Switchable Selectivity

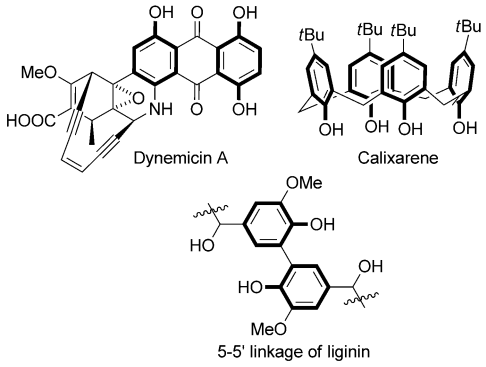
DOI: 10.1002/anie.201403894

# Direct Functionalization with Complete and Switchable Positional Control: Free Phenol as a Role Model**

*Da-Gang Yu, Francisco de Azambuja, and Frank Glorius**

catalysis · C–H activation · C–O activation · free phenol · selectivity

The direct and diverse functionalization of important molecular motifs, especially with good predictability in complex molecules, is a demanding challenge. Many fields, especially the pharmaceutical industry, demand quicker access to diversely functionalized derivatives, which makes direct coupling reactions with complete and switchable selectivity highly desirable. Transition-metal catalysis is one of the most prominent methods to achieve such a goal, and expands retrosynthetic disconnections to inert C–H and C–O bonds.[1] Phenol is not only a cheap chemical commodity but also a ubiquitous core structure in natural products (such as lignin), drugs, and materials (Scheme 1). Thus, transition-metal-catalyzed direct reactions of free phenols at any position are of great interest. Herein, we highlight recent breakthroughs that now allow predictable site-selective and direct functionalization of free phenols by cleaving either the C–O bond (*ipso* position) or one of the C–H bonds (*ortho*, *para*, and, most recently, *meta* positions).




***Scheme 1.*** Free phenol motifs present in important structures.

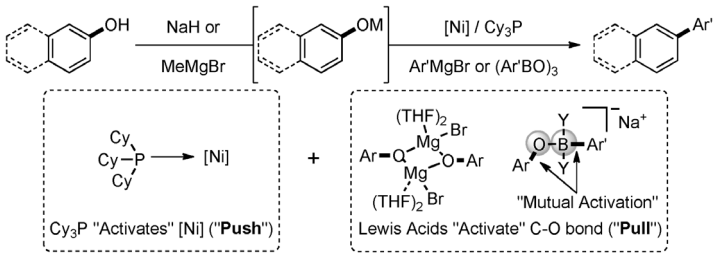
Based on the rational design of C–O activation by a "pull and push" concept,[2a] Shi and co-workers realized the first successful cross-coupling reactions of free naphthols with aryl Grignard reagents[2b] and boroxines[2c] (Scheme 2). In the first case, the strong C–O bond was weakened by the coordination of the oxygen atom to two Lewis-acidic $Mg^{2+}$ ions ("pull"). More interestingly, in the second case, borate formation not only activated the C–O bond but also the C–B bond ("mutual activation"). In both cases, the C–O bond activations were demonstrated by the increased bond lengths in the crystal structures of the intermediates. Additionally, it is also essential to use $Cy_3P$ (Cy = cyclohexyl) as a ligand, which "activates" the Ni catalyst through providing a suitable environment and high electron-density for oxidative addition ("push"). Although only one nonfused phenol was applied, these studies explored the intrinsic reactivity of C–O bonds and revealed a new approach to directly functionalize phenols. In addition, the pioneering report on transition-metal-free fluorination by Ritter and co-workers also deserves much attention.[2d]

For a long time, transition-metal-free electrophilic substitutions and directed *ortho* metalation (DoM) of free phenols have been widely utilized in organic synthesis. However, the application of transition-metal catalysis for selective and diverse *ortho*-C–H activation has been limited by the instability of the four-membered metallacycles and competitive oxidative side reactions. Inspired by the pioneering work of Trost and Toste,[3a] who realized the $Pd^0$-catalyzed direct synthesis of coumarins from electron-rich phenols and alkynes in formic acid, there are a few recent reports describing the use of different activation strategies and various kinds of transition-metal catalysts (Scheme 3). For example, the research groups of Maiti[3b] and Shi[3c] independently developed $Pd^{II}$-catalyzed annulations to produce coumarins in the presence of a base and an oxidant. Under these two sets of conditions, C–H activation might be the rate-limiting step, and all kinds of phenols, whether electron-rich, -neutral, or -poor, underwent the reactions smoothly.[3d] In the system developed by Maiti and co-workers, benzofurans were also efficiently generated when styrenes and unactivated alkenes were employed. Another novel strategy to generate benzofurans from free phenols with internal alkynes was discovered independently in 2013 by the research groups of

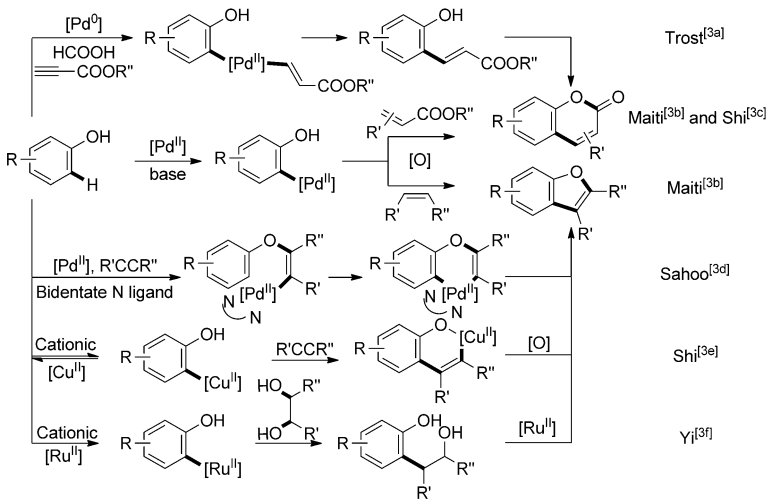
[*] Dr. D.-G. Yu, F. de Azambuja, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/

[**] We thank Dr. Matthew Hopkinson for kind help, and the Alexander von Humboldt Foundation (D.-G.Y.), the São Paulo Research Foundation (grant 2013/14209-9, F.deA.), and the Deutsche Forschungsgemeinschaft (DFG; Leibniz award) for generous financial support.



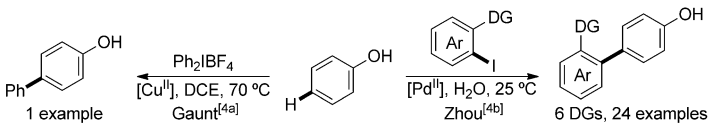

***Scheme 2.*** Direct *ipso* cross-coupling reactions of free phenols by Shi and co-workers.




***Scheme 3.*** Selective *ortho*-C–H activation of free phenols.

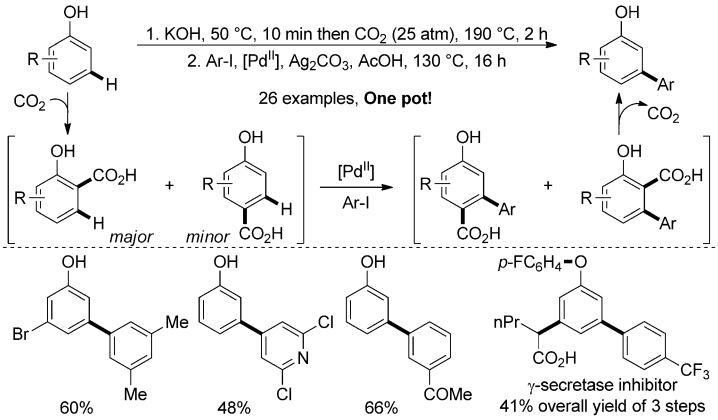
Sahoo[3d] and Shi[3e] (Scheme 3). In the study by Sahoo and co-workers, bidentate N ligands played a pivotal role in effecting the $Pd^{II}$ catalysis. The mechanistic study suggested a sequence involving insertion of the alkyne into bis(aryloxo)-$Pd^{II}$ complexes, intramolecular C–H activation, and a subsequent reductive elimination to generate the benzofuran product. In the report by Shi and co-workers, cationic $Cu(OTf)_2$ was found to undergo reversible electrophilic cupration to form the intermediate, which further undergoes insertion and reductive elimination to generate the C–O bond. Notably, Yi and co-workers developed a robust $Ru^{II}$-catalyzed selective *ortho*-C–H alkylation and alkenylation of free phenols with alcohols, in which $H_2O$ was the by-product (Scheme 3).[3f] The kinetic isotopic effect indicated that the C–H activation is a rapid and reversible step. In the reports by the research groups of Maiti, Shi, and Yi, the excellent *ortho* selectivity might arise from the interaction of the cationic catalysts with the electron-rich C2-position and the oxygen atom in the phenol, with the possibility of forming aryloxo–metal complexes. More importantly, these methods were applied to selectively functionalize many complex phenols, which are highly useful for late-stage derivations (Scheme 1). In addition to these studies, another two elegant strategies by Bedford et al.[3g] and Lei and co-workers[3h] are also highly important for the *ortho*-functionalization of free phenols.

In contrast to many examples of *ortho* selectivity, transition-metal-catalyzed *para*- (Scheme 4) or *meta*-C–H activation of free phenols is far less common. While the established Friedel–Crafts reactions afford mixtures because of the minor difference in the electron density between the *ortho* and *para* positions, the use of transition metals played a key role in recognizing the slightly higher reactivity to achieve high *para* selectivity.[4] Impressively, Gaunt and co-workers reported one nice example of the $Cu^{II}$-catalyzed *para*-selective phenylation of free phenol as well as anisoles.[4a] Another beautiful example was achieved by Zhou and co-workers, who realized the *para*-selective arylations of phenols with aryl iodides bearing different directing groups (DGs).[4b] In both reactions, highly reactive sterically crowded transition-metal complexes with high valence, which hamper




***Scheme 4.*** Selective *para* arylation of free phenols by the research groups of Gaunt and Zhou.




***Scheme 5.*** One-pot *meta* arylation of free phenols by Larrosa and co-workers.

the *ortho* reaction, might be generated and could be pivotal for the high *para* selectivity.

Strikingly, an unprecedented approach to the *meta* functionalization of free phenols was recently described by Larrosa and co-workers that was based on an innovative traceless directing group relay strategy (Scheme 5).[5a,b] The use of the Kolbe–Schmidt reaction to install a carboxylic group at the *ortho* or *para* position, followed by a convergent directed C–H arylation and then decarboxylation resulted in an overall clean one-pot *meta* arylation of free phenols. This original procedure could be efficiently extended to a number of iodoarenes and substituted phenols. Limited efficiency or no reaction was observed when employing *ortho*-substituted aryl iodides or phenols with *para* substituents, both of which hampered activation of the C–H bond. Despite the harsh reaction conditions, the present method proved itself powerful enough to generate *meta*-arylated free phenols, as exemplified by preparing a γ-secretase inhibitor in a concise route. This provides an alternative to recent great achievements by Yu and co-workers for the direct *meta*-selective functionalization of phenol derivatives.[5c]

With the advent of the traceless directing group relay strategy by Larrosa and co-workers, all the positions of free phenol moieties have now been addressed by transition-metal catalysis. Many kinds of catalytic systems can be chosen to directly and selectively functionalize free phenols at the position of choice. However, although some specific transformations have been realized, many limitations still exist, such as limited scope, high catalyst loading, and harsh reaction conditions. Much more research work is required to render these transformations broadly applicable routine operations of organic synthesis. This will enable the programmable and diversity-oriented introduction[1] of different (functional) groups to free phenols, especially at a late stage of drug synthesis, to find many applications. Moreover, we believe that the highlighted transformations of phenols will act as role models, inspiring direct reactions with positional control of other important core motifs.

Received: April 1, 2014
Published online: June 24, 2014

[1] a) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864; b) J. Yamaguchi, K. Muto, K. Itami, *Eur. J. Org. Chem.* **2013**, 19; c) M. Tobisu, N. Chatani, *Top. Organomet. Chem.* **2013**, *44*, 35; d) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369.

[2] a) N. Yoshikai, H. Matsuda, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 9590; b) D.-G. Yu, B.-J. Li, S. F. Zheng, B.-T. Guan, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2010**, *122*, 4670; *Angew. Chem. Int. Ed.* **2010**, *49*, 4566; c) D.-G. Yu, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 7235; *Angew. Chem. Int. Ed.* **2011**, *50*, 7097; d) P. Tang, W. Wang, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 11482.

[3] a) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1996**, *118*, 6305; b) U. Sharma, T. Naveen, A. Maji, S. Manna, D. Maiti, *Angew. Chem.* **2013**, *125*, 12901; *Angew. Chem. Int. Ed.* **2013**, *52*, 12669; c) X.-S. Zhang, Z.-W. Li, Z.-J. Shi, *Org. Chem. Front.* **2014**, *1*, 44; d) M. R. Kuram, M. Bhanuchandra, A. K. Sahoo, *Angew. Chem.* **2013**, *125*, 4705; *Angew. Chem. Int. Ed.* **2013**, *52*, 4607; e) R. Zhu, J. Wei, Z.-J. Shi, *Chem. Sci.* **2013**, *4*, 3706; f) D.-H. Lee, K.-H. Kwon, C. S. Yi, *J. Am. Chem. Soc.* **2012**, *134*, 7325; g) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem.* **2003**, *115*, 116; *Angew. Chem. Int. Ed.* **2003**, *42*, 112; h) Z. Huang, L. Jin, Y. Feng, P. Peng, H. Yi, A. Lei, *Angew. Chem.* **2013**, *125*, 7292; *Angew. Chem. Int. Ed.* **2013**, *52*, 7151.

[4] a) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 478; *Angew. Chem. Int. Ed.* **2011**, *50*, 458; b) Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang, X. Zhou, *Chem. Commun.* **2013**, *49*, 7653; c) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu, J. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 6904.

[5] a) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc.* **2014**, *136*, 4109; b) P. MacLellan, *Nat. Chem.* **2014**, *6*, 375; c) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567.