

## Martin Research Group



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### Abstract

The major goal in the Martin group is to provide solutions to relevant and challenging synthetic problems from the scientific and industrial standpoint, without losing sight its environmental impact. In order to meet these challenges, the group is mainly focused on the metal-catalyzed, selective activation of relatively inert entities of great significance, such as CO<sub>2</sub>, C-H bonds, C-C

bonds and C-O bonds, as these motifs rank amongst the most widespread and fundamental linkages in organic chemistry. We are also interesting on the design and implementation of metal-catalyzed domino reactions since a high degree of molecular complexity can be achieved in a one-step, hence allowing a rapid access to key backbones occurring in many natural products.

Activation of inert entities has been and continues to be of extreme interest to any organic chemist. This is especially true with activation of atmospheric molecules such as CO<sub>2</sub> or also the activation of relatively inert C-H, C-C or C-O bonds. Certainly, the development of catalytic methods for the activation of the above-mentioned entities would be highly desirable, as many of the current methods involve the use of stoichiometric amounts of metal complexes. The research of our group is mainly directed towards the development of novel methodologies for the metal-catalyzed activation of inert entities with the aim of producing synthetically relevant molecules (Figure 1). We are also interested in the mechanism of these reactions, as the understanding of these processes on a fundamental level will in turn lay the foundation for future applications of this chemistry.

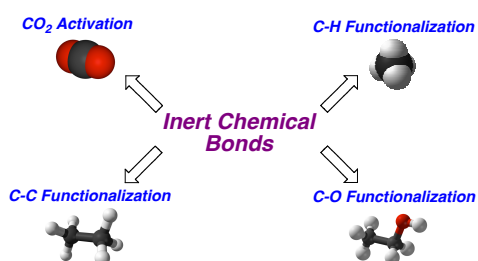


Fig. 1 – Research at Martin Laboratories

### Ni-catalyzed Functionalization of C-O Bonds

In recent years, the use of phenol derivatives as aryl C(sp<sup>2</sup>)-O electrophiles in cross-coupling reactions have emerged as a high cost-effective and environmentally friendly alternative to aryl halide counterparts. Unlike the use of activated aryl sulfonates, the employment of more simple aryl ester derivatives or aryl methyl ethers has received much less attention. Recently, our research group described that benzamides, molecules that display significant biological properties, could be within reach by a reductive event using C-O electrophiles and isocyanates, thus providing a unique opportunity to improve the efficiency and applicability of C-O electrophiles in the cross-coupling arena while offering an innovative bond-disconnection not apparent at first sight. This method was characterized by its wide scope and excellent chemoselectivity profile, including challenging substrate combinations (Figure 1). By definition, such transformation constitutes an “umpolung” strategy for preparing benzamides and a straightforward alternative to classical protocols requiring condensation techniques via the

homologation of benzoic acids or activated substrates. Interestingly, the transformation was not limited to  $\pi$ -extended systems, and simpler aromatic motifs could be utilized with no problems, obtaining high yields in virtually all cases analyzed.

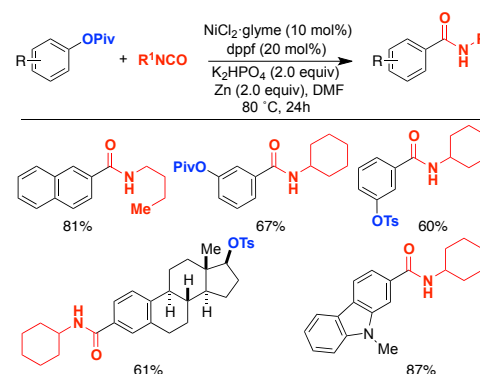


Fig. 2 – Ni-catalyzed umpolung reductive amidation of C-O bonds

Despite the advances realized in the C-O bond-cleavage arena, the vast majority of these reactions are restricted to C-C bond-forming endeavors. Challenged by such perception, our group recently reported a C-Si bond-formation via C-O bond-cleavage (Figure 3). Such a method constitutes an alternative to classical metal/halogen exchange, the coupling of aryl halides with silanes or C-H functionalization techniques that are conducted at high temperatures and using *ortho*-directing groups. Specifically our group found that an unprecedented Ni/Cu catalytic couple allowed for effecting a C-Si bond-forming reaction. Such a method was distinguished by its mild conditions, robustness and wide substrate scope, including the formation of particularly elusive C(sp<sup>3</sup>)-Si bonds without compromising its application profile. At present, we believe the mild conditions are primarily attributed to the unique role of Cu-cocatalysts, ultimately generating silyl copper species.

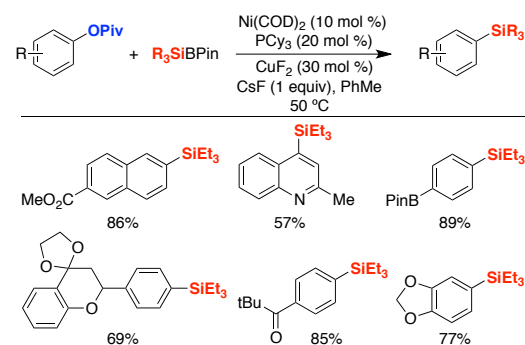


Fig. 3 – C-Si bond-forming reactions via Ni/Cu-catalyzed C-O bond-cleavage

### Metal-catalyzed C-H bond-functionalization

The field of C-H functionalization has gained considerable momentum over recent years, holding great promise for preparing highly complex molecules from simple precursors. While synthetically very attractive, most of these protocols still suffer from relatively high catalyst loadings, harsh conditions, and site selectivity; additionally, the C-H functionalization arena is mainly limited to the use of expensive noble metals as catalysts such as Pd, Rh, or Ir. In 2013, we described a direct and efficient hydroxylation via Cu-catalyzed C(sp<sup>2</sup>)-H functionalization, with carboxylic acids as weakly directing groups. As global demand and prices for noble metals continue to rise, chemists are being challenged to design metal-free processes. To such end, we have recently described a mild and benign ArI-catalyzed C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-H functionalization/C-O bond-formation (Figure 4). The method is user-friendly, operates with a wide substrate scope under mild conditions, and in open-air. Initial studies show an unprecedented and intriguing selectivity profile depending on the nature of the catalyst employed.

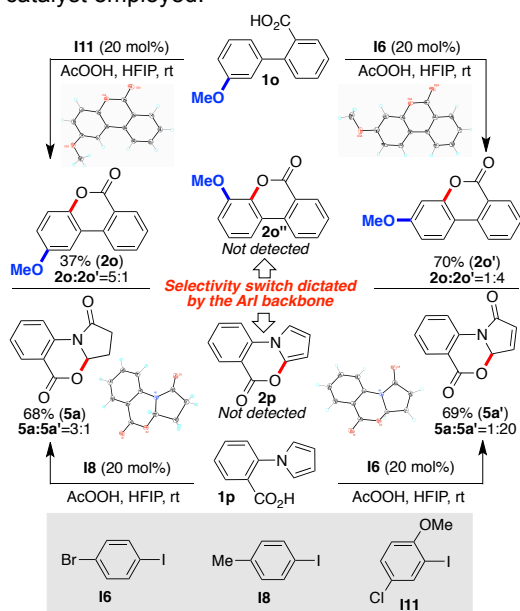


Fig. 4 – ArI-catalyzed C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-H functionalization/C-O bond-formation: An intriguing selectivity switch depending on the catalyst of choice.

### Ni-catalyzed CO<sub>2</sub> Activation

Carbon dioxide (CO<sub>2</sub>) is abundant, inexpensive,

nonflammable, and attractive as an environmentally friendly chemical reagent. Indeed, the fixation of CO<sub>2</sub> holds great promise for revolutionizing approaches toward the elaboration of chemicals of industrial significance. In this regard, metal-catalyzed carboxylation protocols have become excellent alternatives to the classical methods for preparing carboxylic acids. In recent years, our group launched a program aimed at providing new vistas in the area of CO<sub>2</sub> activation en route to the preparation of carboxylic acids. In 2014, we developed a novel Ni-catalyzed carboxylation of C-O electrophiles with CO<sub>2</sub> (Figure 5). The described carboxylation reaction proceeds under mild conditions and at atmospheric pressure of CO<sub>2</sub>. Unlike other routes for similar means, our method does not require well-defined and sensitive organometallic reagents and thus is a user-friendly and operationally simple protocol for assembling carboxylic acids without the classical utilization of halide counterparts. Interestingly, the reaction could be extended to C(sp<sup>3</sup>)-O electrophiles by including a hemilabile group in the alkyl side chain. Preliminary mechanistic studies suggested that the reaction involves the intermediacy of Ni(I) species that are generated upon single-electron transfer processes either in the presence of Mn or via comproportionation events.

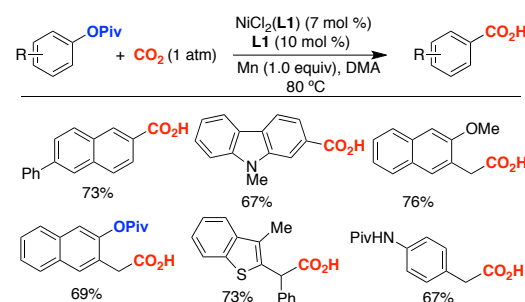


Fig. 5 – Ni-catalyzed carboxylation of C(sp<sup>2</sup>)-O and C(sp<sup>3</sup>)-O bonds with carbon dioxide

While a significant step-forward, reductive carboxylation protocols are inherently restricted to substrates that rapidly undergo oxidative addition such as aryl or benzyl halides. Ideally, this field should include the use of *unactivated* alkyl electrophiles possessing β-hydrogens. Indeed, these substrates are the most challenging in the cross-coupling arena due to their reluctance towards oxidative addition and

the proclivity of *in situ* generated alkyl metal species for  $\beta$ -elimination, homodimerization or hydrogen abstraction pathways, among others. We recently found that the field of reductive carboxylation technologies can be applied with *unactivated* alkyl bromides and sulfonates with CO<sub>2</sub> (Figure 6). The protocol represents a convenient method to rapidly access carboxylic acids from simple precursors without handling air-, moisture-sensitive reagents or cyanide sources. Preliminary mechanistic experiments suggested a scenario consisting of single electron transfer processes (SET) via Ni(I) species. In line with this notion, we observed ring-opened products with radical clocks.

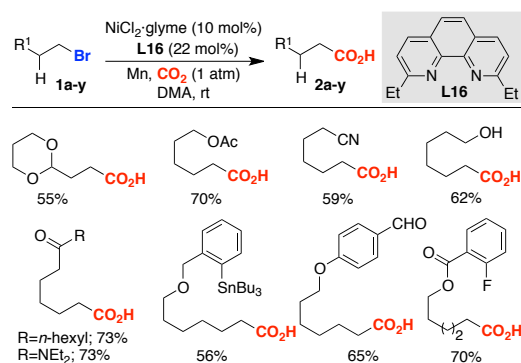


Fig. 6 – Ni-catalyzed carboxylation of unactivated primary alkyl bromides

Although catalytic reductive carboxylation reactions have reached remarkable levels of sophistication, a ligand-controlled selectivity in carboxylation events is unknown, leaving ample opportunities to improve upon existing carboxylation techniques. Among the different possibilities, the ability to promote a regiodivergent event can hardly be overestimated, representing a powerful tool for molecular diversity. We recently found conditions for effecting such catalytic transformation with excellent yields and regioselectivities (Figure 7). The protocol is inherently modular, allowing for the introduction of the carboxylic motif at any site of the allyl terminus depending on the ligand employed. To the best of our knowledge, this constitutes the *first time that the nature of the ligand dictates the outcome of carboxylation events*. The transformation is mild and user-friendly, constituting an added value when compared with classical techniques based on well-defined allyl organometallic species, halide counterparts and/or high CO<sub>2</sub> pressures.

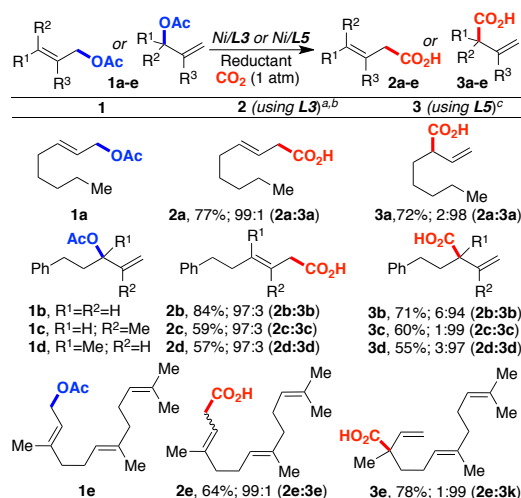


Fig. 7 – Ligand-controlled regiodivergent Ni-catalyzed reductive carboxylation of allyl esters

## Articles

“Ligand-controlled regiodivergent Ni-catalyzed reductive carboxylation of allyl esters with CO<sub>2</sub>”  
*J. Am. Chem. Soc.* **2014**, *136*, 17702-17705  
 Moragas, T.; Cornella, J.; Martin, R.

“Metal-catalyzed activation of ethers via C-O bond-cleavage: a new strategy for molecular diversity”  
*Chem. Soc. Rev.* **2014**, *43*, 8081-8097  
 Cornella, J.; Zarate, C.; Martin, R.

“Mild ArI-catalyzed C(sp<sup>2</sup>)-H or C(sp<sup>3</sup>)-H functionalization/C-O formation: an intriguing catalyst-controlled selectivity switch”  
*Angew. Chem. Int. Ed.* **2014**, *53*, 11084-11087  
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“Ni-catalyzed reductive cleavage of methyl 3-methoxy-2-naphthoate”  
*Org. Synth.* **2014**, *91*, 260-272  
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*J. Am. Chem. Soc.* **2014**, *136*, 11212-11215  
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“Ni-catalyzed direct reductive amidation via C-O bond-cleavage”  
*J. Am. Chem. Soc.* **2014**, *136*, 7253-7256  
 Correa, A.; Martin, R.

## 2014 Annual Scientific Report

“A mild Ni/Cu-catalyzed silylation via C-O cleavage”

*J. Am. Chem. Soc.* **2014**, *136*, 2236-2239

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“Ni-catalyzed carboxylation of C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-O bonds with CO<sub>2</sub>”

*J. Am. Chem. Soc.* **2014**, *136*, 1062-1069

Correa, A.; León, T.; Martin, R.