## Introduction

Csp^3-Csp^3 bonds are extremely important in medicinal chemistry. It has been found that increased complexity, often arising from more Csp^3 hybridized carbons, has been correlated to the increased clinical success of drugs. However, forming Csp^3-Csp^3 bonds has remained a challenge. Traditionally carbon-carbon bonds have been synthesized via polar disconnections. These routes often require multiple steps to forge a single bond. For example, in **figure 1**, the unnatural amino acid can be synthesized in seven steps
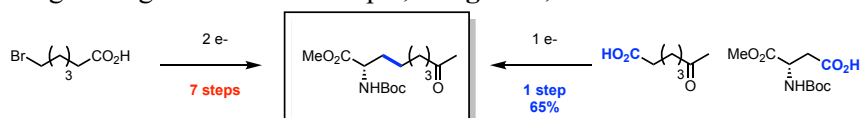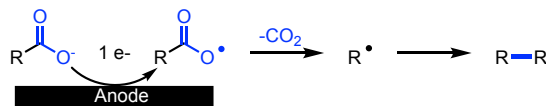

Figure 1: Comparing polar bond disconnection to radical based disconnections.

using traditional methods. Including a Wittig reaction followed by hydrogenation to form a carbon-carbon bond. The overall yield for this seven-step synthesis is 30%.[1] However, using a doubly

decarboxylative cross-coupling reaction, the bond can be formed in a single step from 2 commercially available starting materials in a 65% yield. In addition to traditional polar disconnections, transition metal-mediated catalysis is often used to form Csp^3-Csp^3 bonds. However, traditional cross-coupling methods with alkyl groups are plagued by many challenges. Problems that arise in Csp^3-Csp^3 cross-couplings include inefficient oxidative additions, β-hydride elimination, and slow rates of reductive elimination.[2,3,4,5] Forming a quaternary Csp^3-Csp^3 bond is extremely challenging using traditional cross-coupling methods and often requires highly reactive tertiary Grignard reagents or alkyl iodides.[2]

Kolbe Electrolysis

Kolbe electrolysis, discovered in 1849, is a method that uses platinum electrodes and high potentials to

Figure 2: Kolbe electrolysis mechanism.

forge Csp^3-Csp^3 bonds. In Kolbe electrolysis, a carboxylate is oxidized at the anode to a carboxyl radical, it then undergoes decarboxylation to form an alkyl radical.[6] While this reaction is efficient for homocoupling of carboxylic acids, it is not well suited for heterocoupling of carboxylic acids. To get synthetically useful yields of heterocoupled products, 5-10 equivalents of one

carboxylic acid must be used. The major product is the homocoupled product. Additionally, due to the high potentials used in this reaction, these conditions are strongly oxidative, greatly limiting the scope of the reaction. In 2022, Baran discovered a modified Kolbe electrolysis.[7] Using rapid alternating potential (rAP) and reticulated vitreous carbon (RVC) electrodes, Baran was able to successfully broaden the scope of Kolbe electrolysis. For heterocoupling reactions, an excess of one carboxylic acid is still required. Previously, open benzylic positions were incompatible with Kolbe electrolysis because arene oxidation was the major product. However, with the new method, no arene oxidation was observed.

Electrochemical Methods
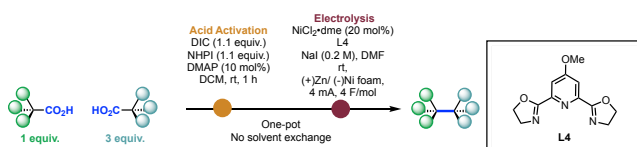
Figure 3: General scheme for electrochemical mediated doubly decarboxylative cross coupling
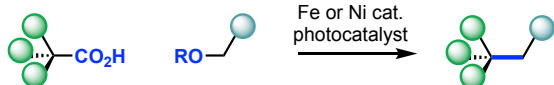
In 2022, Baran developed a doubly decarboxylative cross-coupling method.[1] In this method, both acids are activated in situ to the redox active ester, and in one pot, the subsequent electrolysis reaction is performed. This method was successful for primary-primary, primary-secondary, and secondary-

secondary Csp^3-Csp^3 cross-couplings. This method can tolerate free alcohols, free benzylic sites, pinacol boranes, sulfones, alkyl chlorides, and a variety of heterocycles. Using this method, it is possible to perform enantiodivergent couplings from dissymmetric diacids. By simply changing the order of the two

consecutive cross couplings, two different enantiomers of a product can be generated. Some limitations of this method include that 3 equivalence of one carboxylic acid is still required, the major side product is homocoupling of the carboxylic acid used in excess, and only one tertiary carboxylic acid is tolerated.

Photochemical Methods

In 2021, MacMillan looked to enzymatic reactions for inspiration for radical cross-couplings.[2] One of nature's free radical carriers is a cobalt porphyrin system that can undergo S_H2 reactions to form Csp^3-Csp^3 bonds. Using a biomimetic approach, Macmillan developed a method using an iron porphyrin for Csp^3-Csp^3 decarboxylative cross-coupling.[3] In this method, a primary radical generated from an alkyl bromide reagent is trapped by iron. It reacts with a tertiary nucleophilic radical, formed from the redox-active ester, via an S_H2 reaction to form the new carbon-carbon bond. This reaction successfully forms quaternary centers. However, this reaction is limited to primary alkyl bromides. Wanting to be able to cross-couple two carboxylic acids, due to how readily available they are, MacMillan used a similar method with a nickel catalyst.[3] This reaction proceeds through the same mechanism and therefore is limited by the same requirements: one carboxylic acid must be primary and the other must form a stable alkyl radical.[4,5] However, this method is tolerant of a limited scope of primary-primary cross-couplings and is tolerant of more functionality on secondary carboxylic acids. In a similar method, MacMillan was able to directly cross-couple carboxylic acids with alkyl bromides, via SET from an Ir photocatalyst to the carboxylic acid. This radical can be trapped by a nickel catalyst, which then undergoes oxidative addition into the alkyl halide bond. Following reductive elimination, the product is formed. While this method is beneficial because it directly cross-couples carboxylic acids, reducing the step count of the transformation, it cannot be used for forming quaternary centers because reductive elimination is too challenging.

Figure 4: General scheme for photochemically mediated decarboxylative cross coupling reactions

Outlook

While these methods greatly improve the functional group tolerance on both coupling partners compared to traditional cross-coupling methods and the traditional Kolbe reaction, they have some major limitations. Most methods require excess carboxylic acid for efficient couplings because the carboxylic acid can undergo unproductive pathways including dimerization or reduction, so to increase the yield to synthetically useful yields, an excess is required. Additionally, a more general method for asymmetric induction is necessary. Recently, both Wu and Baran developed methods for asymmetric decarboxylative cross-couplings. In Wu's method[8], stryrenyl carboxylic acids are cross-coupled with TMSCN to form cyanylated products with high ee's. Additionally, Baran[9] was able to cross-couple primary carboxylic acids alpha to a benzyl-protected alcohol with primary alkyl zinc reagents with high ee's. However, both methods require a group capable of stabilizing a radical for good enantioinduction. Additionally, both substrate scopes were limited to simple substrates with limited functionality, so a more general method capable of cross-coupling densely functionalized and sterically hindered substrates with enantiomeric and diastereomeric control is needed.

Sources

1: *Nature, 2022, 606*, 313-319.
2: *Science,* **2021**, *374*, 1258-1263.
3: *J. Am. Chem. Soc., 2022, 144, 21278-212-86.*
4: *Nature,* **2016**, *536*, 322-325.
5: *J. Am. Chem. Soc., 2022, 144*, 6185-6192.
6: *Acc. Chem. Res.* **2020**, *53*, 121−134.
7: *ChemRxiv*, **2022**, 10.26434/chemrxiv-2022-3cj82-v2.

8: *Cell Reports Physical Science 3*, **2022,** *101104*.
9: *J. Am. Chem. Soc.* **2022**, *144*, 10992−11002.