

# RECENT ADVANCES IN DECARBOXYLATIVE COUPLINGS

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## INTRODUCTION

Decarboxylation reactions stem back to the Kolbe electrolysis in 1849, where carboxylic acids and carboxylate salts were homocoupled.<sup>1</sup> Then came the Hunsdiecker reaction,<sup>2</sup> Barton decarboxylation,<sup>3</sup> and Minisci reaction.<sup>4</sup> Finally, the Tsuji-Trost allylation allowed for the facile generation of all-carbon quaternary stereocenters through the intermediacy of a palladium-allyl species and nucleophilic enolate.<sup>5</sup>

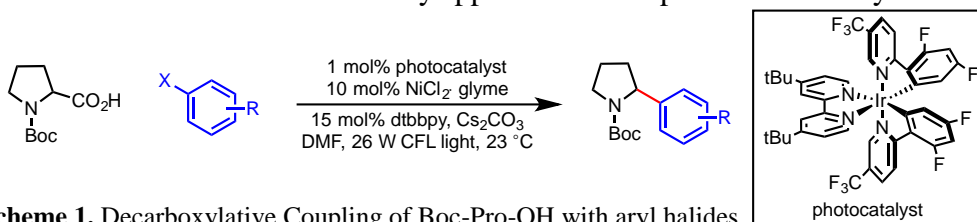
In the realm of transition-metal-mediated decarboxylative transformations, Myers and coworkers functionalized benzoic acid derivatives via a Heck-type olefination employing palladium catalysis.<sup>6</sup> The substrate scope for this transformation was broad, encompassing electron poor and rich aromatic acids, styrene and  $\alpha,\beta$ -unsaturated enone Heck partners. Then, Gooßen *et al.* described the synthesis of biaryls through the coupling of electron deficient benzoic acid derivatives and aryl bromides.<sup>7</sup> This was achieved through the intermediacy of stoichiometric  $\text{CuCO}_3$  and catalytic  $\text{Pd}(\text{acac})_2$ .

Notably, the previously described transition-metal-mediated decarboxylative couplings involved the formation of  $\text{C}_{\text{sp}2}\text{-C}_{\text{sp}2}$  bonds and could not access  $\text{C}_{\text{sp}3}\text{-C}_{\text{sp}2}$  and  $\text{C}_{\text{sp}3}\text{-C}_{\text{sp}3}$  bonds.

## RECENT ADVANCES

### Photoredox Catalysis

In 2014, MacMillan reported the arylation of  $\alpha$ -amino acids via an iridium photoredox-catalyzed decarboxylation and subsequent coupling with aryl nitriles.<sup>8</sup> This allowed for the transformation of feedstock amino acids to high-value added chemicals in a single operation. The carboxylic acid, a relatively ubiquitous functionality in organic chemistry, could now be considered a handle for coupling reactions much in the same way halides and pseudohalides are. The relative generality and potential of this transformation became readily apparent in the report from the Doyle and MacMillan groups involving



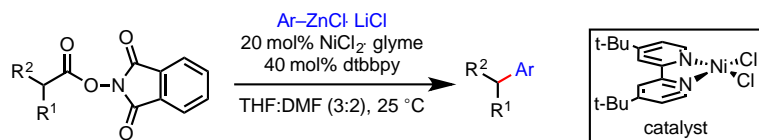
photoredox dual catalysis (Scheme 1).<sup>9</sup> Despite the broad scope and novel reactivity of

**Scheme 1.** Decarboxylative Coupling of Boc-Pro-OH with aryl halides

this transformation, one disadvantage is the complete erosion of the inherent stereochemistry of the proline substrate. While this is not an issue in medicinal chemistry, this is quite inhibitory for those who wish to make use of this chemistry in synthesis.

## Redox Active Esters

Recently, the Baran group published a method that capitalized on the reductive and oxidative potentials of a Ni(I) catalyst and *N*-hydroxyphthalimide ester, respectively (Scheme 2).<sup>10</sup> This



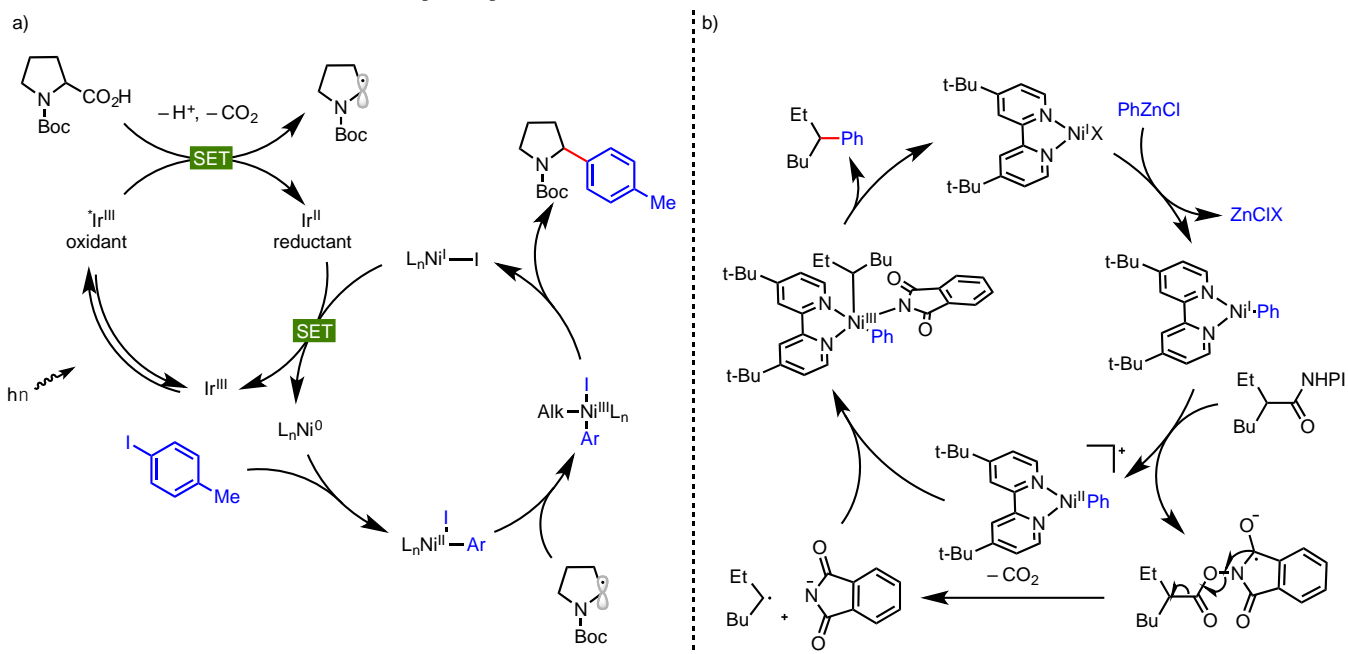
**Scheme 2.** Decarboxylative coupling with redox active esters

methodology coupled redox active esters (RAE) with aryl zinc reagents. Under this principle, a number of esters were screened and those that were successful are: Barton,

*N*-hydroxyphthalimide (NHPI) and its tetrachloro derivative, HOAt, and HOBt. When considering this transformation, it is apparent that a distinct disadvantage takes form in atom economy as the RAE often has a mass greater or equal to that of the substrate.

## Comparison

Comparing the two approaches, each mechanism relies on radical intermediates being trapped by a Ni(II) species (Figure 1); however, the generation of the radical differs by employing a photosensitizer (MacMillan) or RAE (Baran). Furthermore, each mechanism has its own shortcoming to overcome (*vide supra*). Yet, this is overshadowed by the fact that carboxylic acids have now been shown to be competent coupling partners in forming C<sub>sp3</sub>-C<sub>sp2</sub> bonds.



**Figure 1.** a) Doyle and MacMillan's photoredox catalytic cycle b) Baran's redox active ester catalytic cycle

## References

- (1) Kolbe, H. *Justus Liebigs Ann. Chem.* **1849**, 69, 257–294.
- (2) Hunsdiecker, H. *Berichte Dtsch. Chem. Ges. B Ser.* **1942**, 75, 291–297.
- (3) Barton, D. H. R. *Proc. Chem. Soc.* **1962**, 309.
- (4) Minisci, F. *Tetrahedron* **1971**, 27, 3575–3579.
- (5) Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis; Kazmaier, U., Ed.; *Top. Organomet. Chem.*; Springer Berlin Heidelberg: Berlin, Heidelberg, **2012**; Vol. 38.
- (6) Myers, A. G. *J. Am. Chem. Soc.* **2002**, 124, 11250–11251.
- (7) Gooßen, L. J. *Science* **2006**, 313, 662–664.
- (8) MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, 136, 5257–5260.
- (9) Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, 345, 437–440.
- (10) Baran, P. S. *J. Am. Chem. Soc.* **2016**, 138, 2174–2177.

