ORTHO C–H METHYLATION

Pin a methyl on it

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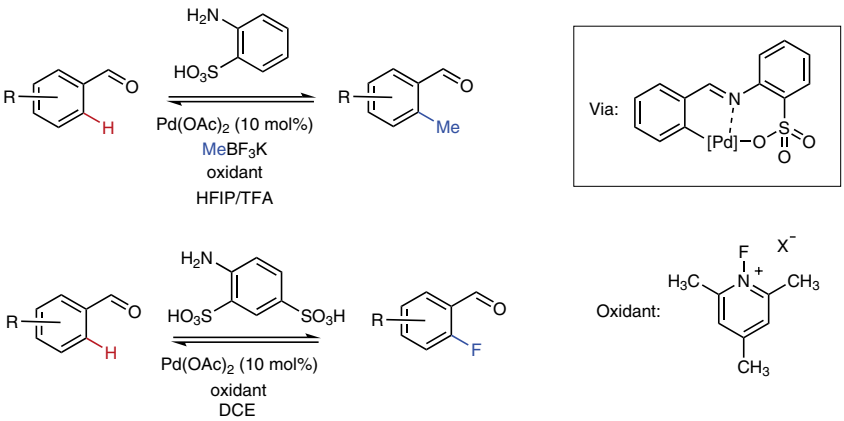

Site-selective C–H functionalization of aromatics is a difficult process. Not only is there the problem of the inherently unreactive C–H bond, but also the frequent presence of a number of sites with relatively similar steric and electronic properties that make finding a general solution difficult. One of the major strategies is to use a coordinating group on the substrate — often pyridinyl or related groups — that directs the metal catalyst to one specific site. Although this method is very successful, it limits the structural variety of the product due to the difficulty of removing such groups. Another appealing option is a transient directing group. For example, aldehydes can be temporarily converted to directing groups by the reversible, in situ, formation of coordinating imines. The final product simply contains the original aldehyde, itself a useful and flexible functional handle.

It was this latter approach that Xiao-Yang Chen and Erik Sorensen from Princeton University employed. Rather than the more common amino carboxylic acid transient directing groups, they used amino sulfonic acid derivatives. This allowed them to methylate the *ortho* C–H position of a range of benzaldehydes, providing complementary reactivity to the previously reported arylation procedures. In order to be compatible with the acidic reactions, potassium methyl trifluoroborante was chosen as the methylating agent, and a fluoropyridinium salt was used as oxidant to form the Pd(IV) intermediate required for C–C bond formation. A diverse range of substituted benzaldehydes were tolerated as reaction partners, though electron-poor aromatic rings were preferred.

The authors then proceeded to examine the highly desirable C–H fluorination reaction. By careful choice of transient directing group and reaction conditions, *ortho* fluorination was achieved in good yields, with the fluoropyridinium oxidant acting as a source of electrophilic fluorine. As with the methylation procedure, a preference for less electron-rich aromatic rings was observed. Finally, crystallographic evidence for the formation of a palladacycle intermediate — coordinated to the transient directing group — was provided by trapping the C–H insertion intermediate with triphenylphosphine.

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