C–H Activation

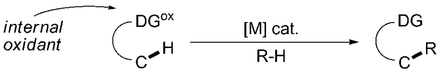
DOI: 10.1002/anie.201007241

Oxidizing Directing Groups Enable Efficient and Innovative C–H Activation Reactions**

Frederic W. Patureau and Frank Glorius**

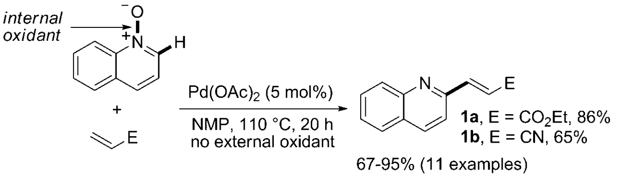
C–H activation · cross-coupling · oxidation · sustainable chemistry

The development of the concepts of green chemistry[1] has resulted from the desire of chemists to minimize synthetic steps and the amount of toxic waste formed, and, moreover, to find milder and more selective transformations. Transition-metal-catalyzed cross-coupling reactions through C–H activation processes have emerged in recent years because such transformations circumvent the need for prior steps to activate the substrate. As a consequence of the often oxidative character of these coupling reactions, the use of an external oxidant is generally required to regenerate the catalyst. An alternative emerging strategy is the use of oxidizing directing groups (acting as an internal oxidant) in C–H activation processes, which was recently and independently introduced by the research groups of Cui and Wu,[2a] Hartwig,[3a] Yu,[4] and Guimond and Fagnou.[5a] This approach can lead to improved levels of reactivity and selectivity and also to a broader scope compared to the use of external oxidants. The internal oxidant strategy typically involves a covalent bond within the directing group, which oxidizes the metal catalyst (for example, through an oxidative addition), but is distinct from the C–H activated and functionalized position. The result is a multifunctional, oxidative directing group (DG^{ox}) that combines many attractive features [Eq. (1)]. In this Highlight we discuss, compare, and analyze the benefits, drawbacks, and opportunities resulting from this novel concept of oxidizing directing groups.



(1)

An external-oxidant-free C–H oxidative C–C cross-coupling reaction was recently reported by Wu, Cui et al. [Eq. (2); NMP = *N*-methyl-2-pyrrolidone].[2a] While the palladium-catalyzed oxidative olefination of the *ortho*-C–H bond of pyridine *N*-oxides is well-known, stoichiometric amounts of quite expensive silver salts are required as an external oxidant. Furthermore, the deprotection of the *N*-oxide products required an additional step, typically by treatment with a (toxic) phosphine derivative.[2b] The new method of Cui and co-workers skillfully utilizes the *N*-oxide functionality as both a directing group and an internal oxidant, thus resulting in the efficient formation of cross-coupled, deoxygenated quinoline products **1** [Eq. (2)] that do not require any further deprotection or deoxygenation steps (*N*-oxide substrates can be easily prepared).



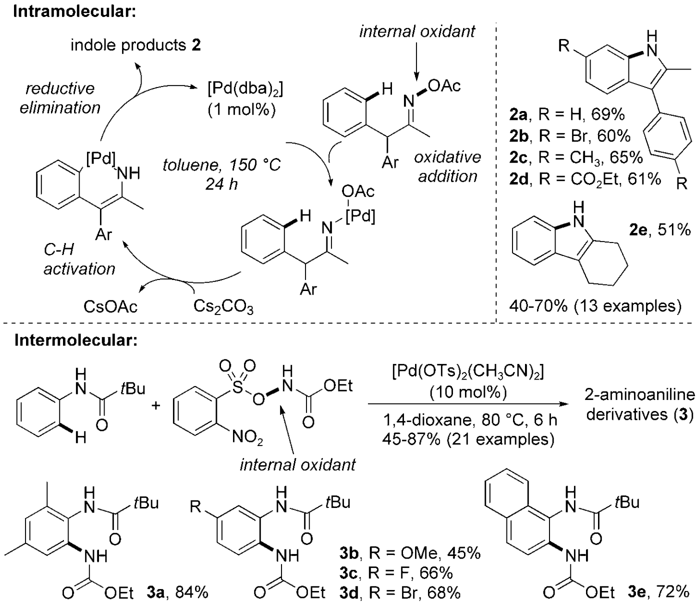
(2)

An impressive external-oxidant-free oxidative amination reaction was recently reported by Tan and Hartwig, who used an oxime ester as both a directing group and an internal oxidant for the preparation of indole derivatives.[3a] The authors propose a Pd^0/Pd^{II} catalytic system in which the oxidative insertion of a Pd^0 species into the N–O bond would be the first step. The resulting intermediate would then undergo a directed *ortho*-C–H bond activation, with a subsequent reductive elimination to give the observed indole products **2**. The clear advantage of the internal oxidant in this case is that the oxidative addition pre-positions the metal center for the C–H activation step, thus allowing the reaction to occur efficiently. Furthermore, the method allows the selective synthesis of 3-arylated and even annulated indoles, albeit in moderate yields (**2a–e**; Scheme 1). A previous and related intramolecular oxidative amination reaction, which utilizes various external oxidants, was typically limited to N-triflated indolines.[3b] An interesting study by Yu and co-workers showed that the N–O bond could also be used for related intermolecular oxidative C–H aminations, although in this particular case the oxidizing function is no longer associated with the directing group.[4] The authors showed that anilines can be *ortho*-aminated under palladium catalysis by using *N*-nosyloxycarbamates as the coupling partner as

---

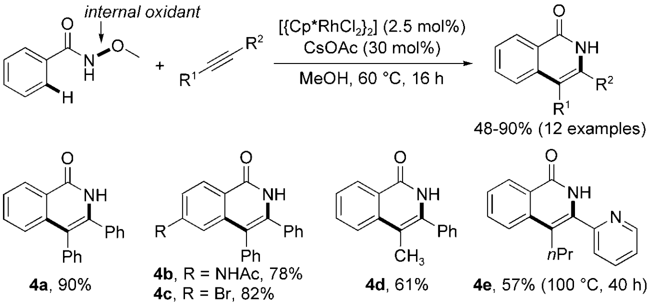
[*] Dr. F. W. Patureau, Prof. Dr. F. Glorius
Organic Chemistry Institute
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-33202
E-mail: patureau@uni-muenster.de
glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/en/index.html

[**] We thank the Alexander von Humboldt foundation (F.W.P.), the European Research Council (ERC), and the Alfried Krupp von Bohlen und Halbach Foundation for generous financial support.



Scheme 1. Application of internal oxidants in C–H oxidative amination processes, by using oxime esters (intramolecular reaction, top) and *N*-nosyloxycarbamates (intermolecular transformation, bottom).

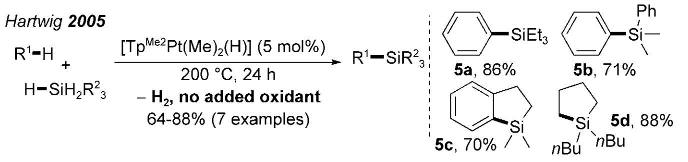
well as the internal oxidant (**3a–e**; Scheme 1). The main drawback of this approach is the poor atom economy (pivaloyl directing group, carbamate protecting group, large nosyl group being part of the internal oxidant). Nevertheless, intermolecular C–H oxidative amination processes are known to be very challenging, and practical solutions are rare,[5c] which makes this example a remarkable advance in the field.

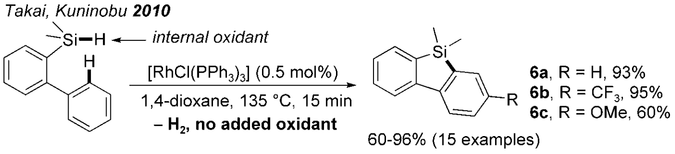


Scheme 2. *N*-Methoxybenzamides as internal oxidants in the rhodium-catalyzed synthesis of isoquinolones. Cp* = η^5-C_5Me_5.

In another key example, Guimond et al. recently reported the rhodium-catalyzed external-oxidant-free synthesis of isoquinolones by C–H activation of *N*-methoxybenzamides and sequential coupling to internal alkynes (Scheme 2).[5a] *N*-Methoxyamides were already known to be powerful directing groups in palladium-catalyzed C–H arylation and amination reactions in the presence of external oxidants, with the integrity of the N–O bond maintained.[5b,c] In contrast to the above-mentioned indole formation by Tan and Hartwig, the first step in this case is not the oxidative addition of the metal center into the N–O bond (Scheme 1).[3a] The authors have proven through deuteration experiments that the integrity of the N–O bond is preserved during the C–H cyclometalation step, thus indicating that the cleavage of the internal oxidant must occur at a later stage of the catalytic cycle. Here, this internal oxidant method presents a number of advantages, such as very mild conditions and broader functional group tolerance compared to analogous methods in which copper salts are used as external oxidants (see, for example, the tolerated pyridine moiety in **4e**). Interestingly, Miura and co-workers simultaneously reported the corresponding rhodium-catalyzed cross-coupling of benzamides and internal alkynes, by using $Cu(OAc)_2$ as an external oxidant. While the direct use of unactivated benzamides is convenient because of their ready availability, it is very difficult in this case to avoid overreaction by multiple cross-coupling events. Indeed, isoquinolones can be further reacted through rhodium-catalyzed C–H activation and subsequent coupling to a second equivalent of the internal alkyne to afford interesting polycyclic structures.[5d] In contrast, the oxidizing directing group of Guimond and co-workers affords very high levels of selectivity towards the monocoupling products, because each internal oxidant can only react once and, as was proven, only internally (Scheme 2).[5]

From a broader perspective, we would like to also highlight an inspiring self-oxidation strategy—acceptorless dehydrogenative coupling reactions[6]—from Tsukada and Hartwig[6a] [Eq. (3); $\mathrm{Tp^{Me2}}$ = hydrotris(3,5-dimethylpyrazolyl)borate], and more recently from Kuninobu, Takai, and co-workers[6b] [Eq. (4)]. The latter approach is a rhodium-

 (3)



(4)

catalyzed C–H activation and silylation method[7] to prepare silafluorene derivatives **6** under quite mild and efficient conditions.[6b] In our view, this process, an oxidative insertion of the metal into the Si–H bond, followed by directed *ortho*-C–H activation and reductive elimination to the product, is conceptually related to the indole formation of Tan and Hartwig (Scheme 1).[3]

In conclusion, an efficient strategy—the use of internal oxidant functionalities, typically built in to the directing group—has emerged in the field of oxidative C–H activation reactions which obviates the need for an external co-oxidant. Analysis of the literature examples and their comparison with analogous C–H activations in the presence of external oxidants clearly shows the distinct advantages of utilizing internal oxidants: novel or increased reactivity under milder reaction conditions, substantially greater selectivity (in part by specifically limiting the number of oxidation equivalents per molecule), larger functional group tolerance, and reduction of the amount of waste formed. Since internal oxidants generally require additional synthetic efforts for their preparation, the level of the overall attractiveness will depend on many different parameters and has to be evaluated in each single case. Nevertheless, it is clear that the internal oxidant strategy will open up new avenues in the field of C–H activations in particular, and synthetic chemistry in general.

Received: November 17, 2010
Published online: February 3, 2011

---

[1] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301.

[2] a) J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888; b) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254.

[3] a) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; b) T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806.

[4] K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862.

[5] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190; c) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058; d) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744; e) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064; f) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* DOI: 10.1021/ja109676d.

[6] a) N. Tsukada, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 5022; b) T. Ureshino, T. Yoshida, Y. Kuninobu, K. Takai, *J. Am. Chem. Soc.* **2010**, *132*, 14324; c) M. Murata, N. Fukuyama, J.-i. Wada, S. Watanabe, Y. Masuda, *Chem. Lett.* **2007**, *36*, 910.

[7] For selected examples of the alternative oxidative formation of Si–C bonds using external oxidants, see a) E. M. Simmons, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 17092; b) S. Furukawa, J. Kobayashi, T. Kawashima, *J. Am. Chem. Soc.* **2009**, *131*, 14192; c) H. Ihara, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 7502; d) M. Tobisu, Y. Ano, N. Chatani, *Chem. Asian J.* **2008**, *3*, 1585; e) F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 422.