

RECENT DEVELOPMENTS IN META-SELECTIVE C—H FUNCTIONALIZATION

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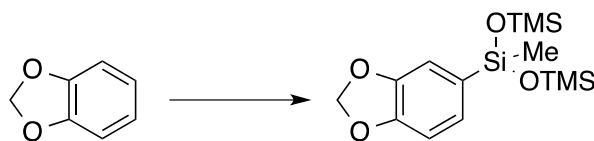
March 17th, 2015

INTRODUCTION

Aromatic rings are ubiquitous structures in natural and pharmaceutical products. Although aromatic C—H bonds are relatively easy to functionalize, the subtle differences within the C—H bonds make regioselectivity challenging to accomplish. While ortho- and para-C—H's can be functionalized through chelation-directed cross-coupling and electrophilic substitution such as Friedel-Crafts reactions, functionalization of meta C—H's is hard to achieve due to deactivation by the necessary electron-withdrawing directing groups. The dependence on directing group's electronic effects further limits the application of the conventional methods. Functionalization of meta-C—H bonds therefore remains a major challenge in organic synthesis. To address this challenge, chemists in recent years developed a series of synthetic strategies taking advantage of steric effects, templates and directing groups.

STERIC-CONTROLLED FUNCTIONALIZATION

The well-developed iridium-catalyzed borylation allows pinacolboranyl groups to insert onto the least hindered positions of arenes.¹ With 1,3-disubstituted arenes, the reaction gives good yield and selectivity for the position meta to both substituents. The selectivity results mainly from steric effects of substituents with electronic effects as the secondary. However, the selectivity diminishes with other substitution patterns or with small-sized substituents. In 2014, Hartwig and co-workers reported the method of stereospecific silylation (Scheme 1).² With the bulky phosphine ligands and a comparatively larger silyl group, the regioselectivity was greatly improved for other disubstitution patterns. However, this method does not necessarily work for monosubstituted arenes, as silylation in most cases happens preferably on the less hindered para position.



Scheme 1. Regioselective Silylation of Benzodioxole.²

TEMPLATE-ASSISTED FUNCTIONALIZATION

For the past decade, numerous studies were done to selectively functionalize ortho C—H's with transition metals through a six-membered ring transition state.³ To activate meta C—H likewise requires an extended chain to deliver the transition metal near the C—H bond. Much earlier, this concept was introduced by Breslow employing a long-chain template to selectively dehydrogenate 3 α -cholestanol.⁴ Later work by Schwarz demonstrated long alkyl nitriles can weakly bind to iron to direct oxidative

addition of their ω -C—H bonds.⁵ In light of these discoveries, Yu and co-workers in 2012 designed templates for meta-C—H activation of toluene and hydrocinnamic acid derivatives based on geometry of the intermediates (Figure 1).⁶ A series of other templates for different substrates were later designed analogously. The major limitation for the application involves the templates' high synthetic overhead and their substrate-dependent nature.

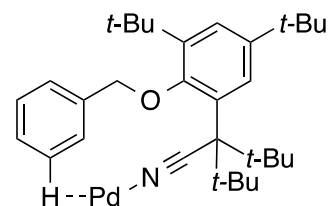
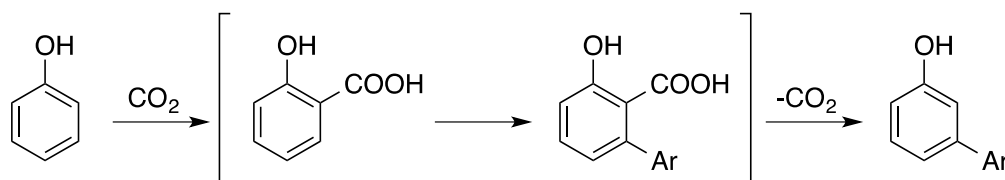


Figure 1. Template-Directed meta-C—H Activation.⁶

DIRECTING GROUP-ASSISTED FUNCTIONALIZATION

Direct meta-functionalization can be achieved with certain directing groups. In 2009, Gaunt and co-workers reported a copper-catalyzed method for meta-arylation of aniline derivatives.⁷ The reaction was proposed to go through a dearomatizing oxy-cupration mechanism to direct Cu onto the meta position and transfer the positive charge to nitrogen for stabilization. Larrosa and co-workers developed a traceless meta-arylation strategy for phenols in 2014 (Scheme 2),⁸ utilizing a carboxyl group formed and removed *in situ* on the ortho-position that directs ortho-arylation to afford the meta-arylated final products. Other examples include Ru-catalyzed sulfonation⁹ and alkylation¹⁰ with *N*-heteroaryl groups, where ruthenium binds to the lone pair on nitrogen, inserts onto the phenyl ring ortho to *N*-heteroaryl and serves as a strong para-directing group, therefore giving the meta-functionalized final product.



Scheme 2. Traceless meta-Arylation of Phenol.⁸

SUMMARY

All three strategies allow meta-C—H functionalization with certain types of substrates, and can potentially compensate for each other. While a more general strategy remains to be developed, these methods have proven fruitful in organic synthesis for designing more efficient synthetic routes.

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