

Martin Research Group



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Summer fellows: José Manuel González (July-Sept.)

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 CO₂, 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.

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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 CO₂ 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.

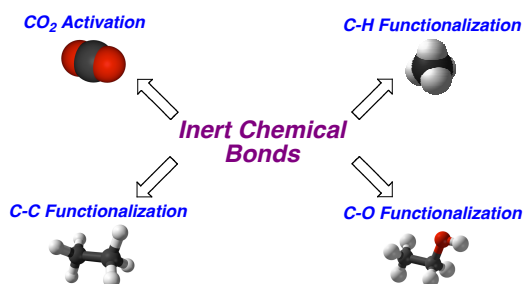


Fig. 1 – Research at Martin Laboratories

Ni-catalyzed CO₂ Activation

Carbon dioxide (CO₂) is abundant, inexpensive, nonflammable, and attractive as an environmentally friendly chemical reagent. Indeed, the fixation of CO₂ 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 CO₂ activation en route to the preparation of carboxylic acids. In 2017, we have discovered that the carboxylation of unactivated allylic alcohols with CO₂ at atmospheric pressure can give rapid access to the corresponding carboxylic acids (Figure 2). 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. Additionally, the geometry of the ligand completely dictated the site-selectivity of the reaction, with bidentate ligands providing access to linear acids whether tridentate ligands furnished selectively the corresponding branched carboxylic acids.

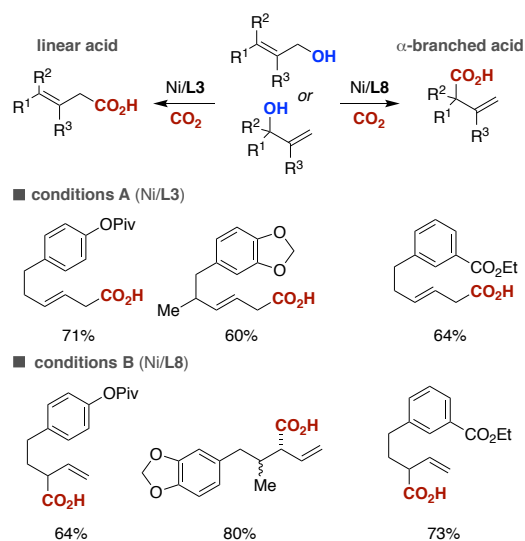


Fig. 2 – Ni-catalyzed reductive carboxylation of allylic alcohols

Although our research group has contributed extensively to the field of catalytic reductive carboxylation of organic halides, all these transformations essentially operate by functional group interconversion, necessarily requiring functionalization at the initial reaction site. From an ideal perspective, the best case scenario would be the development of a direct catalytic carboxylation of simple saturated hydrocarbon feedstocks by means of a sp³ C-H activation. Although the design of such a technique is potentially hampered by reactivity problems (inertness of both CO₂ and sp³ C-H bonds) as well as by site-selectivity issues due to the presence of multiple, yet similar, sp³ C-H bonds, our group has recently provided an alternative that can trigger such a process in a highly efficient manner. Specifically, we have recently discovered the means to trigger a catalytic relay of simple unactivated alkyl halides, by inserting CO₂ at distal, and previously unfunctionalized remote sp³ C-H sites by means of a dynamic displacement of a Ni catalyst throughout the side-chain (Figure 3). More importantly, we have

found that the site-selectivity can be controlled by a dichotomy exerted by the control elements through the alkyl side-chain, allowing to discriminate the CO₂ insertion at multiple sp³ C–H sites. Notably, such a reaction enables to streamline the synthesis of fatty acids from simple alkanes or unrefined mixtures of alkenes in a two-step, one-pot protocol.

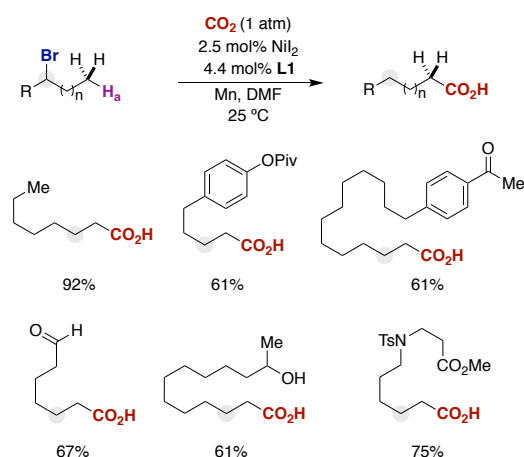


Fig. 3 – Ni-catalyzed reductive carboxylation of alkyl halides at remote sp³ C–H reaction sites

Following up our interest in designing catalytic reductive carboxylation techniques, we have recently found that simple unsaturated chemical feedstocks can trigger a catalytic carboxylation by using water as a safe, inexpensive, hydride source (Figure 4). Site-selectivity can be tuned and controlled by changing the degree of unsaturation; thus, while alkenes gives access to linear carboxylic acids, the utilization of alkynes furnishes branched carboxylic acid derivatives. Mechanistic studies suggests a classical hydrometallation event for the preparation of linear carboxylic acids by the generation of Ni-hydride intermediates, ultimately ending up in the targeted linear carboxylic acids. In contrast, the utilization of alkynes leads to an initial oxidative cycloaddition that results in a nickelalactone that subsequently reacts with water to give access to the corresponding acrylic acids that subsequently are reduced in situ to the targeted branched acids.

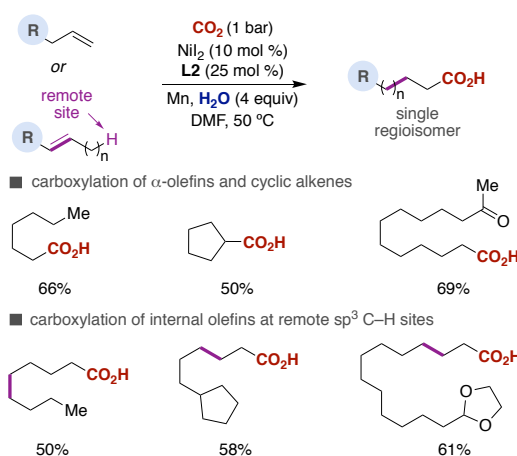


Fig. 4 – Ni-catalyzed direct reductive carboxylation of olefins with water.

Photoredox catalysis

In recent years, visible-light photocatalysis has arguably gained momentum for generating carbon centered radical intermediates via single-electron transfer (SET) processes. Unlike classical SET protocols based on radical initiators or metal catalysts initiated by a chemical activation mode and inner-sphere mechanisms, photoredox catalysis offers the opportunity to promote otherwise analogous processes using simple visible light via outer-sphere mechanisms. Our group has recently described an unconventional photocatalytic redox-neutral atom transfer radical cyclization (ATRC) of unactivated alkyl iodides under visible-light irradiation. The salient features of this transformation are the mild conditions, broad scope, and exquisite chemoselectivity, thus enabling the preparation of highly versatile building blocks susceptible to further functionalization (Figure 5). Preliminary mechanistic experiments leave some doubt about a canonical photoredox cycle, reinforcing the notion that an exciplex might come into play.

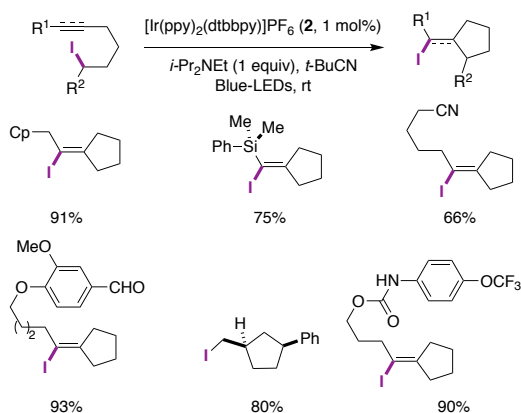


Fig. 5 – Visible light ATRA of alkyl iodides.

In collaboration with the Iwasawa group (Tokyo, TIT), we have described the means to promote a photoredox Pd-catalyzed carboxylation of aryl halides with CO₂ under visible light irradiation, thus becoming a powerful and straightforward alternative to classical reductive carboxylation events that typically require the employment of stoichiometric amounts of metal reductants (Figure 6). Initial mechanistic studies suggest that this reaction is likely initiated via the intermediacy of aryl-Pd(I) complexes that are obtained from the corresponding aryl-Pd(II) via SET reduction prior CO₂ insertion.

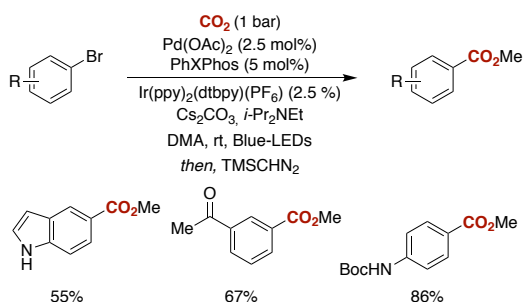
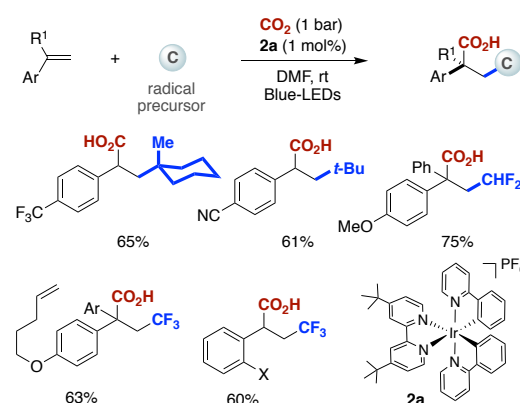


Fig. 6 – Visible light photoredox Pd-catalyzed carboxylation of aryl halides.

Driven by the ability of iridium photoredox catalysts to trigger outer-sphere SET processes, we have recently described a dicarboxylation of simple styrenes with radical precursors and CO₂ (Figure 7). This mild and versatile protocol offers a reactivity principle that is complementary to classical catalytic carboxylations, thus unlocking previously inaccessible scenarios in the carboxylation

arena based on multiple C–C bond-forming events from π -components and in the absence of stoichiometric reductants. Mechanistic studies suggested a pathway consisting of an initial SET oxidation of a radical precursor followed by addition across the alkene and subsequent SET reduction, resulting in a transient carbanion. Such carbanion then further reacts with CO₂ under atmospheric pressure. Interestingly, such a technique obviates the need for metal reductants or sophisticated nickel catalysts, thus opening up new avenues in the carboxylation arena, and suggesting that other related pathways might be conceivable as well.


 Fig. 7 – Dicarboxylation of alkenes with CO₂ by means of photoredox catalysis.

Ni-catalyzed Functionalization of C–O Bonds

In recent years, the use of phenol derivatives as aryl C(sp²)-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 group has reported the first stannylation of aryl ester counterparts via C–O bond-cleavage. This method was characterized by its wide substrate scope and results in the formation of densely functionalized stannyl reagents, even with nitrogen-containing heterocycles, arguably the backbones of excellence in pharmaceutical laboratories (Figure 8). Such a transformation constitutes a straightforward alternative to classical protocols requiring the utilization of aryl halides or well-defined, yet highly reactive, stoichiometric organolithium derivatives.

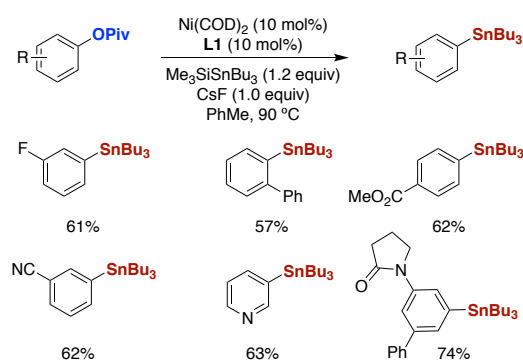


Fig. 8 – Ni-catalyzed stannylation of aryl esters.

Following up our interest in ester derivatives as C-O electrophiles, we have recently described a stereoselective borylation of enantioenriched benzyl ester derivatives, resulting in the formation of versatile benzyl boronates with total control of the stereochemistry at the benzylic position (Figure 9).

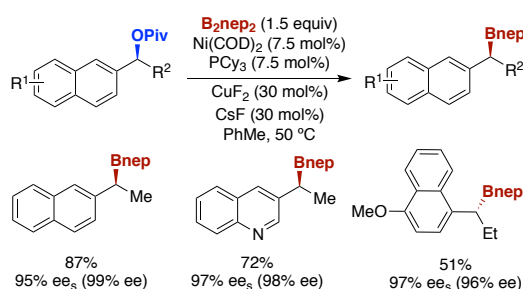


Fig. 9 – Stereoselective Ni-catalyzed borylation of benzyl ester derivatives.

Despite the advances realized in the utilization of aryl esters as surrogates of aryl halides, the utilization of simple anisoles, the simplest derivatives from phenol, still remains at its infancy. Although some progress has been achieved, the ability to trigger C-heteroatom bond-forming reactions still is rather problematic, as it remains confined to the utilization of π -extended systems. Our group has recently described an unprecedented catalytic ipso-silylation of aryl methyl ethers under mild conditions and without recourse to external ligands (Figure 10). The method is distinguished by its wide scope, which includes the use of benzyl methyl ethers, vinyl methyl ethers, and unbiased anisole derivatives, thus representing a significant step forward for designing new C-heteroatom bond formations via C-OMe scission. Applications of this transformation in orthogonal silylation techniques as well as in

further derivatizations are also described. Preliminary mechanistic experiments suggest the intermediacy of Ni(0)-ate complexes, leaving some doubt that a canonical catalytic cycle consisting of an initial oxidative addition of the C-OMe bond to Ni(0) species comes into play.

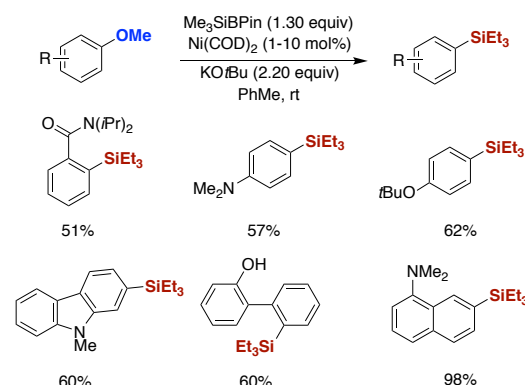


Fig. 10 – Stereoselective Ni-catalyzed borylation of benzyl ester derivatives.

Articles

“Versatile synthesis and enlargement of functionalized distorted heptagon-containing nanographenes”

Chem. Sci. **2017**, *8*, 1068-1074

Marquez, I. R.; Fuentes, N.; Cruz, C. M.; Puente-Muñoz, V.; Sotorrios, L.; Marcos, M. L.; Choquesillo-Lazarte, D.; Biel, B.; Croveto, L.; Gomez-Bengoa, E.; Gonzalez, M. T.; Martin, R.; Cuerva, J. M.; Campaña, A. G.

“Visible light-promoted atom transfer radical cyclization of unactivated alkyl iodides”

ACS Catal. **2017**, *7*, 409-412

Shen, Y.; Cornella, J.; Juliá-Hernández, F.; Martin, R.

“A mild and ligand-free Ni-catalyzed silylation via C-OMe cleavage”

J. Am. Chem. Soc. **2017**, *139*, 1191-1197

Zarate, C.; Nakajima, M.; Martin, R.

“Ni-catalyzed stannylation of aryl esters via C-O bond-cleavage”

Angew. Chem. Int. Ed. **2017**, *56*, 3187-3190

Gu, Y.; Martin, R.



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“Switchable site-selective catalytic carboxylation of allylic alcohols with CO₂”

Angew. Chem. Int. Ed. **2017**, *56*, 6558-6562

Van Gemmeren, M.; Börjesson, M.; Tortajada, A.; Sun, S. -Z.; Okura, K.; Martin, R.

“Forging C-C bonds through decarbonylation of aryl ketones”

Angew. Chem. Int. Ed. **2017**, *56*, 6708-6710

Somerville, R. J.; Martin, R.

“Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide”

Nature **2017**, *545*, 84-88

Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R.

“Visible light-driven carboxylation of aryl halides by the combined use of palladium and photoredox catalysis”

J. Am. Chem. Soc. **2017**, *139*, 9467-9470

Shimomaki, K.; Murata, K.; Martin, R.; Iwasawa, N.;

“Catalytic intermolecular dicarbofunctionalization of styrenes with CO₂ and radical precursors”

Angew. Chem. Int. Ed. **2017**, *56*, 10915-10919

Yatham, V. R.; Shen, Y.; Martin, R.

“Site-selective catalytic carboxylation of unsaturated hydrocarbons with CO₂ and water”

J. Am. Chem. Soc. **2017**, *139*, 12161-12164

Moragas, T.; Gaydou, M.; Martin, R.

“Stereospecific Nickel-catalyzed borylation of secondary benzyl pivalates”

Synlett **2017**, *28*, 2604-2608

Martin-Montero, R.; Krolkowski, T.; Zarate, C.; Manzano, R.; Martin, R.