meta-Directing Groups

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Directed Functionalization of C–H Bonds: Now also *meta* Selective

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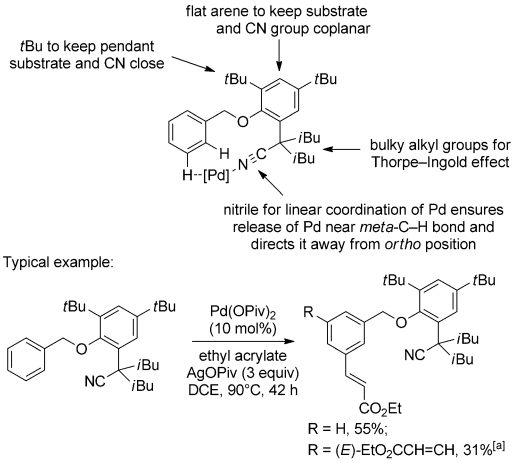
During the last decade, C–H bond functionalization methodology has undergone rapid development and is now used in the synthesis of natural products and medicinally relevant compounds.[1] The ability to employ C–H bond as a transformable functional group allows to shorten reaction pathways, thus leading to more efficient methods for producing the desired substances. Another important feature of C–H bond functionalization is the ability to achieve unique regioselectivities that are often unattainable by employing classical methods such as Friedel–Crafts chemistry.[2] Herein, we discuss an ingenious concept of using *meta*-directing groups, which has recently been reported by Yu and co-workers.[3]

Chemists have used metals in C–H bond functionalization for over 120 years.[4a] Today, many arenes can be regioselectively functionalized by employing transition-metal catalysis. For example, heterocycles can be arylated under copper, rhodium, and palladium catalysis.[4b–e] Regioselectivity of the functionalization is determined by the acidity of C–H bonds of heterocycles or factors that influence a concerted metalation–deprotonation (CMD) pathway. Unusual regioselectivity of thiophene arylation has been achieved by employing a palladium catalyst in the presence of electron-poor phosphite ligands.[4c] Another prominent example of C–H bond functionalization is the transition-metal-catalyzed arene borylation.[5] This breakthrough has allowed thus far unprecedented *meta* functionalization of electron-rich arenes. Regioselectivity of the borylation is determined primarily by steric factors. A recent breakthrough methodology has resulted in *meta*-selective arylation of anilides and arylcarbonyl compounds.[6a,b] Unfortunately, mechanistic reasons for the regioselectivity are not apparent. Ruthenium-catalyzed *meta* sulfonylation of 2-phenylpyridines has been reported recently.[6c] Initial pyridine-directed metalation is followed by electrophilic aromatic substitution that determines the regioselectivity of the functionalization. Alternatively, regioselective functionalization of disubstituted arenes may be achieved by optimization of the ligand environment at the metal center.[7] Finally, regioselectivity of the functionalization can be imparted by directing groups. This methodology has its origins in cyclometalation reactions discovered by Cope and Kleiman, and cobalt-catalyzed carbonylation of benzaldehyde imines reported by Murahashi in 1955.[8] It is generally assumed that the coordinating group directs the metal toward the *ortho*-C–H bond.[9] However, several other mechanistic possibilities have been suggested. Lenges and Brookhart showed that $[Cp^*Rh(CH_2{=}CHTMS)_2]$ (Cp^* = pentamethylcyclopentadienyl, TMS = trimethylsilyl) activates all aromatic positions in acetophenone; however, only *ortho*-arylated products were observed.[10] The barrier to product-determining reductive elimination is apparently reduced by a chelating ketone substituent, resulting in exclusive formation of *ortho*-alkylated acetophenones. Goldman and co-workers have shown that oxidative addition of arene C–H bonds to a (κ^3-C_6H_3-2,6-$(CH_2PtBu_2)_2$)Ir fragment is kinetically hindered by directing groups.[11] Once C–H bond activation occurs at the *ortho* position to a directing group, the metal is trapped by coordination.

The *ortho* functionalization of directing-group-containing arenes has been investigated extensively. In fact, the statement "directing group" in C–H bond functionalization assumes direction of substitution to the *ortho* position. In a recent paper, Yu and co-workers reported removable, nitrile-containing directing groups that allow the functional-



Scheme 1. Development of *meta*-directing groups. [a] Selectivity for *meta*-substituted product relative to other isomers was 88:12. DCE = dichloroethane, Piv = pivaloyl.

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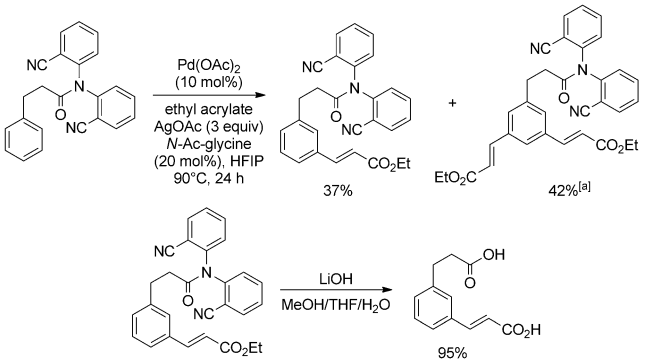
ization of *meta*-C–H bonds of the aromatic substrate via a cyclophane-type transition state (Scheme 1).[3] The auxiliary development required extensive engineering. The authors proposed that the nitrile group, with its linear coordination to Pd^{II}, would produce high local concentration of palladium at the *meta*-C–H bond. Additionally, linear coordination of Pd to nitrile would prevent the activation of *ortho*-C–H bonds. A flat arene template was employed in order to keep the directing group and the *meta*-C–H bond of the substrate coplanar. A bulky *tert*-butyl group in *ortho* position of the removable auxiliary was used to direct the nitrile near the *meta*-C–H bond. Additionally, the nitrile group was connected to the removable auxiliary through a tertiary alkyl group to result in a Thorpe–Ingold effect.[12] The directing group proved to be highly efficient in *meta* alkenylation of arenes, with selectivities for *meta* positions from 100:0 to about 75:25, and typical values of 90:10 to 95:5. Acrylates, ethyl vinyl ketone, diethyl vinyl phosphonate, and a number of disubstituted and cyclic trisubstituted alkenes that possess an ester substituent were reactive. The authors propose that the [Pd^{II}–Ar] intermediate is weakly bound to the nitrile. Thus, hindered olefin substrates can be employed, which is an unusual feature for palladium-catalyzed olefination reactions. The directing group was removed by hydrogenolysis, affording *meta*-substituted toluene derivatives.

To show the generality of the concept of using *meta*-directing groups, alkenylation of hydrocinnamic acid derivatives was investigated next (Scheme 2). An external *N*-acetylglycine ligand, previously shown to accelerate vinylation reactions,[13] was required to achieve high yields and selectivities. Hydrocinnamic acid derivatives were efficiently *meta*-functionalized as well, with selectivities similar to the ones described for benzyl ethers. These examples are the first high-yielding *meta*-selective substitutions of electron-rich monosubstituted arenes.

While this method has considerable synthetic value, its main importance is perhaps conceptual. Yu and co-workers have shown that by rational design of the directing group, both *ortho* and *meta* functionalization of aromatic rings can be achieved. An obvious application of the concept is the remote directed functionalization of aliphatic chains, currently demonstrated in gas phase for transition metals. Schwarz has shown that in gas phase, Fe^+ activates remote C–H bonds in aliphatic nitriles.[14] A recent report shows that copper can promote gas-phase oxygenation of remote aliphatic positions in bipyridine-3-carboxylic acid esters.[15] In solution, directed β-, γ-, or δ-C–H bond functionalization has been described.[1,16b] Remote C(sp^3)–H bond functionalization by radical chemistry has been described earlier by Breslow.[16a]

In summary, the new concept of rationally designed, removable *meta*-directing groups opens up new exciting opportunities for the functionalization of C–H bonds. Although the development of a mechanistic understanding and the expansion of the reaction scope is still highly desirable, current advances show the possibility of attaining unusual selectivities in arene functionalization.



Scheme 2. *meta* Functionalization of hydrocinnamic acid amides. [a] Selectivity for *meta*-substituted product relative to other isomers was 88:12. HFIP = hexafluoroisopropanol.

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