Cross-Coupling

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Decarboxylative Alkyl–Alkyl Cross-Coupling Reactions

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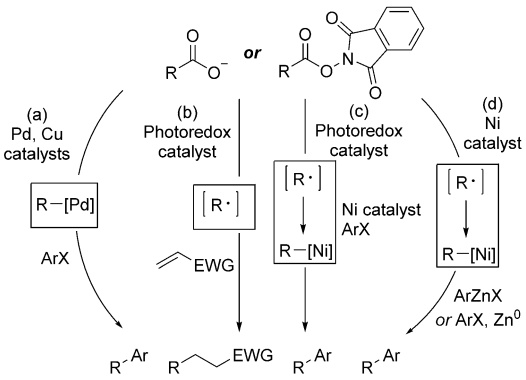
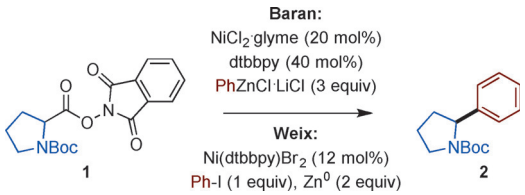
Enzymatic decarboxylation reactions engage carboxylic acid building blocks in key biosynthetic transformations, for example, as part of cellular respiration and syntheses of essential neurotransmitters, including dopamine and serotonin. Chemists have also employed decarboxylation, that is, the extrusion of CO_2, as a means of forming reactive anionic and radical intermediates. Metal-catalyzed protodecarboxylation of aryl carboxylic acid derivatives has been known since the 1930s and has been proposed to proceed through aryl metal intermediates. In 2006, Gooßen and co-workers reported the Cu/Pd dual catalytic decarboxylative synthesis of biaryl compounds (Scheme 1 a), reinvigorating interest in this area.[1] Aside from generating carbanionic intermediates, decarboxylation can also reveal alkyl and aryl radical intermediates when performed under Barton-type or photocatalytic conditions. Okada and co-workers introduced the use of redox-active *N*-hydroxyphthalimide (NHP) esters as activating groups for the generation of alkyl radicals using photoredox catalysts (Scheme 1 b).[2] More recently, Overman and co-workers employed this strategy for the construction of sterically encumbered quaternary centers (Scheme 1 b).[3]



Scheme 1. a) Bimetallic decarboxylative cross-coupling. b) Photocatalysis-enabled radical additions. c) Synergistic photoredox and nickel-catalyzed cross-coupling. d) Decarboxylative $C(sp^3)$–$C(sp^2)$ cross-coupling. EWG = electron-withdrawing group.

Experimental evidence that organonickel intermediates can trap carbon-centered radicals as part of cross-coupling manifolds[4] has sparked a new field in nickel catalysis.[5,6] The Doyle and MacMillan groups demonstrated that combining a photoredox catalyst with a nickel catalyst enables decarboxylative $C(sp^3)$–$C(sp^2)$ couplings between alkyl carboxylic acids and aryl halides (Scheme 1 c).[5b] Based on earlier work from the MacMillan laboratory,[7] they employed an iridium photocatalyst to affect the photomediated oxidation of a carboxylate; subsequent CO_2 expulsion generates a carbon-centered radical. This alkyl radical is proposed to enter the cross-coupling catalytic cycle by intercepting an aryl nickel(II) complex. Since these first reports, many creative strategies for generating radical intermediates in the presence of nickel complexes have been reported.[5] A new advance in decarboxylative $C(sp^3)$–$C(sp^2)$ coupling resulted from the realization that NHP esters can readily accept an electron from a low-valent nickel catalyst without the need for photooxidation (Scheme 1 d).[8] Baran and co-workers demonstrated this concept by developing cross-couplings of secondary NHP esters with aryl zinc halide reagents (Scheme 2). Contemporaneously, Weix et al. reported a cross-electrophile variant, coupling primary and secondary NHP esters with aryl halides with zinc metal as the stoichiometric reductant.[9] Notably, these reactions proceed without the need for a co-catalyst or light and forge a $C(sp^3)$–$C(sp^2)$ bond.



Scheme 2. Decarboxylative alkyl–aryl cross-couplings by nickel catalysis with redox-active esters. Boc = *tert*-butoxycarbonyl, dtbbpy = 6,6′-di-*tert*-butyl-2,2′-bipyridine.

The application of this strategy towards alkyl–alkyl cross-couplings has recently been described by Baran and co-workers. In general, metal-catalyzed $C(sp^3)$–$C(sp^3)$ bond-forming reactions present substantial difficulties when compared to the corresponding $C(sp^3)$–$C(sp^2)$ coupling reactions. Alkyl metal complexes are significantly less stable than their aryl metal counterparts and are prone to a range of side

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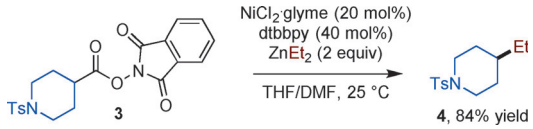
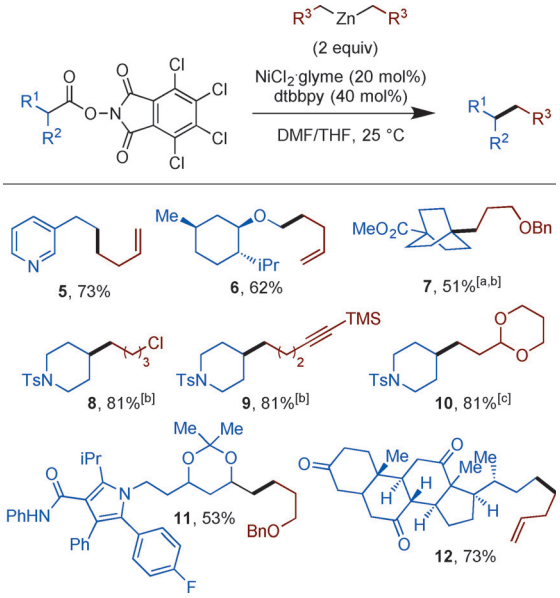
reactions, including β-hydride elimination, reduction, and dimerization. Furthermore, cross-coupling reactions of secondary substrates by traditional mechanisms are challenging, and reactions of tertiary substrates are scarce. Despite these anticipated challenges, direct implementation of the previously developed reaction conditions allowed for effective alkyl–alkyl cross-couplings with dialkylzinc reagents (Scheme 3).[10] Part of the success of this transformation can



Scheme 3. Decarboxylative alkyl–alkyl cross-coupling. Ts = *para*-toluenesulfonyl.

be attributed to replacing a secondary alkyl halide or pseudohalide partner with the NHP ester. By doing this, the challenging oxidative addition reaction of a secondary alkyl electrophile is avoided; instead, a favorable SET reaction engages the substrate.

An impressive scope was demonstrated with a broad range of carboxylic acid derivatives (Scheme 4). Indeed, having the NHP ester trigger formation of the alkyl radical allows the reaction to be somewhat blind to the identity of the alkyl substituent: primary, secondary, and tertiary substrates afford the desired products. Impressively, tertiary bridgehead carboxylic acid derivatives, such as adamantanecarboxylic acid and bicyclo[2,2,2]octane **7**, also participated in the reaction. A variety of functional groups were tolerated, both on the carboxylic acid and the zinc reagent, including aryl and alkyl chlorides, alkenes, alkynes, and ketones. The reaction proceeded in the presence of acidic amides as well (e.g., **11**).

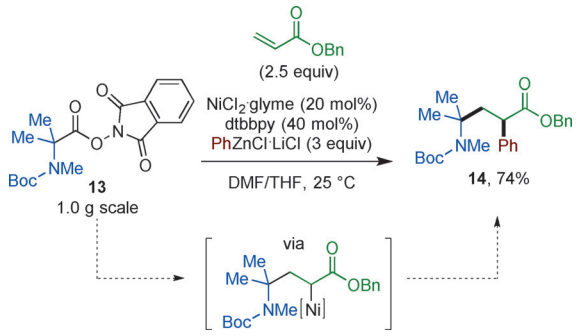


Scheme 4. Scope of the decarboxylative alkyl–alkyl cross-coupling. [a] With $Ni(acac)_2$ (40 mol%; acac = acetylacetonate), 6,6′-dimethyl-2,2′-bipyridine (40 mol%), MeCN/THF, 80 °C. [b] From the phthalimide ester. [c] 2,2′-Bipyridine (40 mol%). Bn = benzyl, TMS = trimethylsilyl.

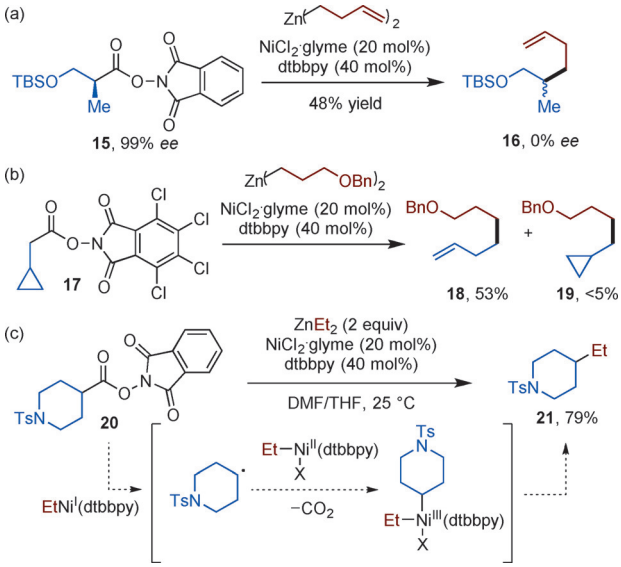
Furthermore, an impressive range of 15 primary organozinc reagents were employed. The selectivity of the coupling reaction was further displayed in the context of derivatization of complex pharmaceuticals and natural-product-derived substrates (e.g., products **11** and **12**).

The use of a conjugate acceptor allowed for a three-component reaction with tertiary NHP esters and aryl zinc halides (Scheme 5). The three-component coupling tolerates a broad range of tertiary acyclic carboxylic acid derivatives, forming congested quaternary centers in good yields on gram scale. Furthermore, these reactions are amenable to application in solid-phase synthesis, as demonstrated by the functionalization of peptides that also contain synthetic handles for further modification. Therefore, activated esters such as **13** can now be envisioned as starting materials for traditional acylation reactions such as amide couplings or decarboxylative reactions.

Preliminary mechanistic investigations are consistent with the formation of an alkyl radical from the fragmentation of the NHP ester. Subjecting enantioenriched secondary substrate **15** to the decarboxylative cross-coupling conditions led to racemic product (Scheme 6a). Coupling of the radical-



Scheme 5. Three-component coupling reaction.



Scheme 6. Mechanistic experiments. a) Racemization of an enantioenriched NHP ester. b) Reaction with a radical-clock substrate. c) Proposed mechanism. TBS = *tert*-butyldimethylsilyl.

clock substrate **17** provided the ring-opened product, alkene **18** (Scheme 6b). Both of these experiments are consistent with the formation of a discrete alkyl radical intermediate, as outlined in Scheme 6c. These findings may have significant practical implications. For example, it may be possible that a chiral nickel catalyst could enable a stereoconvergent, enantioselective cross-coupling reaction akin to Fu's early work in alkyl cross-coupling reactions.[11]

Decarboxylative cross-coupling reactions have traditionally been employed to stitch together biaryl linkages. Expanding these reactions to include alkyl partners has been of great interest and activity, with recent reports achieving the coupling of alkyl carboxylic acids and derivatives with aryl partners. The latest transformation achieved by Baran and coworkers allows for the construction of alkyl–alkyl linkages by coupling with alkyl zinc reagents. This nickel-catalyzed decarboxylative $C(sp^3)$–$C(sp^3)$ cross-coupling reaction is a straightforward and practical strategy, which will likely see application in related target-oriented synthesis and enantioselective cross-coupling reactions.

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