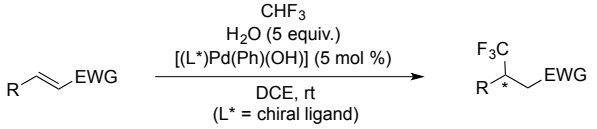
Palladium-catalyzed enantioselective 1,4-conjugate trifluoromethylation of Michael acceptors

The effort to attain novel fluorinated organic compounds continues to be an active area of research in the pharmaceutical and agrochemical industries. This continued effort is due to the enhanced lipophilicity and bioavailability that ensues following the replacement of hydrogen atoms with fluorine.[1] In regards to α,β-unsaturated systems, enantioselective 1,2-trifluoromethylations have been well documented with the use of TMS-CF_3 and cinchona alkaloids, yielding good to high enantioselectivities.[1] However, racemic 1,4-conjugate trifluoromethylation of Michael acceptors still languishes well behind the respective 1,2-addition, mainly due to the mismatch between the "hard" nature of the trifluoromethyl anion and the "soft" nature of the alkene.[1] A handful of reports have demonstrated the 1,4-conjugate trifluoromethylation of Michael acceptors, albeit in poor to fair yields and only in a racemic fashion.[1,2] A method for the enantioselective 1,4-conjugate trifluoromethylation of Michael acceptors is still lacking in the literature.[1,2] Herein, I propose the first enantioselective and catalytic 1,4-conjugate trifluoromethylation of Michael acceptors using palladium, fluoroform, and a chiral bidentate phosphine ligand (Scheme 1).

In 2011, Stoltz and coworkers published work on the Pd(II)-catalyzed conjugate addition of aryl groups—from arylboronic acids—to various cyclohexenones to form new asymmetric quaternary centers.[3,4] Although trifluoromethyl trifluoroborate (F_3C-BF_3^-) is known and could possibly be used in an analogous fashion, it would be advantageous to eliminate the need of super-stoichiometric boron reagents altogether. Work published by Grushin and coworkers in 2013 offers a practical route to access a Pd-CF_3 complex **2** using fluoroform and palladium complex **1** at room temperature (Figure 1).[5] Conjugate trifluoromethylation via carbopalladation would afford intermediate **3**, which could then be protonated by water—avoiding the unwanted β-hydride elimination pathway[6]—yielding the target product and regenerating the active catalyst.



Scheme 1. Proposed Pd-catalyzed 1,4-conjugate trifluoromethylation of α,β-unsaturated systems

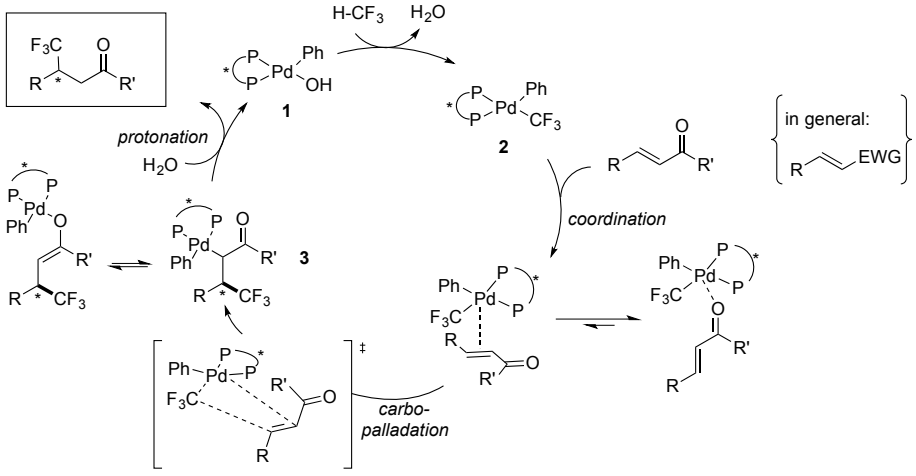


Figure 1. Proposed catalytic cycle

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