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$Sc(OTf)_3$-Catalyzed Direct Alkylation of Quinolines and Pyridines with Alkanes

Guojun Deng and Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec, Canada H3A 2K6

cj.li@mcgill.ca

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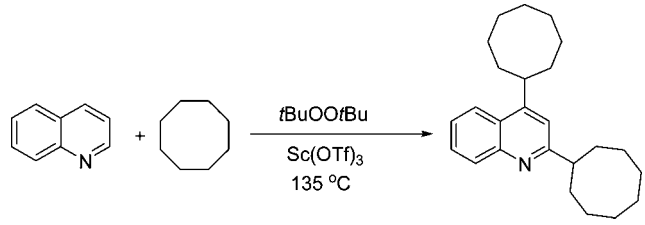
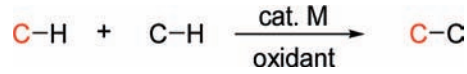
ABSTRACT



The $Sc(OTf)_3$-catalyzed C−C bond formation by direct alkylation of quinolines and pyridines using simple alkanes was developed. Various alkanes reacted with quinolines and pyridines to give the corresponding alkylation products in 50−91% yields in the presence of *tert*-butyl peroxide.

The direct conversion of C−H bonds into C−C bonds can potentially lead to more efficient synthesis with a reduced number of synthetic operations and thus attracted great interest recently.[1] Since the seminal work reported by Murai,[2] great progress has been achieved in the transition-metal-catalyzed activation and subsequent reaction of C−H bonds.[3,4] On the other hand, we[5] and others[6] have developed various methods to generate C−C bonds directly from two different C−H bonds in the presence of an oxidizing reagent through an overall cross-dehydrogenative-coupling (CDC) (Scheme 1).

Scheme 1. C−C Bond Formation via C−H/C−H Reaction



Pyridine and quinoline moieties are key components of a wide range of natural products, pharmacophores, chiral ligands, and synthetic building blocks.[7] Thus, the functionalization of pyridines and quinolines has sustained research attention over the decades. However, the direct functionalization of pyridine rings through C−H bond activation is still challenging due to their electron-deficient nature which results in a low reactivity.[8] In most cases, the nitrogen atom was activated via its conversion to the corresponding pyridine *N*-oxide or *N*-iminopyridinium ylide.[9] The enhanced reactivity was attributed to the increased acidity of the C(2)−H bond caused by an electron-deficient nitrogen. However, this approach requires two additional steps: activation of the pyridine or quinoline starting materials and removal of the activating group from the product. The use of pyridines directly clearly represents the ideal situation in terms of cost and simplicity.

Recently, we have reported that the CDC reaction of simple unactivated alkanes with 1,3-dicarbonyl compounds or 2-phenylpyridine derivatives can be catalyzed by iron and ruthenium catalysts, respectively.[10] We also developed an alkylation method of pyridine *N*-oxide derivatives by reacting with

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(3) For reviews on the reactions of C−H bonds, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Dyker, G. *Angew Chem., Int. Ed.* **1999**, *38*, 1698. (c) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (f) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

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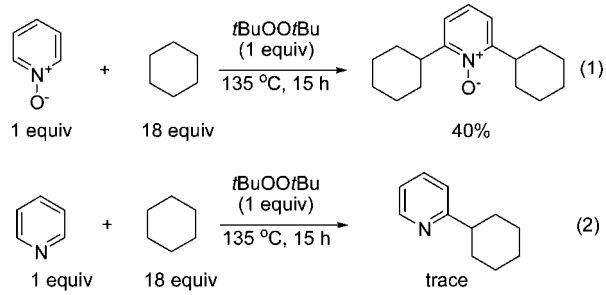
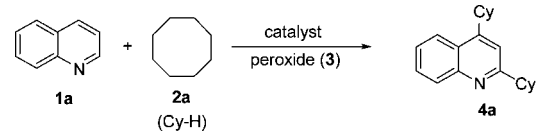
unactivated alkanes and a peroxide in the absence of a transition metal (eq 1).[11] Under similar conditions, however, unactivated pyridines or quinolines did not react with simple alkanes even when increasing the *tert*-butyl peroxide to 3 equiv (eq 2). Alternatively, we rationalized that it may be possible to increase the acidity of the C(2)−H bond on these heteroaromatic rings by using a Lewis acid (LA) catalyst and, thus, to increase the reactivity of pyridine derivatives similar to the use of pyridine *N*-oxide substrates. In a previous mechanistic study, Minisci found that direct alkylation of pyridine could be achieved in a very low yield by using iron catalyst (the yield based on pyridine is only 0.88%).[12] Obviously, an alternative catalyst is necessary to make the direct alkylation of pyridine derivatives more efficient.



We used quinoline as the standard substrate to look for an efficient catalyst. No desired product (**4a**) was observed when quinoline was reacted with cyclooctane together with **3a** in the absense of Lewis acid catalyst (Table 1, entry 1). Then, we tested various silver salts as Lewis acid catalysts for the reaction and are pleased to find that the bisalkylation product was obtained in 22% yield when adding 10 mol % silver fluoride (entry 2). Other silver salts such as $AgBF_4$, $AgPF_6$, and AgOTf are more efficient for this reaction, and the bisalkylation product was achieved in 66%, 77%, and 73% yields, respectively. Subsequently, various Lewis acid metal complexes were investigated under similar conditions and all showed catalytic activity in various efficiencies (entries 6−10). Among the Lewis acids tested, $Sc(OTf)_3$ showed the best catalytic activity, which gave 91% yield of the bisalkylation product with 10 mol % $Sc(OTf)_3$ as catalyst (entry 10).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)		peroxide (equiv)		yield [b]
1	------			(2.0)	trace
2	AgF	(10)	(3a)	(2.0)	22
3	$AgBF_4$	(10)	(3a)	(2.0)	66
4	$AgPF_6$	(10)	(3a)	(2.0)	77
5	AgOTf	(10)	(3a)	(2.0)	73
6	$In(OTf)_3$	(10)	(3a)	(2.0)	78
7	$La(OTf)_3$	(10)	(3a)	(2.0)	68
8	$Yb(OTf)_3$	(10)	(3a)	(2.0)	81
9	$Bi(OTf)_3$	(10)	(3a)	(2.0)	78
10	$Sc(OTf)_3$	(10)	(3a)	(2.0)	91
11	$Sc(OTf)_3$	(10)		(3b) (2.0)	74
12	$Sc(OTf)_3$	(10)		(3c) (2.0)	trace
13	$Sc(OTf)_3$	(10)		(3d) (2.0)	20
14	$Sc(OTf)_3$	(10)		(3e) (2.0)	56
15 [c]	$Sc(OTf)_3$	(10)	(3a)	(2.0)	46
16	$Sc(OTf)_3$	(10)	(3a)	(1.0)	52
17 [d]	$Sc(OTf)_3$	(10)	(3a)	(2.0)	61
18	$Sc(OTf)_3$	(5)	(3a)	(2.0)	93
19	$Sc(OTf)_3$	(1)	(3a)	(2.0)	57

[a] Conditions: **1a** (0.5 mmol), **2a** (7.45 mmol, 1.0 mL), **3** (1.0 mmol), 135 °C, 16 h, under air unless otherwise noted. [b] Determined by ^{1}H NMR using 1,2-dichloroethane as an internal standard; yields based on quinoline utilized. [c] Reaction was carried out at 120 °C. [d] 5 equiv of **2a** was used.

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(5) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (c) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (g) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (h) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (i) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (j) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (k) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505. For an account, see: Li, C.-J. *Acc. Chem. Res.* **2009**, ASAP.

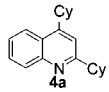
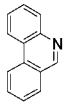
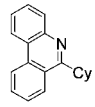
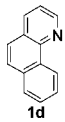
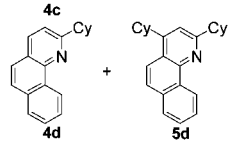
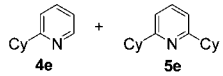
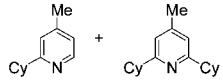
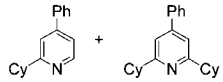
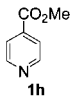
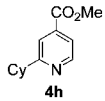
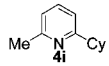
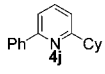
(6) (a) Eberson, L.; Gomez-Gonzalez, L. *Acta Chim. Scand.* **1973**, *27*, 1249. (b) Yoshimoto, H.; Itatani, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2490. (c) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (f) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew Chem., Int. Ed.* **2008**, *47*, 1301. (g) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (h) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew Chem., Int. Ed.* **2008**, *47*, 1115. (i) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (j) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (k) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 7666.

The uses of other peroxides are less effective (entries 11−14). Dicumyl peroxide (**3b**) gave the bisalkylation product in 74% yield (entry 11). Only a trace amount of the coupling product was obtained with *tert*-butyl peroxybenzoate (**3c**) (entry 12). Decreasing the reaction temperature (entry 15) or the amount of peroxide (entry 16) lowered the product yield. A good yield could still be obtained by decreasing the amount of cycloalkane to 5 equiv (entry 17). When the reaction was carried out in an atmosphere of nitrogen, the yield was slightly lower than in air. It is worth noting that a high yield could be achieved when the amount of the catalyst loading was decreased to 5 mol % (entry 18). A lower yield was obtained when we further decreased the catalyst loading to 1 mol % (entry 19).

With the optimized conditions in hand, various quinolines and pyridines were investigated (Table 2). Only monoalkylation products were obtained when isoquinoline (**1b**) and phenanthridine (**1c**) were used as the substrates, and the desired products were obtained in 74% and 91% yields, respectively (entries 2 and 3).[13] With 7,8-benzoquinoline (**1d**), however, mono- and bisalkylation products were formed in an 84% combined yield (entry 4). Interestingly, the alkylation of pyridine only occurred at the ortho position of nitrogen, and no para alkylation product was observed (entry 5) which is in sharp contrast to the pyridine *N*-oxide substrate.[11] Various substituents at the para position did not affect the reaction significantly (entries 5−7). However, only a trace amount of the alkylation product was observed when there is a methoxy group at the 4-position of pyridine. The reaction could also tolerate an ester functional group, which afforded the monoalkylation product as the major product in a moderate yield (entry 8). With substituents at the 2-position, the reactions only occurred at the 6-position to give the desired products in moderate yields (entries 9 and 10).[14]

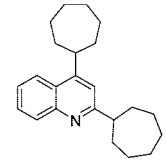
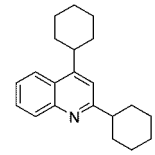
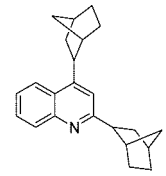
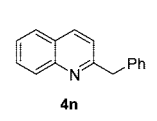
Cycloheptane, cyclohexane, and norbornane all reacted smoothly with quinoline to give the desired C−H/C−H coupling products (Table 3, entries 1−3). When toluene was used as a reagent, both monoalkylation and bisalkylation products were obtained in a good overall yield (entry 4). The

Table 2. Alkylation of Quinolines and Pyridines with Cyclooctane (**2a**)[a]

entry	substrate	product	isolated yield (%)
1	 **1a**	 **4a**	72
2	 **1b**	 **4b**	74
3	 **1c**	 **4c**	91
4	 **1d**	 **4d** + **5d**	84 (**4d**:**5d** = 2.5:1)
5	 **1e**	 **4e** + **5e**	64 (**4e**:**5e** = 1:1.3)
6	 **1f**	 **4f** + **5f**	68 (**4f**:**5f** = 1:1)
7	 **1g**	 **4g** + **5g**	71 (**4g**:**5g** = 1:1.5)
8	 **1h**	 **4h**	52
9	 **1i**	 **4i**	53
10	 **1j**	 **4j**	52

[a] Conditions: **1a** (0.5 mmol), **2a** (1.0 mL, 7.4 mmol), **3a** (1.0 mmol), $Sc(OTf)_3$ (0.025 mmol), 135 °C, 16 h, under air.

Table 3. Quinoline (**1a**) Reacts with Alkanes (**2**)[a]

entry	alkanes	products	isolated yield (%)
1	 **2b**	 **4k**	71
2	 **2c**	 **4l**	51
3	 **2d**	 **4m**	51
4	 **2e**	 **4n** + **5n**	62 (4n:5n=1:1)

[a] Conditions: $Sc(OTf)_3$ (0.025 mmol), quinoline (0.5 mmol), **2** (7.4 mmol), **3a** (1.0 mmol), 135 °C, 16 h, under air.

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(8) For recent successful examples of direct functionalization of pyridines and quinolines, see: (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (b) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.

reaction between quinoline and linear alkane such as heptane also gave the alkylation product in >70% yield (measured by ^{1}H NMR); however, we were unable to separate the different regioisomers due to the reactions of different carbons of heptane.

In conclusion, a novel C−C bond formation based on the direct oxidative C−H/C−H coupling involving nitrogen−heteroarenes and cycloalkanes has been developed. The alkylation occurs selectively at the carbon adjacent to the nitrogen. The reaction was succeeded by using a Lewis acid to increase the reactivity of pyridine and quinoline derivatives. $Sc(OTf)_3$ showed the best activity among all Lewis acids tested. The scope, mechanism, and application of this reaction are under investigation.

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Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For recent examples of direct functionalization of pyridine *N*-oxide and *N*-iminopyridinum ylide, see: (a) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J. P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.

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(13) Tetrahydroisoquinoline also reacted with cyclooctane and gave **4b** in 64% yield when 3 equiv of *tert*-butyl peroxide was used.

(14) In all cases, no alkylation of pyridine and quinoline derivatives at the meta-position of nitrogen was observed. For quinoline, a trace amount of monoalkylation product was observed with alkylation occurring at the ortho position of nitrogen.