DOI: 10.1002/chem.200801893

Coupling of Nitrogen Heteroaromatics and Alkanes without Transition Metals: A New Oxidative Cross-Coupling at C–H/C–H Bonds

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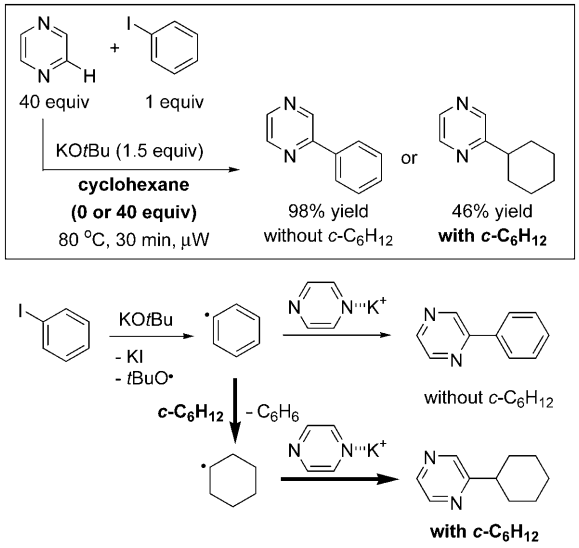
The direct conversion of C–H bonds into C–C bonds can potentially lead to more efficient synthesis and provide benefits in terms of resource conservation and environmental sustainability.[1] Since the seminal work reported by Murai,[2] extensive research has been carried out on C–C bond formation through transition-metal-catalyzed C–H bond functionalization.[3,4] We[5] and others[6] have developed various methods to generate C–C bonds directly from two different C–H bonds (cross-dehydrogenative-coupling, CDC) in the presence of an oxidizing reagent and a transition metal. Since these reactions proceed best with activated C–H bonds, including those of 1,3-dicarbonyls, alkynes, and nitroalkanes, such cross-coupling involving an unactivated sp^3-hybridized C–H bond has been a challenging target. Very recently, we have established that the CDC reactions of simple unactivated alkanes with 1,3-dicarbonyl compounds or 2-pyridylbenzene derivatives can be promoted by iron and ruthenium catalysts.[7] However, in all previous reports of C–C bond formations by C–H activation of alkanes, the use of a transition-metal catalyst is essential both for activating the alkyl C–H bond and for subsequent coupling to form C–C bond. Herein, we report on the coupling of nitrogen heteroaromatics and alkanes as an example of new oxidative cross-coupling at two different C–H bonds in the absence of a transition metal (Scheme 1).

Scheme 1. Transition-metal-free oxidative cross-coupling of N-heteroaromatics and alkanes.

Very recently, we demonstrated that the biaryl coupling of electron-deficient nitrogen heteroaromatics and haloarenes (C–H bond arylation) can be promoted by potassium *tert*-butoxide alone, without the addition of any exogenous transition-metal species.[8] A typical example using pyrazine is shown in Scheme 2. Several control experiments indicate that the coupling involves the KO*t*Bu-induced generation of an aryl radical from haloarene, followed by homolytic aromatic substitution[9] or $S_{RN}1$ reaction.[10] Furthermore, we observed the formation of 2-cyclohexylpyrazine when the reac-



Scheme 2. KO*t*Bu-promoted arylation and alkylation of nitrogen heteroaromatics.

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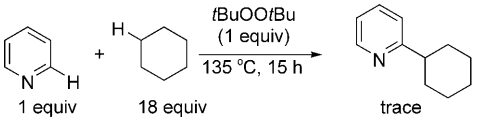
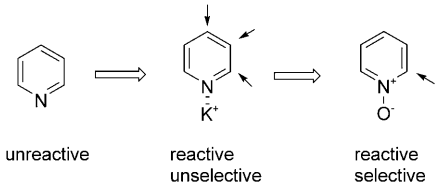
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801893.

tion was conducted in the presence of cyclohexane (Scheme 2). This last reaction most likely proceeds through cyclohexyl radical, generated by the radical exchange reaction of phenyl radical and cyclohexane.[11]

The successful coupling of nitrogen heteroaromatics and alkanes not only supports the radical nature of previous KO*t*Bu-promoted biaryl coupling,[8] but also serves as a starting point toward the development of new transition-metal-free cross-coupling at two different C–H bonds. However, at the early stage of investigation, we became aware of two critical drawbacks of the present KO*t*Bu/PhI system: 1) indirect generation of alkyl radical and 2) lack of regioselectivity for some heteroaromatics (e.g., the reaction of pyridine and cyclohexane produces 2-, 3-, and 4-cyclohexylpyridines in 5, 5, and 10% yield, respectively). In an effort to find a more efficient and direct method to generate alkyl radical from alkane, peroxides have been chosen as a potential promoter. However, the cross-coupling of pyridine and cyclohexane does not proceed under the influence of peroxides such as *t*BuOO*t*Bu [Eq. (1)]. The coordination of nitrogen to potassium ion has been suspected as an additional promoting factor for KO*t*Bu in the previous two coupling reactions (Schemes 2 and 3).[12]

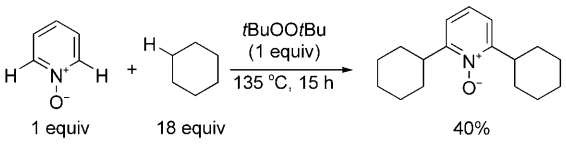


(1)



Scheme 3. Enhancement of reactivity and selectivity by "nitrogen atom activation" of pyridine ring.

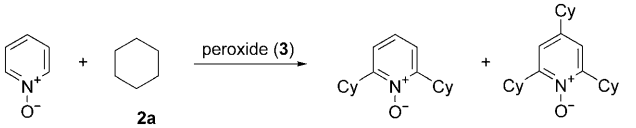
On the basis of our hypothesis that "nitrogen-atom activation" might be a key to achieving the desired coupling, we found that pyridine *N*-oxide derivatives are superior substrates for the radical-based arene/alkane cross-coupling. For example, the reaction of pyridine *N*-oxide (1.0 equiv) and cyclohexane (18 equiv) in the presence of *t*BuOO*t*Bu (1.0 equiv) at 135 °C for 15 h furnishes 2,6-dialkylated product in 40% yield [Eq. (2)], whereas only trace product was obtained when pyridine reacts with cyclohexane under similar conditions and no change was observed by increasing the amount of peroxide to three equivalents [Eq. (1)]. The additional *N*-oxide moiety clearly enhances both the reactivity and regioselectivity (Scheme 3). It should be noted that efficient alkylation method of pyridine *N*-oxide is still rare in comparison to the recently emerging arylation/alkenylation method using transition metal catalysts.[13]



(2)

In view of the importance of pyridine *N*-oxide derivatives in medicinal chemistry[14] as well as their facile conversion (deoxygenation)[13] to the more fertile pyridine derivatives,[15] further optimization of reaction conditions was conducted (Table 1). In this study, pyridine *N*-oxide (**1a**) and cyclohexane (**2a**) were used as model substrates. As mentioned earlier, 2,6-dicyclohexylated pyridine *N*-oxide (**4a**) is obtained in 40% yield when the reaction is conducted with *t*BuOO*t*Bu (**3a**) at 135 °C for 15 h under air (Table 1, entry 1). Increasing the amount of **3a** (2–3 equiv) results in the formation of both di- and trialkylation products (**4a** and **5a**) in good combined yield (entries 2 and 3). In particular, **5a** becomes a major product when three equivalents of **3a** are employed. Although the coupling occurs at 120 °C with reasonable efficiency and selectivity, further decrease of reaction temperature to 100 °C results in nearly no reaction (entries 4 and 5). The choice of peroxide promoter is also important. The reactions using cumyl *tert*-butyl peroxide (**3b**), dicumyl peroxide (**3c**), and *tert*-butyl peroxybenzoate (**3d**) result in much lower product yields (entries 6–8). Only trace amount of coupling product is obtained with *tert*-butyl hydroperoxide (**3e**) (entry 9).

Table 1. Optimization of reaction conditions.[a]



	Peroxide (equiv)	*T* [°C]	Yield [%][b]
1	**3a** (1.0)	135	40 (**5a** trace)
2	**3a** (2.0)	135	77 (3.5:1)
3	**3a** (3.0)	135	66 (1:2.3)
4	**3a** (2.0)	120	59 (11:1)
5	**3a** (2.0)	100	trace
6	**3b** (2.0)	135	6 (**5a** trace)
7	**3c** (2.0)	135	48 (7.0:1)
8	**3d** (2.0)	135	16 (**5a** trace)
9	**3e** (2.0)	135	trace

[a] Conditions: **1a** (0.5 mmol), **2a** (9.2 mmol, 1.0 mL), **3** (0.5–1.5 mmol), 100–135 °C, 15 h, under air. [b] Determined by ^{1}H NMR spectroscopy using 1,2-dichloroethane as an internal standard.

With the optimized conditions in hand, the scope of the reaction with respect to pyridine *N*-oxide derivatives and cy-

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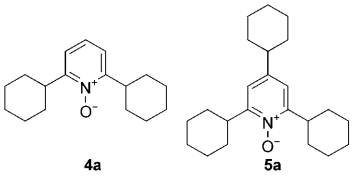
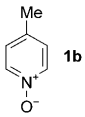
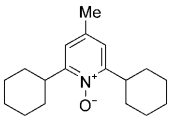
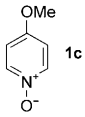
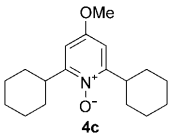
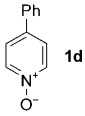
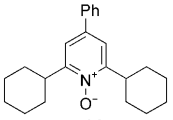
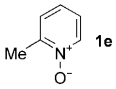
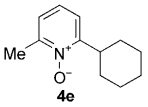
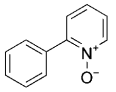
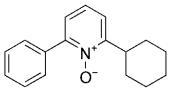
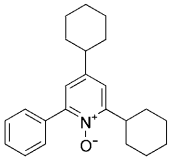
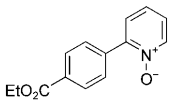
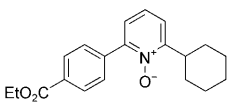
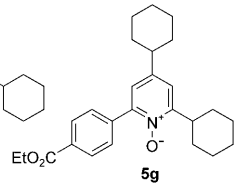
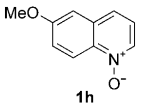
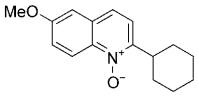
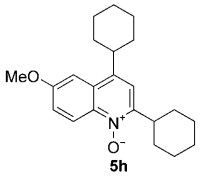
cloalkanes was investigated (Tables 2 and 3). Under the influence of *t*BuOO*t*Bu (**3a**), various electronically and structurally diverse pyridine *N*-oxide derivatives (**1a**–**1h**) react with cyclohexane (**2a**) to give the corresponding alkylated products (**4** and **5**) in good yields (Table 2). The coupling takes place with various electron-donating and withdrawing substituents on the pyridine ring of **1** without affecting the efficiency (entries 2–7). With a substituent at 4-position, the 2,6-dialkylation product (**4**) is predominantly produced (entries 2–4). With a substituent at 2-position, the monoalkylation product becomes the major product (entries 5–7). The *N*-oxides of other nitrogen heteroaromatics such as quinoline *N*-oxide derivative **1h** also react smoothly with **2a** (entry 8). It should be noted that the reaction always takes place on the oxygenated *N*-heteroaromatic ring leaving other aromatic rings on the substrate intact (entries 4, 6–8).

The present C–H/C–H cross-coupling reaction occurs with a range of sp^3-hybridized C–H bonds. Representative results using cycloalkanes (**2**) as coupling partners for pyridine *N*-oxide (**1a**) are shown in Table 3. In a similar manner to the reaction of **2a**, cyclooctane (**2b**) and cycloheptane (**2c**) react smoothly with **1a** (entries 1 and 2). Presumably because of the low boiling point of cyclopentane (**2d**), its reaction furnishes 2,6-dialylation product **4k** selectively (entry 3). The reactions also take place with norbornane (**2e**) and 1,4-dioxane (**2f**) to give structurally interesting molecules in good yields (entries 4 and 5).

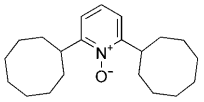
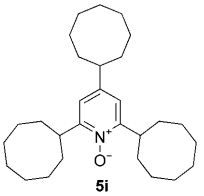
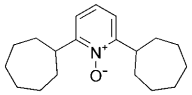
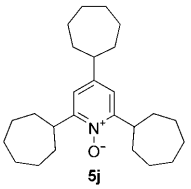
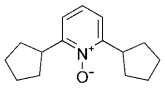
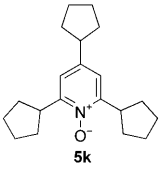
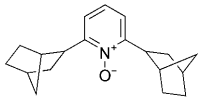
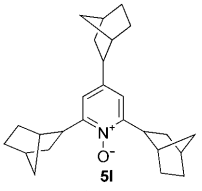
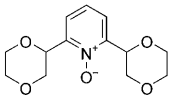
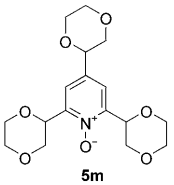
In summary, transition-metal-free systems for the cross-coupling reactions of nitrogen heteroaromatics and alkanes

Table 2. Cross-coupling of nitrogen heterocycles (**1**) with cyclohexane (**2a**).[a]

	N-Heterocycles	Products	Isolated yield [%]
1	 **1a**	 **4a** **5a**	70[b]
2	 **1b**	 **4b**	55
3	 **1c**	 **4c**	66
4	 **1d**	 **4d**	65
5	 **1e**	 **4e**	75
6	 **1f**	 **4f**  **5f**	81[c]
7	 **1g**	 **4g**  **5g**	71[d]
8	 **1h**	 **4h**  **5h**	72[e]

[a] Conditions: **1** (0.5 mmol), **2a** (9.2 mmol, 1.0 mL), **3a** (1.0 mmol), 135 °C, 15 h, under air. [b] **4a**:**5a** = 4.8:1. [c] **4f**: **5f** = 2.2:1. [d] **5g** trace. [e] **4h**:**5h** = 2:1.

Table 3. Cross-coupling of pyridine *N*-oxide (**1a**) with cycloalkanes (**2**).[a]

	Alkanes	Products	Isolated yield [%]
1	 **2b**	 **4i**  **5i**	71[b]
2	 **2c**	 **4j**  **5j**	61[c]
3	 **2d**	 **4k**  **5k**	40[d]
4	 **2e**	 **4l**  **5l**	56[e]
5	 **2f**	 **4m**  **5m**	61[f]

[a] Conditions: **1a** (0.5 mmol), **2** (9.2 mmol), **3a** (1.0 mmol), 135 °C, 15 h, under air. [b] **4i**:**5i** = 6:1. [c] **4j**:**5j** = 4:1. [d] **5k** trace. [e] **4l**:**5l** = 6:1. [f] **4m**:**5m** = 2.2:1.

are described. Under the influence of *t*BuOO*t*Bu, pyridine *N*-oxide derivatives react with alkanes to furnish the corresponding cross-coupling products (alkylated nitrogen heterocycles) in good yields. We believe that the present oxidative cross-coupling reactions at two different C–H bonds not only contributes to the realization of "greener" synthesis, but also unlocks opportunities for markedly different strategies in chemical synthesis. Moreover, in view of the current strict guidelines limiting transition-metal levels in pharmaceuticals,[16] the realization of C–C bond-forming reactions without using a transition metal is noteworthy. The elucidations of reaction mechanism and full scope of present methodology are the focus of ongoing research efforts.

Experimental Section

A representative experimental procedure (4a and 5a): A reaction vessel was charged with pyridine *N*-oxide (**1a**, 47.5 mg, 0.5 mmol), *tert*-butyl peroxide (**3a**, 146 mg, 1.0 mmol) and cyclohexane (**2a**, 1.0 mL, 9.2 mmol). Then the reaction vessel was sealed and the resulting solution was stirred at 135 °C for 15 h. After cooling to room temperature, the resulting mixture was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 6:1) to give **4a** (75 mg, 58 %) and **5a** (21 mg, 12 %) as pale yellow oils.

Data for 4a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.16$–7.12 (m, 1H), 7.03–7.02 (m, 2H), 3.55–3.47 (m, 2H), 2.04–2.00 (m, 4H), 1.83–1.73 (m, 6H), 1.53–1.41(m, 4H), 1.29–1.17 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7$, 125.4, 120.2, 38.1, 31.2, 26.7, 26.6 ppm; IR (liquid film): $\tilde{\nu} =$ 3076, 2912, 2846, 1520, 1442, 1389, 1230, 835, 749 cm^{-1}; MS (EI): *m*/*z* (%): 259, 242 (100), 214, 188, 175, 158, 144, 119, 91, 77; HRMS calcd for $C_{17}H_{25}NO$: 259.1936; found: 259.1933.

Data for 5a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.85$ (s, 2H), 3.56–3.48 (m, 2H), 2.45–2.41 (m, 1H), 2.05–2.01 (m, 4H), 1.84–1.72 (m, 11H), 1.58–1.42 (m, 4H), 1.32–1.18 ppm (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 155.9, 146.1, 118.4, 43.8, 38.2, 33.9, 31.4, 26.8, 26.6, 26.1 ppm; IR (liquid film): $\tilde{\nu} = 2925$, 2846, 1553, 1454, 1415, 1270, 1237, 845 cm^{-1}; MS (EI): *m*/*z* (%): 341, 324 (100), 296, 270, 257, 214; HRMS calcd for $C_{23}H_{35}NO$: 341.2719; found: 341.2716.

The experiments in Tables 2 and 3 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

Acknowledgements

We are grateful to PRESTO program of Japan Science and Technology Agency (to K.I.), a Grant-in-Aid for Scientific Research from MEXT, Japan (to K.I.), Canada Research Chair (Tier I) foundation (to C.J.L.), the NSF-EPA joint program for a Sustainable Environment (to C.J.L.), and NSERC (to C.J.L.) for support of our research. S.Y. is a recipient of the JSPS Predoctoral Fellowships for Young Scientists.

Keywords: alkanes · C–C coupling · C–H activation · nitrogen heterocycles

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Received: September 15, 2008
Published online: November 26, 2008

