% yield.

Several (2-hydroxyalkyl)pyridine *N*-oxides were subjected to the transfer reaction as (*N*-oxido-2-pyridinyl)methyl sources (Scheme 1). The two isopropyl groups of **1a** were not essential, and less sterically hindered alcohols were also applicable for the reaction. Alcohols **1b** having two methyl groups and **1c** bearing a methyl and a phenyl group could be employed to afford the corresponding product **3a** in moderate yields. An attempted reaction of **1d** gave only a trace amount of the desired product **3a**.[12]



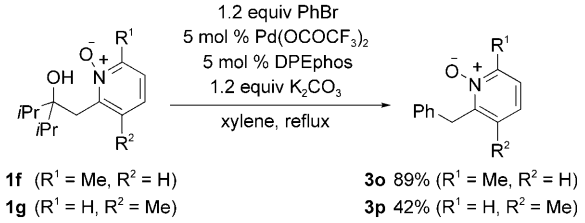

Scheme 1. Pd-catalyzed transfer reaction with alcohols **1**.

Alcohol **1e** would react as an allyl source through retro-allylation under palladium catalysis (Scheme 2).[13] Selective carbon–carbon bond cleavage occurred at the pyridinyl-methyl moiety under the (*N*-oxido-2-pyridinyl)methyl-group-transfer conditions to yield **3m**. In this reaction, no allylated product was detected even in using triphenylphosphine and cesium carbonate, which are effective for the retro-allylation.



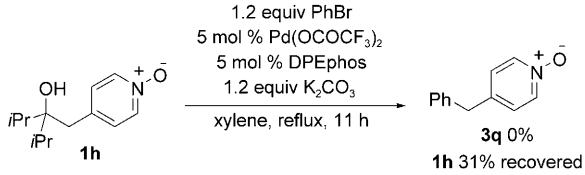

Scheme 2. Pd-catalyzed selective (*N*-oxido-2-pyridinyl)methyl transfer from homoallyl alcohol **1e**. $^{1}$Np = 1-naphthyl.

(2-Hydroxyalkyl)pyridine *N*-oxides **1f** having a methyl group at the 6-position on the pyridine ring were also applicable for the reaction (Scheme 3). In contrast, in the reaction of **1g** bearing a methyl group at the 3-position, the corresponding product was obtained in lower yield, probably owing to the steric hindrance. An attempted reaction of the quinoline *N*-oxide analogue of **1** gave 2-methylquinoline quantitatively instead of the desired 2-benzylquinoline.



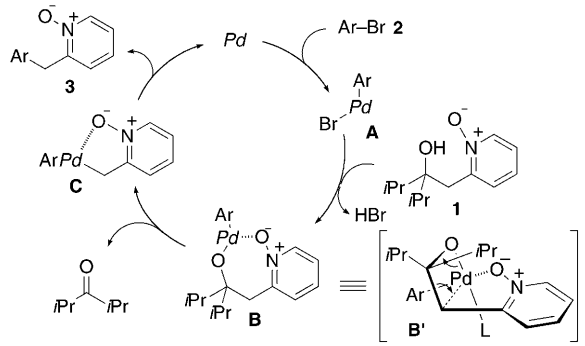

Scheme 3. Scope of the pyridine moiety.

Notably, (*N*-oxido-4-pyridinyl)methyl transfer reactions with **1h** yielded no desired product, and a small amount of starting alcohol was recovered (Scheme 4). This result suggests that the coordination of the oxygen atom on the nitrogen to the palladium center is essential for the success of the transfer reaction.




Scheme 4. Unsuccessful Pd-catalyzed transfer reaction with 4-(2-hydroxyalkyl)pyridine *N*-oxide **1h**.

We tentatively assume that the reaction mechanism for the transfer can be described as follows (Scheme 5). After oxidative addition of aryl bromide **2** to the low-valent palladium species,[14] ligand exchange takes place under basic conditions to afford arylpalladium alkoxide **B** with intramolecular coordination of the basic oxygen atom on the pyridine ring. Subsequent β-C($sp^3$) elimination[15,16] would proceed via a four-membered transition state from conformation **B′**. Finally, reductive elimination would produce **3** along with the starting palladium complex to complete the catalytic cycle.




Scheme 5. Plausible reaction mechanism.

Transformation of the products was investigated (Scheme 6). Treatment of 2-benzylpyridine *N*-oxides **3** with acetic anhydride provided aryl(2-pyridinyl)methyl acetates **4** in high yield.[17] This method provides a facile route to highly functionalized aryl(2-pyridinyl)methanols which are found in some biologically active compounds.[18]

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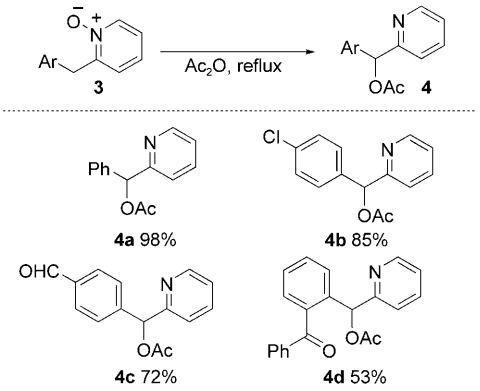


Scheme 6. Rearrangement of **3** to aryl(2-pyridinyl)methyl acetates by use of acetic anhydride.

In conclusion, we have discovered an efficient palladium catalyst system for (*N*-oxido-2-pyridinyl)methyl transfer from (2-hydroxyalkyl)pyridine *N*-oxide derivatives to aryl bromides. The reaction proceeds via β-carbon elimination which involves cleavage of an unstrained $C(sp^3)$–$C(sp^3)$ bond and provides a facile access to 2-benzylpyridine *N*-oxides under mild conditions.

## Experimental Section

Typical procedure for palladium-catalyzed (*N*-oxido-2-pyridinyl)methyl transfer to aryl bromides: Synthesis of 2-benzylpyridine *N*-oxide (**3a**) is representative (Table 1, entry 1). Potassium carbonate (166 mg, 1.2 mmol), palladium(II) trifluoroacetate (17 mg, 0.050 mmol), and bis[2-(diphenylphosphino)phenyl] ether (27 mg, 0.050 mmol) were placed in a 20 mL two-necked reaction flask equipped with a Dimroth condenser under Ar atmosphere. Xylene (4.0 mL), bromobenzene (**2a**, 0.13 mL, 1.2 mmol), and alcohol **1a** (223 mg, 1.0 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 3 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (AcOEt/MeOH = 10:1) gave 2-benzylpyridine *N*-oxide (**3a**, 149 mg, 0.80 mmol) in 80% yield.

Rearrangement of benzylpyridine *N*-oxides **3** to aryl(2-pyridinyl)methyl acetates by means of acetic anhydride (Scheme 6): Synthesis of phenyl(2-pyridinyl)methyl acetate (**4a**) is representative. A solution of benzylpyridine *N*-oxide (**3a**, 93 mg, 0.5 mmol) in acetic anhydride (10 mL) was placed in a 50 mL flask. After the mixture was heated at 110 °C for 3 h, the mixture was concentrated in vacuo. Silica gel column purification (hexane/AcOEt = 1:1) gave **4a** (111 mg, 0.49 mmol) in 98% yield.

## Acknowledgements

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**Keywords:** alcohols · cleavage reactions · palladium · pyridines

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[8] Product **3a** was isolated in 64% yield by using palladium(II) acetate.

[9] DPEphos: bis[2-(diphenylphosphino)phenyl] ether. binap: 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl.

[10] The effects of the ligands are summarized in the Supporting Information.

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[14] We prepared a palladium complex, *trans*-$[PdBr(Ph)(PPh_3)_2]$, and performed the stoichiometric reaction of the arylpalladium complex with **1a** in the presence of 1.2 molar equivalents of potassium carbonate in boiling xylene for 5 h. The reaction afforded **3a** in 62% yield.

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