J|A|C|S
COMMUNICATIONS

Published on Web 04/06/2007

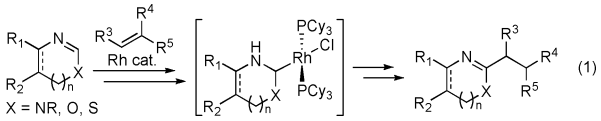
Rh(I)-Catalyzed Alkylation of Quinolines and Pyridines via C−H Bond Activation

Jared C. Lewis, Robert G. Bergman,* and Jonathan A. Ellman*

Department of Chemistry, University of California, and Division of Chemical Sciences, Lawrence Berkeley National Laboratory, Berkeley, California 94720

Received January 18, 2007; E-mail: jellman@berkeley.edu; rbergman@berkeley.edu

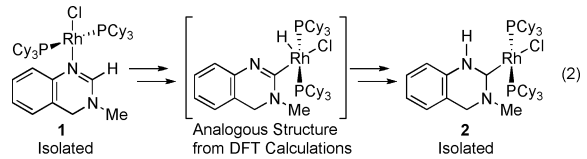
Elaboration of heterocycles through the application of carbon−carbon bond forming reactions via C−H bond activation constitutes a powerful approach for the preparation of functional molecules ranging from ligands for biomolecular targets to electroactive materials.[1] Our group developed a general method for the *ortho*-alkylation of nitrogen-containing heterocycles with olefins using a Rh(I)−phosphine catalyst[2] and gathered extensive evidence supporting the intermediacy of substrate-based *N*-heterocyclic carbene (NHC) complexes (eq 1).[3]



(1)

Consistent with this mechanism, the catalytic alkylation reaction to date has been reported only for heterocycles with two heteroatoms adjacent to and thereby capable of stabilizing the carbene center of the proposed intermediates.[4] Herein, we report dramatic expansion of substrate scope for this reaction by demonstrating the catalytic alkylation of heterocycles containing a single nitrogen, specifically pyridines and quinolines, which are extensively used in the pharmaceutical industry.[5] The alkylation of these *electron-deficient* heterocycles marks a significant departure from other direct functionalization methods,[6] which typically require directing groups[7] or electron-rich (hetero)arenes and proceed via electrophilic metalation.[8]

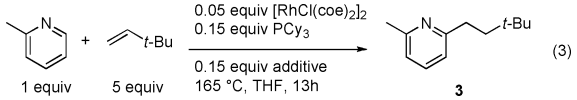
We recently conducted a detailed kinetic analysis of the conversion of heterocycle complex **1** to NHC complex **2** (eq 2) and utilized the acquired data, along with DFT calculations, to propose a reaction coordinate.[9] This work provided strong evidence that coordination of the heterocycle to the catalytically active $RhCl(PCy_3)_2$ fragment precedes an intramolecular C−H activation step, which provides a Rh−H intermediate that ultimately tautomerizes to the observed carbene complex.



(2)

The Carmona and Esteruelas groups have since reported the synthesis of (2-substituted)-pyridine- and quinoline-based Os, Ru, and Ir−NHC complexes directly from the corresponding heterocycles and a late transition metal complex.[10] The authors propose mechanisms analogous to that shown in eq 2, with substitution *ortho* to the heterocycle ring nitrogen being necessary to drive the equilibrium from an N-bound to the desired NHC complexes. We therefore sought to determine whether our Rh/PCy_3 catalyst system could be used to not only activate but also alkylate these heterocycles, presumably via an NHC intermediate.[11]

Table 1. Alkylation of 2-Methylpyridine[a]

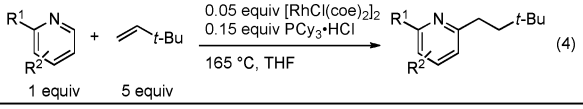


(3)

entry	phosphine	additive	conc (M)[b]	yield (%)[c]
1	PCy_3	none	0.1	0
2	PCy_3	$MgBr_2$	0.1	0
3	PCy_3	LutBr	0.1	16
4	PCy_3	LutCl	0.1	20
5	PCy_3·HCl	none	0.1	17
6	PCy_3·HCl	none	0.4	42
7	PCy_3·HCl	none	0.8	64

[a] coe = *cis*-cyclooctene; Lut = lutidinium. [b] Concentration of heterocycle in total reaction volume. [c] Determined by ^1H NMR spectroscopy relative to internal standard.

Table 2. Investigation of Heterocycle Scope



(4)

entry	heterocycle		time (h)	#	yield (%)[a]
1	R =	Me	14	**3**	59
2	R =	*i*-Pr	14	**4**	83
3	R =	TIPS	24	**5**	64
4	R =	OMe	14	**6**	96
5	R =	H	9.5	**7**	98
6	R =	CO_2Me	7	**8**	96

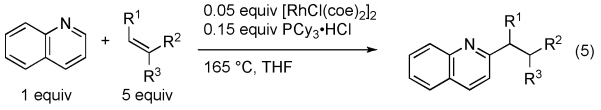
[a] Isolated yield of pure product.

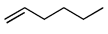
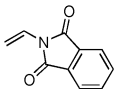
Our investigation commenced with an examination of catalysts and additives to affect the coupling of 2-methylpyridine and 3,3-dimethylbutene (eq 3, Table 1).[12] No conversion was observed when no additive or Lewis acids such as $MgBr_2$ were used. However, we were pleased to find that the use of the Rh/PCy_3 catalyst system in combination with a Brønsted acid provided the desired alkylated product, **3**. PCy_3·HCl was found to be the optimal acid additive as was previously observed for azoles.[2b] Notably, increasing the substrate concentration to 0.8 M greatly improved the yield of **3** to 64%.

The scope of heterocycles compatible with the optimized alkylation conditions was next investigated (eq 4, Table 2). Increasing the bulk of the group located *ortho* to the pyridine ring nitrogen from methyl to isopropyl led to an increase in both alkylation rate and isolated yield of alkylated product **4**. *o*-Triisopropylsilyl (TIPS)-substituted pyridine was also an effective substrate (entry 3). This has significant synthetic utility because the silyl group can be removed, enabling additional transformations (vide infra). Consistent with the findings of Carmona and Esteruelas

10.1021/ja070388z CCC: $37.00

Table 3. Investigation of Olefin Scope[a]



entry	olefin	time (h)	#	yield (%)[a]
1		9.5	**7**	98
2		9.5	**9** **10**	80 (linear) 14 (branched)
3		9.5	**11**	96
4		19	**12**	91
5		19	**13**	90[c]
6		3.5	**14**	53
7		16	**15**	53[d]
8		14	**16**	57

[a] Unless specified, only the linear isomer was observed in cases where linear and branched products were possible. [b] Isolated yield of pure product. [c] A ca. 2:1 mixture of diastereomers. [d] 0.1 equiv of $[RhCl(coe)_2]_2$ and 0.3 equiv of PCy_3•1HCl used.

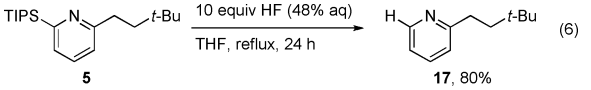
for carbene formation,[10] pyridine itself was alkylated in less than 5% yield when heated in the presence of excess olefin and catalyst.

A variety of quinolines were also alkylated under the reaction conditions. Parent quinoline provided nearly quantitative conversion to the corresponding alkylated quinoline (entry 5). Both ether and ester substitution were tolerated in the quinoline 6-position (entries 4 and 6). On the other hand, isoquinoline was not alkylated, which again supports the fact that *ortho* substitution, not simply the differing electronics of the benzo-fused heterocycle, is responsible for alkylation.

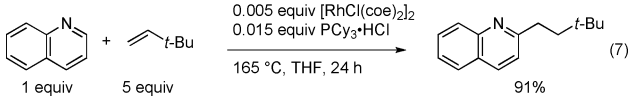
We next investigated the scope of olefins compatible with the reaction conditions (eq 5, Table 3). The isomerizable olefin, *n*-hexene, coupled to quinoline to provide quantitative conversion to the alkylated quinoline (entry 2). An 80:14 mixture of linear to branched isomers was observed which, in addition to providing a synthetically useful yield of the linear isomer, also indicated the feasibility of using disubstituted olefins as coupling partners. Indeed, cyclohexene could be used to alkylate quinoline in extremely high yield (entry 3). 1,1-Disubstituted olefins, including 2-methylpropene and camphene, were also effective coupling partners (entries 4 and 5). In a very preliminary investigation of functional group tolerance, both esters and phthalimides were found to be compatible with the reaction conditions (entries 6−8); however, styrene was not.

While substitution *ortho* to the pyridine nitrogen was required to obtain high yields of alkylated products, an *ortho*-silyl group serves as a suitable blocking group that can readily be removed to provide monoalkylated pyridines. For example, treatment of **5** with aqueous HF in refluxing THF provided the monoalkylated pyridine product **17** in good yield (eq 6).

We were also able to substantially reduce the catalyst loading required to affect the alkylation reaction. Specifically, quinoline



was alkylated with 3,3-dimethylbutene in 91% yield using only 1% of the Rh catalyst (eq 7).



In summary, we have developed a method for the Rh(I)-catalyzed alkylation of pyridines and quinolines. Consistent with the work of Carmona and Esteruelas, steric interactions provided by the *ortho*-substituent presumably increase the equilibrium from an N-bound to a C-bound Rh complex. We are currently investigating this hypothesis by undertaking efforts to isolate intermediate complexes and by performing DFT calculations on model structures. Continued expansion of the catalytic alkylation process to new classes of heterocycle and alkene inputs is also in progress.

Acknowledgment. This work was supported by the NIH GM069559 to J.A.E. and by the Director and Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC03-76SF00098 to R.G.B.

Note Added after ASAP Publication. A production error in Table 1, column 2, entry 5 was corrected after this paper was published ASAP on April 6, 2007. The corrected version was published ASAP on April 10, 2007.

Supporting Information Available: Experimental details, including analytical data for all compounds described, are included. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Kakiuchi, F.; Murai, S. *Top. Curr. Chem.* **1999**, *3*, 47. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (f) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, *20*, 3382.

(2) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (c) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329. (d) Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685. (e) Wiedemann, S. H.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2006**, *71*, 1969.

(3) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202. (b) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35.

(4) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1047.

(5) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(6) Ru-catalyzed heterocycle acylation is an exception. (a) Moore, E. J.; Pretzer, W. R.; O'Connel, T. J.; Harris, J.; LaBounty, L.; Cou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. (b) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493.

(7) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

(8) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

(9) Wiedemann, S. H.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 2452.

(10) (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.

(11) Jordan reported the Zr-catalyzed alkylation of 2-picoline using simple olefins. In all cases, the branched isomer of the product was favored. (a) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. (b) Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 4491. Murakami reported the Ru-catalyzed alkenylation of pyridine using alkynyl silanes. (c) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720.

(12) Reactions were conducted in sealed tubes fitted with Kontes stoppers and heated in an oil bath.

JA070388Z