

## 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.

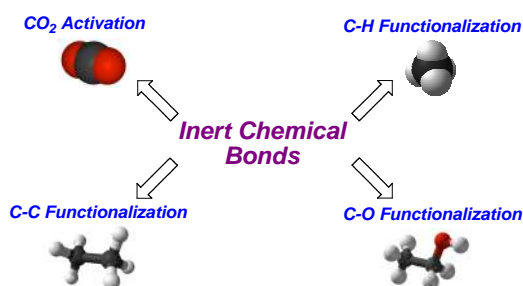


Fig. 1 – Research at Martin Laboratories

### Ni-catalyzed reductive cleavage of C-OMe 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 other C(sp<sup>2</sup>)-O electrophiles, catalytic cross-coupling reactions based upon cleavage of C(sp<sup>2</sup>)-OMe bonds are still scarce. In this context, our research group reported in 2010 a Ni-catalyzed protocol that was capable of promoting the reductive cleavage of C-OMe bonds. However, the mechanistic understanding behind the results obtained was rather obscure. Recently, we provided compelling evidence that the cleavage of C-OMe bonds occur along more than one pathway depending on the catalyst of choice and that a classical mechanism based upon a Ni(0)/Ni(II) couple is not operative. Computational and experimental studies suggested Ni(I)-SiR<sub>3</sub> as the key propagating species with migratory insertion into the naphthalene backbone being the rate-determining step. Such assumption is in perfect analogy with all the recorded kinetic data,

isotope-labeling studies, and the significantly greater reactivity of extended π-systems as compared with simpler anisole derivatives (Figure 2).

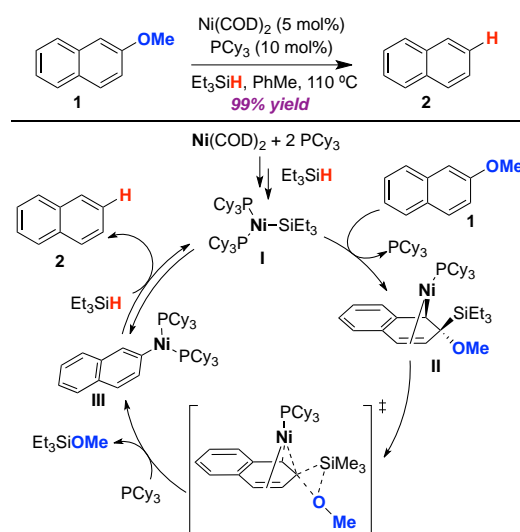


Fig. 2 – Mechanistic interpretation of the Ni-catalyzed reductive cleavage of C-OMe bonds.

Prompted by such mechanistic study, we have recently reported a Ni-catalyzed arylation event of inert C-O bonds that operates at temperatures as low as -40 °C (Figure 3). Unlike other methods for C-O bond-cleavage utilizing organometallic species, this protocol allows the presence of sensitive functional groups with excellent site-selectivity. The high reaction rates are translated into an excellent chemoselectivity profile, allowing for the preparation of Z-configured homoallylic alcohols. Preliminary mechanistic studies suggest a Lewis acid-aided oxidative addition, an issue that can be turned into a strategic advantage in the presence of more reactive electrophilic counterparts

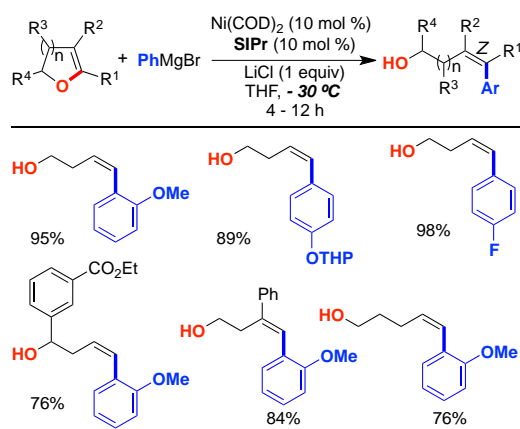


Fig. 3 – Ni-catalyzed arylation of inert C-O bonds at low temperatures.

### 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. We have recently described a direct and efficient hydroxylation via Cu-catalyzed C(sp<sup>2</sup>)-H functionalization with carboxylic acids as weakly directing groups (Figure 4). This protocol constitutes a user-friendly, operationally simple reaction for preparing remote hydroxylated arenes under mild reaction conditions with excellent chemoselectivity. Interestingly, the observed reactivity is complementary to methodologies based upon the use of Pd catalysts.

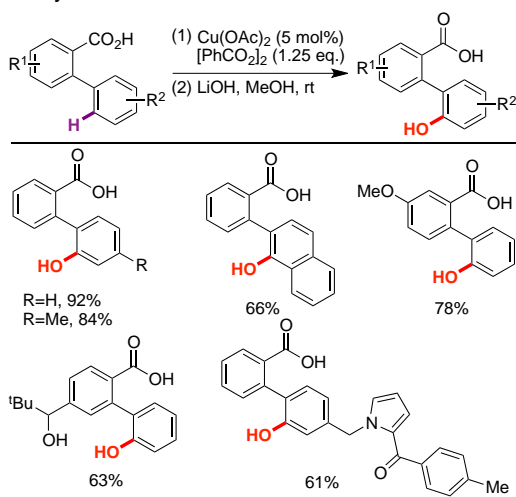


Fig. 4 – Cu-catalyzed remote hydroxylation of arenes.

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

In the last decade, C-C bond-functionalization protocols have profoundly changed the landscape of organic synthesis through unconventional bond-disconnection strategies for the assembly of complex organic molecules. Despite the available background knowledge, the development of catalytic methods for activating C-C bonds is still in its infancy. In this regard, we wondered whether we could implement a protocol based on a C-C bond-activation to naturally-occurring compounds. We decided to face the challenge for preparing  $\gamma$ -alkynylated ketones via C-C bond-cleavage from easily accessible *tert*-cyclobutanol derivatives (Figure 5). As shown, we developed a highly

active Pd-catalyzed ketone  $\gamma$ -alkynylation via C-C cleavage with alkynyl halides. The broad scope and high chemoselectivity profile makes this method a straightforward alternative to the existing methods for the synthesis of  $\gamma$ -alkynylated ketones.

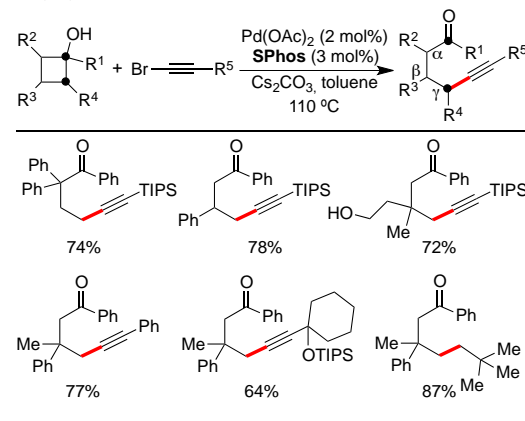


Fig. 5 – Pd-catalyzed synthesis of  $\gamma$ -alkynylated ketones via C-C bond-cleavage

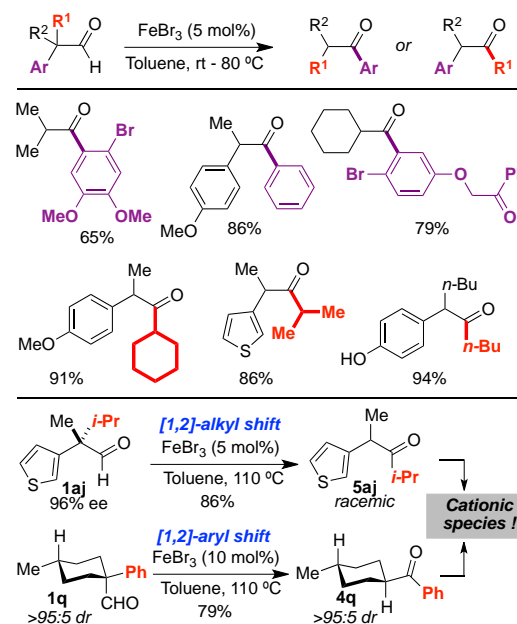


Fig. 6 – Fe-catalyzed stereodivergent [1,2]-shift

Beyond any reasonable doubt, carbonyl compounds rank among the most versatile synthons in organic synthesis. Despite the robustness of classical protocols for their synthesis, the search for alternatives, particularly in a catalytic fashion, still represents a formidable challenge. Among all available scenarios, the means for catalytically interconverting carbonyl compounds with total control of selectivity would be highly desirable, hence increasing molecular complexity while following the principles of both atom and step economy. Recently, we have discovered a

simple and straightforward Fe-catalyzed conversion of aldehydes to ketones via [1,2]-shift (Figure 6). This skeletal rearrangement shows a wide substrate scope and chemoselectivity profile while exhibiting an excellent [1,2]-aryl or [1,2]-alkyl shift selectivity that is easily switched by electronic effects. Preliminary experiments suggested that the reaction involved the intermediacy of cationic species, as illustrated by the examples shown in Figure 6 (bottom). The wide scope and the selectivity profile suggest that this protocol could be a powerful alternative en route to ketone derivatives from available precursors without requiring stoichiometric amounts of metal complexes.

### 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.

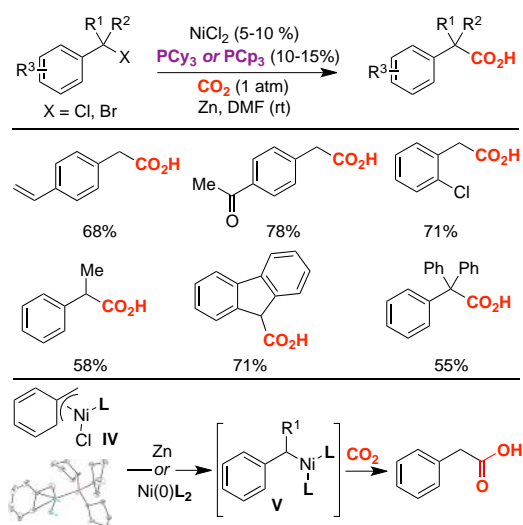


Fig. 7 – Ni-catalyzed carboxylation of benzyl halides en route to phenyl acetic acids

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 2013, we developed a novel Ni-catalyzed carboxylation of benzyl halides with CO<sub>2</sub> (Figure 7). The described carboxylation reaction proceeds under mild conditions at room temperature 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 phenylacetic acids. Interestingly, primary, secondary and even tertiary benzylic halides could be equally carboxylated under relatively similar reaction conditions. 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 Zn or via comproportionation events, an assumption corroborated by the isolation of putative reaction intermediates **IV**.

### Articles

“Ni-catalyzed decarbonylative C-H coupling reactions: A strategy for preparing bis(heteroaryl) backbones”

*Angew. Chem. Int. Ed.* **2013**, *52*, 1878-1880  
Correa, A.; Cornella, J.; Martin, R.

“Formal  $\gamma$ -alkynylation of ketones via Pd-catalyzed C-C cleavage”

*Chem. Commun.* **2013**, *49*, 4286-4288  
Ziadi, A.; Correa, A.; Martin, R.

“Combined experimental and theoretical study on the reductive cleavage of inert C-O bonds with silanes: ruling out a classical Ni(0)/Ni(II) catalytic couple and evidence for Ni(I) intermediates”

*J. Am. Chem. Soc.* **2013**, *135*, 1997-2009  
Cornella, J.; Gómez-Bengoña, E.; Martin, R.

“Ni-catalyzed direct carboxylation of benzyl halides with CO<sub>2</sub>”

*J. Am. Chem. Soc.* **2013**, *135*, 1221-1224  
León, T.; Correa, A.; Martin, R.

“Recent advances in the synthesis and application of benzocyclobutenones and related compounds”

*Synthesis* **2013**, *45*, 563-580

“Ni-catalyzed stereoselective arylation of inert C-O bonds at low temperatures”

*Org. Lett.* **2013**, *15*, 6298-6301  
Cornella, J.; Martin, R.

“Fe-catalyzed regiodivergent [1,2]-shift of  $\alpha$ -aryl aldehydes”

*J. Am. Chem. Soc.* **2013**, *135*, 12576-12579  
Gutiérrez-Bonet, A.; Flores-Gaspa, A.; Martin, R.

“Cu-catalyzed mild C(sp<sup>2</sup>)-H functionalization assisted by carboxylic acids en route to hydroxylated arenes”

*J. Am. Chem. Soc.* **2013**, *135*, 9350-9353  
Gallardo-Donaire, J.; Martin, R.