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Palladium-Catalyzed Minisci Reaction with Simple Alcohols

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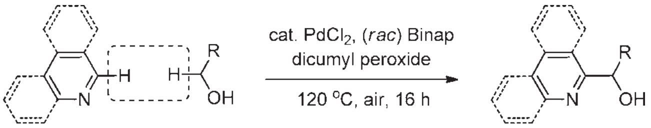
ABSTRACT



A palladium-catalyzed coupling of N-heterocycles with simple alcohols was achieved. The reaction is initiated by peroxide and does not require the use of stoichiometric acid for activation of the heterocycle.

C–H activation of alcohols and ethers has garnered much interest due to the ease of generating a new C–C bond and simple introduction of an oxygen-containing functional group into the molecule at the same time.[1] Although great progress has been made for the coupling of alcohols to alkynes and alkenes, through a transfer hydrogenative pathway,[2] the direct and selective activation of the α sp^3 C–H of alcohols still remains particularly challenging to chemists.

Early studies in this field by Minisci[3] describe the hydroxymethylation and hydroxyethylation of heterocyclic bases, in the presence of peroxides and stoichiometric amounts of acid, in moderate and low yields respectively. In 2006, a $Co(acac)_2$/*N*-hydroxyphthalimide (NHPI) catalyzed addition of secondary alcohols to electron-deficient alkynes was explored by Ishii.[4] Similar to Minisci's work, this reaction was initiated by an α H-radical abstraction from the alcohol by the phthalimide *N*-oxyl (PINO) radical. In 2009, Liu[5] and co-workers published a *tert*-butyl hydroperoxide (TBHP) initiated addition of alcohols to alkynes in the absence of metal catalysts.

Recently, Tu demonstrated the metal-catalyzed C–C coupling of alcohols and alkenes.[6] The reaction could be performed using Ru, Rh, or Pd catalysts, in the presence of a strong Lewis acid ($BF_3 \cdot OEt_2$) for activation of the alcohol. More recently, they were able to perform this reaction with $FeCl_3$.[7]

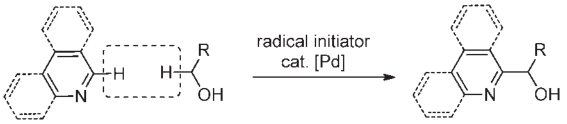


Figure 1. Palladium-catalyzed dehydrogenative coupling between ethanol and isoquinoline.

We considered the possibility of a cross-coupling between alcohols and N-heterocycles via metal catalysis, circumventing the need for stoichiomeric acid for protonation of the heterocycle. Herein we describe a palladium-catalyzed

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(1) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937.

(2) For reviews, see: (a) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008**, *41*, 95. (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (c) Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron* **2009**, *65*, 5024.

(3) (a) Minisci, F. *Synthesis* **1973**, 1. (b) Minisci, F; Vismara, A.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1986**, *51*, 476. (c) Minisci, F; Cetterio, A.; Vismara, A.; Giordano, C. *Tetrahedron Lett.* **1985**, *26*, 617.

(4) Oka, R.; Nakayama, M.; Sakaguchi, S.; Ishii, Y. *Chem. Lett.* **2006**, *35*, 1104.

(5) Liu, Z.-Q.; Sun, L.; Wang, J.-G.; Han, J.; Zhao, Y.-K.; Zhou, B. *Org. Lett.* **2009**, *11*, 1437.

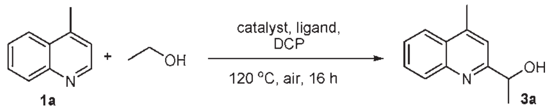
(6) (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836. (b) Jiang, Y.-J.; Tu, Y.-Q.; Zhang, E.; Zhang, S.-Y.; Cao, K.; Shi, L. *Adv. Synth. Catal.* **2008**, *350*, 552. (c) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Shi, L.; Cao, K.; Zhang, E. *Chem.—Eur. J.* **2008**, *14*, 10201.

(7) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8761.

10.1021/ol201774b

Minisci reaction of quinolines and isoquinolines with simple alcohols (Figure 1).

Table 1. Optimization of Reaction Conditions



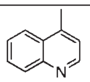
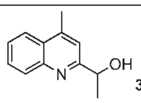
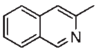
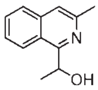
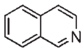
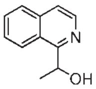
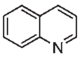
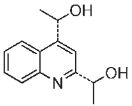
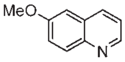
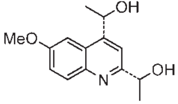
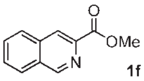
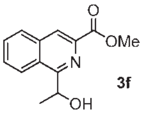
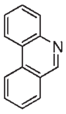
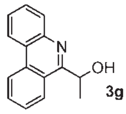
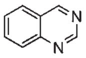
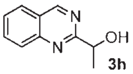
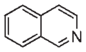
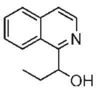
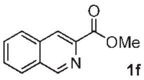
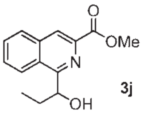
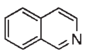
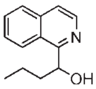
entry[a]	catalyst (mol %)	DCP	yield (%)[b]
1	$Sc(OTf)_3$ (5)	3	8
2	$FeCl_3$ (5)	3	n.d.
3	$InCl_3$ (5)	3	21
4	–	3	n.d.
5	$PdCl_2$ (5)	3	44
6	(*rac*)Binap (5)	3	n.d.
7	$PdCl_2$/(*rac*)Binap (5)	3	74
8	$RhCl_3/PPh_3$ (5/10)	3	45
9	$PdCl_2$/(*rac*)Binap oxide (5)	3	21
10	$PdCl_2$/(*rac*)Binap (5)	3.5	78
11	$PdBr_2$/(*rac*)Binap (5)	3.5	43
12	$PdCl_2(PPh_3)_2$	3.5	41
13[c]	$PdCl_2$/(*rac*)Binap (5)	3.5	68
14[c]	–	3	24

[a] Conditions: 0.2 mmol of **1a**, 1 mL of ethanol, catalyst, ligand, and DCP at 120 °C in air for 10 h unless otherwise noted. [b] NMR yield %. [c] 10 mol % HCl. n.d.: none detected. DCP: dicumyl peroxide.

We chose ethanol and lepidine as initial substrates owing to the ease of identification of the product (**3a**) and lack of regioisomers formed. Interestingly, unlike our previous work[8] with cycloalkanes and N-heterocycles, we found $Sc(OTf)_3$ to be an inefficient catalyst for this reaction; **3a** could only be obtained in very low yields (Table 1, entry 1). Other Lewis acids were tested; no product was detected with $FeCl_3$; however a slightly better yield was achieved with $InCl_3$. We were happy to find that the yield could be increased to 44% with palladium dichloride (entry 5) and, in the presence of *(rac)*Binap, **3a** could be furnished in 74% yield (entry 7). Rhodium could also afford the product, but at a lower yield (entry 8). A decreased yield was obtained if *(rac)*Binap was replaced with *(rac)*Binap oxide (entry 9). Increasing the amount of dicumyl peroxide (DCP) in the system increased the conversion of the starting material thereby increasing the yield (entry 10). Other palladium catalysts were also tested (entries 11 and 12); however they were found to be inferior to the $PdCl_2$/*(rac)*Binap system. The reaction cannot be realized in the presence of dicumyl peroxide alone or in the absence of palladium (entries 4 and 6). As the Minisci reaction requires stoichiometric amounts of acid, we wondered whether a catalytic amount of HCl could improve the yield. However, we found that the yield decreased slightly upon addition of HCl (compare entries 10 and 13). Moreover, a control experiment was run using only 10 mol % HCl and no palladium catalyst with only 24% of the product obtained.

A variety of nitrogen containing heterocycles were subjected to these optimized conditions. Quinolines and isoquinolines were found to be acceptable substrates for this reaction affording the product in moderate to good yields. Owing to the lack of regioselectivity of quinoline and 6-methoxyquinoline, alkylation on the 2- and 4-positions as well as bis-addition products were obtained (Table 2, entries 4 and 5). As expected, the electron-rich substrate, 6-methoxyquinoline, provided the product in low yields. On the other hand, the electron-poor substrate, methyl 3-isoquinolinecarboxylate, reacted smoothly and with

Table 2. Scope of the Reaction between Simple Alcohols and N-Heterocycles

entry[a]	heterocycle	alcohol	product	yield %[b]
1	 **1a**	ethanol	 **3a**	71
2	 **1b**	ethanol	 **3b**	64
3	 **1c**	ethanol	 **3c**	76
4	 **1d**	ethanol	 **3d** (C2:C4 bis)	62 (38:10:14)
5	 **1e**	ethanol	 **3e** (C2:C4:bis)	39 (27:6:6)
6	 **1f**	ethanol	 **3f**	78
7	 **1g**	ethanol	 **3g**	74
8	 **1h**	ethanol	 **3h**	n.d.
9[c]	 **1a**	*n*-propanol	 **3i**	25
10[c]	 **1f**	*n*-propanol	 **3j**	60
11[c]	 **1a**	*n*-butanol	 **3k**	27

[a] Conditions: 0.2 mmol of heterocycle, 1 mL of alcohol, 5 mol % $PdCl_2$, 5 mol % (*rac*) Binap, 3.5 equiv of DCP at 120 °C in air for 16 h unless otherwise noted. [b] Isolated yields. [c] At 135 °C with 3 equiv of DCP.

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[8] (a) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171. For an account on CDC reactions, see: (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

good yield (entry 6). These reaction conditions were found to be ineffective for the addition of ethanol to quinazoline (entry 8). Unfortunately the reaction scope is limited to simple alcohols at this time. A small change in the reaction conditions (higher temperature and decrease in amount of peroxide) was found to be optimal for reaction with propanol and butanol (entries 9–11).

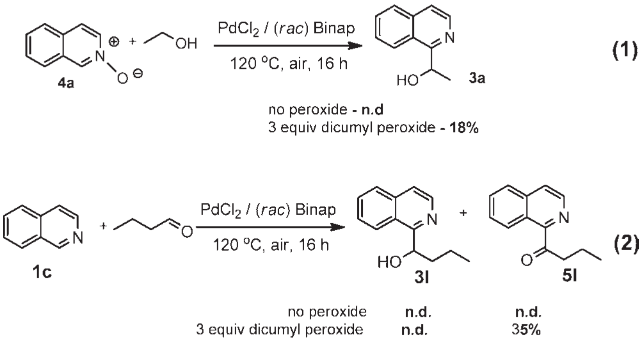

Figure 2. (1) Reaction of isoquinoline *N*-oxide with ethanol. (2) Reaction of isoquinoline with butryaldehyde.

To determine whether the peroxide was used as an oxidant to create a highly reactive *N*-oxide *in situ*, isoquinoline *N*-oxide was subjected to the reaction conditions.[9] An 18% yield of **3a** was obtained in the presence of DCP, and no product was detected in the absence of peroxide. This led us to eliminate *N*-oxide as an intermediate in this reaction (Figure 2, eq 1). Similarly, we tested the possibility of the peroxide oxidizing the alcohol to the aldehyde *in situ* and the subsequent addition of the heterocycle to the aldehyde. On reacting isoquinoline with *n*-butanal, **3l** was not detected, in either the presence or absence of peroxide. However, ketone **5l** was obtained in the presence of peroxide (Figure 2, eq 2).

From these results we believe that the reaction proceeds through a radical mechanism[10] similar to the Minisci reaction.[3] Initiation of the reaction involves generation of the cumyl peroxide radical under heating. This radical next abstracts the α hydrogen of the alcohol. The nucleophilic carbon centered radical can add to the N-heterocycle, and rearomatization of the heterocycle is achieved through H-atom abstraction. We are unsure of the role that palladium plays in this reaction;[11] however it is possible that palladium may be participating in the generation or stabilization[6b] of the radical intermediate.

In summary we have established a transition-metal-catalyzed Minisci reaction. Unlike previous studies on carbon centered radical additions to N-heterocycles,[3,12] this reaction can be performed without the need for a stoichiometric amount of acid. Further development of this chemistry and expansion of the scope to different alcohols are currently underway in our group.

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Supporting Information Available. Experimental detail and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Deng, G. J.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem.—Eur. J.* **2009**, *15*, 333.

[10] Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50* 5018.

[11] Although HCl may be formed in situ from palladium-catalyzed activation of the alcohol, we do not believe that this is the primary role of the catalyst. In addition to the control experiment with 10 mol % HCl (Table 1, entry 11), the reaction of lepidine and ethanol was also performed in the presence of 10 mol % lepidine·HCl but in the absence of palladium dichloride; 35% of the product was obtained. Like the traditional Minisci reaction, acids can catalyze the addition in low yields; however we found that the metal catalyst system was needed to obtain good yields.

[12] (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *13*, 13194. For photochemical reactions, see: (b) Stermitz, F. R.; Wei, C. C.; O'Donnell, C. M. *J. Am. Chem. Soc.* **1970**, *92*, 2745. (c) Castellano, A.; Catteau, J. P.; Lablache-Combier, A.; Planckaert, B.; Alan, G. *Chem. Heterocycl. Compd.* **1974**, *10*, 755 and references cited therein.