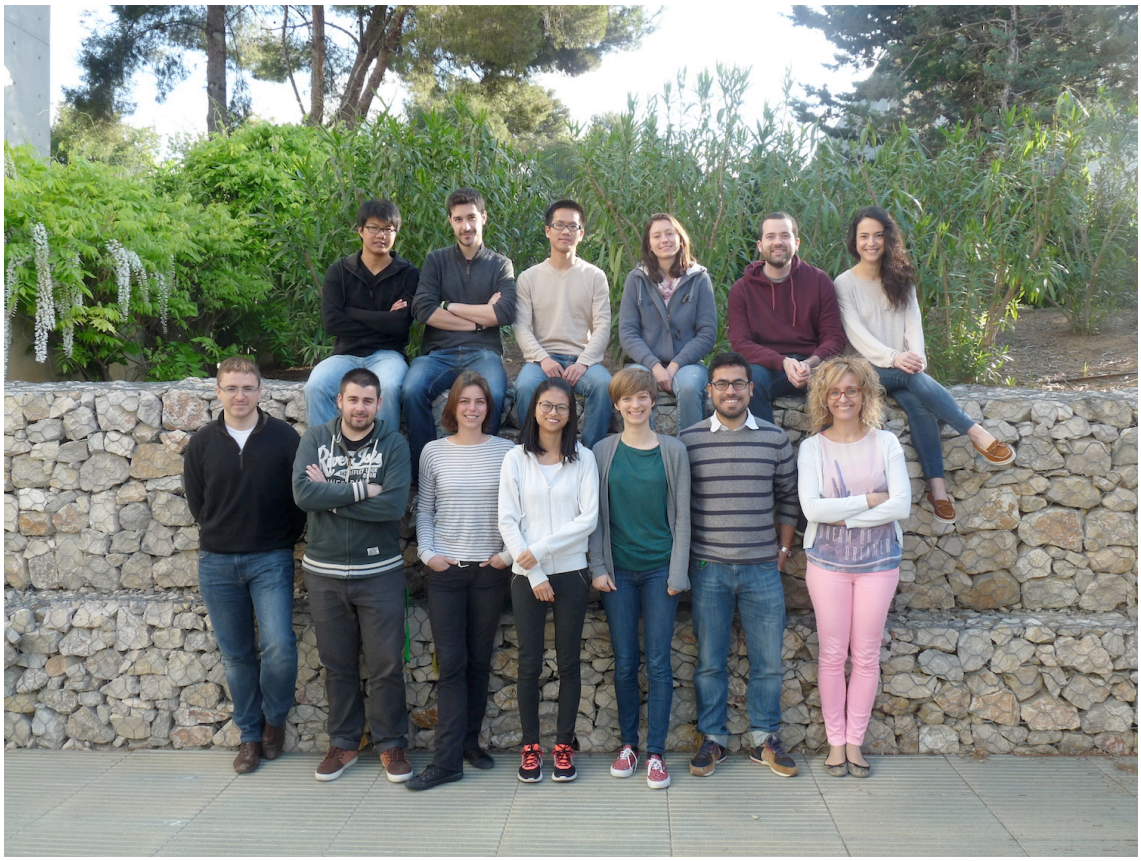
Martín Research Group



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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_2, 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 interested 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_2 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 stochiometric 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.

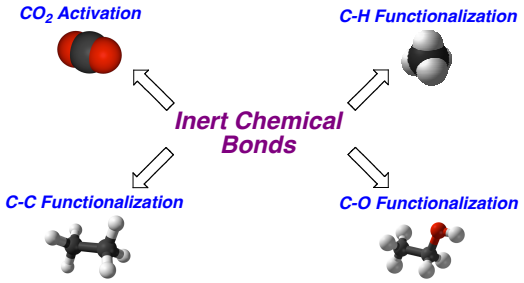

Fig. 1 – *Research at Martin Laboratories*

Ni-catalyzed functionalization of C-O Bonds

In recent years, the use of phenol derivatives as aryl C(sp^2)–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 reported the first enantioselective C-C bond-formation through C-O bond-cleavage using aryl ester counterparts. This method was characterized by its wide substrate scope and results in the formation of quaternary stereogenic centers with high yields and asymmetric induction for a wide number of challenging substrate combinations (Figure 2). Such a transformation constitutes a straightforward alternative to classical protocols requiring the utilization of aryl halides or activated pronucleophiles. Interestingly, the transformation was not limited to π–extended systems, a common drawback associated to other C-O bond-activation processes.

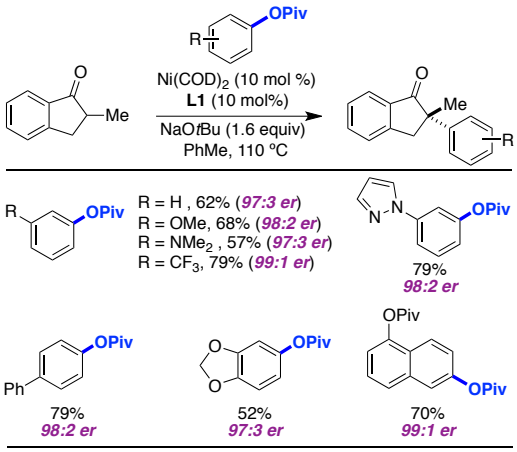

Fig. 2 – *Ni-catalyzed enantioselective C–O bond-cleavage of aryl esters*

Despite the advances realized in the C–O bond-cleavage arena, the coupling of aryl methyl ethers via C-OMe bond-cleavage still constituted a daunting challenge. Challenged by such perception, our group has recently reported a C-OMe borylation/C-B bond-formation technique. By definition, such *ipso*-borylation complements classical *ortho*-, *meta*- and *para*-borylation processes that have been reported using Pd, Rh or Ir catalysts using otherwise identical starting materials. This protocol is distinguished by its broad substrate scope and intriguing selectivity switch depending on the boron reagent employed ; while the utilization of bis(pinacol)boronates result in C(sp^3)-OMe cleavage using fluoride bases, a C(sp^2)-OMe borylation occurs effectively using bis(neopentyl) boronate derivatives (Figure 3).

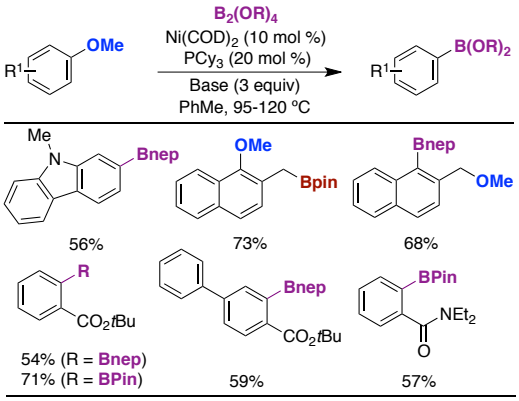

Fig. 3 – *Ni-catalyzed ipso-borylation of aryl methyl ethers via C-OMe bond-cleavage*

During our study on the ipso-borylation of aryl methyl ethers, we found that aryl fluorides were partially borylated via C-F bond-cleavage. This

observation was particularly remarkable taking into consideration that C-F bonds are the strongest C-heteroatom bonds in nature, conferring a remarkable metabolic activity that makes them particularly attractive in pharmaceuticals. Intrigued about these results, we discovered an optimized Ni-catalyzed borylation protocol capable of promoting the targeted reaction with high levels of efficiency (Figure 4). Indeed, such a transformation constitutes a rare example of C-heteroatom bond-formation via catalytic C-F cleavage of unactivated monofluoroarenes. The protocol is distinguished by its wide scope without compromising its practicality and efficiency.

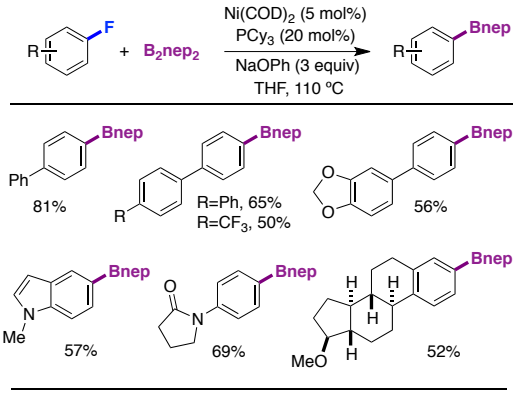

Fig. 4 – *Ni-catalyzed ipso-borylation of aryl fluorides via C-F bond-cleavage*

Ni-catalyzed CO_2 activation

Carbon dioxide (CO_2) is abundant, inexpensive, nonflammable, and attractive as an environmentally friendly chemical reagent. Indeed, the fixation of CO_2 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_2 activation en route to the preparation of carboxylic acids. In 2015, we developed a novel Ni-catalyzed t cyclization/carboxylation of unactivated primary and secondary alkyl halides with CO_2 at atmospheric pressure en route to carboxylated carbocyclic skeletons. The protocol operates under mild conditions and is characterized by an unconventional divergence in syn/anti selectivity that can be easily dictated by the ligand backbone or substrate utilized (Figure 5). Preliminary mechanistic studies suggested that the reaction involves the intermediacy of Ni(I) species that are generated upon single-electron transfer processes (SET) promoted by Mn or comproportionation events with $Ni(0)L_n$ and $RNi(II)L_n$ intermediates. Such assumption was corroborated by the isolation, characterization and the study of the reactivity of some putative reaction intermediates.

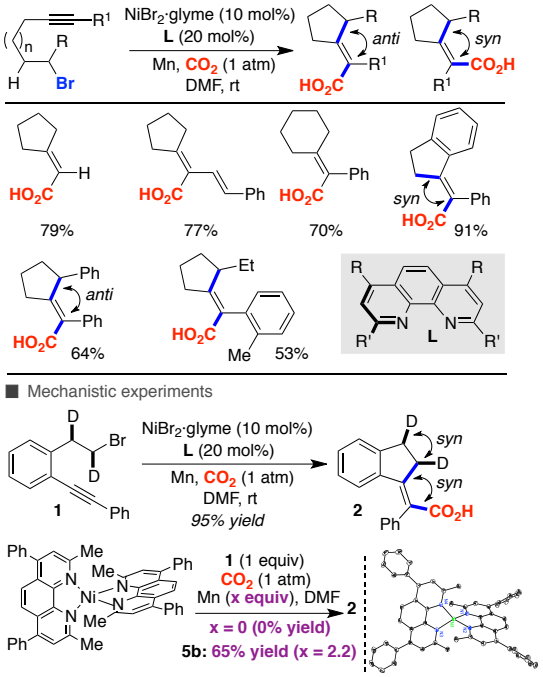

Fig. 5 – *Ni-catalyzed cyclization/carboxylation of unactivated alkyl halides*

Although the means to promote reductive carboxylation techniques has gained considerable momentum, a limited number of catalytic carboxylation protocols of alkynes with CO_2 has been decribed. Among these, hydrocarboxylation events are particularly appealing, providing rapid access to industrially relevant acrylic acids. Unlike the known methodologies using well-defined reducing agents such as silanes or organometallic species, that ultimately end up in acrylic acids with a C1-selective motion where the carboxylic acid function is adjacent to the aromatic site, we have recently discovered an exceedingly practical and user-friendly hydrocarboxylation of alkynes that obviates the need for air-sensitive or organometallic reagents. Such a method is characterized by a remarkable chemoselectivity profile with CO_2 at atmospheric pressure (Figure 6). While counterintuitive at first sight, the inclusion of simple alsochols as proton sources results in an exquisite and predictable selectivity

switch, even for sterically unbiased unsymmetrical alkynes, exploiting a previously unrecognized opportunity in reductive carboxylation events. The regioselectivity profile observed does not match the inherent propensity of metal hydride complexes to undergo addition across the alkyne motif, suggesting that the mechanism likely proceeds via the intermediacy of nickelalactone intermediates that might react with an alcohol donor, thus preceding the protonolysis event. A final reduction mediated by Mn affords the targeted carboxylic acid while regenerating the propagating $Ni(0)L_n$ species. Stoichiometric studies with some of the putative reaction intermediates corroborated this notion.

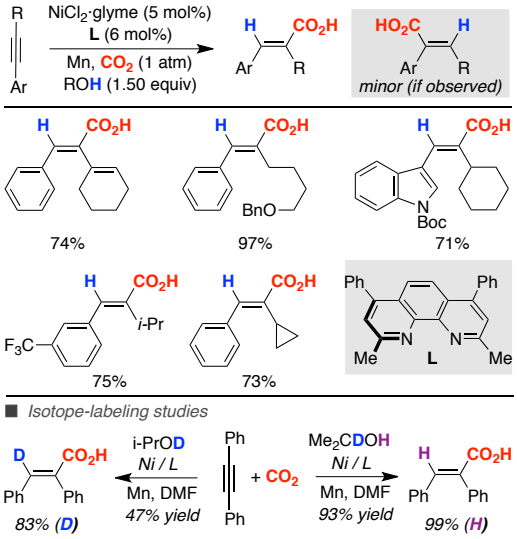

Fig. 6 – *Ni-catalyzed hydrocarboxylation of alkynes using simple alcohols as proton sources*

Metal-catalyzed C-C bond-functionalization

The field of C−C 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−C functionalization arena is mainly limited to the use of expensive noble metals as catalysts such as Pd, Rh, or Ir. As part of our interest for designing C-C bond-functionalization reactions, we have described the first catalytic intermolecular proximal C1-C2 cleavage of benzocyclobutenones (BCB) without prior carbonyl activation or employing noble metals. This method is inherently modular, allowing for preparing a variety of otherwise inaccessible carbocyclic skeletons depending on the synthon utilized, including elusive benzofused eight-membered rings via formal [4+4]-cycloaddition. The reaction operates at room temperature, constituting the lowest temperature achieved for catalytic C-C bond-cleavage events of BCB reported to date. Importantly, this new protocol was distinguished by its exquisite chemo-, regio- and diastereoselectivity profile (Figure 7).

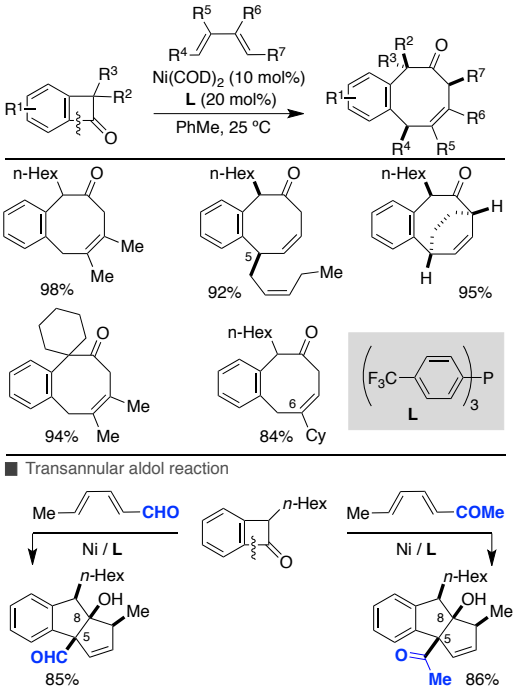

Fig. 4 – *Ni-catalyzed chemo-, regio- and diastereoselective bond-formation through proximal C-C cleavage of benzocyclobutenones*

Articles

"Ni-catalyzed borylation of aryl fluorides via C-F cleavage"
J. Am. Chem. Soc. (**2015**), *137*, 12470-12473
X. W. Liu, J. Echavarren, C. Zarate, R. Martin

"Ni-catalyzed regioselective hydrocarboxylation of alkynes with CO_2 by using simple alcohols as proton sources"
J. Am. Chem. Soc. (**2015**), *137*, 8924-8927
J. Cornella, C. Zarate, R. Martin

"*Ipso*-borylation of aryl ethers via Ni-catalyzed C-OMe cleavage"
J. Am. Chem. Soc. (**2015**), *137*, 6754-6757
X. Wang, J. Gallardo-Donaire, R. Martin

"Nickel-catalyzed chemo-, regio- and

diastereoselective bond-formation through proximal C-C cleavage of benzocyclobutenones"
Angew. Chem. Int. Ed. (**2015**), *54*, 9537-9541
F. Juliá-Hernández, A. Ziadi, R. Martin

"Ni-catalyzed divergent cyclization/carboxylation of unactivated primary and secondary alkyl halides with CO_2"
J. Am. Chem. Soc. (**2015**), *137*, 6476-6479
X. Wang, Y. Liu, R. Martin

"Nickel-catalyzed enantioselective C-C bond-formation through C(sp^2)-O cleavage in aryl esters"
Angew. Chem. Int. Ed. (**2015**), *54,* 4075-4078
J. Cornella, E. P. Jackson, R. Martin