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## Non-covalent organocatalysis in asymmetric oxidative C(sp<sup>3</sup>)-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(sp<sup>3</sup>)-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(sp<sup>3</sup>)-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.<sup>1</sup> In the last decade a large number of practical applications of this C–H coupling methodology have appeared. In this regard, oxidative C(sp<sup>3</sup>)-H

bond functionalization, such as the cross-dehydrogenative coupling (CDC) coined by Li, has attracted great interest.<sup>2</sup> 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).<sup>1,2</sup> 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.<sup>1–3</sup> 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(sp<sup>3</sup>)-H bond functionalization processes.<sup>4</sup> 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.<sup>5,6</sup> On

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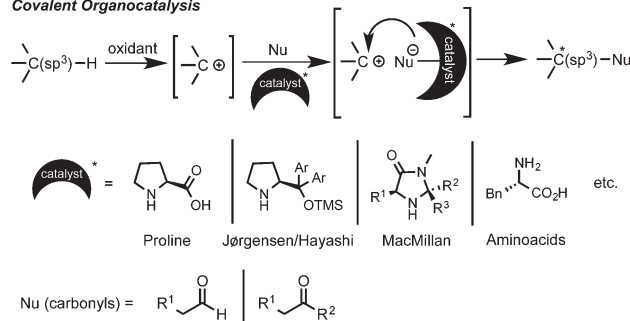


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### Covalent Organocatalysis



Scheme 1 Asymmetric covalent-organocatalysis approach.



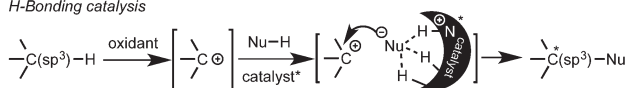
## Highlight

the other hand, the initial parallel studies by Prof. Nicolaou and by Prof. MacMillan in the area of metal-free asymmetric intramolecular oxidative C(sp<sup>3</sup>)-H couplings using SOMO activation of aldehydes with MacMillan-type catalysts and CAN or [Fe(phen)<sub>3</sub>](PF<sub>6</sub>)<sub>3</sub> as oxidants provided moderate to excellent enantioselectivities (70–98% ee).<sup>7</sup> However, the intermolecular reactions of C(sp<sup>3</sup>)-H bonds in the α-position of a nitrogen with ketones proved to be more challenging, showing in some cases to be inefficient (<20% ee) and irreproducible due to fast product racemization processes.<sup>8</sup> 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).<sup>9</sup>

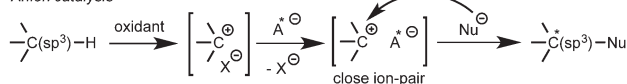
Additionally, efficient bicatalytic systems that combine a metal and an organocatalyst have also been recently developed.<sup>10</sup> Among those combinations, several amines,<sup>10a,b</sup> heterocyclic carbenes (NHC)<sup>10d</sup> and thioureas<sup>10e</sup> have synergistically been employed with 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.<sup>11,12</sup> Herein, the two latest approaches based on non-covalent bifunctional organocatalysis by hydrogen bonding<sup>11</sup> and anion catalysis<sup>12</sup> are highlighted (Scheme 2).

## Non-covalent Bifunctional Organocatalysis

## H-Bonding catalysis



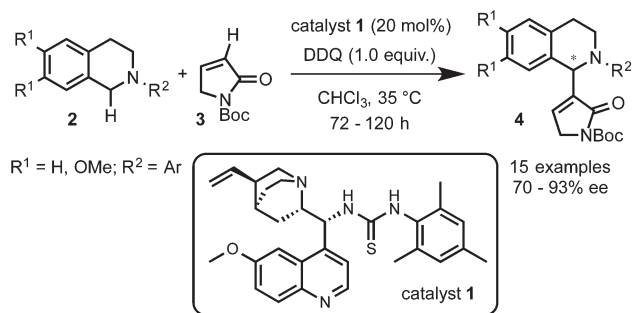
## Anion catalysis



Scheme 2 Non-covalent bifunctional organocatalysis approaches.

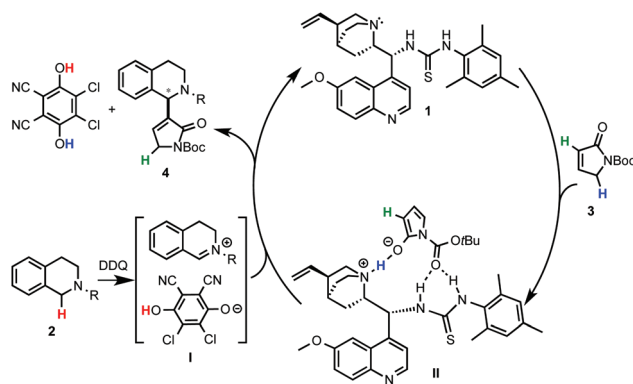
## Intermolecular C–C bond forming reaction

Prof. Wang and coworkers<sup>11</sup> reported the use of a bifunctional quinine-thiourea **1**<sup>13</sup> 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(sp<sup>3</sup>)-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.

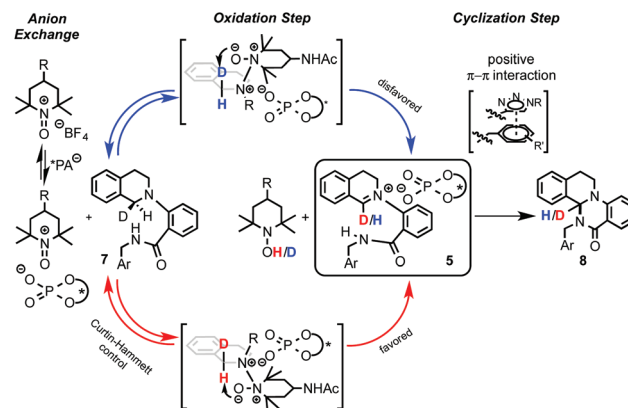
Although a highly selective α-alkylation was observed, based on previous work with the nucleophile **3**, a MBH mechanism was ruled out.<sup>14</sup> In order to explain the regio- and enantioselectivity, the authors proposed a mechanism in which, after deprotonation of the γ-butyrolactam, a H-bonding 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.<sup>1–3</sup> On the other hand, whereas the deprotonation of **3** with tertiary amines such as DABCO or quinuclidine has been described,<sup>14</sup> 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**.

tive approach to the iminium electrophile, explaining the high enantioselectivities observed.

## Intramolecular C–N bond forming reaction

Recently, Toste's group made a great breakthrough in asymmetric organocatalyzed C–H functionalization (Scheme 5).<sup>12</sup> In this case, the *in situ* generation of a chiral close ion-pair<sup>15</sup> with an anionic catalyst by getting advantage of the cationic character of the oxidation-intermediate 5 was exploited. Thus, a chiral counter ion could be introduced by anion exchange between a chiral anion and an ionic oxidant (e.g. [Ox]<sup>+</sup>X<sup>−</sup>) or the iminium salt generated in the first oxidation step. For that reason chiral triazole-containing phosphoric acids (PA) 6 derived from BINOL were employed as precatalysts.<sup>16</sup> The active catalyst, the corresponding phosphonate, was generated in the reaction media by addition of a base such as Na<sub>3</sub>PO<sub>4</sub>. To prove the concept, the intramolecular amidation of *N*-aryl substituted THIQs 7 was chosen as the target reaction using as oxidant a TEMPO-derived oxoammonium salt (4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate, 4-AcNHT<sup>+</sup>BF<sub>4</sub><sup>−</sup>).<sup>17,18</sup> The multifunctional nature of the catalysts was carefully designed in order to enhance the positive interactions between the substrate and the catalyst. Thus, the 1,2,3-triazole units present in the catalyst at the 3 and 3' positions<sup>19</sup> could additionally participate in an attractive interaction with



Scheme 6 Proposed mechanism for the phosphate-catalyzed reaction.

the iminium intermediate and, therefore, lead to an efficient chirality transfer. Consequently, moderate to excellent enantioselectivities were achieved (up to 95% ee).

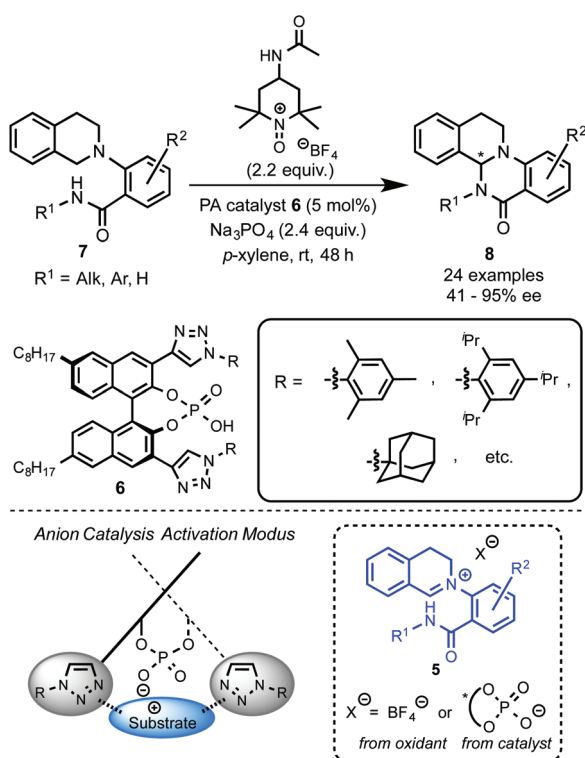
Interestingly, well-established simple PA catalysts designed only to create a sterically hindered environment around the active acid-site failed to provide effective chirality transfer. Although the main task of the substituent at the triazole in the used PA catalyst is also to be steric, positive  $\pi$ - $\pi$  interactions between the substrate and the triazole ring were also proposed.<sup>12b</sup> Kinetic isotope effect (KIE) studies and library-trend analysis led to the mechanistic hypothesis shown in Scheme 6. Different KIEs were observed using the (*R*)- and the (*S*)-PA, suggesting that the catalyst should be already involved in the oxidation step. Thus, the anion exchange might have occurred between the oxoammonium salt and the catalyst prior to the oxidation of the substrate 7 to the iminium intermediate 5 (Scheme 6, left).

## Conclusions

Considering the current importance of direct C–H bond functionalization towards more efficient and sustainable synthesis, the use of organocatalysis for the development of efficient asymmetric strategies provides a valuable alternative to transition-metal catalyzed approaches. In this highlight, two effective methods based on multiple H-bonding and a synergetic combination of Coulomb and  $\pi$ - $\pi$ -interactions have been presented. Although the control of supramolecular non-covalent interactions constitutes a fundamental challenge, non-covalent organocatalysis offers high flexibility and unique cooperative features that will allow the design and discovery of novel asymmetric oxidative C–H functionalization reactions. Thus, significant future advances in this field using multifunctional non-covalent organocatalysis are certainly expected in the next few years.

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Scheme 5 Chiral phosphate catalysis in C(sp<sup>3</sup>)-H functionalization.



## Notes and references

- (a) *Handbook of C–H Transformations*, ed. G. Dyker, Wiley-VCH, Weinheim, 2005; (b) J.-Q. Yu and Z.-J. Shi, in *C–H Activation: Topics in Current Chemistry*, Springer, Berlin, 2010.
- Selected recent reviews on oxidative C–H functionalization: (a) C. J. Scheuermann, *Chem. – Asian J.*, 2010, **5**, 436; (b) M. Klussmann and D. Sureshkumar, *Synthesis*, 2011, 353; (c) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (d) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (e) R. Rohlmann and O. García Mancheño, *Synlett*, 2013, 6; (f) S. A. Girard, T. Knauber and C. J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (g) R. Narayan, K. Matcha and A. P. Antonchick, *Chem. – Eur. J.*, 2015, **21**, 14678, and references cited therein.
- Recent review on asymmetric couplings of  $\alpha$ -C(sp<sup>3</sup>)-H of amines: (a) Y. Qin, J. Lv and S. Luo, *Tetrahedron Lett.*, 2014, **55**, 551. See also: (b) W. Liu, S. Liu, R. Jin, H. Guo and J. Zhao, *Org. Chem. Front.*, 2015, **2**, 288. For a mechanistic study, see: E. Boess, C. Schmitz and M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317.
- Recent review on asymmetric C–H bond functionalization: C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173.
- Pioneer work: Z. Li and C.-J. Li, *Org. Lett.*, 2004, **6**, 4997.
- See also: (a) N. Sasamoto, C. Dubs, Y. Hamashima and M. Sodeoka, *J. Am. Chem. Soc.*, 2006, **128**, 14010; (b) O. Basléand and C.-J. Li, *Org. Lett.*, 2008, **10**, 3661; (c) G. Zhang, Y. Zhang and R. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 10429; (d) W. Cao, X. Liu, R. Peng, P. He, L. Lin and X. Feng, *Chem. Commun.*, 2013, **49**, 3470; (e) J. Yu, Z. Li, K. Jia, Z. Jiang, M. Liu and W. Su, *Tetrahedron Lett.*, 2013, **54**, 2006; (f) I. Perepichka, S. Kundu, Z. Hearne and C.-J. Li, *Org. Biomol. Chem.*, 2015, **13**, 447, and references cited herein.
- (a) K. C. Nicolaou, R. Reingruber, D. Sarlah and S. Bräse, *J. Am. Chem. Soc.*, 2009, **131**, 2086; (b) J. C. Conrad, J. Kong, B. N. Laforteza and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 11640.
- (a) A. Sud, D. Sureshkumar and M. Klussmann, *Chem. Commun.*, 2009, 3169; (b) Y. Pan, C. W. Kee, L. Chen and C.-H. Tan, *Green Chem.*, 2011, **13**, 2682.
- For a recent review, see: (a) Y.-L. Zhao, Y. Wang, Y.-C. Luo, X.-Z. Fu and P.-F. Xu, *Tetrahedron Lett.*, 2015, **56**, 3703. See also: (b) F. Benfatti, M. G. Capdevila, L. Zoli, E. Benedetto and G. Cozzi, *Chem. Commun.*, 2009, 5919; (c) X. H. Ho, S. I. Mho, H. Kang and H. Y. Jang, *Eur. J. Org. Chem.*, 2010, 4436; (d) B. Zhang, S. K. Xiang, L. H. Zhang, Y. X. Cui and N. Jiao, *Org. Lett.*, 2011, **13**, 5212; (e) J. Zhang, B. Tiwari, C. Xing, X. Chen and Y. G. Chi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3649; (f) Z. L. Meng, S. T. Sun, H. Q. Yuan, H. X. Lou and L. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 553.
- Amino/Cu: (a) J. Zhang, B. Tiwari, C. Xing, X. Chen and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3649; (b) G. Zhang, Y. Ma, S. Wang, W. Kong and R. Wang, *Chem. Sci.*, 2013, **4**, 2645. Alcohol/Cu: (c) G. Zhang, Y. Ma, S. Wang, Y. Zhang and R. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 12334. NHC/Ru: (d) D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 8094. Thiourea/Ru: (e) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen and C. R. J. Stephenson, *Chem. Sci.*, 2014, **5**, 112.
- Y. Ma, G. Zhang, D. Yang and R. Wang, *Org. Lett.*, 2014, **16**, 5358.
- (a) A. J. Neel, J. P. Hehn, P. F. Tripet and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 14044; (b) A. Milo, A. J. Neel, F. D. Toste and M. S. Sigman, *Science*, 2015, **347**, 737.
- Bifunctional cinchona-thioureas: (a) C. E. Song, in *Cinchona Alkaloids in Synthesis and Catalysis*, Wiley-VCH, Weinheim, 2009; (b) Q. L. Zhou, in *Privileged Chiral Ligands and Catalysts*, Wiley-VCH, Weinheim, 2011. For the pioneering work, see: (c) B. Vakulya, S. Varga, A. Csmpai and T. Soos, *Org. Lett.*, 2005, **7**, 1967; (d) S. H. McCooney and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (e) J. Yea, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481.
- (a) Z. Duan, Z. Zhang, P. Qian, J. Han and Y. Pan, *RSC Adv.*, 2013, **3**, 10127; (b) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 3300; (c) N. Ramireddy and J. C.-G. Zhao, *Tetrahedron Lett.*, 2014, **55**, 706.
- (a) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518; (b) K. Brak and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 534.
- Selected reviews: (a) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (b) M. Terada, *Synthesis*, 2010, 1929; (c) R. J. Phipps, G. L. Hamilton and D. F. Toste, *Nat. Chem.*, 2012, **4**, 603; (d) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047.
- Reviews on *N*-oxoammonium chemistry: (a) J. M. Bobbitt and M. C. L. Flores, *Heterocycles*, 1988, **27**, 509; (b) J. M. Bobbitt, C. Brückner and N. Merbouh, *Oxoammonium- and nitroxide-catalyzed oxidations of alcohols*, in *Org. Reactions*, ed. S. E. Denmark, Wiley, New York, 2009, vol. 74, p. 103; (c) T. Stopka and O. García Mancheño, *Synthesis*, 2013, 1602. See also: (d) M. A. Mercadante, C. B. Kelly, J. M. Bobbitt, L. J. Tilley and N. E. Leadbeater, *Nat. Protoc.*, 2013, **8**, 666.
- TEMPO oxoammonium salts as oxidants in C–H functionalization: (a) H. Richter and O. García Mancheño, *Eur. J. Org. Chem.*, 2010, 4460; (b) H. Richter and O. García Mancheño, *Org. Lett.*, 2011, **13**, 6066; (c) S. Wetz, S. Kodama and A. Studer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11511; (d) H. Richter, R. Fröhlich, C. G. Daniliuc and O. García Mancheño, *Angew. Chem., Int. Ed.*, 2012, **51**, 8656; (e) R. Rohlmann, T. Stopka, H. Richter and O. García Mancheño, *J. Org. Chem.*, 2013, **78**, 6050; (f) C. Yan, Y. Liu and Q. Wang, *RSC Adv.*, 2014, **4**, 60075; (g) S. Sun, C. Li, P. E. Floreancig, H. Lou and L. Liu, *Org. Lett.*, 2015, **17**, 1684.
- For the first syntheses of 1,2,3-triazole BINOLs and they application in catalysis, see: (a) S. Beckendorf and O. García Mancheño, *Synlett*, 2012, 2162; (b) C. Recsei and S. P. McErlean, *Tetrahedron*, 2012, **68**, 464.

