Double C–H Activation

DOI: 10.1002/anie.201103621

Nickel-Mediated Cycloaddition by Two Sequential C–H Activations**

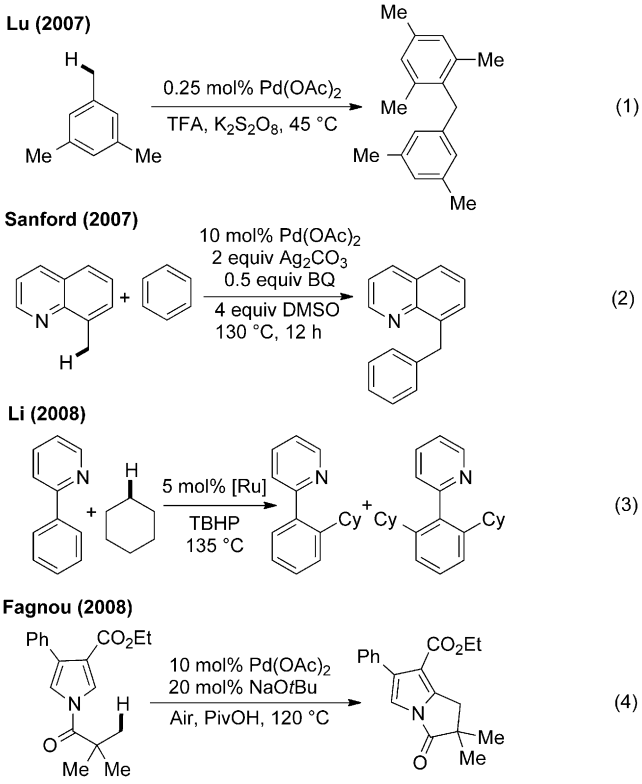
*Puneet Kumar and Janis Louie**

C–H activation · cross-dehydrogenative coupling · cyclometalation · dihydropyridone · nickel

Be it the design of a simple or architecturally complex molecule, carbon–carbon bond formation processes play a pivotal role.[1a] One of the most common adopted strategies to accomplish these tasks is the cross-coupling reaction, where electrophiles and nucleophiles are coupled with the aid of a suitable transition-metal catalyst.[1b] However, a limitation of cross-coupling methods is the amount of waste being produced in these processes.[1c] One solution is the use of less oxidized substrates like arenes or alkanes which would be coupled through selective C–H activations.[2,3] A significant amount of work has been done to understand and utilize $C(sp^2)$–H activation of arenes.[2] In contrast, $C(sp^3)$–H activation of alkanes is still a challenging problem in organometallic chemistry.[4] Not surprisingly, cross-coupling by activation of both $C(sp^2)$–H and $C(sp^3)$–H bonds is quite rare.

A handful of isolated examples of $C(sp^2)$–$C(sp^3)$ cross couplings have been reported in recent years. For example, two mesitylene units can be coupled together through Pd-catalyzed double C–H activation [Eq. (1); TFA = trifluoroacetic acid].[5a] Also, Sanford's group reported an isolated example, where quinoline acts as a directing group for the activation of a $C(sp^3)$–H bond followed by coupling with benzene [Eq. (2); BQ = benzoquinone, DMSO = dimethylsulfoxide].[5b] More general approaches in this direction include a Ru-catalyzed cross-dehydrogenative coupling of 2-arylpyridines with cycloalkanes [Eq. (3); TBHP = *tert*-butyl hydroperoxide][5c,6] and the intramolecular dehydrogenative coupling of *N*-pivalylpyrroles [Eq. (4)].[5d,7] However, in both of these latter cases, products yields were generally only moderate.

Given the difficulty associated with $C(sp^2)$–$C(sp^3)$ cross couplings, a recent report of Hiyama and co-workers on the cycloaddition of formamides and alkynes through activation of both $C(sp^2)$–H and $C(sp^3)$–H bonds is a significant achievement [Eq. (5)].[8] Hiyama et al. originally discovered a nickel catalyst system that facilitates hydrocarbamoylation

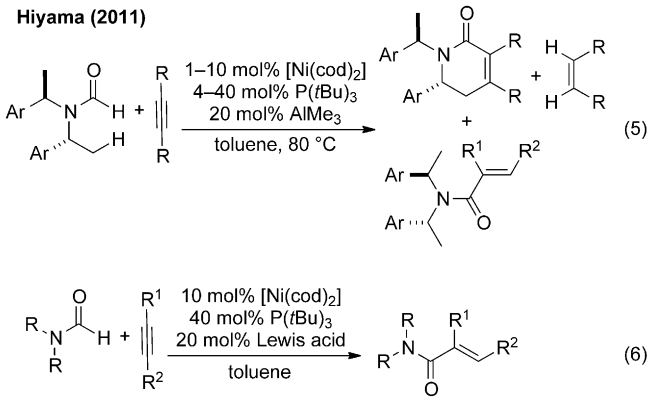


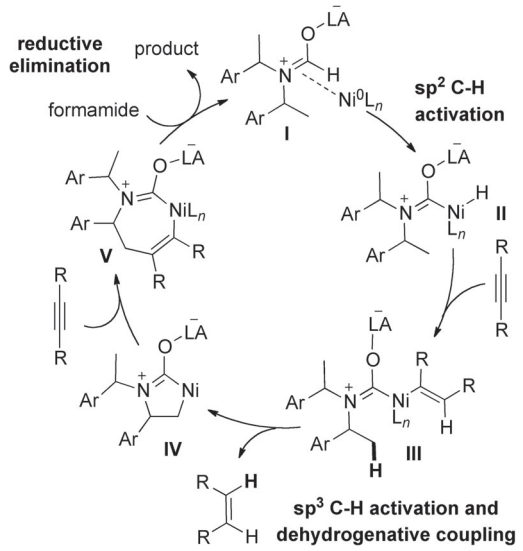
of unsaturated bonds such as alkynes [Eq. (6); cod = cyclooctadiene].[9] This study revealed that Lewis acid plays a critical role in activating the formamides towards $C(sp^2)$–H activation.[10] With this Lewis-acid assistance, [Ni] oxidatively adds the $C(sp^2)$–H bond of the formamide. Alkyne insertion followed by C–C bond-forming reductive elimination provides highly substituted acrylamides.

Building upon this work, Hiyama and co-workers found *N*,*N*-bis(1-arylalkyl)formamides not only undergo the Lewis-acid-assisted oxidative addition of the formamide $C(sp^2)$–H bond, the resultant nickel intermediate inserts an alkyne and undergoes a second C–H activation (Scheme 1). That is, intermediate **III** converts to intermediate **IV** through cyclometalation of the alkyl $C(sp^3)$–H bond and extrusion of a reduced alkyne (i.e., an alkene). Although this type of cyclometalation is prevalent for platinum metals, cyclometalation on nickel is much less prevalent.[11] In addition, examples of Ni-based cyclometalation has been mainly limited to the activation of $C(sp^2)$–H bonds.[12] In contrast,

[*] P. Kumar, Prof. Dr. J. Louie
Department of Chemistry, University of Utah
315 S. 1400 E. Rm. 2020, Salt Lake City, UT 84112 (USA)
E-mail: louie@chem.utah.edu
Homepage: http://www.chem.utah.edu/faculty/louie/index.html

[**] The NIGMS, the NSF, the DOE, and Merck are gratefully acknowledged for financial support.





Scheme 1. Proposed mechanism.

this nickelacycle (**IV**) inserts a second alkyne and reductively eliminates the dihydropyridone product to complete the catalytic cycle.

The dehydrogenative cycloaddition chemistry is not only mechanistically interesting, it is synthetically useful. Symmetrical alkyl as well as aryl alkynes reacted with formamides to afford dihydropyridone in good to excellent yields (Figure 1). The coupling of both *tert*-butyl-methyl alkyne and phenyl-trimethylsilyl alkyne occurred regioselectively. Intriguingly, these two alkynes afforded products with the opposite regioselectivity.

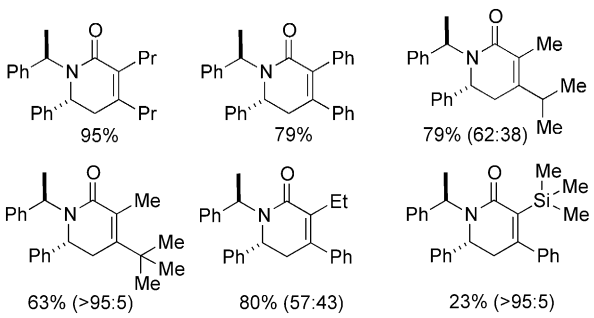


Figure 1. Selected dihydropiperidones prepared by Ni-catalyzed dehydrogenative [4+2] cycloaddition.

The work of Hiyama and co-workers is certainly an outstanding contribution in the field of cross-dehydrogenative coupling. Key to their success was an optimal steric environment around the metal center to promote cyclometalation/dehydrogenative coupling. These findings marks the entry of a cheaper, first-row transition metal catalyst (i.e. nickel) in mediating C–C bond formation through the challenging C(sp^3)–H activation. It will be interesting to see how this chemistry acts as a springboard for the development of future, more general dehydrogenative coupling catalysts.

Received: May 26, 2011
Revised: July 13, 2011
Published online: September 27, 2011

[1] a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B*, 5th ed., Springer, New York, **2007**; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710; c) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202.
[2] For an excellent review on catalytic cross-dehydrogenative coupling, see: C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292.
[3] For discussion related to the use of less oxidized substrates in organic synthesis, see: K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824–828.
[4] H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191–206.
[5] a) Y. Rong, R. Li, W. Lu, *Organometallics* **2007**, *26*, 4376–4378; b) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905; c) G. Deng, L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 6374–6378; *Angew. Chem. Int. Ed.* **2008**, *47*, 6278–6282; d) B. Liégault, K. Fagnou, *Organometallics* **2008**, *27*, 4841–4843.
[6] For leading work on mechanistically distinct approaches to form C(sp^2)–C(sp^3) bonds by dehydrogenative coupling, see: a) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749–5754; b) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344, and references therein.
[7] For other metal-catalyzed C(sp^2)–C(sp^3) bond forming processes involving C(sp^3)–H activations/insertion protocols, see: a) B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557; b) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681.
[8] Y. Nakao, E. Morita, H. Idei, T. Hiyama, *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267.
[9] Y. Nakao, H. Idei, K. S. Kanviya, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 5070–5071.
[10] For other Lewis-acid-assisted Ni-catalyzed oxidative additions, see: a) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449; b) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 15996–15997.
[11] For reviews on cyclometalation, see: a) M. I. Bruce, *Angew. Chem.* **1977**, *89*, 75–89; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 73–86; b) I. Omae, *Chem. Rev.* **1979**, *79*, 287–321; c) G. R. Newkome, W. E. Puckett, V. K. Gupta, G. E. Kiefer, *Chem. Rev.* **1986**, *86*, 451–489; d) A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403–424; e) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; f) J. Cámpora, P. Palma, E. Carmona, *Coord. Chem. Rev.* **1999**, *193–195*, 207–281; g) J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571; h) M. Albrecht, *Chem. Rev.* **2010**, *110*, 576–623; i) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.
[12] For Ni-mediated cyclometalation processes, see: a) E. Carmona, P. Palma, M. Paneque, M. L. Poveda, *J. Am. Chem. Soc.* **1986**, *108*, 6424–6425; b) E. Carmona, E. Gutierrez-Puebla, *Polyhedron* **1989**, *8*, 1069–1075; c) T. N. Tekavec, J. Louie, *Tetrahedron* **2008**, *64*, 6870–6875.

