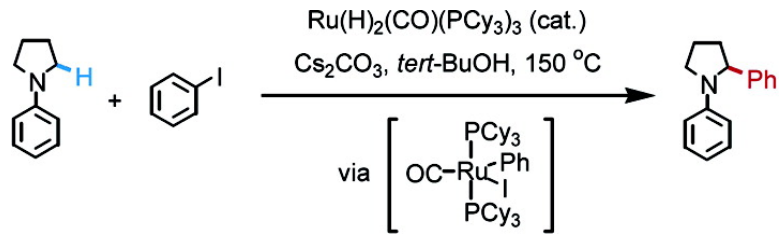
Communication

Selective and Catalytic Arylation of *N*-Phenylpyrrolidine: sp C–H Bond Functionalization in the Absence of a Directing Group

Beng Sezen, and Dalibor Sames

J. Am. Chem. Soc., **2005**, 127 (15), 5284-5285• DOI: 10.1021/ja050269o • Publication Date (Web): 23 March 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 03/23/2005

Selective and Catalytic Arylation of *N*-Phenylpyrrolidine: sp^3 C−H Bond Functionalization in the Absence of a Directing Group

Bengü Sezen and Dalibor Sames*

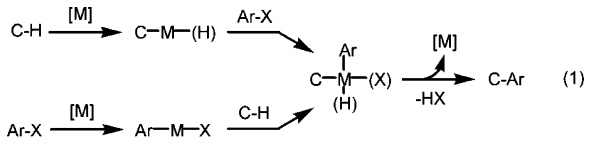
Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

Received January 14, 2005; E-mail: sames@chem.columbia.edu

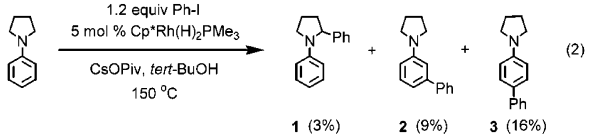
This paper was retracted on March 1, 2006 (*J. Am. Chem. Soc.* 2006, *128*, 3102).

Despite significant progress in the area of C−H bond functionalization, catalytic intermolecular transformations of sp^3 C−H bonds to C−C bonds still remain rare.[1] These few examples depend on the presence of a suitably situated directing group and, hence, suffer from a limited substrate scope.[2,3] In this paper, we report our studies on arylation of *N*-phenylpyrrolidine, which led to the development of a new catalytic system capable of selective arylation of sp^3 C−H bonds in the absence of a directing group.[4]

The direct coupling of an sp^3 C−H bond and a haloarene requires the introduction of an aryl group to the metal system (via oxidative addition of Ar−X) either before or after the C−H bond activation step (eq 1). To translate this simple scheme to practice, however, multiple challenges need to be addressed: (1) the selectivity for sp^3 C−H bonds over arene sp^2 bonds; (2) the suppression of β-hydride elimination; and (3) the suppression of dehalogenation in favor of C−C bond formation (Figure 1).



N-Phenylpyrrolidine was chosen as a suitable substrate for our studies. Although the higher reactivity of the methylene group adjacent to the amine ("activated" C−H bonds) is well recognized, a direct arylation of this position has not been achieved.[5] Our initial results with $Cp^*M(H)_2PR_3$ complexes[6] highlighted the selectivity issue discussed above as the arylation occurred predominantly on the phenyl ring (eq 2). The product distribution was in accord with the well-documented thermodynamic preference for the metalation of sp^2 over sp^3 C−H bonds.[7] Noteworthy is the fact, however, that the phenylation did occur, and these preliminary studies demonstrated the feasibility of intermolecular arylation of benzene rings in the absence of a directing group. It should be noted that the key to success was the judicious choice of base and solvent.



With the focus on sp^3 C−H bonds, however, we decided to explore ruthenium−pyrrolidine carbene complexes, prepared by metalation of pyrrolidines in Caulton's group[8] as possible intermediates in the arylation reaction. Having failed to obtain any stable complexes from the reaction of *N*-phenylpyrrolidine with the Caulton complex $\{Ru(H)(Cl)[P(iPr)_3]_2\}_2$, we turned our attention to the known carbene complex, derived from *N*-methylpyrrolidine. When treated with iodobenzene, this complex gave only traces of the arylation products (Supporting Information).

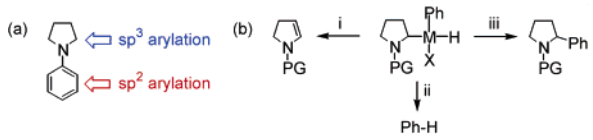
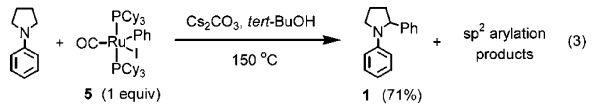


Figure 1. Challenges: (a) sp^3 versus sp^2 C−H bond arylation; (b) competing pathways following the C−H bond activation step; i. β-H elimination, ii. dehalogenation of PhX, and iii. C−C bond formation.

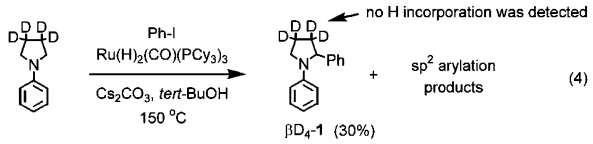
Although the involvement of the carbene complexes seemed unlikely, our interest in ruthenium complexes was not diminished, due to their low propensity for β-hydride elimination.[8] The first lead was obtained with $Ru(H)_2(CO)(PPh_3)_3$, which not only showed good selectivity for the α-CH_2 position but also underwent catalytic turnover (14% yield, Table 1). Encouraged by this exciting discovery, we modified the catalyst by replacing triphenylphosphine with more electron donating and bulkier phosphine ligands, with the aim to stabilize the higher oxidation state intermediates and favor the reductive elimination of the product. Indeed, these alterations led to an improved catalyst as $Ru(H)_2(CO)(PCy_3)_3$ afforded the desired product in 32% yield.

Subsequently, we undertook preliminary mechanistic studies to determine the order of two key steps, namely, the oxidative addition of PhI and the C−H bond activation (eq 1). As the reactions in the absence of iodobenzene yielded no insight, we directed our efforts toward the sequence wherein C−I addition precedes the C−H activation.

The feasibility of this scenario was documented by in situ NMR analysis, which revealed the formation of complex **5** upon heating of the reaction mixture, presumably via elimination of hydrogen followed by oxidative addition of iodobenzene (Figure 2).[9] Moreover, complex **5**, prepared through an independent procedure, reacted with *N*-phenylpyrrolidine directly, furnishing the product in 71% yield (eq 3). Further analysis revealed nearly identical behavior (yields and kinetics) of **4** and **5** in both catalytic and stoichiometric reactions (for details, see Supporting Information).[10]



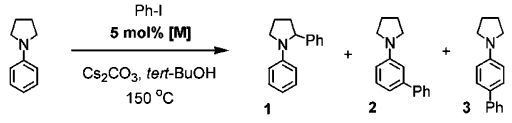
To confirm that this transformation did not proceed via an enamine intermediate formed by β-hydride elimination, *N*-phenylpyrrolidine deuterated at both β-positions was prepared. As expected, no hydrogen incorporation in the product was observed (eq 4).



On the basis of these observations, we propose the following mechanistic model (Figure 2). The reaction is initiated by the

10.1021/ja050269o CCC: $30.25

Table 1. Identification of the Active Catalyst System[a]



[M]	1 / 2 / 3
$Ru(H)_2(CO)(PPh_3)_3$	14 / 3 / 2
$Ru(H)_2(CO)(PCyPh_2)_3$	26 / 4 / 3
$Ru(H)_2(CO)(PCy_2Ph)_3$	28 / 4 / 2
$Ru(H)_2(CO)(PCy_3)_3$ (**4**)	32 / 6 / 4
$Ru(Ph)(I)(CO)(PCy_3)_2$ (**5**)	34 / 5 / 4

[a] Conditions: *N*-phenylpyrrolidine (1 equiv), PhI (1.2 equiv), [Ru] (5 mol % Ru), Cs_2CO_3 (1.2 equiv), *tert*-BuOH, 150 °C, 18 h. The given yields are the average of three runs with deviation of 2−3%. Purification of reagents and anhydrous conditions are required (see Supporting Information for details).

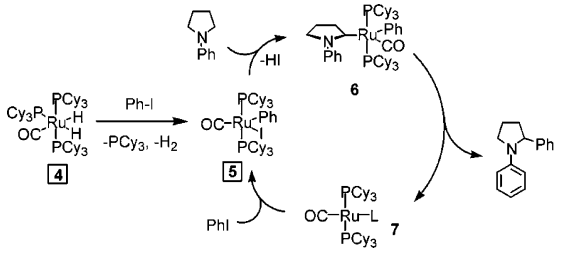
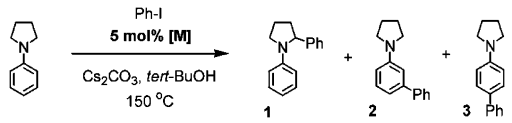


Figure 2. Proposed mechanistic scheme.

Table 2. Catalyst Improvement[a]



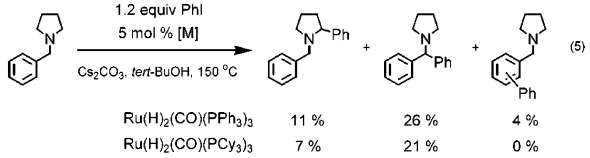
[M]	1 / 2 / 3
$Ru(H_2)(H)_2(PCy_3)_3$	38 / 6 / 4
$Ru(H_2)_2(H)_2(PCy_3)_2$	40 / 7 / 4
$Ru(H_2)_2(H)_2(PCy_3)_2$ (10 mol %)	59 / 9 / 4

[a] Conditions: *N*-phenylpyrrolidine (1 equiv), PhI (1.2 equiv), [Ru] (5 mol % Ru), Cs_2CO_3 (1.2 equiv), *tert*-BuOH, 150 °C, 18 h. The given yields are the average of three runs with deviation of 2−3%. The complexes must be handled under H_2 atmosphere during all experimental manipulations (see Supporting Information for details).

formation of complex **5** in situ, followed by the slow C−H bond activation step, which may proceed via oxidative addition or σ-bond metathesis. Finally, reductive elimination gives the product and Ru(0) species **7**, which is rapidly converted back to complex **5**. A large kinetic isotope effect ($k_H/k_D = 5.4$) observed in the catalytic reaction supports the claim that C−H bond metalation is the slow step of the cycle. The catalytic reaction was found to be first order in *N*-phenylpyrrolidine and zero order in iodobenzene (Supporting Information), consistent with the proposed mechanistic scheme.

Next, having identified the rate-determining step, we examined the potential role of the CO ligand. For this purpose, $Ru(H)_2(H_2)(PCy_3)_3$ and $Ru(H)_2(H_2)_2(PCy_3)_2$[11] complexes were synthesized and evaluated under the reaction conditions. Interestingly, a measurable increase in the arylation yield was observed in comparison to that of **4**, despite the high instability of these complexes (Table 2). These results further support the hypothesis that the *PhRu(X)L$_2$ fragment has the ability to arylate sp^3 C−H bonds* and suggest that CO as a π-acceptor stabilizes (and perhaps deactivates) the low valent ruthenium intermediates.

Last, a preliminary examination of the substrate scope showed that in addition to *N*-phenylpyrrolidine, *N*-methyl- and *N*-benzylpyrrolidine, as well as *N*-benzoylpyrrolidine, were arylated under the reaction conditions. In the case of *N*-benzylpyrrolidine, phenylation occurred preferentially at the α-methylene groups, confirming the selectivity of this system for sp^3 over sp^2 C−H bonds (eq 5; for details, see Supporting Information).



In summary, a novel transformation was identified to achieve the direct and selective arylation of sp^3 C−H bonds in the absence of a directing group. Although rudimentary in its efficiency, this catalytic system sets the precedent for future development in this area.

Acknowledgment. This work was supported by the NIGMS. D.S. is a recipient of the Bristol-Myers Squibb Unrestricted Grants in Synthetic Organic Chemistry Award and Pfizer Award for Creativity in Organic Chemistry. B.S. is a recipient of the Bristol-Myers Squibb graduate fellowship. We thank GlaxoSmithKline, Merck Research Laboratories, Dr. J. B. Schwarz (editorial assistance), and Vitas Votier Chmelar (intellectual support).

Supporting Information Available: Experimental procedures, spectral data for all products, kinetics of stoichiometric and catalytic experiments with complexes **4** and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on C−H activation and functionalization, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770.
(2) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372−13373.
(3) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935−10941.
(4) In this report, the term "directing group" refers to a heteroatom-containing functionality, which facilitates metalation of distant C−H bonds (separated by more than one bond) via formation of a metallacycle (usually five- or six-membered metallacycle). Related terms such as "coordination-directed metalation" are also often used in this sense. In the context of aromatic systems, "*ortho*-metalation" is a widely used (and understood) term.
(5) The greater reactivity of amines also allows for the oxidative approach to C−H → C−C transformations. (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312−15313. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811. (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 13244−13246. (d) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *Organometallics* **2004**, *23*, 5392−5395.
(6) (a) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352−354. (b) Hoyano, J. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1982**, *104*, 3723−3725. (c) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650−1663.
(7) (a) Bergman, R. G. *Science* **1984**, *223*, 902−908. (b) Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91−100.
(8) Ferrando-Miguel, G.; Coalter, J. N.; Gerard, H.; Huffman, J. C.; Eisenstein, O.; Caulton, K. G. *New J. Chem.* **2002**, *26*, 687−700.
(9) Elimination of hydrogen by extrusion from dihydrido complexes is known. (a) Frediani, P.; Salvini, A.; Bianchi, M.; Piacenti, F. *J. Organomet. Chem.* **1993**, *454*, C17−C19. (b) Jessop, P. G.; Rastar, G.; James, B. R. *Inorg. Chim. Acta* **1996**, *250*, 351−357.
(10) Ph−Ru(II) complexes in coupling reactions have not been explored. (a) Faller, J. W.; Chase, K. J. *Organometallics* **1995**, *14*, 1592−1600. (b) Ritleng, V.; Sutter, J. P.; Pfeffer, M.; Sirlin, C. *Chem. Commun.* **2000**, 129−130.
(11) (a) Felkin, H.; Fillebeen-Khan, T.; Gault, Y.; Holmes-Smith, R.; Zakrzewski, J. *Tetrahedron Lett.* **1984**, *25*, 1279−1282. (b) Chaudret, B.; Poilblanc, R. *Organometallics* **1985**, *4*, 1722−1726. (c) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *J. Am. Chem. Soc.* **1998**, *120*, 4228−4229.

JA050269O