ACS central science

FIRST REACTIONS

Directing Remote *Meta*-C–H Functionalization with Cleavable Auxiliaries

Christopher G. Frost and Andrew J. Paterson

Department of Chemistry, Centre for Sustainable Chemical Technologies, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.

The catalytic functionalization of unreactive C–H bonds is an area of great importance for the design of atom economical approaches to useful organic molecules. However, due to the ubiquity of C–H bonds in organic molecules, achieving perfect site-selectivity along with the incorporation of a broad range of functional groups has been one of the major challenges in the area. In this context, the "directing group" strategy has been one of the prevailing methodologies to address issues of selectivity whereby pre-existing functionality within a molecule can direct a metal catalyst to the vicinity of a C–H bond and position it for insertion (Figure 1). Cyclometalated

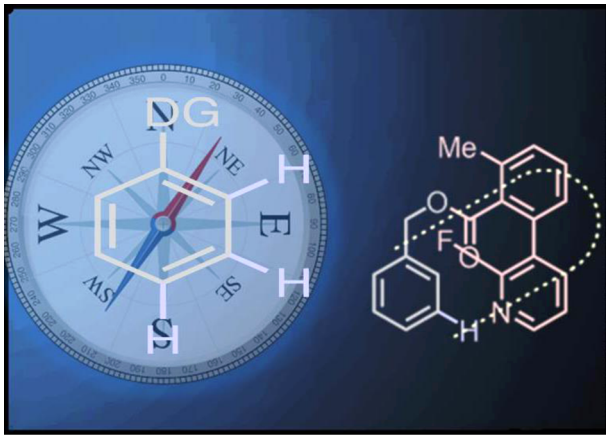

Figure 1. Directing groups (DG) are the gold standard approach in CH activation. Jin-Quan Yu and co-workers have extended their utility with the pictured DG. Image credit: American Chemical Society.

complexes are key intermediates in these transformations and have enabled a broad range of direct *ortho*-C–H functionalizations due to the conformational stability of these intermediates. Within this area, the pyridine directing group has perhaps been the most widely explored, as its superior coordinative ability allows the formation of a particularly stable metallocycle which can be readily manipulated (Figure 2). In a significant recent breakthrough, Jin-Quan Yu and co-workers report a rationally designed

Frost and Paterson discuss various methods of "going meta", notably the report from Jin-Quan Yu and co-workers.

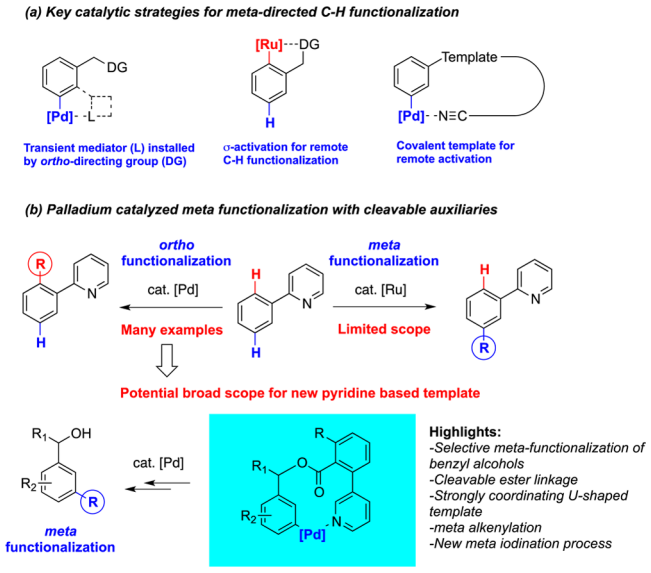

Figure 2. (a) Key catalytic strategies for meta-functionalization. (b) Palladium catalyzed *meta*-functionalization with cleavable auxiliaries.

cleavable auxiliary incorporating a more strongly coordinating pyridine group to direct palladium complexes to functionalize the *meta* position of benzyl ethers.[1]

Cyclometalated complexes are key intermediates in these transformations and have enabled a broad range of direct *ortho*-C–H functionalizations due to the conformational stability of these intermediates.

Published: November 11, 2015

DOI: 10.1021/acscentsci.5b00358
ACS Cent. Sci. 2015, 1, 418–419

Although many successful strategies involve palladium-catalyzed *ortho*-functionalization of 2-phenylpyridine, it should be highlighted that achieving selectivity beyond the *ortho*-C−H bond in aromatic substrates is an area still in its infancy. While a number of elegant directing group strategies have emerged to achieve *meta*-functionalization, σ-activation strategies are often limited to privileged substrates[2,3] and other regioselective C−H functionalizations require the use of specialized ligands to control secondary interactions with the substrate.[4] One specific way to broaden the substrate scope is to use a removable auxiliary directing group. Ackermann and co-workers have recently reported exactly this strategy to overcome the limitations of catalytic σ-activation by cyclo-ruthenation and specifically the reliance on 2-phenylpyridine.[5] This powerful approach employs *N*-(pyrimidin-2-yl)anilines in *meta*−C-H *tert*-alkylations. The removable auxiliary provides access to *meta*-substituted anilines which are challenging to access by conventional synthetic routes.

This is a literal extension of the core concepts of direct *ortho*-functionalization, and initial studies utilized cleavable, nitrile containing auxiliaries to access remote *meta*-C−H bonds resulting in the formation of cyclophane-like metallacycles, a methodology often referred to as the "Yu-turn".

One of the most exciting advances in this area arises from the "potential of achieving site selectivity in C−H activation via the recognition of distal and geometric relationship between existing functional groups and multiple C−H bonds in organic molecules." In this context, Yu introduced the concept of utilizing a covalent U-shaped template for remote C−H activation.[6] This is a literal extension of the core concepts of direct *ortho*-functionalization, and initial studies utilized cleavable, nitrile containing auxiliaries to access remote *meta*-C−H bonds resulting in the formation of cyclophane-like metallacycles, a methodology often referred to as the "Yu-turn". This approach has given rise to an ever growing number of auxiliaries from his own group and others that convert simple functional groups including amines,[7] alcohols,[8] and carboxylic acids[9] into *meta*-selective directing groups. The use of weakly coordinating nitrile directing groups does however have intrinsic limitations, for example, competing coordination from other functional groups or solvents. Furthermore, the variable binding modes of nitrile groups can afford potentially unwanted switches in selectivity.[10]

The latest pyridine-based auxiliary addresses some of the shortcomings associated with nitrile based templates by using extended, conformationally restricted pyridine based directing groups. Of course there are the still the obvious challenges of having to prepare and attach/cleave the auxiliary which require additional synthetic steps. Nevertheless, this advance provides a selective and effective method for achieving a palladium-catalyzed *meta*-alkenylation reaction which itself is impressive on benzyl and phenyl ethyl alcohol derivatives. However, it is the ability to extend the *meta*-functionalization toolbox to include iodination that provides new opportunities. This is a valuable functional group to incorporate in terms of a reactive site for further functionalization, and it indicates that this strategy could prove effective for the selective incorporation of other useful functional groups. Given the wealth of knowledge in utilizing palladium complexes to incorporate a wide range of functional groups in to the *ortho*-position of 2-phenylpyridine, the prospects of developing a practical toolbox of synthetically useful site-selective C−H functionalizations appears ever closer.

Author Information
E-mail: c.g.frost@bath.ac.uk.

REFERENCES

(1) Chu, L.; Shang, M.; Tanaka, K.; Chen, Q.; Pissarnitski, N.; Streckfuss, E.; Yu, J.-Q. *ACS Cent. Sci.* **2015**, *1*, 394−399.
(2) Paterson, A. J.; John-Campbell, S., St; Mahon, M. F.; Press, N. J.; Frost, C. G. *Chem. Commun.* **2015**, *51*, 12807−12810.
(3) Teskey, C. J.; Lui, A. Y. W.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 11677−11680.
(4) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712−717.
(5) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. *J. Am. Chem. Soc.* **2015**, *137*, 13894−13901.
(6) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518−522.
(7) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215−220.
(8) Dai, H.; Li, G.; Zhang, X.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567−7571.
(9) Deng, Y.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 888−891.
(10) Li, S.; Ji, H.; Cai, L.; Li, G. *Chem. Sci.* **2015**, *6*, 5595−5600.

DOI: 10.1021/acscentsci.5b00358
ACS Cent. Sci. 2015, 1, 418−419