

HIGHLIGHT

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Non-covalent organocatalysis in asymmetric oxidative C(sp³)-H bond functionalization – broadening C–H bond coupling reactions

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Among the current huge development activities in C–H functionalization, asymmetric oxidative C(sp³)-H bond coupling strategies have remained underrepresented. Beyond the initial examples using chiral metal complexes, the use of organocatalysis provides a new direction for the design of new asymmetric C–H bond cross-coupling reactions. This highlight focuses on the latest advances in metal-free asymmetric oxidative C(sp³)-H bond functionalization using cooperative non-covalent organocatalysis.

C–H bond functionalization has emerged as a powerful synthetic method for the efficient and straightforward construction of C–C or C–heteroatom bonds.¹ In the last decade a large number of practical applications of this C–H coupling methodology have appeared. In this regard, oxidative C(sp³)-H

bond functionalization, such as the cross-dehydrogenative coupling (CDC) coined by Li, has attracted great interest.² This type of chemistry is conceptually very simple and easy to perform. From a mechanistic point of view, it implies an initial substrate oxidation to form a cationic intermediate (or in some cases a radical) that can then undergo a nucleophilic attack to form the new C–Nu bond (Scheme 1).^{1,2} However, one of the intrinsic selectivity issues in C–H functionalization relies on the ubiquitous presence of C–H bonds in organic molecules. Therefore, in order to attain high levels of regio- and chemoselectivity, substrates such as 1,2,3,4-tetrahydroisoquinolines (THIQ), which possess a distinct prominent easily oxidizable benzylic C–H bond alpha to a N-atom, have extensively been explored.^{1–3} Although a large variety of nucleophiles have already been enrolled as reaction partners, there is still a limited number of effective and synthetically valuable enantioselective oxidative C(sp³)-H bond functionalization processes.⁴ In the earlier examples, a Cu–metal catalyst was used in combination with a chiral ligand, such as BOX or PyBOX, providing moderate to good enantioselectivities.^{5,6} On

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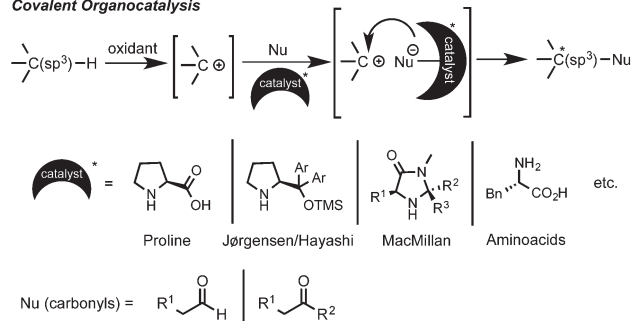


Olga García Mancheño

Olga García Mancheño received her PhD in 2005 from the Universidad Autónoma de Madrid under the supervision of Prof. Juan C. Carretero. During her PhD she carried out two–three month research-stays with Prof. Manfred T. Reetz (Max-Planck-Institut für Kohlenforschung) and Prof. Karl Anker Jørgensen (University of Aarhus). Next she moved to RWTH-Aachen University for her postdoctoral stay in the group of Prof. Carsten Bolm (2005–2008). At the end of 2008 she started her independent career as Assistant Professor (Habilitation, mentor: Prof. Frank Glorius) at the University of Münster. In 2013 she was appointed as Professor for Organic Chemistry at the University of Regensburg and the Straubing Center of Science for Renewable Resources. Her main research interests include the development of new synthetic methods, with a special focus on catalytic approaches, and their application in the synthesis of bioactive compounds and heterocycles.

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Covalent Organocatalysis



Scheme 1 Asymmetric covalent-organocatalysis approach.

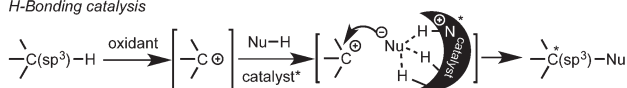


the other hand, the initial parallel studies by Prof. Nicolaou and by Prof. MacMillan in the area of metal-free asymmetric intramolecular oxidative C(sp³)-H couplings using SOMO activation of aldehydes with MacMillan-type catalysts and CAN or [Fe(phen)₃](PF₆)₃ as oxidants provided moderate to excellent enantioselectivities (70–98% ee).⁷ However, the intermolecular reactions of C(sp³)-H bonds in the α-position of a nitrogen atom with ketones proved to be more challenging, showing in some cases to be inefficient (<20% ee) and irreproducible due to fast product racemization processes.⁸ Fortunately, several efforts have proven that the appropriate choice of the substrate, carbonyl nucleophile, oxidant and amino organocatalyst can lead to high levels of enantioinduction (Scheme 1).⁹

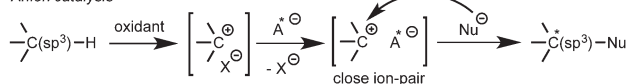
Additionally, efficient bicatalytic systems that combine a metal and an organocatalyst have also been recently developed.¹⁰ Among those combinations, several amines,^{10a,b} heterocyclic carbenes (NHC)^{10d} and thioureas^{10e} have synergistically been employed with copper salts or metal-based photoredox catalysts. The metal catalyst is generally added to promote the oxidation of the substrate, but in some cases it is also involved in the asymmetric step. The few examples using non-covalent organocatalysis are quite appealing since they opened new opportunities for a broader nucleophile scope and the development of novel enantioselective reactions. Thus, other non-carbonylic nucleophiles can now be also enrolled. However, due to multiple possible positioning and coordination points, the control of non-covalent interactions still represents a great challenge. Consequently, complete metal-free processes are still quite rare within these types of interactions.^{11,12} Herein, the two latest approaches based on non-covalent bifunctional organocatalysis by hydrogen bonding¹¹ and anion catalysis¹² are highlighted (Scheme 2).

Non-covalent Bifunctional Organocatalysis

H-Bonding catalysis



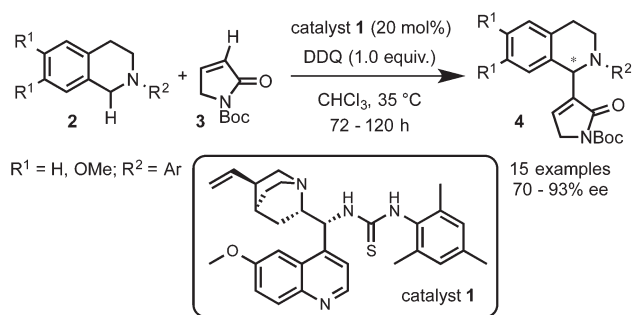
Anion catalysis



Scheme 2 Non-covalent bifunctional organocatalysis approaches.

Intermolecular C–C bond forming reaction

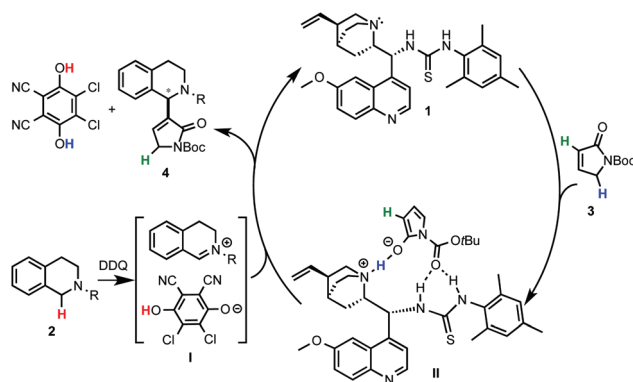
Prof. Wang and coworkers¹¹ reported the use of a bifunctional quinine-thiourea **1**¹³ for the coupling of *N*-aryl-THIQs **2** with α,β-unsaturated *N*-Boc γ-butyrolactam **3** to produce Morita-Baylis-Hilman (MBH) products **4** (Scheme 3). In this strategy the use of the bifunctional catalyst **1** allowed the simultaneous activation by deprotonation and orientation by H-bonding with the nucleophile.



Scheme 3 Bifunctional organocatalysis in asymmetric C(sp³)-H functionalization.

be the most efficient for this transformation, providing good to excellent enantioselectivities (up to 93% ee) with a variety of electron-rich *N*-aryl THIQs.

Although a highly selective α-alkylation was observed, based on previous work with the nucleophile **3**, a MBH mechanism was ruled out.¹⁴ In order to explain the regio- and enantioselectivity, the authors proposed a mechanism in which, after deprotonation of the γ-butyrolactam, a H-bonding interaction with the catalyst takes place. However, an unconceivable H-bonding interaction of the thiourea group with the positively charged nitrogen of the THIQ-iminium intermediate **I** was postulated. A more plausible mechanism implying a multiple hydrogen bonding between the catalyst and the nucleophile is depicted in Scheme 4. In one hand, the oxidation of THIQs with DDQ to form the reactive iminium salt **I** is well known.^{1–3} On the other hand, whereas the deprotonation of **3** with tertiary amines such as DABCO or quinuclidine has been described,¹⁴ its exact activation by the cinchona-thiourea catalyst is still unclear. A reasonable H-bonding interaction between the protonated quinuclidine unit and the deprotonated reagent can be envisioned. Furthermore, the additional capture of the nucleophile might be possible by H-bonding between the thiourea moiety and its Boc protecting group to form the species **II**. This might be translated to a more effective orientation and shielding of the reagent for the selec-



Scheme 4 A revisited plausible mechanism for the cinchona thiourea-catalyzed asymmetric C–H coupling of THIQ with **3**.



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