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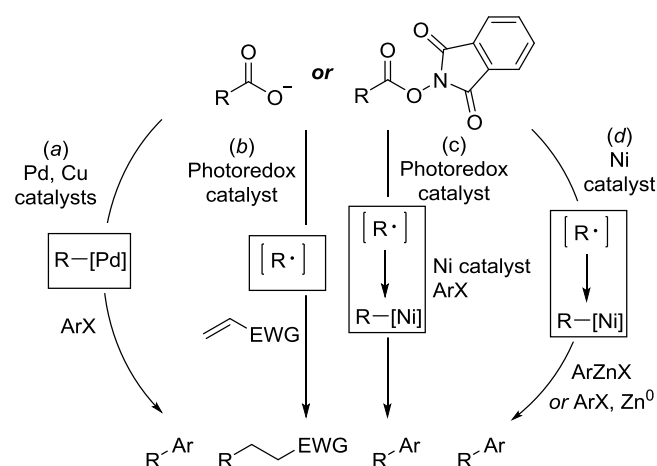
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## Decarboxylative Alkyl-Alkyl Cross-Coupling Reactions

Mikhail O. Konev and Elizabeth R. Jarvo\*

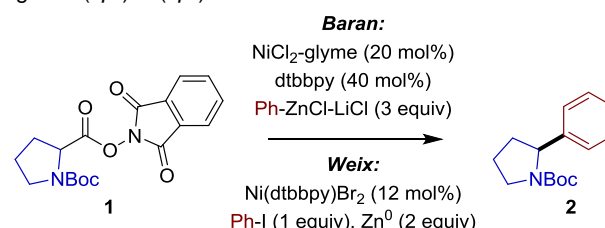
Enzymatic decarboxylation reactions engage carboxylic acid building blocks in key biosynthetic transformations, for example, as part of cellular respiration and the syntheses of essential neurotransmitters including dopamine and serotonin. Chemists have also employed decarboxylation, extruding CO<sub>2</sub> as a means of forming of reactive anionic and radical intermediates. Metal-catalyzed protodecarboxylation of arylcarboxylic acid derivatives has been known since the 1930's and is proposed to proceed through arylmetal intermediates. In 2006 Gooßen and co-workers reported the Cu/Pd dual catalytic decarboxylative synthesis of biaryls (Scheme 1a), reinvigorating interest in this area.<sup>[1]</sup> In addition to 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 1b).<sup>[2]</sup> More recently, Overman and co-workers employed this strategy for construction of sterically encumbered quaternary centers (Scheme 1b).<sup>[3]</sup>



**Scheme 1.** (a) Bimetallic decarboxylative cross-coupling. (b) Photocatalysis-enabled radical additions. (c) Synergistic photoredox and nickel-catalyzed cross-coupling. (d) C(sp<sup>3</sup>)-C(sp<sup>2</sup>) decarboxylative cross-coupling.

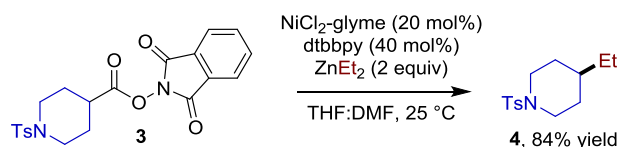
The realization that organonickel intermediates can trap carbon-centered radicals as part of cross-coupling manifolds has sparked a new field in nickel-catalysis.<sup>[4,5]</sup> The Doyle and MacMillan groups demonstrated that combining a photoredox catalyst with a nickel catalyst provided decarboxylative sp<sup>3</sup>-sp<sup>2</sup> coupling between alkyl carboxylic acids and aryl halides (Scheme 1c).<sup>[4b]</sup> Based on earlier work from the MacMillan laboratory,<sup>[6]</sup> they employed an iridium photocatalyst to affect photomediated oxidation of a carboxylate; subsequent CO<sub>2</sub> expulsion generated a carbon-centered radical. This alkyl radical is proposed to enter the cross-coupling catalytic cycle by intercepting an arylnickel(II) complex. Since these first reports, many creative strategies for generation of radical intermediates in the presence of nickel complexes have been reported.<sup>[5]</sup> A

new advance in *decarboxylative* sp<sup>3</sup>-sp<sup>2</sup> coupling resulted from the realization that NHP esters can readily accept an electron from a low valent nickel catalyst without the need of photooxidation (Scheme 1d).<sup>[7]</sup> The Baran group demonstrated this concept by developing cross-coupling of secondary NHP esters with arylzinc halide reagents (Scheme 2). Contemporaneously, Weix reported a cross-electrophile variant, coupling primary and secondary NHP esters with aryl halides with zinc metal as a stoichiometric reductant.<sup>[8]</sup> Notably, these reactions proceed without the need of a co-catalyst or light and forge a C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bond.



**Scheme 2.** Decarboxylative alkyl-aryl cross-couplings via nickel catalysis with redox-active esters. Dtbppy = 6,6'-di-*tert*-butyl-2,2'-bipyridine.

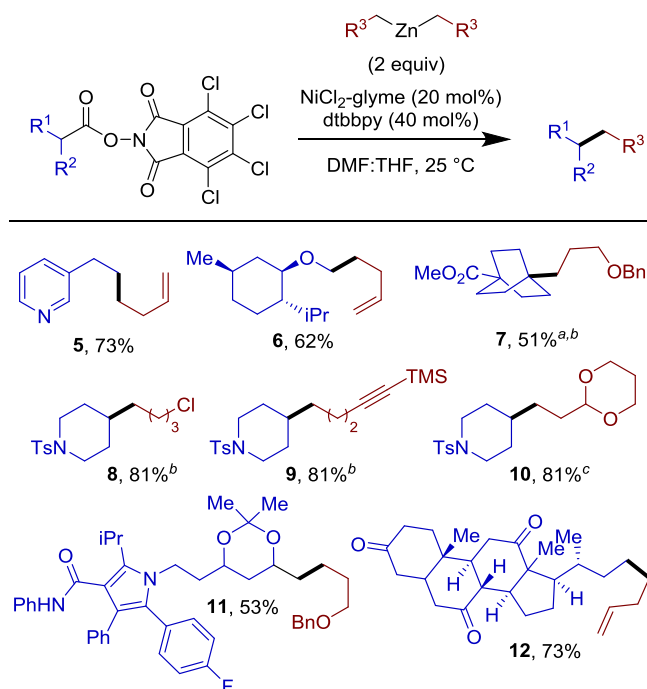
Application of this strategy toward an alkyl-alkyl cross-coupling has recently been described by Baran and co-workers. In general, metal-catalyzed C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formations present increased difficulties when compared to corresponding C(sp<sup>3</sup>)-C(sp<sup>2</sup>) coupling reactions. Alkylmetal complexes are significantly less stable than the arylmetal counterparts and are prone to a range of side 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 previous reaction conditions allows for the effective alkyl-alkyl cross-coupling with dialkylzinc reagents (Scheme 3).<sup>[9]</sup> Part of the success of this transformation can be attributed to replacing a secondary alkyl halide or pseudohalide partner with the NHP ester. By doing this, a challenging oxidative addition reaction of a secondary alkyl electrophile is avoided, instead, a favorable SET reaction engages the substrate.



**Scheme 3.** Decarboxylative alkyl-alkyl cross-coupling.

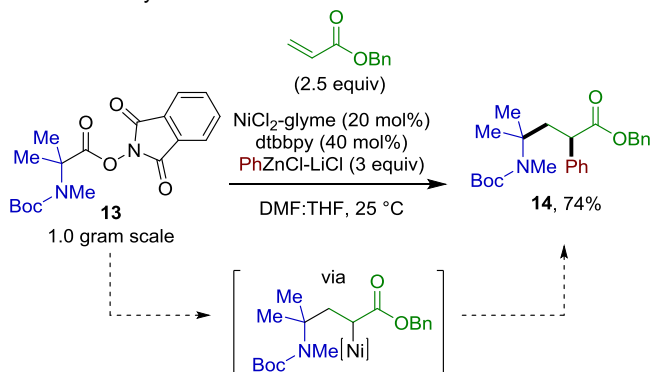
An impressive scope was demonstrated with a broad range of carboxylic acid derivatives (Scheme 4). Indeed, having the NHP ester trigger formation of the alkyl radical allows the reaction to be somewhat blind to the identity of the alkyl substituent: primary, secondary, and tertiary substrates afford products. Impressively, bridgehead tertiary substrates such as adamantantecarboxylic 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**). 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**).

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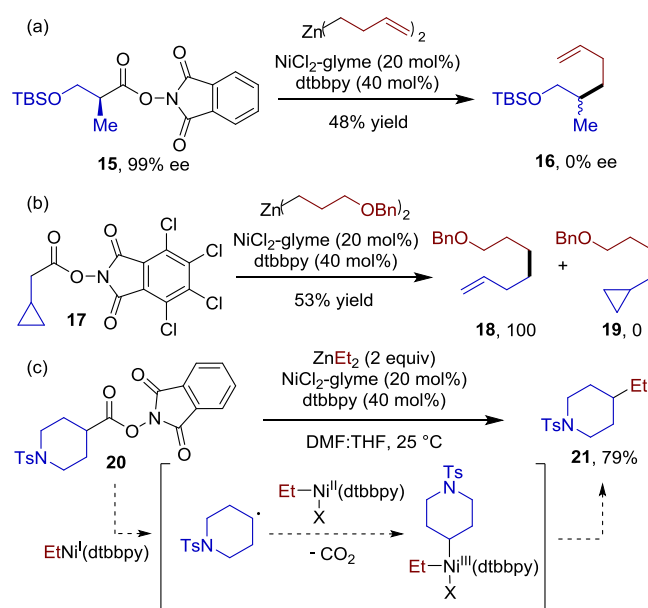
**Scheme 4.** Scope of the decarboxylative alkyl-alkyl cross-coupling. <sup>a</sup>Using 40 mol%  $Ni(acac)_2$ , 40 mol% 6,6'-dimethyl-2,2'-bipyridine, MeCN:THF, 80 °C. <sup>b</sup>Using phthalimide ester. <sup>c</sup>Using 40 mol% 2,2'-bipyridine.

Use of a conjugate acceptor allows for a three-component reaction with tertiary NHP esters and arylzinc 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, demonstrated by the functionalization of peptides that also contain synthetic handles for further functionalization.



**Scheme 5.** Three component coupling reaction.

Preliminary mechanistic investigations are consistent with the formation of an alkyl radical from the fragmentation of the NHP ester. Subjecting an enantioenriched secondary substrate **15** to decarboxylative cross-coupling conditions provided racemic product (Scheme 6a). Coupling of the radical clock substrate **17** provided ring-opened product, alkene **18** (Scheme 6b). Both of these experiments are consistent with 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 provide a stereoconvergent, enantioselective cross-coupling reaction akin to Fu's early work in alkyl cross-couplings.<sup>[10]</sup>



**Scheme 6.** Mechanistic experiments. (a) Racemization of an enantioenriched NHP ester. (b) Radical clock. (c) Proposed mechanism.

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 coupling of alkyl carboxylic acids and derivatives with aryl partners. The latest transformation achieved by Baran and co-workers allows the construction of alkyl-alkyl linkages by coupling with alkylzinc 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.

## Acknowledgements

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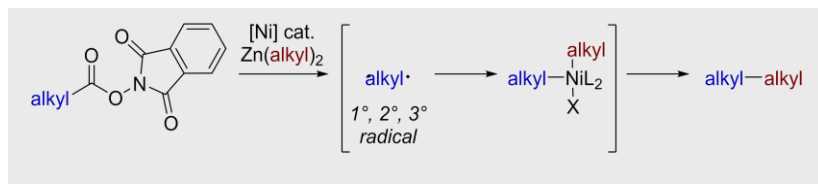
**Keywords:** decarboxylative coupling • Negishi coupling • alkyl-alkyl coupling • nickel

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## Entry for the Table of Contents

## HIGHLIGHT



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Decarboxylative alkyl-alkyl cross-coupling reactions

Baran and co-workers have reported a significant new development in alkyl-alkyl cross-coupling reactions, nickel-catalyzed decarboxylative Negishi coupling of *N*-hydroxyphthamide esters. This reaction provides a practical new method, amenable to synthesis of highly functionalized compounds including natural product derivatives. Three component coupling reactions are also achieved via conjugate addition of the putative radical intermediate.