C–H Activation

DOI: 10.1002/anie.201405714

Functionalization of Remote C–H Bonds: Expanding the Frontier**

*Johannes Schranck, Anis Tlili, and Matthias Beller**

arylation · C–H activation · directing groups · regioselectivity

Selective C–H bond-functionalization reactions constitute an important goal in modern synthetic chemistry. In general, such transformations offer advantages in terms of decreased waste generation and improved reaction step economy. Recent developments in this area have given rise to selective catalytic functionalizations of less reactive (hetero)aromatic C–H bonds.[1] Here, site selectivity constitutes a major challenge. In the past, either steric effects of substituents in *ortho* position relative to the reacting carbon center directed the C–H bond-activation process,[1a] or substituents on the arene that bind to the catalyst enabled the regioselective C–H bond activation.[1c–e] However, the selective functionalization of C–H bonds distal to any substituents was difficult. Initial reports on such *meta* C–H functionalizations of arenes were published by the groups of Hartwig and Smith.[2] In these cases, the selectivity is governed by steric and electronic effects of the substituted arene on the applied catalyst (Figure 1 a). Thus, regioselective borylation and recently also silylation of substituted arenes in the *meta* positon is possible and gives access to interesting building blocks that can be applied in further transformations using well-established processes such as C–C or C–heteroatom bond formations. A second approach applies the directing-group-assisted concerted metalation–deprotonation (CMD) mechanism that has been reported for a variety of selective *ortho* C–H bond functionalizations.[1c–e] In some examples it has been shown that the C–H bond cleavage and the subsequent formation of the desired product occurs in the *meta* position relative to the directing group.[3] A remote *para* activation of the intermediate metallacycle is discussed to account for the observed regioselectivity. However, these reactions have been found to be highly dependent on the electrophile applied as the coupling partner. In order to circumvent the limitations of current C–H bond functionalizations, the group of Yu designed new templates that promote the selective remote C–H bond activation of arenes (Figure 1 b).[4,5] Similarly,

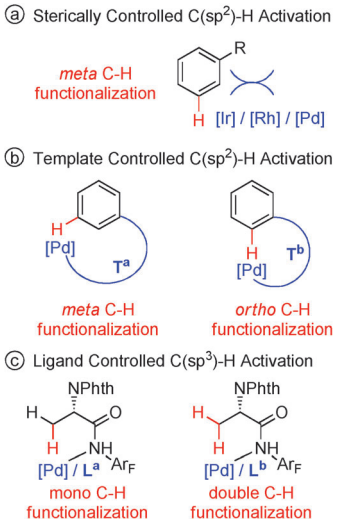


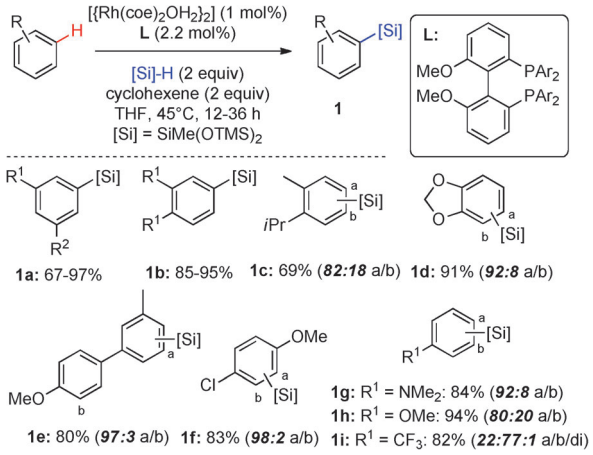
Figure 1. Remote C–H activation. PG = protecting group, Phth = phthalimido.

mono- as well as diarylation of a C(sp^3) center can be conducted selectively by the application of simple amide auxiliaries (Figure 1 c).[6]

More specifically, Hartwig and co-workers have developed a rhodium-catalyzed intermolecular C–H silylation of unactivated arenes that enables excellent control of regioselectivity.[7] Their protocol describes the formation of arylsilanes, which are of interest for silicone polymers and also as intermediates for accessing more complex molecules (Scheme 1). Compared to the products of related borylation reactions, the generated arylsilanes are more stable and can be formed with significantly higher regioselectivities. The key to success was the application of a $[Rh(coe)_2OH]_2$/2,2′-biphenylphosphine catalyst (coe = cyclooctene) in conjunction with the commercially available silane $HSiMe(OTMS)_2$ (TMS = trimethylsilyl). It was found that the steric effects of the ligand as well as the bulky silane account for the high regioselectivities. Thus, silylation of 1,3-difunctionalized arenes occurred in the 5-position with selectivities of > 89:11 (**1a**, Scheme 1). Similarly, symmetrically 1,2-disubstituted arenes reacted in one of the free *meta* positions (**1b**) with selectivities of > 99:1. In the case of *o*-cymene the C–H bond silylation proved to be very sensitive to the steric effect of substituents in the position *meta* relative to the site of reactivity since

[*] J. Schranck, Dr. A. Tlili, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
E-mail: Matthias.Beller@catalysis.de
Homepage: http://www.catalysis.de

[**] We thank the State of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support.

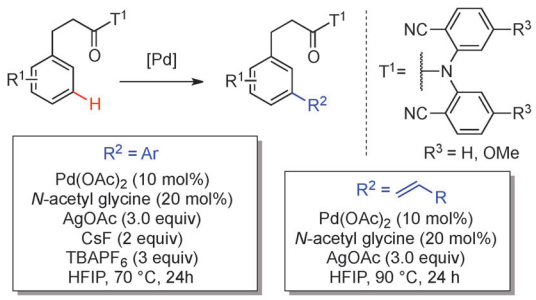


Scheme 1. Rh-catalyzed regioselective C–H silylation. di = a and b.

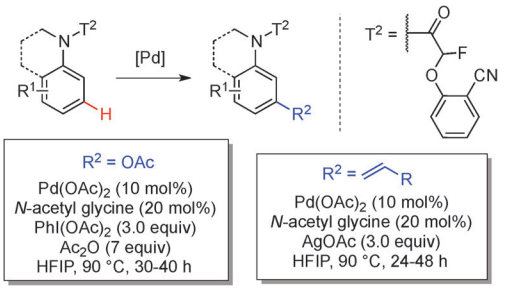
a selectivity of 82:18 towards silylation in the position *para* to the bulkier isopropyl group was observed (**1c**). However, in some examples steric effects even override *ortho* preferences known from analoguous borylations (**1d**). Notably, the catalyst system is also suitable for the selective silylation at the least hindered position of biaryls (**1e**). When 4-chloroanisole was reacted, secondary electronic effects accounted for a highly selective functionalization in the position *ortho* to the methoxy group. However, monosubstitution of the arene proved to be detrimental to the selectivity of the silylation process due to an increased impact of electronic effects (**1g–i**).

Complementary to Hartwig's work, the selective *meta* C–H bond functionalization of arenes was reported by Yu and co-workers (Scheme 2).[4,5] The design of a new end-on-coordinating template allowed for the selective remote C–H bond functionalization. The concept utilizes an induced regioselectivity through the weak coordination of a nitrile group to the catalyst which is realized through the application of a corresponding cleavable template (i.e. T^1). This allows for selective olefination[4] as well as arylation[5] of arenes in *meta* position with very good selectivities and high yields. The corresponding olefins and arylboronic acids react with the template-substituted arene by means of a Pd^{II}/Pd^0 redox cycle.

In order to generalize this concept for other arenes and nucleophiles, more recently the same group introduced another removable template (i.e. T^2). In this way the olefination and acetoxylation of distal *meta* C–H bonds on



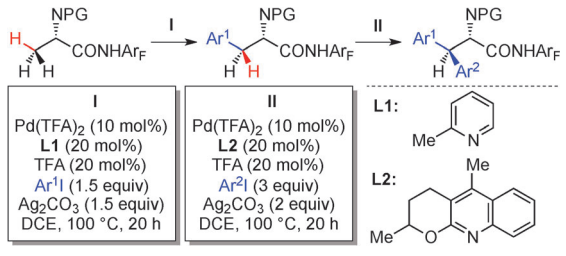
Scheme 2. Pd-catalyzed regioselective remote C–H bond activation. HFIP = hexafluoroisopropanol, TBA = tetrabutylammonium.



Scheme 3. Pd-catalyzed regioselective remote C–H bond activation of the alkenylation and acetoxylation of *N*-methylanilines.

anilines and benzylic amines is possible (Scheme 3).[8] Switching from dimethyl to a single fluorine substituent in the template has been found to account for a change from *ortho*- to *meta*-selective C–H bond functionalization through a significant conformational change in the intermediate metallacycle. The C–H bond olefination of *N*-methylanilines, conducted by a Pd^{II}/Pd^0 cycle, proceeds with moderate to very good yields regardless of whether the starting material bears electron-withdrawing or -donating substituents. However, the selective *meta* C–H bond acetoxylations of *N*-methylanilines and benzylamines bearing the same template also proceeded with very good selectivities and yields, although a Pd^{IV}/Pd^{II} cycle is proposed for these cases.

In contrast to $C(sp^2)$–H bond functionalizations, selective functionalization of $C(sp^3)$–H bonds have been even more challenging, since the latter are less acidic and lack the proximal empty low-energy or filled high-energy orbitals that readily interact with orbitals of a metal.[9] In this respect, it is noteworthy that the group of Yu described a ligand-controlled procedure that allows for the selective β-$C(sp^3)$–H mono- as well as diarylation of amino acid derivatives through the application of simple amide auxiliaries with excellent diastereoselectivities (Scheme 4).[6] The incorporation of perfluorinated arylamides in the substrate enables a weak coordination to the palladium catalyst. Depending on the applied ligand, either monoarylation (in the case of pyridine ligands) or diarylation (in the case of quinoline ligands) occurred. Sequential application of the two systems facilitates the incorporation of two different aryl moieties into the β-Ar-β-Ar′-α-amino acid product. The removal of the auxiliary can be conducted under mild conditions in 95 % yield and without loss in enantiomeric purity. Hence, this protocol allows for



Scheme 4. Ligand-controlled $C(sp^3)$–H mono- and diarylation of amino acid derivatives. Ar_F = 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, DCE = 1,2-dichlorethane, TFA = trifluoroacetic acid.

a straightforward and selective synthesis of a wide range of amino acid derivatives in high yields.

In conclusion, remote site selectivity, a major challenge of C–H bond functionalization, has been achieved by different approaches, each of which offers unique features in terms of selectivity and substrate scope; overall, a complementary tool set has been devised.

Received: May 28, 2014
Published online: July 27, 2014

[1] a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; b) J. Wencel Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; f) X. Bugaut, F. Glorius, *Angew. Chem.* **2011**, *123*, 7618; *Angew. Chem. Int. Ed.* **2011**, *50*, 7479; g) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; h) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885.

[2] a) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864; b) D. W. Robbins, J. F. Hartwig, *Angew. Chem.* **2013**, *125*, 967; *Angew. Chem. Int. Ed.* **2013**, *52*, 933; c) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith III, *Science* **2002**, *295*, 305.

[3] M. Gagliardo, D. J. Snelders, P. A. Chase, R. J. Klein Gebbink, G. P. van Klink, G. van Koten, *Angew. Chem.* **2007**, *119*, 8710; *Angew. Chem. Int. Ed.* **2007**, *46*, 8558.

[4] D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[5] L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056.

[6] J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216.

[7] C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853.

[8] R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215.

[9] a) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; b) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937; c) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654.

