C–H Activation

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Meta-Selective Transition-Metal Catalyzed Arene C–H Bond Functionalization**

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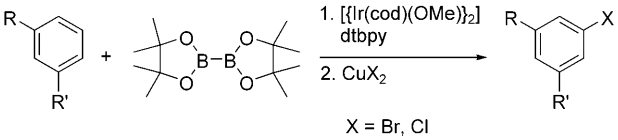
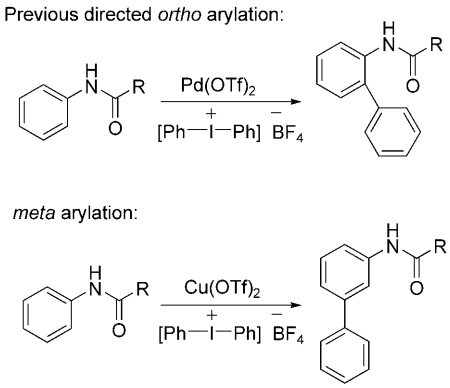
Transition metal catalyzed functionalization of aromatic C–H bonds is of great contemporary interest.[1] This synthetic strategy provides novel approaches as alternatives to the traditional electotrophilic aromatic substitution and the Friedel–Crafts reactions[2] for the preparation of substituted arenes. Different reactivity and selectivity patterns are observed in these metal-catalyzed transformations, which facilitate the preparation of isomers which are not readily formed by traditional approaches. Specifically, in Friedel–Crafts-type reactions, electron-donating substituents direct the incoming electrophiles to the *ortho* and *para* positions, whereas electron-withdrawing groups steer the electrophile to the *meta* position. *Ortho*-substituted products form predominantly in the recently popularized palladium-catalyzed C–H activation reactions through functional group directed cyclometalation,. One of the remaining challenges is to develop catalytic methods for the functionalization of aromatic C–H bonds selectively at the *meta* or *para* position only.

Previously, Hartwig et al. and Smith et al. described the functionalization of the *meta* position of arenes by iridium-catalyzed C–H borylation (Scheme 1).[3] In a one-pot fashion, *meta*-selective boronic esters or halides could be obtained. Because this *meta* selectivity arises from a steric effect, both electron-rich and electron-deficient arenes gave products with similar selectivity. Functional groups including nitriles, esters, amides, and protected alcohols can all be tolerated.

Recent breakthroughs by Phipps and Gaunt and Yu et al. shed some new light on how *meta* selectivity can be realized by clever catalyst design (Scheme 2).[4] In the study by Phipps and Gaunt, a copper-catalyzed arylation reaction can selectively add phenyl electrophiles at the aromatic C–H sites *meta* to an electron-donating amido substituent.[4a] The inspiration



Scheme 1. Iridium-catalyzed C–H bond functionalization (Hartwig et al.). cod = 1,5-cyclooctadiene, dtbpy = 4,4′-di-tert-butyl-2,2′-bipyridine.



Scheme 2. Copper-catalyzed C–H bond arylation. Tf = trifluoromethanesulfonyl (Phipps and Gaunt).

of the study came from the observation of an intriguing copper(I)-catalyzed C–H bond arylation on the indole skeleton at the C3-position as opposed to the C2 selectivity in palladium(II) catalysis. It was speculated that the use of a copper catalyst might enable one to override the *ortho* selectivity observed from other electrophilic palladium(II)-catalyzed arene C–H funtionalizations. Indeed, when acylanilides were treated with the arylating agent (Ph_2IOTf or Ph_2IBF_4) in the presence of 10 mol% a $Cu(OTf)_2$ catalyst in dichloroethane at approximately 70 °C, arylation occurred at the position *meta* to the amide. No reaction occurred in the absence of the copper catalyst, and no products arising from monoarylation at the *ortho* or *para* position were observed. The reaction proceeded most efficiently with benzamides and pivanilides, producing good yields of the desired biaryl products (ca. 80%). Additional experiments showed that the reaction tolerated a wide array of substituents in all positions of the aromatic ring. Even tri- or tetra-substituted

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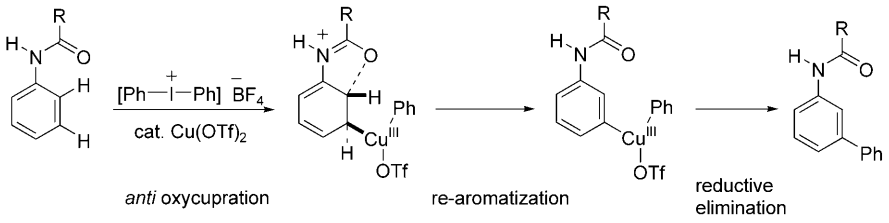
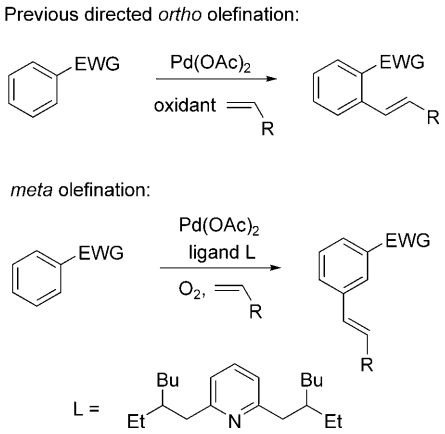
anilides were compatible with the reaction, leading to highly functionalized products in reasonable to good yields. Moreover, by using unsymmetrical iodonium salts, a range of steric, electronic, and functionally diverse aryl groups could be successfully installed within the pivanilide systems. Therefore, this study provides a novel and elegant approach to circumvent the inherent *ortho*/*para* selectivity of electron-rich aromatic systems to generate the *meta*-substituted products.



Scheme 4. Proposed mechanism for palladium-catalyzed olefination of arenes (Phipps and Gaunt).

Complementary to the work by Phipps and Gaunt, Yu and et al. studied the *meta*-C–H functionalization of electron-deficient arenes using palladium-based catalysts (Scheme 3).[4b] Their initial goal was to extend the Fujiwara-



Scheme 3. Palladium-catalyzed olefination of arenes (Yu et al.).

type arene olefination reaction[5] to electron-deficient aromatic systems.[6,3d] Preliminary screening results suggested that coordination between an electron-deficient arene and palladium(II) is poor, so that the commonly used catalyst ($Pd(OAc)_2$ + pyridine) tends to remain as $[Pd(OAc)_2Py_2]$ without binding to the arene. To overcome the problem, Yu et al. designed novel ligands, namely, 2,6-disubstituted pyridines having minimal steric hindrance immediately surrounding the nitrogen atom, and steric hindrance placed instead on the side chain carbon atoms. Such ligands would strongly coordinate to palladium(II) in a singly bound fashion in solution to allow arene binding. It was found that these ligands indeed promoted the olefination of electron-deficient arenes in reasonable to good yields (ca. 70%). More interestingly, *meta*-olefinated arenes were found to be the major products of the reaction. No olefination was observed at the *ortho* position, although small amounts of *para*-olefination products were produced. Thus the study provides an unprecedented approach for *meta*-selective C–H functionalization of electron-deficient arenes under catalytic conditions.

Mechanistically, two explanations may be proposed to explain the *meta* selectivity in transition metal catalyzed arene C–H functionalization:

1) Directed metalation at the *meta* position though a cyclic intermediate (a closed transition-state mechanism): In this proposal, the original substituent of the arene explicitly participates into the metalation process by producing an *anti*-metalated cyclohexa-1,3-diene intermediate (Scheme 4). This process can be compared to the *ortho*-directing cyclometalation process, but it is the *meta*-carbon atom that forms a covalent bond with the metal. Rearomatizing deprotonation of the cyclohexa-1,3-diene intermediate and subsequent reductive elimination would deliver the *meta*-functionalized product. It appears that the Gaunt's copper-catalyzed arylation of electron-rich arenes may undergo the directed metalation at the *meta* position though a cyclic intermediate because no *para* product was observed.

2) Higher C–H acidity at the *meta*-position (an open transition state mechanism): In recent studies on palladium-catalyzed direct arylation of arenes it was found that the arene reactivity depended on C–H acidity, not on nucleophilicity.[7] This theory predicts that for substituted arenes with no or weakly metal-coordinating groups (such as CF_3, NO_2, ketone carbonyls, esters), the *meta* selectivity may be preferred simply because of the higher C–H acidity at the *meta* position. *Ortho* selectivity in the process can be easily prevented by installing sterically hindered ligands at the catalytic center, which makes it difficult to be functionalized close to the substituent. However, unless the C–H acidities at *meta* and *para* positions differ dramatically, the *para*-activation pathway cannot be fully switched off in this mechanism. In Yu's work both *meta* and *para* products were observed, strongly suggesting the involvement of competitive C–H abstractions at both positions on the electron-deficient arenes. This acidity mechanism was proposed by Yu et al.

The studies by Phipps and Gaunt, and Yu et al. on the *meta*-selective arene C–H bond functionalization not only provide powerful tools to the synthetic community, but also open doors for numerous possibilities for developing new transition-metal catalysts. More detailed understanding on the reaction mechanisms will certainly be welcomed in future work. C–H bond functionalizations with novel reactivity and higher selectivity will continue to command the attention of organometallic chemists in the future.

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