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Synthesis of Multicyclic Pyridine and Quinoline Derivatives via Intramolecular C−H Bond Functionalization

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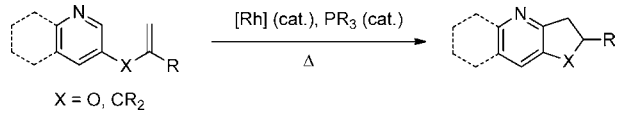
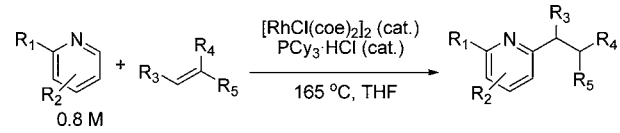
ABSTRACT



An efficient method is reported for the preparation of multicyclic pyridines and quinolines by a rhodium-catalyzed intramolecular C−H bond functionalization process. The method shows good scope for branched and unbranched alkyl substituents on the pyridine ring and at the R position of the tethered alkene group. Starting materials capable of undergoing olefin isomerization to provide terminal 1,1-disubstituted alkenes also proved to be effective substrates.

The synthesis of *N*-heterocycles is an important area of research due to their prevalence in natural products and drugs.[1] Of the *N*-heterocycles, pyridines are the most extensively used in pharmaceutical research,[2] and much effort has been devoted to their synthesis.[3,4] The functionalization of C−H bonds provides an atom-economical and direct approach for the preparation of substituted pyridines.[5,6] Our group has previously developed a method for the Rh(I)-catalyzed intermolecular alkylation of pyridines and quinolines to produce *ortho*-alkylated products (Scheme 1).[6] Significantly, pyridines lacking substitution at the 2-position (R^1 = H) as well as 2,5-disubstituted pyridines did not undergo alkylation. Presumably, substituents at the 2- and 5-positions introduce steric interactions that either promote or attenuate, respectively, the propensity of forming the

Scheme 1. Rh(I)-Catalyzed Intermolecular Alkylation of Quinolines and Pyridines via C−H Bond Activation



(1) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, 2000.

(2) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347. (b) Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627.

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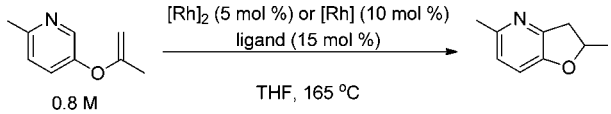
C-bound Rh complex necessary for C−H functionalization relative to the *N*-bound form.[7] Herein, we report an expansion of substrate scope for pyridine alkylation to include intramolecular cyclization of pyridines with alkenes tethered to the 5-position of the pyridine substrates. This cyclization method provides a new reaction pathway for the efficient preparation of underrepresented classes of complex bicyclic pyridines and tricylic quinolines that have considerable potential as useful scaffolds in drug discovery.[8]

Our investigation started with an examination of the enol ether tethered 2-methylpyridine substrate **1** using the optimized conditions for the intermolecular alkylation of pyridines: $[RhCl(coe)_2]_2$ as the precatalyst and PCy_3·HCl as an optimal ligand−additive combination (Table 1).[9,10] Under

Table 1. Alkylation of Enol-Tethered 2-Methylpyridine[a]



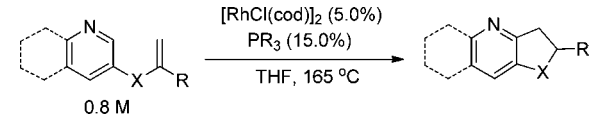
entry	catalyst	ligand[b]	yield[c] (%)
1	$[RhCl(coe)_2]_2$	PCy_3·HCl	70 (24 h)
2	$[RhCl(coe)_2]_2$		0
3		PCy_3·HCl	0
4	$[RhCl(coe)_2]_2$	PCy_3	70 (15 h)
5	$RhCl(PPh_3)_3$		0
6	$[RhCl(coe)_2]_2$	PPh_3	0
7	$[RhCl(coe)_2]_2$	$P(t\text{-}Bu)_3$	31 (24 h)
8	$[RhCl(coe)_2]_2$	PAd_2Bu	100 (24 h)
9	$[RhCl(cod)]_2$	PCy_3	99 (24 h)
10	$[RhCl(cod)]_2$	PAd_2Bu	99 (24 h)

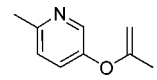
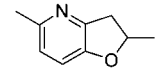
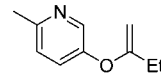
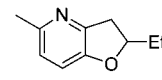
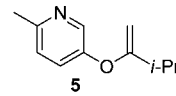
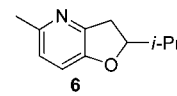
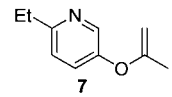
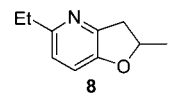
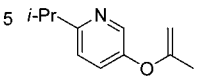
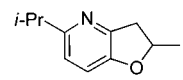
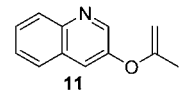
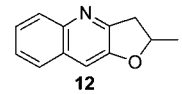
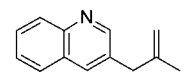
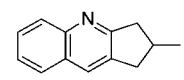
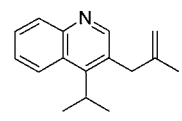
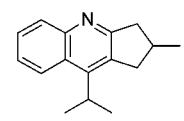
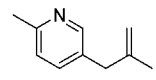
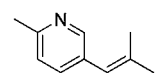
[a] Partial screening data are listed. See the Supporting Information for more details. [b] coe = *cis*-cyclooctene, cod = cyclooctadiene. [c] Reported yields are NMR yields, determined by ^1H NMR spectroscopy relative to an internal standard.

these conditions, cyclized product **2** was obtained in 70% yield (Table 1, entry 1). Thus, the tethered enol ether function located at the *meta* position of pyridine substrates does not block the intramolecular *ortho* C−H activation. Upon examination of the effects of other reaction parameters[9] (Rh-catalysts, ligands, additives, solvents, temperatures, and concentrations), no cyclization was observed in the absence of phosphine ligand or rhodium (entries 2 and 3). Notably, the HCl additive does not have a dramatic effect on the reaction (entry 4), which contrasts with the corresponding intermolecular reactions where alkylation only occurred in the presence of the acid catalyst.[6] We then undertook extensive ligand screening (partial ligand screening data are listed in Table 1, entries 5−10) and found that PCy_3 and PAd_2Bu are optimal (entries 4 and 8−10). Although both $[RhCl(coe)_2]_2$ and $[RhCl(cod)]_2$ precatalysts gave good results (entries 2 and 8−10), we elected to use $[RhCl(cod)]_2$ for all subsequent studies due to its air and thermal stability, commercial availability, and higher reaction yield.

After investigation of other parameters, we found that optimal reaction conditions are 5% $[RhCl(cod)]_2$ loading with 15% phosphine ligand and 0.8 M of substrate in THF at 165 °C.[11] Investigation of substrate scope (Table 2) revealed that PCy_3 in general gives similar or slightly better yields than PAd_2Bu for enol ether tethered substrates (Table 2, entries 1−7). Variation of the R group on the tethered enol ether

Table 2. Investigation of Substrate Scope



entry	substrate	product	ligand	yield (%)[a]
1	 1	 2	PCy_3	100 (96)
2	 3	 4	PCy_3	99 (95)
3	 5	 6	PCy_3	58 (50)
4	 7	 8	PCy_3	80 (78)
5	 9	 10	PCy_3	58 (55)
6	 11	 12	PCy_3	80 (78)
7	 13	 14	PAd_2Bu	72 (71)
8	 15	 16	PAd_2Bu	70 (65)
9	 17	 18	PAd_2Bu	100 (95)

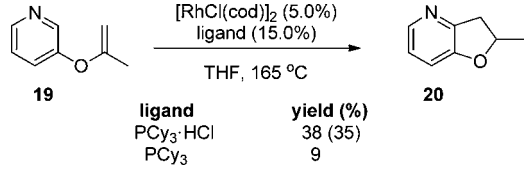
[a] NMR yields determined by ^1H NMR spectroscopy relative to an internal standard. Yields in parentheses correspond to isolated yields of pure product after column chromatography.

(7) Carmona and Esteruelas have provided careful studies of the effect of steric interactions upon the equilibrium between *N*- and *C*-bound transition-metal complexes. (a) Alvarez, E.; Conejero, S.; Paneque, M.; Petronilho, A.; Poveda, M. L.; Serrano, O.; Carmona, E. *J. Am. Chem. Soc.* **2006**, *128*, 13060. (b) Esteruelas, M. A.; Fernandez-Alvarez, F. J.; Onate, E. *J. Am. Chem. Soc.* **2006**, *128*, 13044.

group from methyl (**1**) to ethyl (**3**) or isopropyl (**5**) leads to the formation of cyclized products in 99% (**2** and **4**) and 58% (**6**) yields, respectively (entries 1−3). Variation of the *ortho*-pyridine substituent from methyl (**1**) to ethyl (**7**) or isopropyl (**9**) also results in good conversion to the fused products in 80% (**8**) and 58% (**10**) yields, respectively (entries 4 and 5). Enol ether tethered quinoline substrate **11** also undergoes cyclization in 80% yield (entry 6). On the other hand, for the allyl-tethered quinoline substrates (entries 7 and 8), the PAd_2Bu ligand was found to minimize the competitive double-bond isomerization pathway, resulting in higher cyclization yields. Unfortunately, for allyl-tethered pyridine substrate **17** only the conjugated pyridine product **18** that resulted from double-bond isomerization was observed (entry 9).

In contrast to intermolecular pyridine alkylation where *ortho* substitution is required for alkylation to proceed,[6] substrate **19**, which lacks alkyl substitution at the *ortho* position, undergoes cyclization under the reaction conditions (Scheme 2). In the case of substrate **19**, using PCy_3·HCl as a ligand results in a great improvement in yield (PCy_3·HCl gives 38% cyclized product while PCy_3 gives <10% product). It is likely that Rh coordination to the tethered alkene helps to promote C−H bond functionalization at the proximal site. In addition to no substitution and alkyl substitution at the 2-position of the pyridine ring, 2-chloro substitution was also investigated, but no reaction was observed.

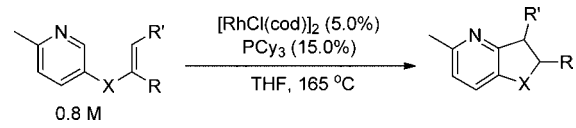
Scheme 2. Cyclization of Unsubstituted Pyridine[a]

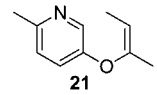
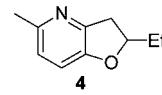
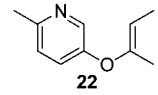
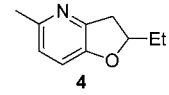
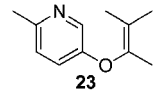
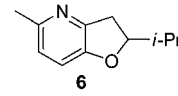
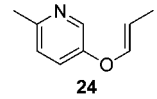
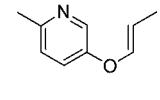
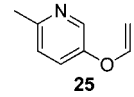
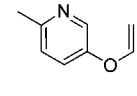


[a] NMR yields determined by ^{1}H NMR spectroscopy relative to an internal standard. Yield in parentheses corresponds to isolated yields of pure product after column chromatography.

We also investigated the effects of different alkyl substituents on the tethered enol ether function (Table 3). Substrates **21**−**23** (entries 1−3) undergo intramolecular alkylation; however, the bicyclic pyridine products (**4** and **6**) were observed as a consequence of olefin isomerization to the less substituted 1,1-disubstituted regioisomer prior to cyclization (Scheme 3). Olefin isomerization is well-documented with Rh catalysts, including for intramolecular azole alkylation substrates.[12] The observation that 1,2-disubstituted alkenes (**24**) do not cyclize is also consistent with the presence of β-substituents on the vinyl ether group impeding the cyclization rate (entry 4). However, α-substitution on the vinyl ether group also appears to be required for cyclization because the unsubstituted vinyl ether **25** was found to be unreactive (entry 5).

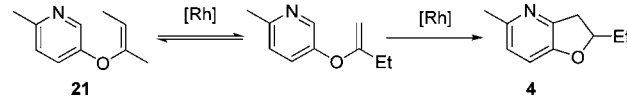
Table 3. Cyclization of Isomerizable Tethered Alkene Substrates



entry	substrate	product	yield (%)[a]
1	 **21**	 **4**	99
2	 **22**	 **4**	83
3	 **23**	 **6**	60
4	 **24**		No Reaction [b]
5	 **25**		No Reaction [c]

[a] Reported yields are NMR yields, determined by ^{1}H NMR spectroscopy relative to an internal standard. [b] *E*/*Z* isomerization was observed. [c] Hydrolysis of the enol group was observed.

Scheme 3. [Rh]-Catalyzed Olefin Isomerization Prior to Cyclization Reaction



(8) For recent literature on fused pyridines as potent kinase inhibitors, see the following: (a) Chiou, M.; Samadi, A.; Soriano, E.; Lozach, O.; Meijer, L.; Marcro-Contelles, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4566. (b) Saavedra, O.; Claridge, S.; Zhan, L.; Raeppel, F.; Granger, M.-C.; Raeppel, S.; Mannion, M.; Gaudette, F.; Zhou, N.; Isakovic, L.; Bernstein, N.; Déziel, R.; Nguyen, H.; Beaulieu, N.; Beaulieu, C.; Dupont, I.; Wang, J.; Macleod, A. R.; Besterman, J. M.; Vaisburg, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6836. (c) Cusack, K.; Allena, H.; Bischoffa, A.; Clabbersa, A.; Dixona, R.; Stenzela, S. F.; Friedmana, M.; Gaumonta, Y.; Georgea, D.; Gordona, T.; Grongsaarda, P.; Janssena, B.; Jiaa, Y.; Moskeya, M.; Quinna, C.; Salmerona, A.; Thomasa, C.; Wallacea, G.; Wisharta, N.; Yua, Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1722. (d) Wu, J.-P.; Fleck, R.; Brickwood, J.; Capolino, A.; Catron, K.; Chen, Z.; Cywin, C.; Emeigh, J.; Foerst, M.; Ginn, J.; Hrapchak, M.; Hickey, E.; Hao, M. H.; Kashem, M.; Li, J.; Liu, W.; Morwick, T.; Nelson, R.; Marshall, D.; Martin, L.; Nemoto, P.; Potocki, I.; Liuzzi, M.; Peet, G. W.; Scouten, E.; Stefany, D.; Turner, M.; Weldon, S.; Zimmitti, C.; Spero, D.; Kelly, T. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5547. (e) Tumey, L. N.; Boschelli, D. H.; Lee, J.; Chaudhary, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4420.

(9) See the Supporting Information for experimental details of substrate preparation and screening of reaction conditions.

(10) These conditions were also found to be optimal for intermolecular azole alkylation: Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329.

In conclusion, cyclization of tethered pyridines and quinolines produces multicyclic derivatives via C−H activation. The cyclization reactions show good scope for branched and unbranched alkyl substituents on the pyridine ring and at the α-position of the vinyl ether group. Morever, isomerization of the double bond on the alkene tether enables cyclization to be accomplished via isomerization of trisubstituted enol ether substrates. Expansion of the synthetic utility of this method, including exploration of enantioselective catalytic cyclizations, is currently in progress.

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Supporting Information Available: Full experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Lowering catalyst loading, effective concentration of substrate and temperature result in much lower yield and slower rate of reaction. See the Supporting Information for more details.

(12) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685. (b) Rech, J. C.; Yato, M.; Duckett, D.; Ember, Brian; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490. (c) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 5th ed.; Wiley: Hoboken, 2009; pp 229−230.