Martin Research Group

Group Leader: Ruben Martin
Postdoctoral researchers: Antoni Moragas / Francisco Julià / Xinag -Wei Liu / Veera Reddy Yatham / Yasuhiro Okuda / Morgane Gaydou (until Nov.) / Masaki Nakajima (until July) / Manuel van Gemeren (until Mar.)
PhD students: Cayetana Zárate / Eloisa Serrano / Marino Börjesson / Yangyang Shen / Rosie Somerville / Yiting Gu / Andreu Tortajada / Raúl Martin / Alberto Tampieri / Shang-Sheng Sun
Laboratory engineer: Míriam Sau
Visiting students: Keisho Okura (until Nov.) / Lilian Hale (until Aug.)
Administrative support: Ingrid Mateu

Group of Catalytic Activation of Inert Chemical Bonds

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 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_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.

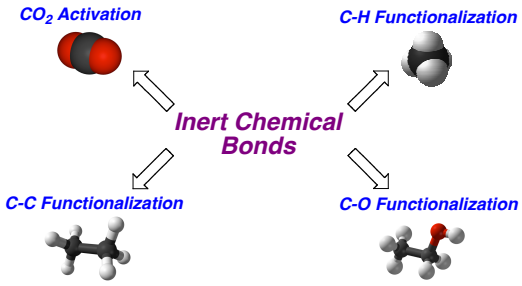

Fig. 1 – *Research at Martin Laboratories*

Ni-catalyzed Functionalization of C-N Bonds

In recent years, the use of C-O electrophiles have emerged as a high cost-effective and environmentally friendly alternative to organic halide counterparts. In contrast, the utilization of C-N electrophiles in cross-coupling reactions have received considerable less attention. Recently, our research group reported the first direct catalytic carboxylation of C-N electrophiles with CO_2 at atmospheric pressure. This method was not only characterized by its wide substrate scope, including challenging substrate combinations, but also outperforms state-of-the-art techniques for the carboxylation of benzyl electrophiles by avoiding commonly observed parasitic pathways such as homodimerization or β-hydride elimination, thus leading to new knowledge in cross-electrophile coupling reactions. Importantly, the ligand used exerted a profound influence on both reactivity and selectivity, allowing for obtaining a variety of different phenyl acetic acids under remarkable mild conditions (Figure 2). Importantly, mechanistic studies with isolable, well-defined putative nickel intermediates allowed for establishing a rationale that indicates that the mechanism proceeds via initial oxidative addition followed by single-electron-transfer, generating Ni(I) intermediates that subsequently trigger CO_2 insertion en route to phenyl acetic acids.

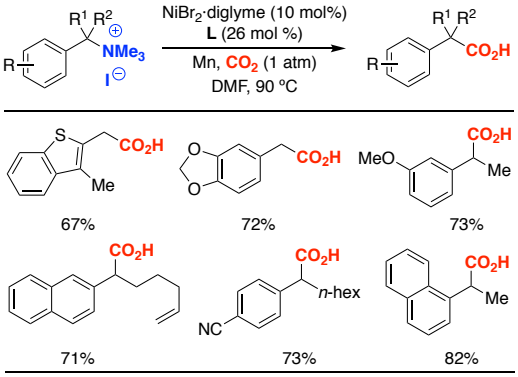

Fig. 2 – *Ni-catalyzed carboxylation of benzyl C-N electrophiles with CO_2*

Pd-catalyzed C-H Activation

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 deal with the utilization of well-defined directing groups located at a proximal position to the targeted C-H site. This is likely due to the presence of multiple, yet similarly reactive, C-H bonds that are amenable for the subsequent functionalization. Additionally, the vast majority of these processes deal with the activation of C(sp^2)-H bonds, probably due to the neat stabilization of the corresponding aryl or vinyl metal entities. Prompted by these observations, we recently questioned whether it would be possible to design a catalytic technique capable of activating much more challenging C(sp^3)-H bonds without the need for using directing group methodologies. Indeed, we discovered a Pd-catalyzed platform consisting of a tandem C(sp^3)-H functionalization/carbenoid insertion (Figure 3). The method allowed for the rapid synthesis of bicyclic frameworks, generating all-carbon quaternary centers via multiple C-C bond-formations in a straightforward manner. The reaction turned out to be rather general for a number of substrates, including particularly challenging combinations. More importantly, we gathered evidence for the mechanism by studying the reactivity of the putative reaction intermediates that could be obtained in pure form as judged by X-ray crystallography and spectroscopical techniques.

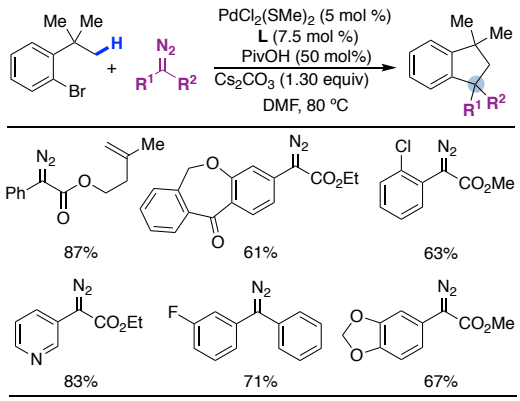

Fig. 3 – *Pd-catalyzed synergistic C(sp^3)-H functionalization/carbenoid insertion en route to indane derivatives*

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 2016, we have discovered that the carboxylation of unactivated primary alkyl chlorides with CO_2 at atmospheric pressure can give rapid access to the corresponding fatty acids, molecules of utmost relevance in pharmaceuticals (Figure 4). The protocol was characterized by its generality and by a distinctive mechanism that differs from previous carboxylation reactions, an observation that was corroborated by in depth mechanistic studies. These findings set the stage for the development of a carboxylation/cyclization of alkyl chlorides, affording carbocyclic skeletons. Notably, we found 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. This assumption could finally be corroborated by the isolation of the putative, yet highly sensitive, Ni(I) reaction intermediates, demonstrating that these species are catalytically competent as reaction intermediates in the targeted carboxylation event.

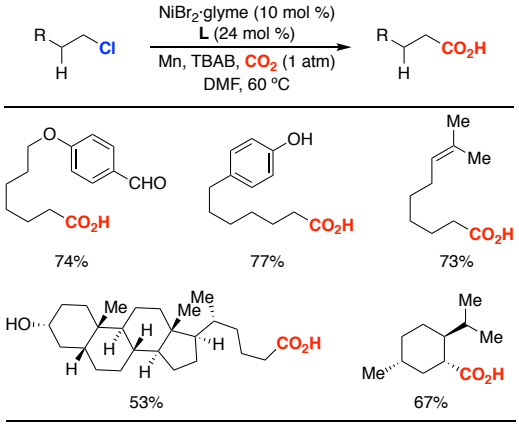

Fig. 4 – *Ni-catalyzed reductive carboxylation of unactivated alkyl chlorides*

Prompted by these findings, we have recently found a nickel-catalyzed reductive carboxylation technique for the straightforward synthesis of cyclopropanecarboxylic acids (Figure 5). This user-friendly and mild transformation operates at atmospheric pressure of CO_2 and utilized either organic halides or alkene precursors. Interestingly, the diastereoselective of the process is dictated by the substrate employed, obtaining in some cases a single diastereoisomer.

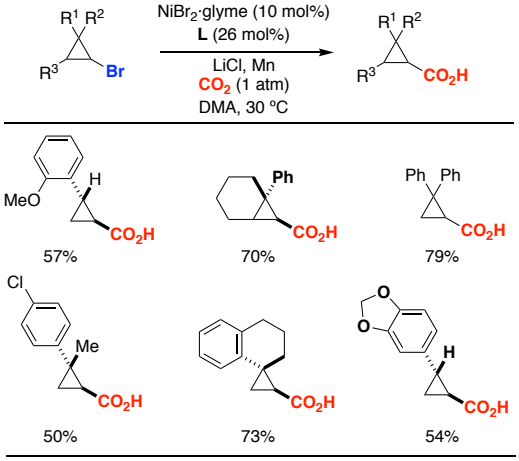

Fig. 5 – *Ni-catalyzed reductive carboxylation of cyclopropyl motifs*

Catalytic Reductive Amidation

Although our group has been particularly prolific in the area of carbon dioxide fixation into organic matter, we recently wondered whether we could extend the scope of these reactions to heterocumelenes other than CO_2. Among the different alternatives, we focused our attention on the utilization of isocyanates, as it would provide a rapid access to amides, key structural motifs in a myriad of pharmaceuticals. Recently,

we have found a user-friendly, Ni-catalyzed reductive amidation of unactivated primary, secondary or even the always-elusive tertiary alkyl bromides with isocyanates. This catalytic strategy offers an efficient synthesis of aliphatic amides under mild conditions and with an excellent chemoselectivity profile while avoiding the use of stoichiometric and sensitive organometallic reagents (Figure 6).

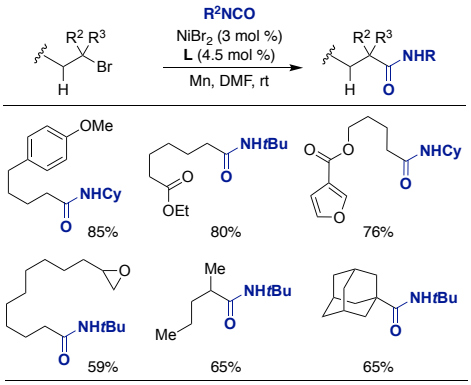

Fig. 6 – *Ni-catalyzed direct reductive amidation of unactivated alkyl halides*

While the results in Figure 5 constituted a proof of concept for the utilization of isocyanates in catalytic reductive coupling reactions, we turned our attention on the viability for extending these reactions to acrylamides. Specifically, we found a rather intriguing catalytic hydroamidation of alkynes with isocyanates using light alkyl bromides as hydride sources. The method essentially turns commonly perceived parasitic β-hydride elimination into a strategic advantage, rapidly affording acrylamides with excellent chemo- and regioselectivity (Figure 7).

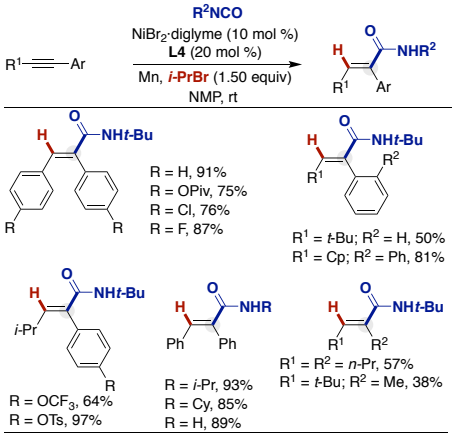

Fig. 7 – *Ni-catalyzed hydroamidation of alkynes using light alkyl halides* as hydride sources

Articles

"Alkyl bromides as mild hydride sources in Ni-catalyzed hydroamidation of alkynes with isocyanates"
J. Am. Chem. Soc. **2016**, *138*, 15531-15534
Wang, X. ; Nakajima, M. ; Serrano, E.; Martin, R.

"Phenol derivatives: modern electrophiles in cross-coupling reactions"
Adv. Organomet. Chem. **2016**, *66*, 143-222
Zarate, C.; van Gemmeren, M.; Somerville, R.; Martin, R.

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

"Metal-catalyzed carboxylation of organic (pseudo)halides with CO_2"
ACS Catal. **2016**, *6*, 6739-6749
Börjesson, M.; Moragas, T.; Gallego, D.; Martin, R.

"Ni- and Fe-catalyzed carboxylation of unsaturated hydrocarbons with CO_2"
Top. Curr. Chem. **2016**, 374:45
Juliá-Hernández, F.; Gaydou, M.; Serrano, E.; van Gemmeren, M.; Martin, R.

"Nickel-catalyzed reductive carboxylation of cyclopropyl motifs with carbon dioxide"
Synthesis **2016**, *48,* 2816-2822
Moragas, T.; Martin, R.

"Nickel-catalyzed reductive amidation of unactivated alkyl bromides"
Angew. Chem. Int. Ed. **2016**, *55*, 11207-11211
Serrano, E.; Martin, R.

"Ni-catalyzed carboxylation of unactivated alkyl chlorides with CO_2"
J. Am. Chem. Soc. **2016**, *138*, 7504-7507
Börjesson, M; Moragas, T.; Martin, R.

"Pd-catalyzed C(sp3)-H functionalization/carbenoid insertion: All-carbon quaternary centers via multiple C-C bond-formation"
J. Am. Chem. Soc. **2016**, *138*, 6384
Gutiérrez-Bonet, A.; Juliá-Hernández, F.; de Luis, B.; Martin, R.

"Nickel-catalyzed carboxylation of benzylic C-N bonds with CO_2"
Angew. Chem. Int. Ed. **2016**, *55*, 5053-5057
Moragas, T.; Gaydou, M.; Martin, R.