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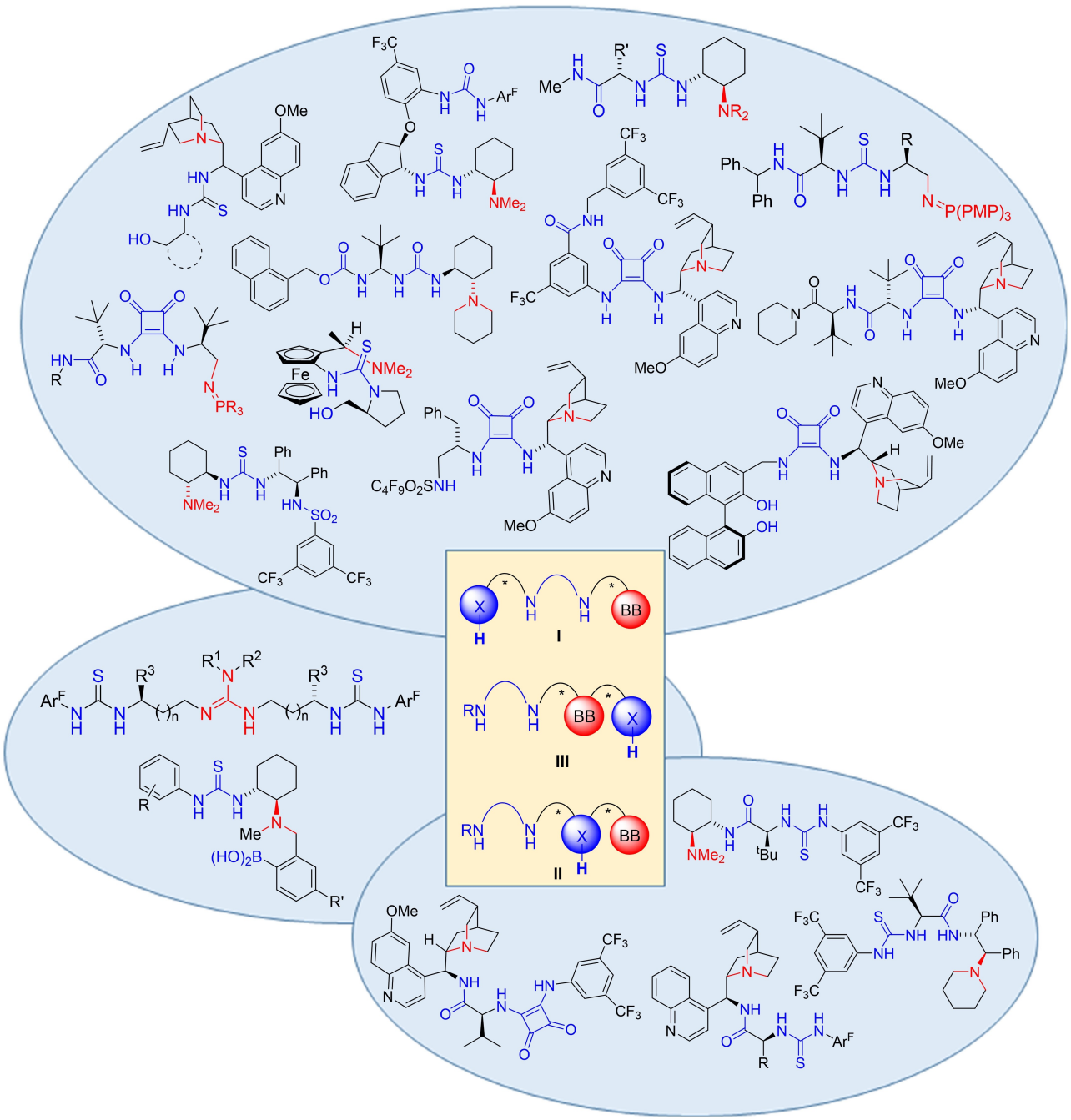
Progress in (Thio)urea- and Squaramide-Based Brønsted Base Catalysts with Multiple H-Bond Donors

Silvia Vera,[a] Ane García-Urricelqui,[a] Antonia Mielgo,*[a] and Mikel Oiarbide*[a]

Dedicated to Prof. Cesare Gennari on the occasion of his 70th birthday



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Thiourea- and squaramide-based bifunctional base catalysts represent nowadays a powerful tool in the field of asymmetric catalysis and have demonstrated very efficient for promoting a wide variety of transformations enantioselectively. New versions that incorporate one or various additional H-bond donor site(s) in the catalyst structure have been developed recently which led to more active (reduced catalyst loadings) and selective catalysts. This review highlights the pioneering ideas and the most recent contributions to the area with the material organized according to the nature of the additional H-bond donor functionality. The advantages, current limitations and perspectives of these new multifunctional catalysts are discussed.

1. Introduction

Multifunction is inherent to the mode of action of enzymes in catalysing bond forming/breaking processes with extremely high efficiency and selectivity.[1] In the realm of small-molecule catalysis, and particularly organocatalysis, the potential advantages of catalysts capable of displaying bi(multi)functional activation mechanisms were postulated quite long time ago, but its realization has progressed with paucity.[2] Notably, in 1981 (more than four decades ago) the bifunctional character of naturally occurring cinchona and ephedra alkaloids –which integrate as key structural moiety a chiral β-hydroxy amine fragment– was already noted by Wynberg et al.[3] Their studies on the enantioselective conjugate addition of arenethiols to enones in the presence of such organocatalysts led to the conclusion that "[these compounds] *can be regarded as bifunctional catalysts…They activate the thiol* via *ion-pair formation and the enone* via *hydrogen bonding*". While moderate enantioselectivities were achieved, in their 1981 paper authors concluded that "*the development of new chiral catalysts with the principle of multifunctional catalysis in mind will certainly enhance the importance of catalytic chiral synthesis as a method for obtaining optically active substances.*" and that "*the scope of the utility to other Michael reactions can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen bond donor.*"

Over the last two decades, that prediction has come true and several chiral catalysts integrating a Brønsted base (BB) and a hydrogen-bond (HB) donor moiety have demonstrated effective in promoting C–C and C-heteroatom bond-forming reactions enantioselectively.[4] In this evolution, BB's other than tertiary amines have been introduced in the catalysts design, but these latter remain dominant.[5] On the contrary, the search of HB donor units other than simple alcohols has resulted quite fruitful, with urea and thiourea being among the most successful in this context.[6] Thus, fundamental and independent discoveries by the groups of Jacobsen[7] and Schreiner[8] in the late 1990's/early 2000's uncovered the capacity of α-amino acid-derived chiral (thio)ureas and electron-poor *N,N*-bisaryl (thio)ureas, respectively, as effective HB catalysts. Ground on these studies, in 2003 Takemoto realized the highly enantioselective, direct Michael reaction between 1,3-dicarbonyl compounds (malonates) and nitroolefins using tertiary amine/(thio)urea catalyst (Figure 1a),[9] a realization that set a trend. Five years later, Rawal expanded this category of tertiary amine/HB catalysts by introducing the squaramide functionality as a highly efficient HB donor unit (Figure 1a).[10] Since these ground-breaking findings, a large body of work involving both (thio)urea- and squaramide-based bifunctional BB catalysts[11] has been developed based on refining catalysts design, thus broadening the portfolio of reactions within reach.

In the above developments, it is generally recognized that HB interactions during substrate activation and, ultimately, control of the reaction outcome, including stereoinduction, play a critical role. The perception that catalysts incorporating additional HB donor units in their structure may perform superior, while vague, has guided the design of new catalysts

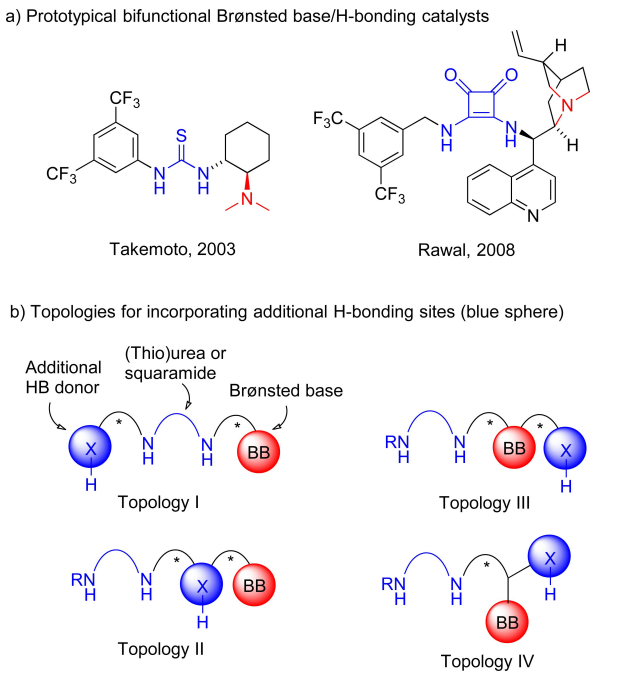

Figure 1. a) First BB catalysts incorporating thiourea/squaramide units. b) Various topologies explored within multifunctional Brønsted base/H-bonding catalyst architectures. Asterisk denotes chiral backbone.

[a] *Dr. S. Vera, Dr. A. García-Urricelqui, Prof. Dr. A. Mielgo, Prof. Dr. M. Oiarbide*
Departamento de Química Orgánica I
Universidad del País Vasco
Manuel de Lardizábal 3, 20018 Donostia-San Sebastián (Spain)
E-mail: antonia.mielgo@ehu.eus
mikel.oiarbide@ehu.eus

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that, in fact, resulted comparatively more efficient in many instances. A practical consequence of this idea is that preparation of catalysts with increasing structural and functional complexity is necessary, which means slightly longer catalyst preparation sequences. However, benefits in terms of more effective substrate activation, better catalyst pre-organization, tighter transition state geometries, and ultimately higher degree of stereoinduction, often override. This review describes the most salient contributions in the area with a focus on the underlying key design elements and, when available, showing any gained efficiency in catalyst activity and selectivity by incorporation of the additional HB donor site(s). As the general pictograms **I**–**IV** in Figure 1b represent, various topological arrangements of the main three active units of the catalyst have been conceived, with **I** being the most frequently explored topology and **IV** the less often studied. Content has been organized based on the catalyst structure/functionality, covering first thiourea and urea-based catalysts, and then squaramide-based developments. In its turn, methods within each section are ordered according to the nature of the additional HB donor functionality, i.e., sulfonamides, alcohols, amides, organoboronic acids, amidines, amines, and bis (thio)urea systems. While some of these developments may have been already discussed in a fractional manner in previous review articles,[2c,12] to the best of our knowledge there is a lack of a focus review, except a *Featured Article* by Wang that mainly covered their own laboratory contributions to the area until year 2015.[5f] Herein we report the main contributions since the first examples until the end of 2021.

2. Thiourea-based Multifunctional Brønsted Base Catalysts

2.1. Thiourea-sulfonamide systems

In 2008 Wang laboratory reported newly designed catalysts of general structure **A** (Scheme 1) as effective promoters of Michael additions of acetylacetone to nitroolefins,[13] thus introducing a new family of bifunctional amine-thiourea catalysts bearing multiple H-bonding donors with efficiencies usually higher than that achieved with previously known Brønsted base/H-bonding bifunctional catalysts. The presence of multiple H-bonding donors in the catalyst structure guided the new design inspired by the mode multidentate enzymes work in Nature. Furthermore, this design allows also variation regarding the BB, the chiral diamine and the sulfonamide group, which set the basis for the synthesis of other related sulfonamide-containing multifunctional BBs as outlined in this section. Subsequently, this research group further expanded the utility of this family of catalysts to various reaction settings, including domino processes, as summarized next.

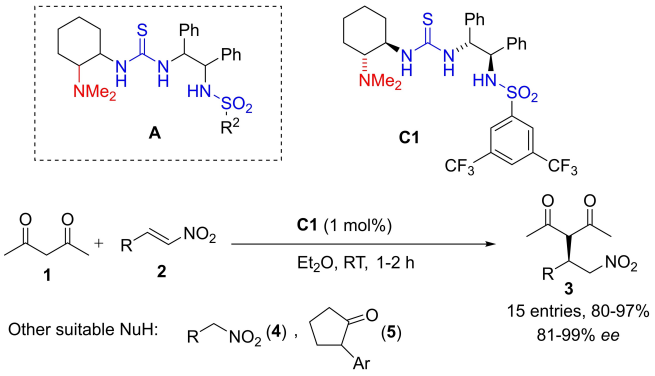
In their initial report, thiourea-sulfonamide **C1** was demonstrated to be able to trigger the Michael addition reaction of

Silvia Vera completed her PhD in 2010 at University of the Basque Country UPV/EHU (Spain) under of supervision of Profs. Claudio Palomo and Antonia Mielgo working on the development of novel organocatalyst for asymmetric synthesis. Then, in 2010, she worked as a postdoctoral researcher with Prof. Paolo Melchiorre at ICIQ, (Tarragona, Spain) and, in 2012, with Prof. M. Gaunt group (Cambridge, England). Then, she moved to the group of Prof. José Luis Serrano (Zaragoza, Spain) to work in the field of liquid crystals and dendrimers. In 2013, she returned to the University of the Basque Country UPV/EHU (Spain) and her current research interests include the asymmetric synthesis and its application.

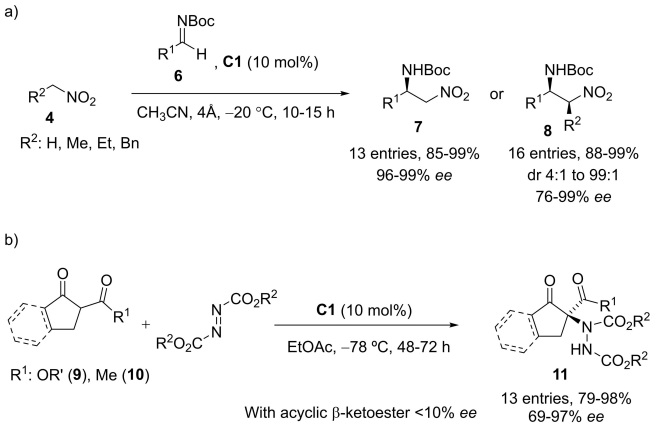
Ane García-Urricelqui was born in Pamplona (Spain) in 1994. She obtained her degree in Chemistry from the University of the Basque Country (UPV-EHU) in 2016 and her master's degree in Synthetic and Industrial Chemistry from the same university the next year. She then carried out her thesis in organic chemistry under the supervision of Profs. Claudio Palomo and Antonia Mielgo, obtaining her PhD in 2022. Her research focuses on designing and synthesizing new chiral multifunctional catalysts to perform new and challenging stereoselective organic transformations.

Antonia Mielgo was born in San Sebastián (Spain) and studied chemistry at the University of the Basque Country. She completed her phD at the same university in 1996 on β-lactam chemistry under the supervision of Prof. Palomo. After a two-year postdoctoral stay as Marie Curie fellow with Prof. Gennari at the Università degli Studi di Milano on combinatorial chemistry and peptidomimetics (1996-1998), she returned to the University of the Basque Country, UPV/EHU. In 2003 she became Associate Professor at the same university. Her current research interest is asymmetric catalysis and the development of new stereoselective reactions.

Mikel Oiarbide obtained his PhD from the University of the Basque Country UPV/EHU (Spain) in 1991 working with Prof. C. Palomo and J.M. Aizpurua. He then spent two years as a postdoctoral research associate with Prof. H. Rapoport at UC Berkeley (USA). In 1994, he took up a tenure position at UPV/EHU and was promoted to Professor in 2003.



Scheme 1. First demonstration by Wang of the efficiency of new multifunctional catalysts **A** in enantioselective Michael additions, 2008.[13]



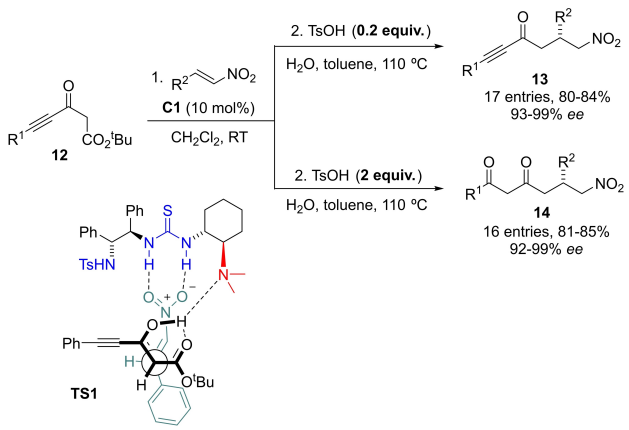
Scheme 2. The new thiourea-sulfonamide catalyst **C1** as promoter of enantioselective aza-Henry and α-amination reactions. Wang, 2008, 2011.[16,17]

acetylacetone **1** to nitroolefins **2** with high enantioselectivities using very low catalyst loading (95% *ee* with catalyst loading as low as 0.1 mol%) (Scheme 1). The substrate scope using 1 mol% catalyst in Et_2O at room temperature was demonstrated wide for aromatic nitroolefins, affording high enantioselectivity (> 95% *ee*). The aliphatic nitroolefins performed slightly inferior, with longer reaction times and 5 mol% catalyst loading being necessary to achieve *ee* values in the range of 81–85%. Still, these figures are among the best in the literature for Michael additions to aliphatic nitroolefins. Control experiment using as catalyst a methylated sulfonamide derivative (instead of the free sulfonyl NH) led to less efficient and selective addition reaction, thus demonstrating the relevant role played by the third H-bonding donor group in the present design. In subsequent work by Wang group it was demonstrated that this same catalyst **C1** is also effective in the Michael reaction to nitroolefins of nitroalkanes **4**[14] and cyclopentanones **5**,[15] respectively, as pronucleophiles.

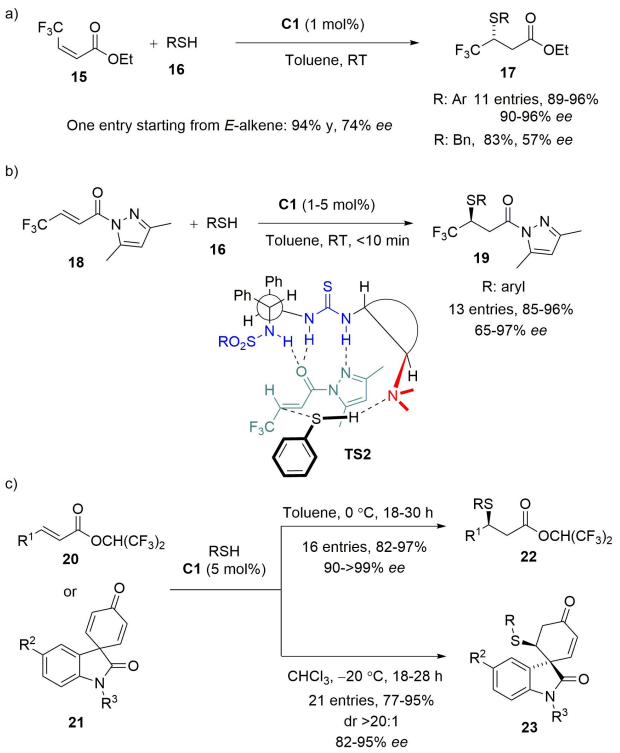
In following up studies Wang and co-workers found that the efficiency of this new family of catalysts can be translated to the aza-Henry reaction between nitroalkanes and *N*-Boc aldimines **6** to afford **7/8** (Scheme 2a).[16] It is significant that among the several isomeric forms tested, **C1** demonstrated again the highest stereoinduction during the new C–C bond forming event, this time in acetonitrile as solvent at −20 °C. Once more, both the free sulfonyl NH and the electron-withdrawing aryl group attached to the sulfonyl in catalyst structure were essential for efficiency. It is important to remark that aliphatic aldimines were also well tolerated in the reaction as well as the fact that the reaction diastereoselectivity when using superior nitroalkanes to give rise adducts **8** remained high. In addition, the authors reported that cyclic β-keto esters **9** and diketones **10** may also react with azodicarboxylate reagents in the presence of 10 mol% catalyst **C1** in cryogenic conditions to afford α-diazo compounds **11**.[17] Cyclic substrates **9** usually provided products in very good yields and enantioselectivity, while acyclic β-keto esters seem to lead to impractical selectivity (Scheme 2b).

A few years later, Pen, Wang, Shao and coworkers found **C1** as the optimum catalyst to achieve Michael additions to nitroolefins in which activated alkynyl methyl ketones **12** were employed as equivalents of acetyl acetone kinetic enolate (Scheme 3).[18] During catalyst screening, the similar amine-thiourea catalyst that lacks the sulfonamide group (Takemoto's catalyst) showed to be also competent but led to somewhat lower isolated yield (73% vs. 84%) and enantioselectivity (80% vs. 85% *ee*). Curiously, in their stereomodel proposal **TS1** authors fail to assign any relevant role to the free sulfonyl NH group during the key C–C bond forming step.

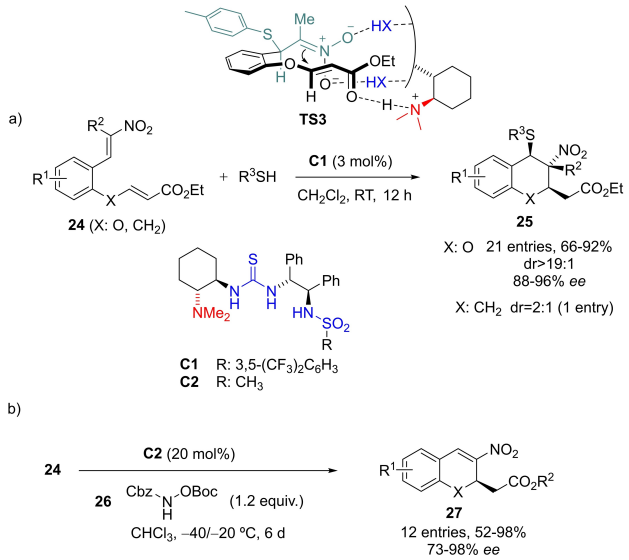
Complementing their pioneering studies on the catalytic performance of thiourea-sulfonamide catalysts of general structure **A**, Wang group carried out further evaluation of this catalyst model in the context of sulfa-Michael reactions. After screening several compounds with varying substituent groups and relative configurations, the catalyst represented by **C1** afforded, once again, the highest activity and enantiocontrol (*ee* ≥ 90%) for the conjugate addition of aryl thiols to *Z*-trifluorocrotonates **15** (Scheme 4a).[19] The reaction with alkyl thiols proceeded with poor selectivity (R = Bn, 52% *ee*). Control experiments with enoates lacking the CF_3 substituent at Cβ



Scheme 3. A decarboxylative Michael addition strategy with alkynyl ketoesters based on Wang's catalyst. Peng, Wang & Shao, 2016.[18]



Scheme 4. Thiourea-sulfonamide catalyst **C1** promoted sulfa-Michael reactions. Wang, 2011–2013.[19–22]



Scheme 5. Stereoselective domino processes promoted by catalysts based on a thiourea-sulfonamide system: a) Sulfa-Michael/Michael reaction of thiols with nitroolefin enoates. Chen, 2010;[23] b) intramolecular crossed Rauhut-Currier reaction. Gu and Xiao, 2014.[24]

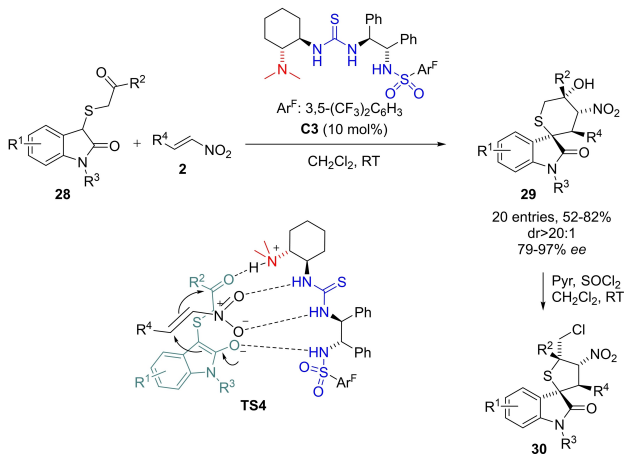
required higher catalyst loading, longer reaction times and provided lower selectivity, indicating the CF_3 group has a critical role. One problem of this method is that the reactions involving the *E*-configured analogs proceeded with considerably low enantioselectivity. Further research from the same group identified a solution to this problem by using the corresponding *E*-configured pyrazolyl amides **18** instead (Scheme 4b). In addition, the resulting adducts **19** are crystalline, so that simple crystallization may afford essentially enantiopure products.[20] A transition-state model **TS2** was proposed for these reactions in which the three thiourea and sulfonamide N–H groups associate through H-bonding to the acylpyrazole moiety of the substrate. Using the same catalyst system, the enantioselective sulfa-Michael reaction could be extended to Michael acceptors lacking the CF_3 group. Thus, addition of thiols to esters **20**[21] and dienone systems like **21**[22] also proceed under smooth conditions affording adducts **22**/**23** in high diastereo- and enantioselectivity (Scheme 4c).

The capacity of thiourea-sulfonamide molecules as efficient catalysts in reactions involving more elaborated Michael acceptors in domino or cascade processes has been explored successfully. Soon after its introduction by Wang group, Chen and co-workers identified **C1** as the best catalyst to trigger the sulfa-Michael/Michael reaction cascade of thiols with nitroolefin enoates **24** to afford polyfunctionalized chromane derivatives **25** in a highly stereoselective manner (Scheme 5a).[23] An array of *C*- and *O*-tethered substrates **24** were suitable and products **25** were obtained in good yield and usually excellent stereoselectivity. For the first sulfa-Michael addition, a transition-state similar to **TS2** (Scheme 4) is proposed with the participation of the sulfonamide NH group in which *Re*-face attack is favored. For the second intramolecular Michael the *Si*-face attack is preferred, as in **TS3**.

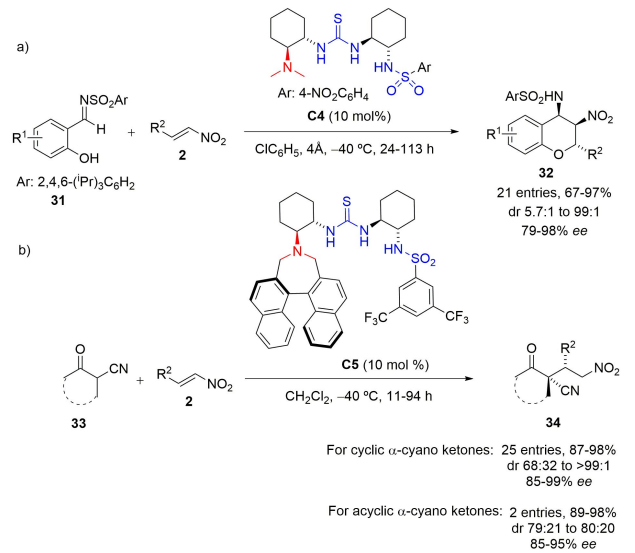
In a variation of the above method, Gu, Xiao and co-workers developed an intramolecular crossed Rauhut-Currier reaction involving the same type of unsaturated nitro-esters **24** to produce bicyclic structures **27** in the presence of thiourea-sulfonamide catalyst **C2**, which again demonstrated to be superior to other similar bifunctional catalysts lacking the sulfonamide group.[24] The key for this chemodivergent reaction outcome was the nucleophilic promoter, which in this latter case could be either stoichiometric *N*,*O*-diacylated hydroxylamine **26** or alternatively substoichiometric amounts of benzotriazole or *p*-thiocresol (Scheme 5b). The reaction afforded bicyclic structures **27** in generally good yields and enantioselectivity with **C1** being also competent catalyst.

More recently, Wang, Sheng and co-workers described the catalytic Michael-Henry reaction cascade between *S*-tethered 2-oxindole-ketones **28** and nitroolefins **2** to afford spiranic products **29** (Scheme 6).[25] Optimal stereoselectivity was attained using Wang's catalyst **C3**, a stereoisomer of **C1**, under very smooth reaction conditions. Interestingly, chlorination of adducts **29** employing the typical pyridine/thionyl chloride system was accompanied with an unexpected rearrangement to afford tricyclic compounds **30**. A transition-state model **TS4** involving multiple H-bonding interactions was proposed for the key stereochemistry-determining step.

In another approach to functionalized chromene systems, Peng described a catalytic oxa-Michael/aza-Henry reaction cascade between *N*-tosyl salicylimines **31** and nitroolefins **2** (Scheme 7a).[26] After screening several multifunctional catalysts,



Scheme 6. Domino Michael-Henry process promoted by multi H-bonding thiourea catalyst leading to enantioenriched spiranic compounds. Wang and Sheng, 2018.[25]



Scheme 7. a) Asymmetric oxa-Michael/aza-Henry reaction cascade between *N*-tosyl salicylimines and nitroolefins promoted by **C4**. Peng, 2012.[26] b) Michael addition of α-cyano ketones to nitroolefins catalyzed by **C5**. Kim, 2012.[27]

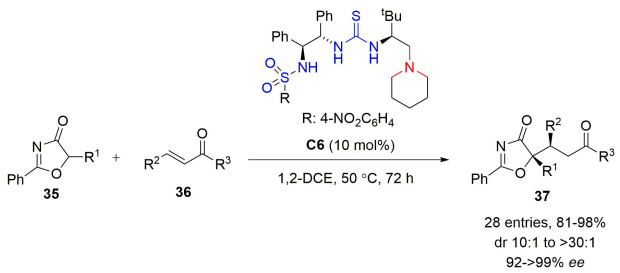
including Wang's catalyst, thiourea-sulfonamide **C4** derived from two *trans*-cyclohexane-1,2-diamine units afforded the best results, thus showing that following general design **A**, other efficient sulfonamide-containing catalysts can also be developed. Chlorobenzene was proven to be better solvent than most commonly used chlorinated and non-chlorinated solvents such as CH_2Cl_2 or acetonitrile, and low temperatures were needed that turned the reaction seemingly slow. However, yields and selectivities were generally high or very high. A comparatively more sophisticated thiourea-sulfonamide catalyst, also derived from two *trans*-cyclohexane-1,2-diamine units, but incorporating a conformationally restricted binaphthyl framework (i.e. **C5**), was developed by Kim. This catalyst proved successful in promoting the asymmetric Michael reaction of cyclic and acyclic α-cyano ketones **33** with nitroolefins to afford the corresponding Michael adducts **34** in high yield, moderate to very good diastereoselectivity and very good enantioselectivity (Scheme 7b).[27]

Ye group investigated the conjugate addition of oxazolones to enones under various BB/H-bonding bifunctional catalysts hoping to broaden the scope of suitable enone substrates for this transformation. Initial screening using some well-established catalysts led to products in good yields and diastereomeric ratios, but poor enantioselectivity (<10% *ee*). Further exploration using Wang's multiple H-bonding catalysts afforded adducts with comparable yields and *dr* values but improved *ee* values (up to 66%). Finally, they synthesized a new thiourea-sulfonamide catalyst subfamily **C6** derived from *tert*-Leucine, which ultimately achieved similar reaction yields and diastereoselectivity but *ee* values above 90% in all cases reported (Scheme 8).[28] It is worth of noting that products **37** with adjacent tertiary and quaternary stereocenters are formed as essentially single stereoisomers using unusually high reaction temperatures (50 °C).

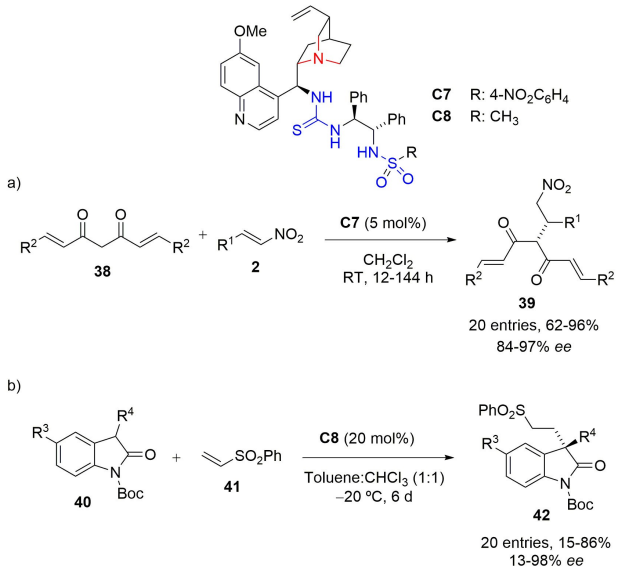
In 2011, almost simultaneously, independent work by the groups of Ye,[29] on the one hand, and Zhao and Shi,[30] on the other, documented the synthesis of novel thiourea-sulfonamide systems (e.g. **C7** and **C8**) derived from 9-amino(9-deoxy)epiquinine and 1,2-diphenylethene-diamine moieties. These multiple H-bonding donor sites bearing catalysts performed exceedingly in conjugate additions of enolizable precursors such as diketones **38** and 2-oxindoles **40** to nitroolefins and vinyl sulfones, respectively (Scheme 9).

Both catalysts **C7** and **C8** were also efficient in triggering addition reactions of enolizable pronucleophiles to isatin and isatin-derived imine substrates. Thus, Zhao and Shi found that **C8** is the catalyst of choice for the addition-trapping reaction cascade involving isatins **43** and α-isonitrile esters **44** to afford spiro-compounds **45** in a stereocontrolled fashion (Scheme 10a).[31] On the other hand, Sha, Wu and co-workers developed a Mannich-type reaction of pyrazole amides **47** to *N*-Boc ketimines **46** (Scheme 10b).[32] The pyrazole moiety in this latter reaction showed to be crucial for attaining desired catalytic reactivity.

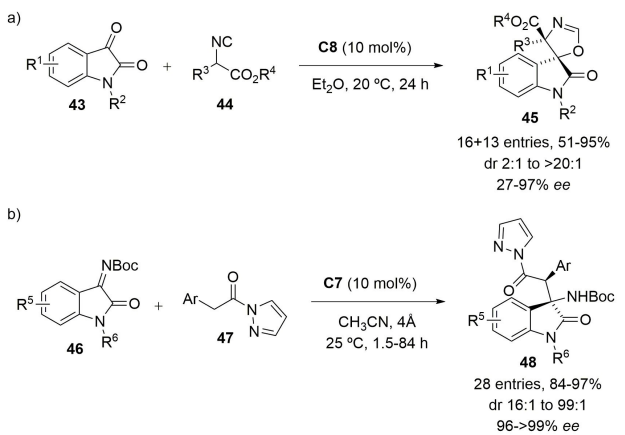
Wu and coworkers examined various bifunctional BB/HB catalysts for the Michael-nitrile addition reaction cascade between β-ketonitriles **49** and isatiliden malonotriles **50** for the



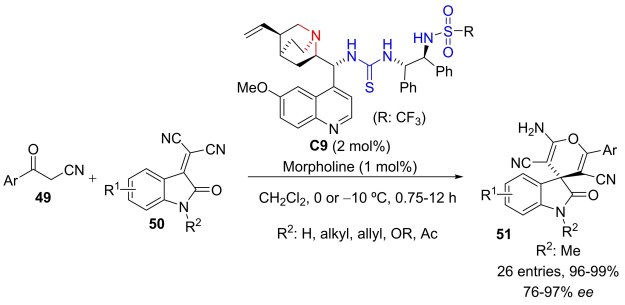
Scheme 8. *tert*-Leucine derived sulfonamide-thiourea tertiary amine base for promoting the asymmetric conjugate addition of oxazolones to enones. Ye, 2012.[28]



Scheme 9. Cinchona-derived thiourea-sulfonamide systems described by Ye and Zhao and Shi simultaneously for conjugate additions, 2011.[29,30]



Scheme 10. Isatin derivatives as electrophiles in asymmetric reactions catalyzed by cinchona-derived thiourea-sulfonamide catalysts. Zhao & Shi, 2013.[31] Sha & Wu, 2014.[32]



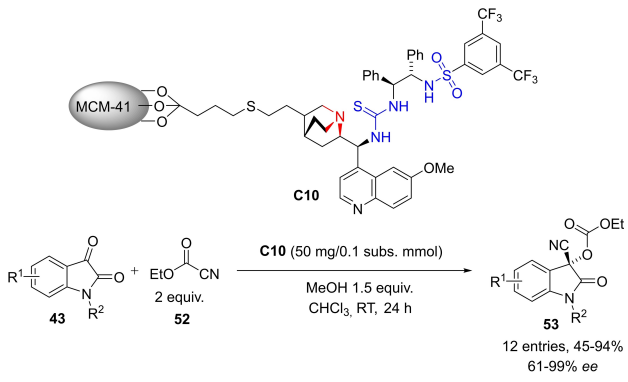
Scheme 11. Enantioselective synthesis of spiranic oxindole derivatives **51** catalysed by quinidine-derived thiourea-sulfonamide **C9**. Wu, 2016.[33]

construction of spiranic oxindole derivatives **51** (Scheme 11).[33] While various catalyst were equally competent for bringing the reaction to completion, the quinidine-derived thiourea-sulfonamide system **C9**, a diastereomer of **C8**, provided the highest enantioselectivities. Control experiments with catalysts affordable from various combinations of cinchona alkaloid derived amine and 1,2-diamine moieties demonstrated that the configuration of the product was dictated by the quinidine moiety mainly, **C9** resulting the optimum catalyst. Upon screening the effect of various additives it was found that addition of a base improved the chemical yield. However, while secondary amines considerably improved the enantioselectivity, both primary and tertiary amine additives have a limited effect on selectivity.

In another approach to immobilization of multiple H-bonding catalysts, Khan group designed quinine- and 1,2-diamine-derived thiourea-sulfonamide catalysts grafted on MCM-41 mesoporous silica (Scheme 12).[34] Before conducting catalysis experiments, the prepared insoluble materials like **C10** could be characterized by techniques such as FTIR and ^{29}Si and ^{13}C CP/MAS solid-state NMR spectroscopy, as well as via nitrogen sorption isotherms or powder X-ray diffraction XRD spectra. Evaluation of the catalytic ability of these heterogenous materials was performed using the isatin cyanoethoxycarbonylation as model reaction. As the results in Scheme 12 show, catalyst **C10** was able to promote formation of adduct **53** in chloroform at room temperature in the presence of MeOH as enabling additive. Yields as well as enantioselectivities with *N*-*p*-nitrobenzyl isatins **43** were consistently high. In parallel reactions conducted under similar but homogeneous conditions using the corresponding soluble catalyst, slightly inferior reactivity and selectivity were obtained. Catalyst recycling could be achieved through centrifugation and washing with chloroform, and the reused material was equally selective along 5 consecutive runs, although yields commenced to decrease.

2.2. Thiourea-alcohol systems

Soon after the introduction of multifunctional thiourea-sulfonamide catalysts of general structure **A**, Wang group found that



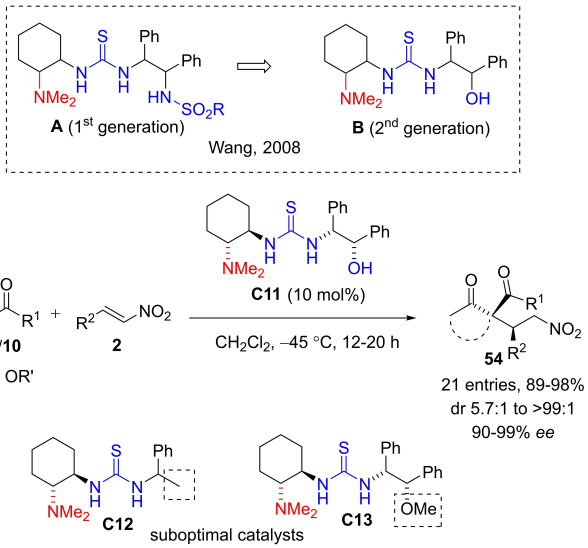
Scheme 12. Multiple H-bond donating thiourea catalysts grafted on MCM-41 mesoporous silica for isatin cyanoethoxycarbonylation reactions. Khan, 2019.[34]

these catalysts, while effective in promoting the addition of α-substituted β-ketoesters **10** to nitroolefins **2**, the resulting adducts **54** were obtained with low diastereoselectivity and low to moderate enantioselectivities (Scheme 13).[35] This lack of selectivity was attributed to unfavorable interactions between the bulky sulfonamide $NHSO_2R$ group and the reactants in the proposed transition-state. Indeed, improved results were obtained by using the second generation catalysts **B**, in which the sulfonyl group is replaced by the less bulky OH group (Scheme 13). In the presence of **C11** the addition reaction of cyclic ketoesters **10** to nitroolefins **2** proceeded smoothly at −45 °C within less than 24 h to afford adducts **54** in high isolated yields and very good diastereo- and enantioselectivity.[35] The method is also compatible with acyclic ketoesters and 1,3-diketones, although slightly lower selectivities accompanied. The significant role multiple hydrogen-bonding donors played in this catalyst system was apparent as catalysts with similar structure but lacking the alcohol group, i.e. **C12**, or presenting blocked alcohol in the form of methyl ether, i.e. **C13**, led to drastically reduced enantioselectivity.

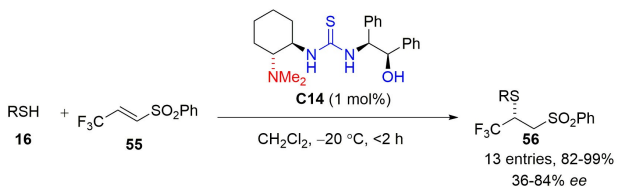
More recently, Wang group explored a new access to chiral β-trifluoromethyl substituted alkylsulfones **56** via catalyst-controlled conjugate addition of thiols to β-trifluoromethyl substituted vinyl phenyl sulfone **55**.[36] Using as low as 1 mol% equivalents of the thiourea-alcohol **C14** the reaction with a range of aryl thiols was brought to completion in less than 2 h at −20 °C affording adducts **56** in good yields with enantioselectivities from moderate to good (Scheme 14). Screening of several bifunctional amine-thiourea catalysts, including various stereoisomers of **C14**, resulted in inferior enantioselectivity (typically *ee* < 25 %) for this transformation. The reaction with alkyl thiols were less selective.

Starting from the corresponding chiral 1,2-aminoalcohol building block, several bifunctional catalysts bearing thiourea-alcohol moiety as multiple H-bonding donor system have been developed in which the amine unit is changed from cyclohexane diamine to quinine or related alkaloid structures. In this context, in 2009 the groups of Koskinen[37] and Lu,[38] independently, reported the preparation and evaluation of quinidine-derived thiourea-alcohol catalysts of general structure **C** (Figure 2). However, initial exploration of these molecules as catalysts for the Michael addition reactions of nitroalkanes to vinyl bis-sulfones and of Meldrum's acid to nitroolefins provided unsatisfactory levels of enantioselectivity.

Further studies by Lu and co-workers led to identify 2-aminoindanol-derived thiourea-alcohol **C15** as optimum catalyst for the tandem aza-Michael-Henry condensation reaction between ortho-sulfamido benzaldehydes **57** and nitroolefins to construct 1,2-dihydroquinolines **58** in high yields and enantioselectivities (Scheme 15).[39] The overall process required considerably long reaction times. Additionally, the trisyl sulfonyl group proved to be crucial for attaining high selectivities, with some common sulfonyl groups such as tosyl, nosyl or mesyl providing poor *ee* values.



Scheme 13. Stereoselective Michael addition of cyclic ketoesters **9** to nitroolefins promoted by multifunctional tertiary amine/thiourea/alcohol catalysts. Wang, 2008.[35]



Scheme 14. Asymmetric Michael addition of thiols to sulfone **55** promoted by thiourea-alcohol bearing catalyst **C14**. Wang, 2013.[36]

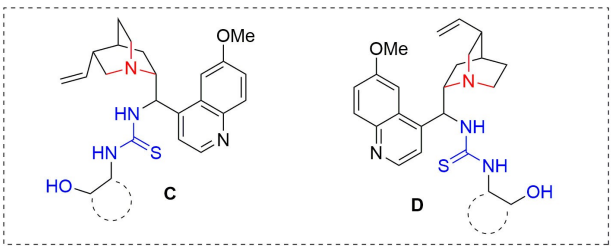
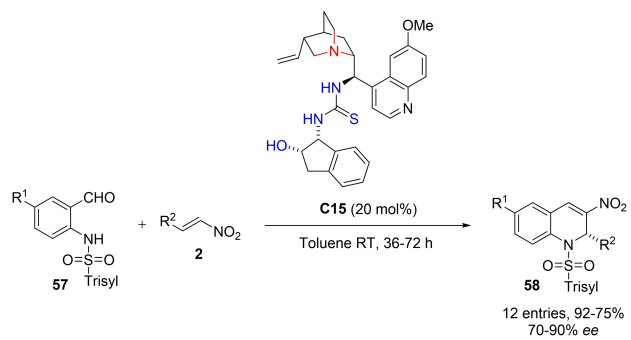
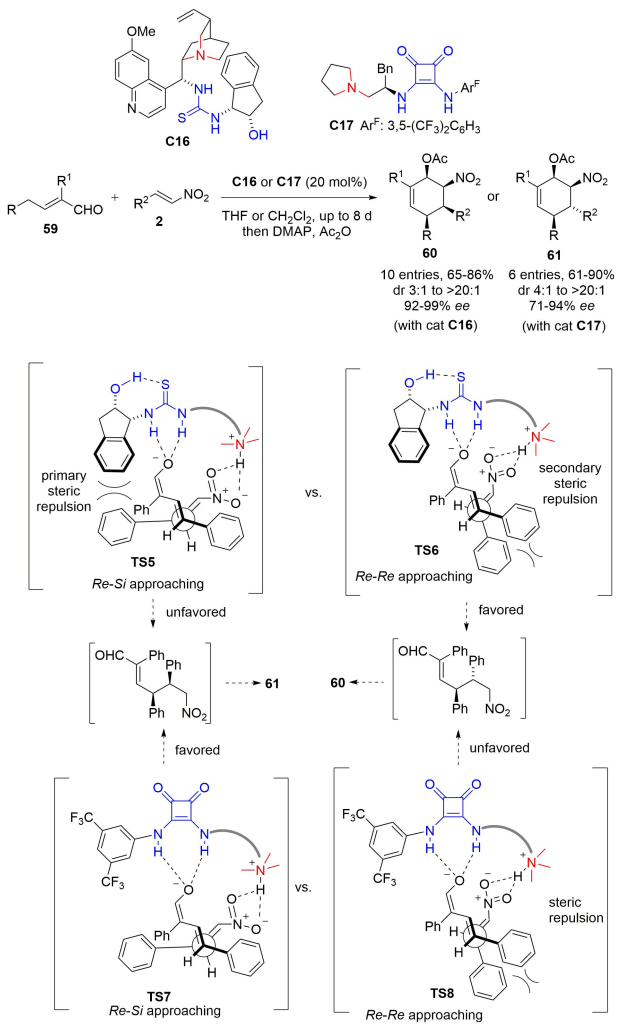


Figure 2. General structures of the alkaloid derived multifunctional thiourea-alcohol catalysts independently reported in 2009 by Koskinen[37] and Lu.[38]



Scheme 15. Enantioselective preparation of 1,2-dihydroquinolines **58** through an aza-Michael-Henry condensation tandem reaction. Lu, 2010.[39]

Thiourea catalysts with multiple H-bonding groups derived from the merging of aminoquinine and aminoindanol fragments have found applications in cascade processes. Xu has reported the domino vinylogous Michael-intramolecular Henry reaction of unsaturated aldehydes **59** and nitroolefins to form pentasubstituted cyclohexene products **60**/**61** in the presence of a bifunctional BB/H-bonding catalyst (Scheme 16).[40] Cycloadduct formation required additional treatment of the reaction mixture with Ac_2O/DMAP system. Examination of a variety of bifunctional catalysts revealed a diastereodivergent behavior of the cascade process, with common bifunctional catalysts such as **C17** affording **61** as major isomer while catalyst **C16**, a diastereomer of **C15**, bearing multiple H-bonding donors, afforded **60** as major isomer. The **C16**-catalyzed process proceeded with high yields, diastereoselectivity ratios of about 4:1 or higher and very high *ee* for a variety of α-branched enals **59** and aromatic nitroolefins **2**. On the basis of X-ray crystallographic analysis and control experiments the authors propose the transition states **TS5**-**TS8** (Scheme 16) for the razionalization of this stereodivergence. For catalyst **C16** the intramolecular H-bonding interaction between the OH group and the thiourea sulfur places the bulky indane moiety in such a way that significant steric repulsion with the phenyl ring of the nitroolefin favors the *Re-Re* approach (**TS6**) over the *Re-Si* one (**TS5**) to provide adduct **60**. For catalyst **C17** this repulsive interaction is not present and, instead, steric repulsion between the substrate substituents dictates the *Re-Si* approach (**TS7**) as the most favorable one, thus leading to adduct **61**.

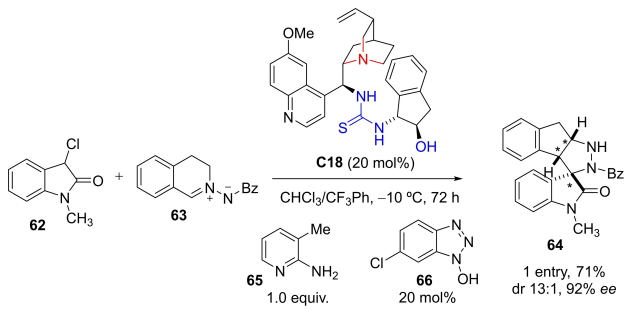


Scheme 16. Stereodivergent Michael/Henry tandem reactions of aldehydes and nitroolefins with thiourea/alcohol containing BBs as catalysts. Xu, 2017.[40]

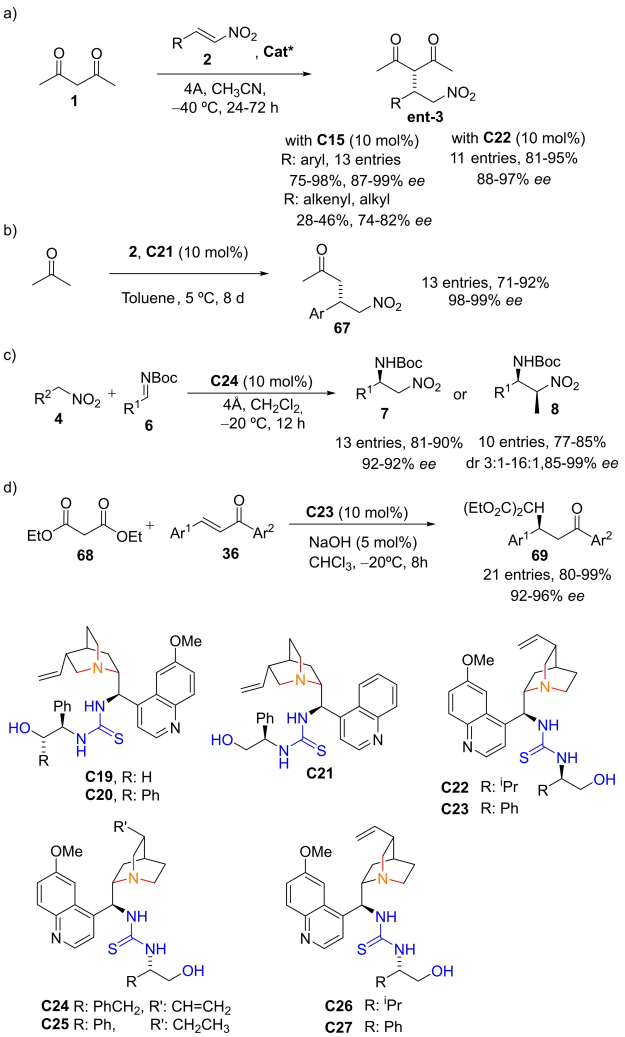
Ouyang, Chen and co-workers discovered a base-promoted addition followed by rearrangement process involving α-chloro 2-oxindoles **62** and azomethine ylides **63** to produce the diaza-spiro systems **64** (Scheme 17).[41] Development of a practical asymmetric version of this transformation was not straightforward. After extensive screening, the authors found that a combination of the multifunctional catalyst **C18**, 20 mol% of 1-hydroxy benzotriazole **66** and 2-amino-3-methylpyridine **65** could successfully induce high diastereoselectivity and enantioselectivity for the transformation to give product **64** in a mixture of chloroform and trifluorotoluene as solvent.

Compounds bearing multiple H-bonding donor groups of general structure **C**, and the related quinine-derived structure **D** (Figure 2), soon became frequently explored in various reaction settings. In 2011 He group evaluated catalysts **C15**,**C19** and **C20** for the Michael reaction of 2,5-propanedione to nitroolefins **2** and found **C15** as the most effective (Scheme 18a).[42] During the reaction optimization, low temperatures and the presence of molecular sieves proved beneficial in terms of enantioselectivity. Selectivity was also highly solvent-dependent, with acetonitrile providing the best figures. As usual, alkyl and alkenyl substituted nitroolefins behaved inferior than aryl analogs leading to a decrease of about 10 or 20 units of *ee*.

The same group also developed similar Michael reactions of simple symmetrical ketones, i.e. acetone, to nitroolefins as well as aza-Henry reactions between nitroalkanes and *N*-Boc aldimines catalyzed by quinine- and cinchonine-derivedthiourea-alcohols (Scheme 18b-c).[43] **C22** was also found efficient for the conjugate addition of 2,5-propanedione to nitroolefins **2** (Scheme 18a). Interestingly, these studies further revealed the high variability of solvent dependence: while acetonitrile was the best option for diketones addition to nitroalkenes in the presence of **C22** as catalyst, the addition of acetone in presence of **C21** worked better in toluene and the aza-Henry reaction



Scheme 17. Multifunctional BB catalyzed asymmetric synthesis of diaza-spiro systems. Ouyang and Chen, 2019.[41]

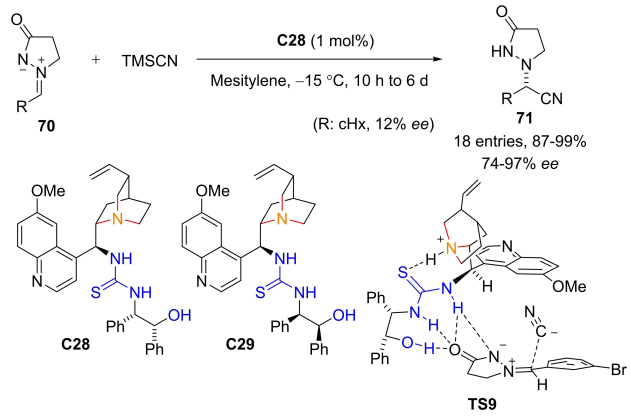


Scheme 18. Alkaloid derived multifunctional thiourea-alcohol catalysed addition reactions: a) He, 2011.[42] a,b,c) He & Zhang, 2012.[43] d) He, 2014.[45]

proceeded better in dichloromethane with catalyst **C24**. In connection to this work, Lin, Duan and co-workers documented the highly diastereo- and enantioselective aza-Henry reaction of nitroalkanes with isatin-derived *N*-Boc ketimines for which the dihydroquinine-derived catalyst **C25** was the best.[44]

The He group also demonstrated the efficacy of these catalysts in promoting the conjugate addition of malonic esters to enones (Scheme 18d). In this particular case, out of various cinchona alkaloid-derived thiourea-alcohol molecules with different configurations, **C23** provided the highest selectivity.[45] Importantly, a small amount of an inorganic base, preferably NaOH (5 mol%), was necessitated for the reactions to proceed.

In the same context Y. Wang, X. W. Wang and co-workers studied the Strecker-type reaction of azomethine imine **70** under the presence of various cinchona alkaloid-derived organocatalysts (Scheme 19).[46] Initial screening showed that both the basic quinuclidine and the acidic thiourea moiety were crucial to catalyze the reaction and for attaining stereoinduction. Moreover, investigation of the reaction conditions

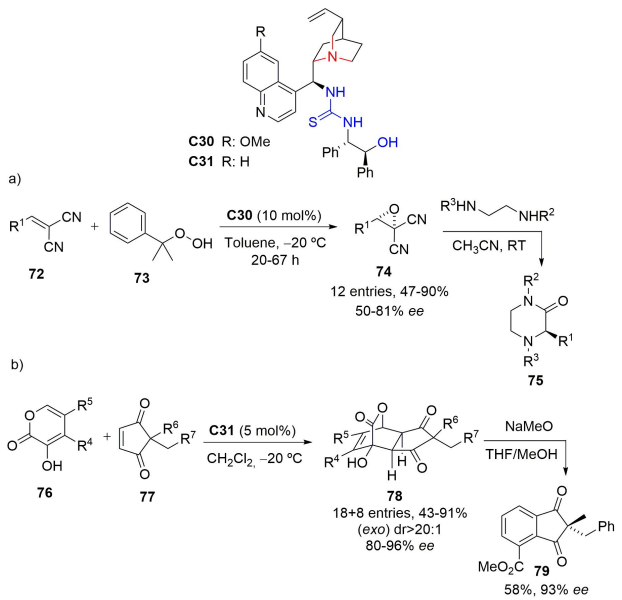


Scheme 19. Aminoalcohol-thiourea containing BBs for the stereocontrol of a Strecker-type reaction through multiple H-bonding. Wang & Wang, 2013.[46]

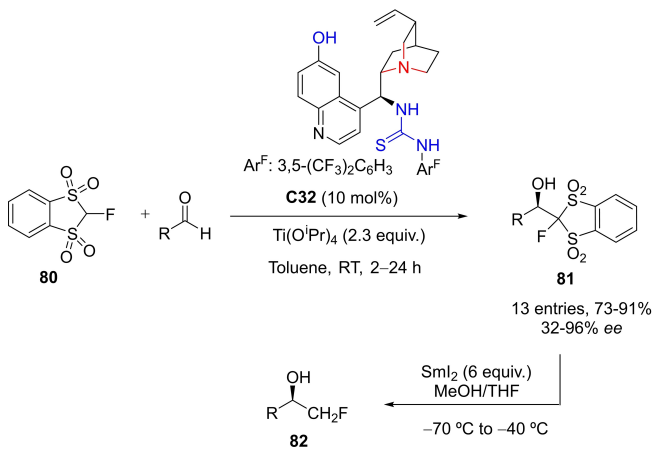
and additives revealed that addition of catalytic amounts of (*S*)-BINOL increased enantioselectivity notably. Considering this latter observation, new catalysts incorporating a 1,2-diphenylethanol fragment, such as **C28/C29**, were tested in the above reaction, being **C28** the best. The reactions tolerated a wide range of aryl substituted azomethine imines **70**, but the alkyl counterparts (e.g. R = cyclohexyl) led to products **71** with drastically diminished *ee*. Computational calculations for this reaction localized a preferred transition-state structure (**TS9**) with multiple hydrogen bonds formed between the catalyst and the acceptor substrate **70**, highlighting the importance of multiple H-bonding donors on catalyst structure.

Applications of cinchona-alkaloid-derived thiourea-alcohol catalysts to other types of reactions, including cycloadditions and tandem reactions, have been demonstrated. Lattanzi[47] reported moderate enantioselectivities in the epoxidation of alkylidenmalononitriles **72** with cumyl hydroperoxide **73** in the presence of **C30** (Scheme 20a), while Dong and Wang[48] realized the highly diastereo- and enantioselective Diels-Alder reaction between 3-hydroxy-2-pyrones **76** and cyclopentenediones **77** in the presence of **C31** to afford adducts **78** (Scheme 20b). In the former case, treatment of adducts **74** with 1,2-diamines afforded piperazine-2-ones **75**, while in the latter treatment of adducts **78** with sodium methoxide led to a decarboxylative aromatization to provide desymmetrisized cyclopentanediones **79**.

Shibata found an interesting synergic effect between organocatalysts bearing multiple H-bonding donors, for example **C32**, and Lewis acids, such as $TiCl_4$, in the cross-aldol reaction between aldehydes and α-fluoro bis-sulfone **80** (Scheme 21).[49] In the absence of any Lewis acid in toluene at rt, bifunctional organocatalyst necessitated 4 days to bring this reaction to full conversion but led to enantioselectivities below 20% *ee*. However, in the presence of 2.3 equivalents of $TiCl_4$, enantiocontrol increased dramatically. Authors recognized the significant role played by the hydroxy group of the organocatalyst in controlling the enantioselectivity of the addition reaction. This method was quite general for aromatic aldehydes which, however, afforded aldols **81** with highly variable *ee*



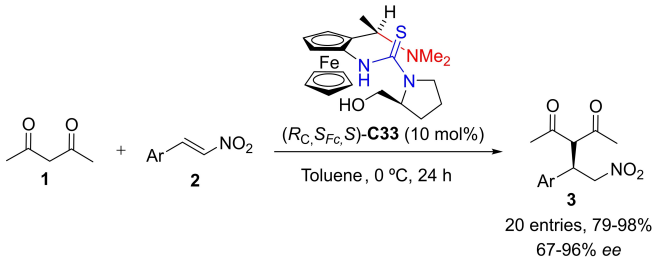
Scheme 20. Cinchona-alkaloid-derived catalysts bearing thiourea and alcohol H-bond donors for promoting: a) epoxidation of alkylidenmalononitriles. Lattanzi, 2015.[47] b) Diels-Alder cycloadditions. Dong & Wang, 2017.[48]



Scheme 21. Synergic Lewis acid/multifunctional BB catalysis for enantioselective cross-aldol reaction between aldehydes and α-fluoro bis-sulfone **80**. Shibata, 2013.[49]

values. The reaction using aliphatic aldehydes tend to be less practical as the reported enantioselectivities keep below 44% *ee*. The reaction adducts can be easily converted into the corresponding monofluoromethyl carbinols **82** by reductive desulfonylation with SmI_2/MeOH.

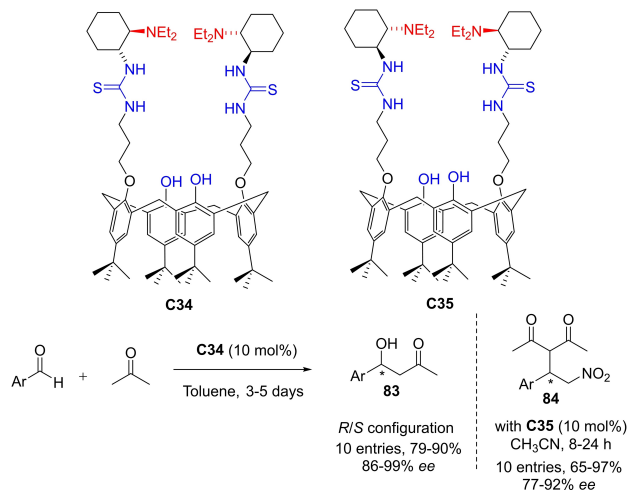
Amine/thiourea catalysts with additional H-bonding donor groups have also been built on less common chiral architectures. Chai, Zhang and co-workers prepared several chiral ferrocenyl tethered amino-thioureas bearing a carbinol sidearm. The screening of these molecules as catalyst candidates for the Michael addition of acetylacetone **1** to nitroolefins identified prolinol-derived **C33** as the most efficient (Scheme 22).[50] It should be noted that while the reaction in protic or polar



Scheme 22. Chiral ferrocenyl tethered amino-thioureas for the asymmetric Michael reaction between 1,3-diketones and nitroolefins. Chai & Zhang, 2015.[50]

solvents such as MeOH or CH_3CN was very fast, these solvents led to racemic product. Instead, toluene was the solvent of choice considering both reactivity and enantioselectivity.

Sirit group developed chiral *p-tert*-butylcalix[4]arene-derived amine-thiourea hybrids, such as **C34** and **C35**, and investigated their behavior as catalysts in various C–C bond forming addition reactions. Catalyst **C34** was the best to promote the cross-aldol reaction between acetone and aromatic aldehydes to provide **83** (Scheme 23).[51] Control experiments demonstrated that the presence of free hydroxyl groups on calixarene structure was crucial for catalyst activity and stereoinduction. The effect of both acidic and basic additives was evaluated, but none of them improved the reaction outcome. Most intriguing, some of the substituted aryl aldehydes provided aldol adducts with opposite configuration randomly. The rationale for this observation was not provided. The same group also showed that this class of multifunctional catalyst is able to promote the Michael addition of acetylacetone to nitroolefins affording adducts **84** enantioselectively.[52]



Scheme 23. Enantioselective cross aldol reaction promoted by chiral *p-tert*-butylcalix[4]arene-derived amine-thiourea hybrids. Sirit, 2016, 2018.[51,52]

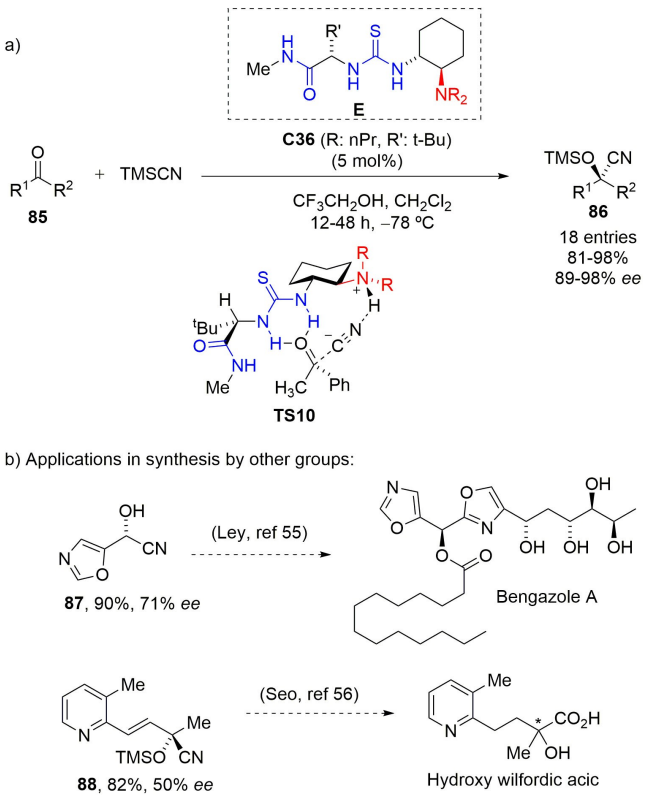
2.3. Thiourea-amide systems

Pioneering studies by Jacobsen group in 2005 identified thiourea-amine bifunctional structures derived from α-amino acids and bearing an amide side arm of general structure **E** as efficient catalysts in the context of the enantioselective cyanosilylation reaction of ketones (Scheme 24).[53] *tert*-Leucine proved to be the optimum amino acid component (R′: *t*Bu) with less sterically demanding amide derivatives, for example secondary methyl amide, leading to improved enantioselectivities. For this particular reaction, replacement of primary amine as the basic functionality with the corresponding *N*,*N*-dimethyl tertiary amine (R: Me) completely supressed the reaction. However, introduction of trifluoroethanol as an additive for in situ generation of HCN restored the reactivity maintaining enantioselectivity high. Upon further catalyst adjustment, **C36** was found to provide the highest enantioselectivity and was adopted for reaction development which resulted to be suitable for a wide range of ketones. Detailed mechanistic studies carried out subsequently confirmed the bifunctional operating nature of the catalyst, and allowed to establish the most favourable transition structure involving amine-bound HCN adding to thiourea-bound ketone, as in **TS10**. Curiously, there was no apparent role ascribed to the amide NH unit thus far.[54] Examples of applications of this catalyst in cyanation reactions by other groups include Ley's synthesis of bengazoles A and B, involving aldehyde-derived cyanohydrin **87**,[55] and Seo's synthesis of hydroxy wilfordic acid, involving ketone-derived cyanohydrin **88**.[56]

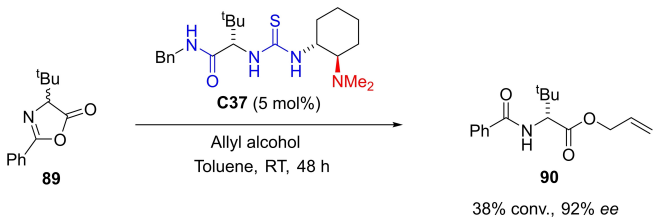
Whether or not the amide NH group in **E** has any role in substrate activation during key catalytic events, as a matter of fact this catalyst system has been demonstrated successful in various unrelated reaction settings. For example, independent work by Berkessel group described the effectiveness of thiourea-based bifunctional organocatalysts in the enantioselective dynamic kinetic resolution of azlactones **89** with alcohols (Scheme 25).[57] A wide variety of thiourea-tertiary amine based structures were screened and those bearing an amide side-arm such as **C37** demonstrated to be the most efficient. It should be noted that for this particular reaction, not only the free NH amide but also *N*-dialkylated amide congeners worked efficiently.

In a more recent application of the Jacobsen's catalyst, Shi described the diastereo- and enantioselective construction of dihydroisocoumarin-based spirooxindole frameworks **92** (Scheme 26).[58] The transformation involves an aldol-intramolecular transesterification cascade between homophthalic anhydride **91** and isatin **43**, and product isolation was preceded by an esterification with diazomethane. In the tentative activation model proposal described (e.g. **TS11**), no specific role was assigned to the free NH amide side arm.

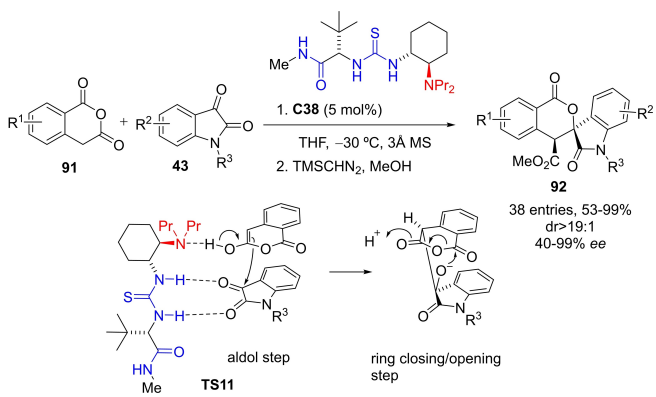
In a series of papers, Mukherjee group demonstrated the effectiveness of Jacobsen-type thioureas in catalysing conjugate additions of transiently generated vinylogous enolates (Scheme 27).[59] In their initial studies, the addition of α-



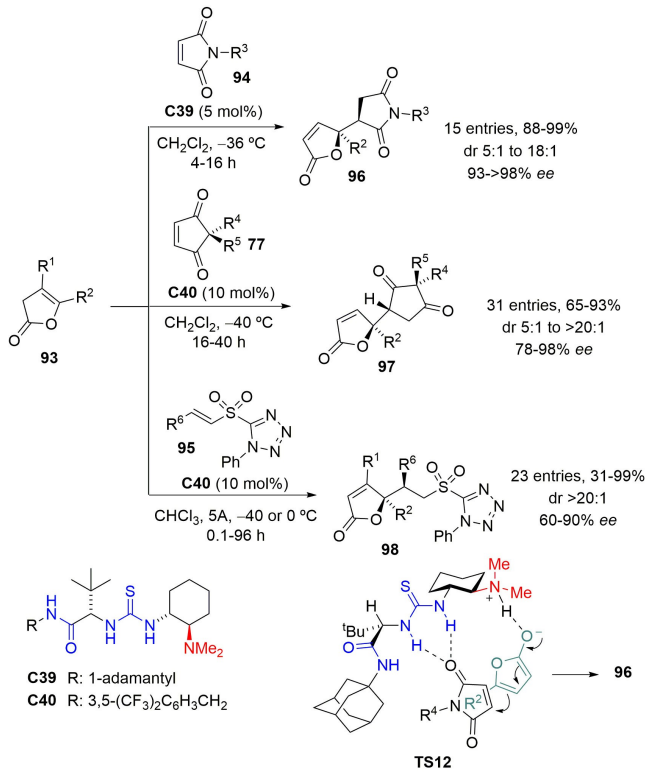
Scheme 24. Enantioselective cyanosilylation of ketones promoted by thioureas bearing an amide as additional H-bond donor,Jacobsen, 2005,[53] 2007;[54] and applications of this catalytic reaction described by other groups, Ley, 2007;[55] Seo, 2009.[56]



Scheme 25. Dynamic kinetic resolution of azlactones employing chiral multifunctional thiourea **C37**. Berkessel, 2006.[57]



Scheme 26. Aldol-intramolecular transesterification cascade reaction between anhydrides **91** and isatins **43** promoted by catalyst **C38**. Shi, 2016.[58]



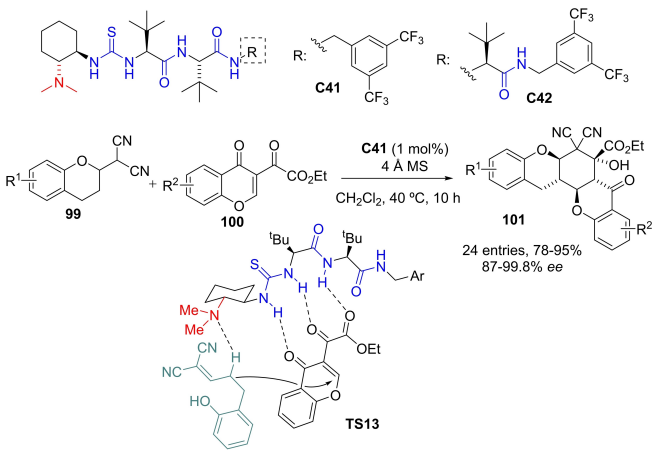
Scheme 27. Various conjugate additions of α-Angelica-type lactones **93** promoted by amide-containing thiourea bases. Mukherjee, 2012–2016.[59]

Angelica-type lactones **93** to *N*-aryl maleimides **94** was shown to proceed smoothly to give adducts **96** in high isolated yields and enantioselectivity.[59a] Cryogenic temperatures were required for the highest enantiocontrol without compromising too much the reactivity. The nature of the R group attached to the catalyst amide moiety proved to have an impact on reaction stereoselectivity. Thus, while the *N*-1-adamantyl derivative **C39** was the most selective catalyst for the above reaction, the addition reaction to cyclopentenones **77** proceeded with suboptimal enantioselectivity with this and the related *N*-propyl and *N*-benzyl catalysts.[59b] However, catalyst **C40**, bearing a *N*-bis(trifluoromethyl)phenylmethyl group achieved increased selectivity for this challenging desymmetrization process. With this latter catalyst products **97** were obtained as essentially single diastereomers in high yields and enantioselectivities from good to very high for a range of substituent patterns. Interestingly, base-promoted decarboxylation of thus generated adducts allowed to develop an enantioselective two-step vinylation of 2,2-disubstitutes cyclopentene-1,3-diones.[59c] This same catalyst was able to promote the addition of **93** to vinylsulfones **95**.[59d] The reactivity attenuation observed at the low temperatures (−40 °C) required for optimum stereocontrol could be avoided by performing the reactions in the presence of molecular sieves. A transition-state structure **TS12** was proposed for the reaction leading to product **96**.

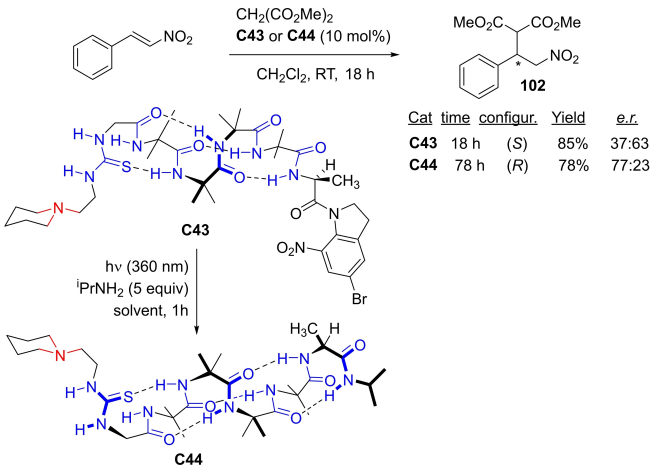
Thiourea-tertiary amine conjugates bearing two or more amide side-arms have been explored as multiple hydrogen-bonding chiral catalysts in enantioselective bond-forming reactions. For instance, in a recent study by Liu and co-workers, a new reaction cascade for accessing polyfused heterocyclic compounds **101** bearing five continuous stereogenic centers, including a quaternary one, was developed (Scheme 28).[60] Evaluation of a variety of thiourea-tertiary amines, with or without NH amide group(s) as additional H-bonding units, revealed increased reactivity and enantiocontrol as the number of amide groups in the catalyst increases, suggesting that multiple H-bonding interactions may be involved. Among the catalysts evaluated, those with two and three NH amide groups, **C41** and **C42**, respectively, outperformed, providing cycloadducts with high yields. The presence of 4 Å molecular sieves in the reaction mixture allowed to diminish the catalyst loading down to 1 mol% without deteriorating the enantioselectivity nor the reactivity. The transition structure **TS13** was proposed to explain the observed stereoselectivity.

A rather spectacular demonstration of multiple H-bonding interactions within thiourea-tertiary amine catalyst was reported by Clayden laboratory in the context of the conjugate addition of malonates to nitroolefins selected as model reaction (Scheme 29).[61] While the moderate enantioselectivity achieved makes this method unpractical at the present stage of development, the study shows how critical a single additional H-bonding unit within catalyst structure may be regarding conformation of the whole catalyst molecule. As the conformational switch between **C43** and **C44** in Scheme 29 shows, insertion/deletion of a NH amide unit in a thiourea-terminated oligopeptide may cause foldamer twist leading to a reversal of the sense of enantioinduction.

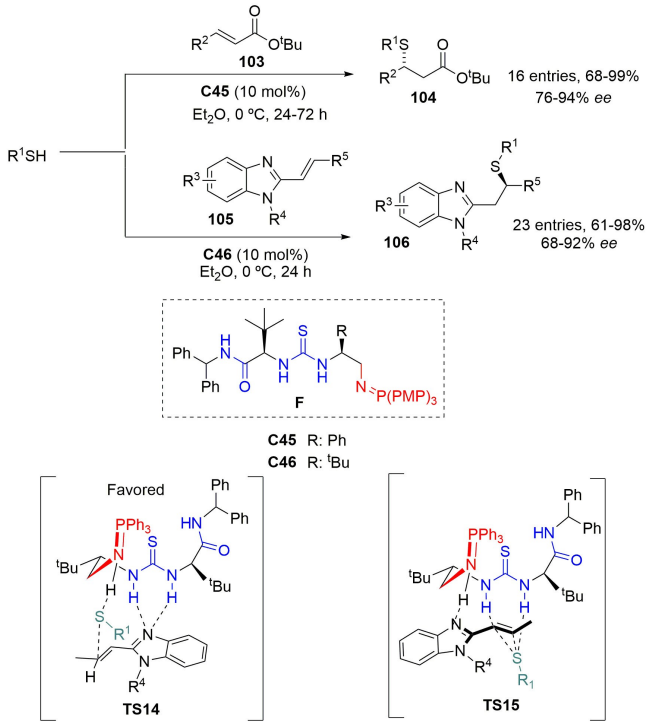
Dixon group further explored the potential of thiourea-amide-based catalysts by incorporating to the catalyst structure an iminophosphorane unit as in **F** (Scheme 30). Stronger organic bases may deprotonate pronucleophiles to a greater extent, thus increasing the actual nucleophile concentration in solution and broaden the repertoire of suitable nucleophile/electrophile combinations. The realization of the highly enantio-



Scheme 28. Multiple amide-containing thiourea-base catalysts for preparing polyfused heterocyclic compounds **101** bearing five consecutive stereocenters. Liu, 2019.[60]



Scheme 29. H-Bonds mediated conformational switch on oligopeptidic catalyst as a base for programable reaction enantioswitch. Clayden, 2016.[61]

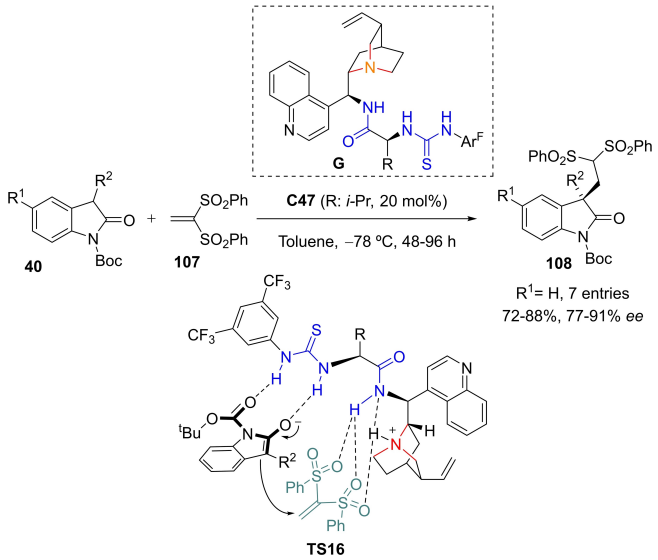


Scheme 30. Multi H-bond donating thioureas bearing an iminophosphorane as BB for the sulfa-Michael addition to unsaturated esters **103** and alkenyl benzimidazoles **105**. Dixon, 2017, 2018.[62,63]

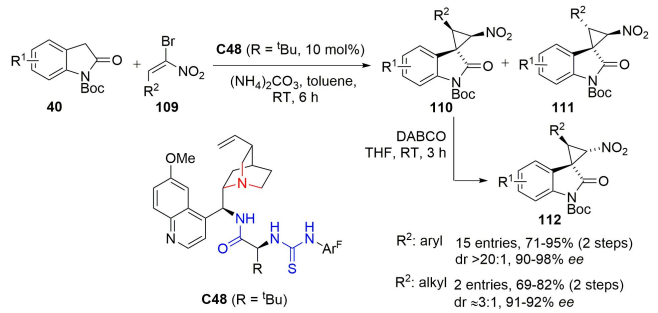
selective conjugate addition of thiols to simple α,β-unsaturated esters **103**, which are recalcitrant Michael acceptors in asymmetric organocatalysis, is a powerful illustration (Scheme 30).[62] The bifunctional iminophosphorane (BIMP) **C45**, which is prepared in situ by treatment of the corresponding chiral azide with a triarylphosphine, was able to promote the reaction with a variety of alkyl thiols quite efficiently to lead to products **104** in high yields and enantioselectivities usually high. Both the amide-thiourea moiety as the H-bond donor group and tris-(4-methoxyphenylphosphine) derived iminophosphorane as the Brønsted basic group were crucial for optimum catalyst performance. The high activity and versatility of this family of chiral organo-superbases was further demonstrated in the context of direct sulfa-Michael addition of alkyl thiols to alkenyl benzimidazoles **105**, most frequently *N*-tosyl benzimidazoles. Using **C46** as the catalyst, this reaction led to products **106** with high yields in most cases and enantioselectivities up to 98% *ee*.[63] During reaction optimization it was observed that the parent thiourea-iminophosphorane catalyst lacking the amide group imparted attenuated selectivity, and that both stereocenters on the new family of multiple H-bonding catalyst have an impact on the level of stereoinduction. In addition, the reaction proved to be solvent-sensitive, with THF and, in most cases, Et_2O being the optimum solvent. The authors investigated by DFT calculations the origins of the reaction enantioselectivity considering the most usual coordination patterns with these Brønsted base catalysts, the so-called Takemoto's[64] and Pápai's[65] models. In Takemoto's coordination geometry the nucleophile interacts with the protonated Brønsted base and the electrophile coordinates to the thiourea NHs via H-bonding. In its turn, in Pápai's coordination mode the nucleophile coordinates to the thiourea NHs while the electrophile interacts with the protonated Brønsted base. For the reactions in Scheme 30, **TS14**, (Takemoto's model) was found to be energetically more favorable than **TS15** (Pápai's model) in 4.3 kcal/mol.

The amide-containing thiourea-organobase systems described until now all feature an amide-thiourea-Brønsted base (A-TU-BB) connectivity pattern as represented by topology **I**. Amide-containing bifunctional catalysts that follow the complementary TU-A-BB arrangement (topology **II**) have also been developed. In 2010, Lu designed a new subfamily of thiourea-amide systems, namely **G**, in which the amide function is intercalated between the thiourea group and the tertiary amine unit, this latter accessible from cinchona alkaloids. In a first demonstration of this subtype of catalysts, the highly enantioselective Michael addition of 2-oxindoles **40** to vinyl bis(sulfones) **107** was achieved (Scheme 31).[66] While the reaction with α-aryl 2-oxindoles **40** (R^2 = aryl) could be performed with known bifunctional amine-thiourea catalysts in highly enantioselective fashion, the α-alkyl derivatives proved to be more challenging leading to poor selectivities. However, using catalyst **C47** even these latter substrates afforded adducts **108** in high enantioselectivity, further underlying the benefits of catalysts bearing various H-bond donors. Transition state model **TS16** nicely matches the observed configuration of products and underlines the role played by the amide NH in merging both reactants during transition state.

Two years later, Lu and co-workers reported a catalytic Michael-intramolecular alkylation cascade involving α-bromo nitroolefins **109** and 2-oxindoles **40** to give spiranic cyclopropanes **110** and **111** as major products (Scheme 32).[67] For this reaction, catalyst **C48** proved to provide the highest enantiocontrol. However, extensive additive and solvent studies were required to achieve useful levels of **110**:**111**:**112** products ratio. Finally, using 5 Å molecular sieves in $CHCl_3$ as solvent, in



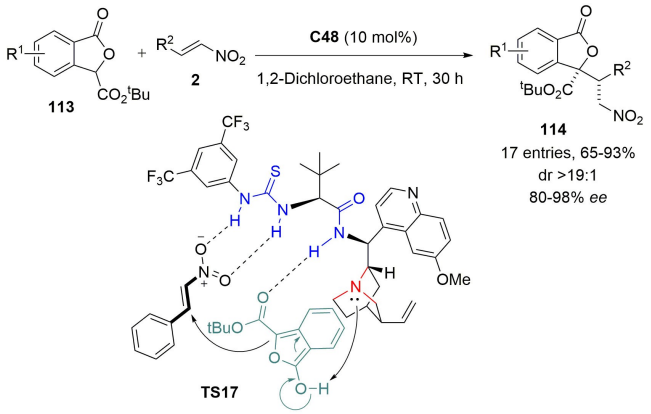
Scheme 31. Enantioselective Michael addition of 2-oxindoles to vinyl bis(sulfone) promoted by thiourea-amide organocatalysts. Lu, 2010.[66]



Scheme 32. Stereodivergent synthesis of spiranic cyclopropanes **110**–**112** promoted by thiourea-amide alkaloid derived **C48**. Lu, 2012.[67]

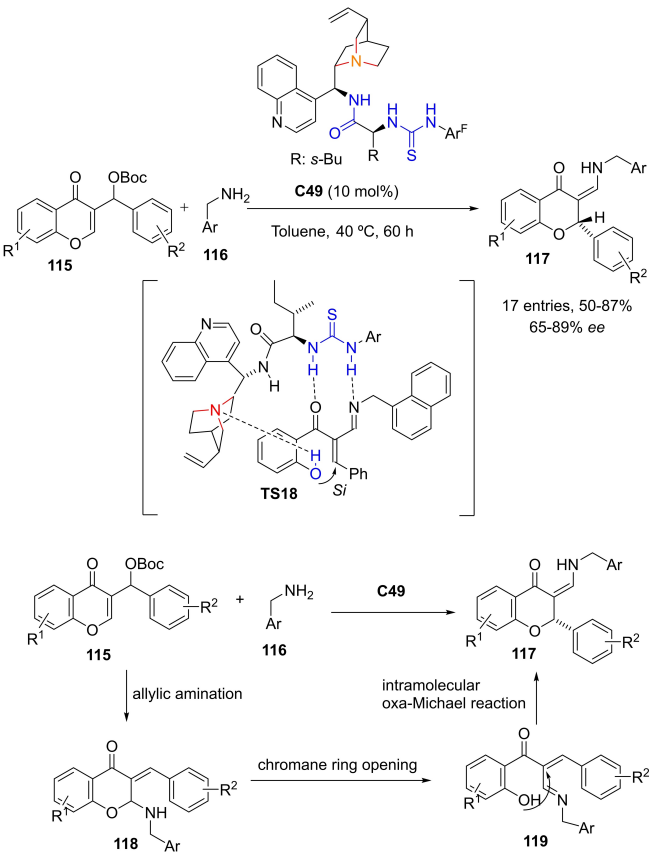
the presence of stoichiometric $(NH_4)_2CO_3$ as acid scavenger, allowed to shift the reaction towards isomer **110** in variable yields, but high selectivity and very high *ee* values for most cases. Importantly, it was found that base-promoted epimerization of **110** to **112** was feasible, especially with nucleophilic bases. This second process was most effective with DABCO in THF, which lead to a one-pot two-step access to compounds **112**. Thus, a highly enantioselective and diastereodivergent entry to either isomer **110** or **112** was uncovered.

Soon thereafter, the same group applied catalyst **C48** to the Michael addition of phthalide derivatives **113** to nitroolefins leading to products **114** as essentially single isomer in highly enantioselective fashion (Scheme 33).[68] A transition-state model **TS17** was proposed in which both the thiourea and amide groups of the catalyst are involved in H-bonding to both reactants during the carbon-carbon bond forming event. Strinckingly, the hydrogen bonding matching between nucleophilic/electrophilic reactants and the catalyst in model **TS17** is just the opposite to that proposed in **TS16** (Scheme 31).



Scheme 33. Michael addition of phthalide derivatives **113** to nitroolefins promoted by **C48**. Lu, 2013.[68]

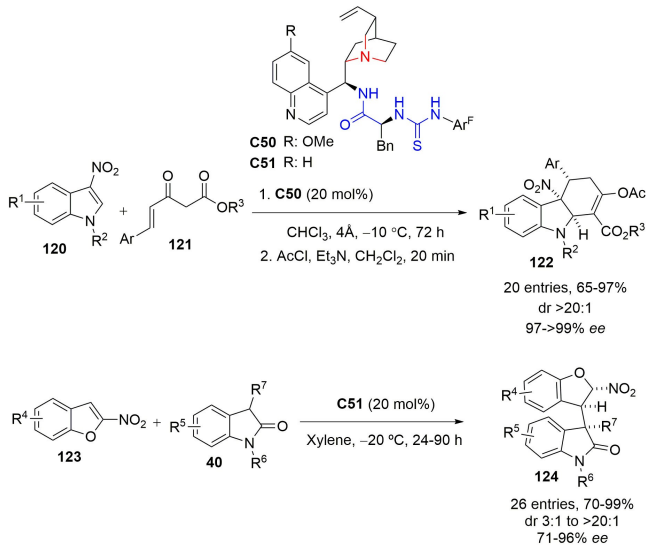
In parallel studies Liu, Chen and co-workers applied this type of catalyst to an *N*-allylic amination-ring opening-oxa-Michael cascade process starting from chromone-derived Morita-Baylis-Hillmann (MBH) carbonates **115** (Scheme 34).[69] The cascade process, the racemic version of which was previously described feasible under $In(OTf)_3$ catalysis by same authors, resulted also amenable for bifunctional catalysis. However, common tertiary amine-thioureas led to products **117** with only



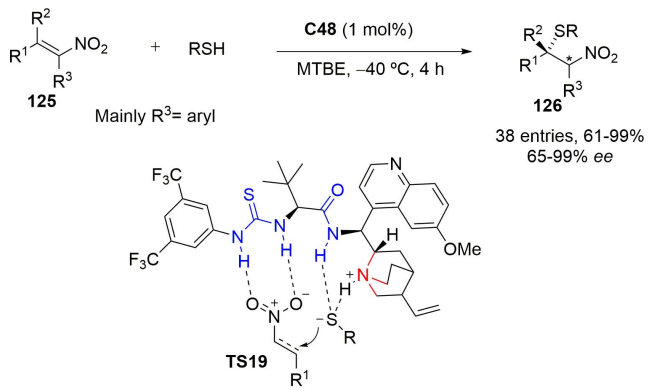
Scheme 34. *N*-allylic amination-ring opening-oxa-Michael cascade process promoted by thiourea-amide catalyst **C49**. Liu and Chen, 2013.[69]

moderate enantioselectivity. Gratifyingly, multifunctional cinchonidine-derived thiourea-amides proved superior catalysts with **C49** leading to the highest enantioselectivity. According to the author's proposal, in the first step, the amine attacks the MBH carbonate allylic position activated by the thiourea-type catalyst providing **118**. Subsequently chromane ring opening would afford intermediate **119**, which then would undergo an intramolecular oxa-Michael addition. In this last step the tertiary amine would assist the OH group deprotonation while the thiourea NHs would coordinate to the carbonyl and imine N inducing *Si* face attack (proposed **TS19**). However, no specific role is assigned to the NH group of the amide function.

Yuan and coworkers studied this type of cinchona alkaloid-derived multiple H-bonding thiourea-amide catalysts in the context of addition reactions involving benzo-fused heterocyclic systems (Scheme 35). In a first development, the cinchonidine-derived thiourea-amide **C50** was the optimum catalyst to promote the dearomative formal [4 + 2] cycloaddition between 3-nitroindoles **120** and Nazarov reagents **121**.[70] Hydrocarbazole skeletons **122** were obtained with generation of three new stereocenters in essentially perfect diastereo- and enantiomeric control. Comparative experiments using as catalysts analogs lacking either NH amide or thiourea groups led to substantially lower reactivity and selectivity, supporting the need of cooperative multiple H-bonding interactions for high stereoselectivity. In a subsequent development, authors identified the quinine-derived thiourea-amide system **C51** as the best catalyst to trigger the dearomative addition of 2-oxindoles **40** to 2-nitrobenzofurans **123**.[71]



Scheme 35. Dearomative reactions involving benzo-fused heterocyclic systems promoted by amide containing thiourea-bases. Xu & Yuan, 2017. Zhao and Yuan, 2020.[70,71]

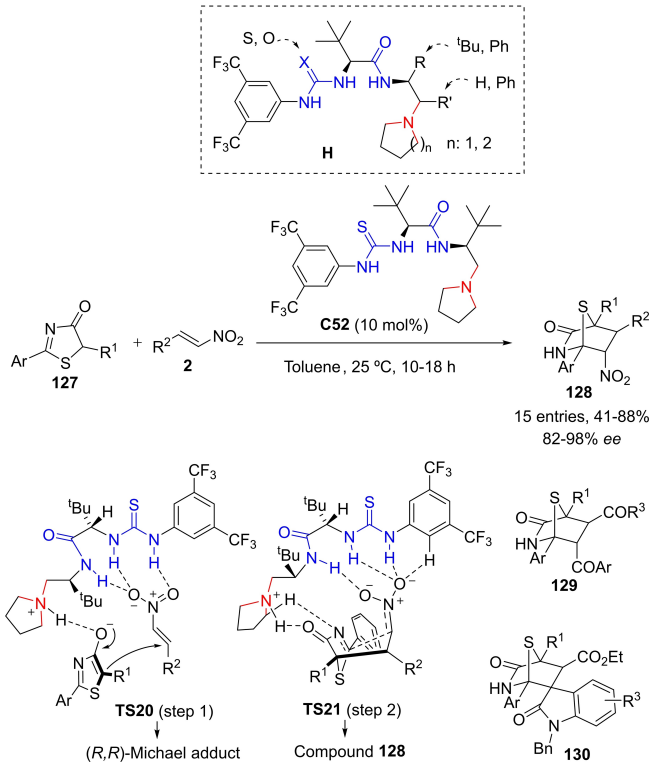


Scheme 36. Enantioselective addition of arenethiols to nitroolefins promoted by multi H-bond donating **C48**. Peng, 2017.[72]

Recently, Lu's catalyst has been applied by Peng and coworkers to an enantioselective addition of arenethiols to substituted nitroolefins **125** (Scheme 36).[72] Several catalytic and enantioselective methods were available for the addition of alkylthiols, but highly enantioselective methods suitable for direct addition of aryl thiols remained rare. Since the resulting sulfa-Michael adducts **126** tend to racemize at ambient temperature, cryogenic conditions were required for both the reaction and the products purification aftermath. The high activity of multiple H-bonding catalysts such as **C48**, even at low temperatures and low catalyst-loading, was a key for success. In the proposed **TS19** by the authors the amide NH coordinates to the thiolate nucleophile.

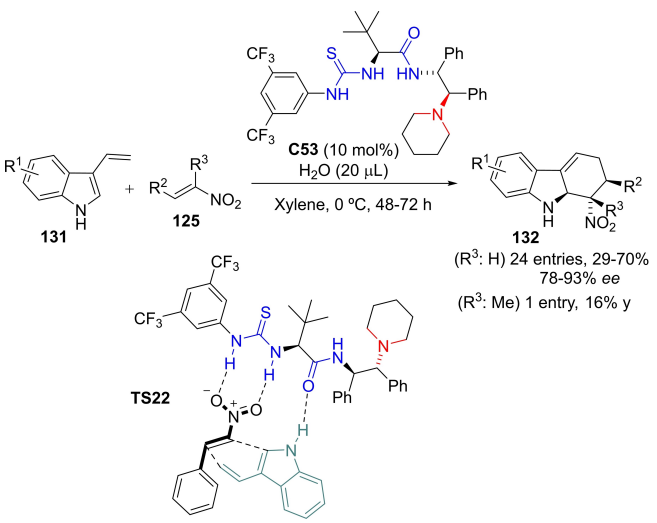
Complementing the above thiourea-amide molecules with TU–A-BB type arrangement derivable from cinchona alkaloids, similar multifunctional catalysts have been designed starting from other chiral cyclic and acyclic 1,2-diamine scaffolds. In this context, Lee, Jiang and coworkers designed dipeptide-based catalysts of general structure **H** derivable from *tert*-Leucine and the corresponding 1,2-diamine moiety (Scheme 37). Formal [4 + 2] annulation of 5*H*-thiazol-4-ones **127** and nitroalkenes to yield 1,4-sulfur bridged piperidones and their derivatives **128** could be carried out with good yields and excellent enantioselectivity with **C52** as a catalyst.[73] DFT calculations on model reaction are compatible with a two-step process involving first Michael-type addition via **TS20**, followed by an intramolecular diastereoselective nitro-Mannich addition via **TS21**. For the Michael addition step four pathways leading to adducts with both (*S*,*S*)- and (*R*,*R*)- configurations according to Takemoto's and Pápai's binding modes were calculated. Among them, **TS20** was found to be the lowest in energy. Furthermore, the authors found that this first step was not the rate determining one. For the second step (intramolecular Mannich reaction) **TS21**, featuring an amide-nitro NH…O H-bonding, is the most kinetically dominant route ($\Delta G^{\neq} = 18.5$ kcal/mol) among all the other possibilities, including the competing protonation reaction. This type of reactivity could be further extended to other dienophiles, opening new stereocontrolled entries to sulfur-containing complex products like **129** and **130**.

Recently, Guo laboratory reported a Diels-Alder cycloaddition reaction between 3-vinyl indoles **131** and substituted nitroolefins **125** promoted by multifunctional thiourea-amide-tertiary amine catalysts leading to cycloadducts **132**.[74] Among various thiourea-amide molecules, including some derived from quinine, **C53** provided the highest enantioselectivity, and



Scheme 37. Formal cycloaddition of 5H-thiazol-4-ones **127** and nitroalkenes promoted by thiourea-amide catalyst **C52**. Lee & Jiang, 2016.[73]

further fine tuning of solvent and conditions led to identify xylene as the solvent of choice along with trace amount of water as additive. Although no conclusive, some control experiments led the authors to suggest the catalyst amide moiety acting as an H-bond acceptor through its C=O moiety rather than H-bond donor through NH (see model **TS22** in Scheme 38).

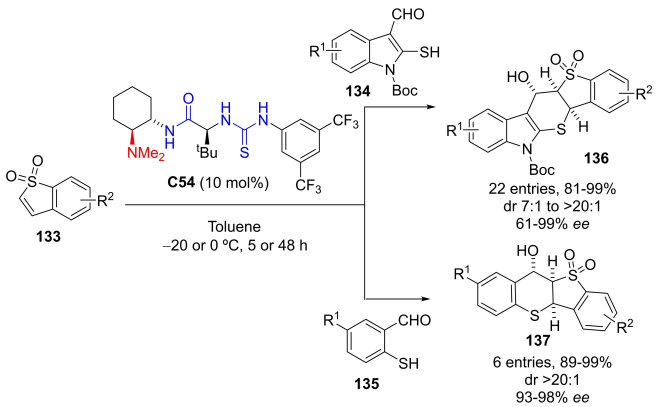


Scheme 38. Diels-Alder reaction between 3-vinyl indoles **131** and nitroolefins promoted by organocatalyst **C53**. Guo, 2019.[74]

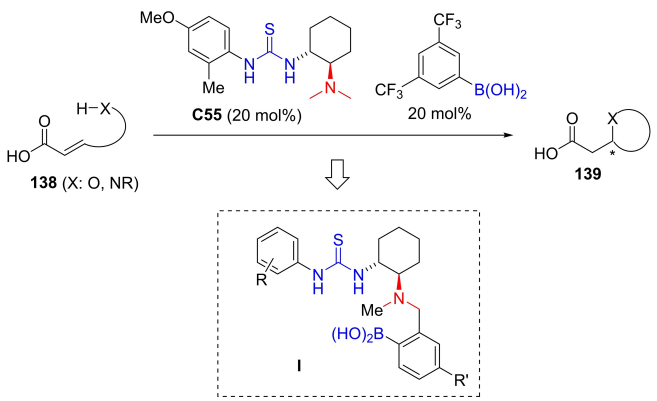
In another recent development, Yuan group reported organocatalyzed tandem sulfa-Michael/aldol reactions between unsaturated sulfolanes **133** and aromatic 1,2-mercapto aldehydes **134** and **135** to access dihydrothiopyran-fused benzosulfolane skeletons **136** and **137**, respectively (Scheme 39).[75] Screening of various related multifunctional molecules led to identify **C54** as the best catalyst, affording the respective products in high yields, diastereo- and enantioselectivities.

2.4. Thiourea-boronic acid systems

In 2016 Takemoto introduced a new amine-thiourea bifunctional catalyst family featuring an organoboronic acid side-arm as additional H-bond donor group, represented by general structure **I** (Scheme 40).[76] The capacity of boronic acids to activate carboxylic acids was previously known in the literature, presumably operating through formation of intermediate mixed anhydride (an acyloxyboronate complex is formed). On this basis, initially Takemoto developed a dual catalysis approach for the intramolecular addition of tethered *N*- and *O*-centered nucleophiles to unsaturated carboxylic acids.[77] That first



Scheme 39. Thiourea-amide structures based on cyclic 1,2-diamines to promote tandem reactions leading to dihydrothiopyran-fused benzosulfolane skeletons **136** and **137**. Yuan, 2020.[75]



Scheme 40. Combining thiourea/amine and boronic acid activation modes. From dual catalysis to bi(multi)functional catalysis. Takemoto, 2014–2016.[76,77]

realization, which required high loading (20 mol%) of each catalyst component, then evolved into the idea of merging both components in the same catalyst molecule, as in **I**.

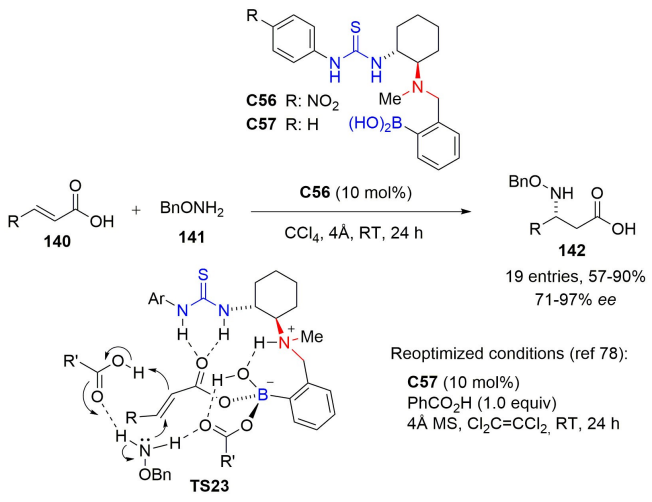
The successful realization of this idea was demonstrated first in the addition reaction of *O*-benzylhydroxylamine **141** to α,β-unsaturated carboxylic acids **140** (Scheme 41).[76] During optimization of catalyst structure, it was observed that the *N*-(4-nitrophenyl) thiourea termination, i.e. **C56**, performed superior than the most commonly used *N*-bis(trifluoromethyl)phenyl thiourea termination. From the point of view of practicality and for safety reasons, the need to use CCl_4 as solvent is a drawback of the method. However, selectivities from moderate to very good were obtained for most cases, which is remarkable considering the fact that free carboxylic acids are employed as substrates. Control experiments using dual catalysis approach instead of catalyst **C56** led to drastically diminished enantioselectivities, further stressing the advantage of using integrated catalysts. Ulterior spectroscopic analysis and detailed kinetic studies of this catalytic process revealed a mechanism more intricate than expected and allowed for reoptimization of the experimental protocol.[78] Thus, more than one discrete molecule of carboxylic acid was involved in key reaction intermediates, which could be experimentally translated in dramatic improvement in product enantioselectivity with the addition of 1 equivalent of benzoic acid. Also, more environmentally friendly halogenated solvents could be used. In addition, catalyst **C57** proved superior and addition of molecular sieves was found critical in generating the ternary borate complexes, which were crucial for obtaining high enantioselectivity. The method was applied to the first chemical enantioselective synthesis of *N*-hydroxyaspartic acid derivatives through regioselective addition of *O*-benzylhydroxylamine to fumaric monoacids.[79] In the transition state proposed by the authors (**TS23**) a H-bonding network with participation of the boronic acid OH group, is key for structure rigidification/stabilization.

During further validation of the present multifunctional thiourea-boronic acid catalyst system, Takemoto group found that the catalyst is competent in promoting the conjugate addition reaction of thiols to unsaturated carboxylic acids. Moreover, it was found that the addition reaction may follow enantiodivergent pathways depending on the solvent employed.[80] As shown in Scheme 42, while nonpolar solvents, for example CCl_4, led to *S*-configured product **144** in the presence of catalyst **C57**, aprotic polar solvents, for example acetone, led to *R*-configured product in the presence of **C58**. Based on spectroscopic data, including detection by mass spectroscopy of the 1 : 2 complex between the catalyst and the unsaturated acid, authors proposed each pathway to proceed through a distinct boron coordination mode. In one case the unsaturated acid would adopt a *s*-trans conformation (**TS24**), with a *s*-cis conformation being adopted in the other (**TS25**).

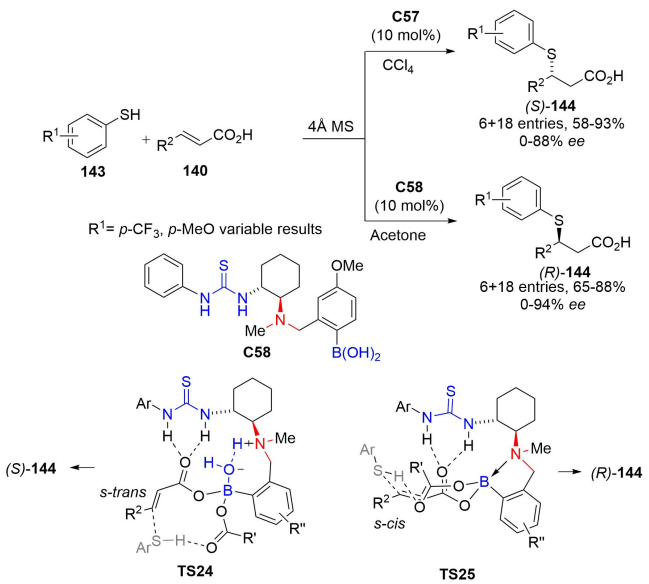
The usefulness of this catalyst system has been extended to the protonation of in situ generated enolate species, such as those formed upon conjugate addition of hydroxylamines to α-aryl acrylic acids (Scheme 43).[81] This reaction could be triggered by the thiourea-boronic acid catalyst **C59** in *p*-chlorotrifluoromethylbenzene with variable levels of enantioselectivity. Here, while the rate-limiting step appears to be the C–N bond forming step, product configuration is set during the subsequent protonation. The transition-state model **TS26** was proposed by authors to justify the configuration of major enantiomer. The method was applied to a short enantioselective synthesis of (−)-nakinadine B.

2.5. Thiourea-(thio)urea systems

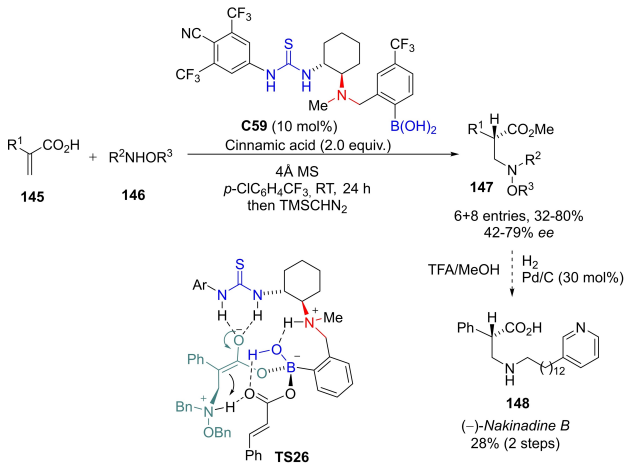
Bifunctional base/H-bonding catalysts featuring thiourea-thiourea (bis-thiourea) and thiourea-urea systems have also been



Scheme 41. Addition of *O*-benzylhydroxylamine to α,β-unsaturated carboxylic acids promoted by new chiral thiourea-amine-boronic acid systems. Takemoto, 2016–2019.[77–79]



Scheme 42. Boronic acid-BB thioureas for the enantiodivergent sulfa-Michael addition of thiols to unsaturated carboxylic acids. Takemoto, 2020.[80]

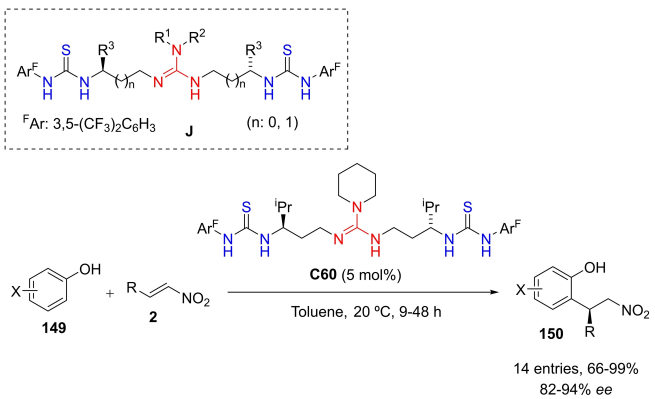


Scheme 43. Conjugate addition of hydroxylamines to α-aryl acrylic acids promoted by **C59**, and subsequent transformation of the obtained chiral product into (-)-nakinadine B. Takemoto, 2021.[81]

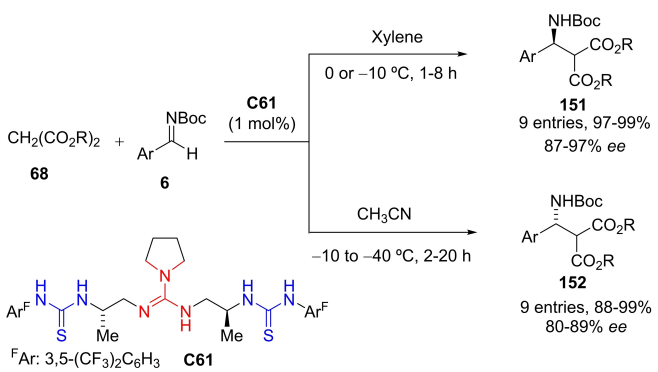
developed. Based on previous observations on the effectiveness of dual catalysis using a combination of amine bases and bis-thioureas on MBH-type reactions,[82] and also the unique catalytic properties of *C*2-symmetric guanidinium-bisthiourea under phase-transfer conditions,[83] Sohtome and Nagasawa developed carbon-linked guanidine/bisthiourea catalysts of general structure **J** (Scheme 44). Authors first applied these new multifunctional catalysts to the Friedel-Crafts type 1,4-addition reaction of phenols and naphthols **149** with nitroolefins **2**. Extensive optimization of catalyst structure for this reaction suggested both six-membered ring containing the guanidine moiety and the α-branched alkyl substituent on the chiral spacer are crucial for the achievement of high levels of asymmetric induction. With **C60** identified as the best catalyst, the *ortho*-addition adducts **150** were obtained in generally good yields and high enantioselectivity.[84] Kinetic studies provided evidence that differences in the activation entropies play a main role in the stereodiscrimination of this catalytic reaction. It was also observed that high levels of enantioselectivity are attained over a wide temperature range (optimum at 20 °C), making the reaction operationally simple.

The above finding that stereodiscrimination is governed by differential activation entropy rather than differential activation enthalpy opened the possibility of dynamic control over the reaction stereochemical outcome. This idea crystallized in a solvent-dependent enantiodivergent Mannich reaction between *N*-Boc aldimines **6** and malonates **68** (Scheme 45). The reaction catalyzed by 1 mol% guanidine/bisthiourea **C61** afforded either adduct **151** or **152** in high yields and enantioselectivity when using nonpolar solvents (e.g. xylene) and polar aprotic solvents (e.g. acetonitrile), respectively.[85] More detailed kinetic data suggested that the solvent-dependent enantioswitch may be explained assuming entropy differences are determinant in the former solvents while enthalpy differences in the latter. The data also suggested that the stereo-determining steps in both (*R*)- and (*S*)-selective Mannich reactions are governed by cooperative effect of guanidine and thiourea and that both enantiodivergent pathways follow similar mechanisms. Based on this principle, a sequential enantiodivergent process was discovered which allows enantio-switching with single-flaks operation and high in situ tunability.[86]

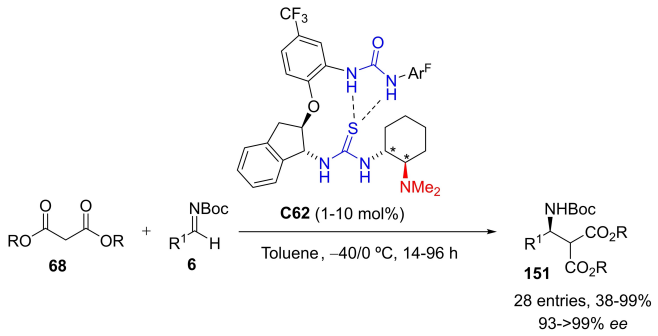
The impact additional H-bonding donor units installed within a bifunctional amine-thiourea system have during catalysis is well recognized. However, whether these units interact directly with the reactant(s) or just do it internally within the catalyst, tuning its conformation and electronics, remains unanswered for the majority of cases. In 2012 Pihko reported purposefully designed thiourea-urea systems like **C62** (Scheme 46) and demonstrated that in these systems the H-bonds established internally between each urea NH site and thiourea sulfur atom are maintained intact during catalysis.[87] **C62** efficiently catalyzes the Mannich reaction of malonates with *N*-Boc aldimines affording products **151** in high yields for most cases and very high *ee* values. Analogs of **C62** derived from different 1,2-diamines and 1,2-aminols were prepared and evaluated, but **C62** resulted the most active and selective owing probably to an optimum structure preorganization. Combination of crystal X-ray determination and solution NMR studies



Scheme 44. Design of the new guanidinium/bis-thiourea catalyst subfamily **J** and its application in the asymmetric Michael addition of phenols to naphthols. Sohtome & Nagasawa, 2010.[84]



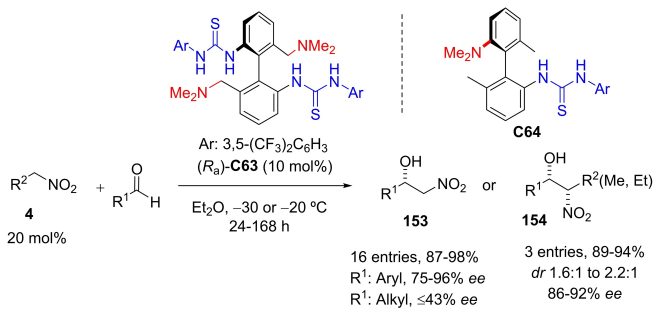
Scheme 45. Enantiodivergent Mannich reaction between *N*-Boc aldimines and malonates promoted by H-bond donating bifunctional guanidine **C61**. Sohtome & Nagasawa, 2010,2013.[85,86]



Scheme 46. Thiourea-BB catalysts bearing a demonstrated stabilizing intramolecular H-bond system for the enantioselective Mannich reaction of malonates. Pihko, 2012, 2019.[87,88]

along with model DFT calculations of both the catalyst alone and ion paired to anions were insightful.[88] In its native form, the catalyst folds through intramolecular H-bonds between the urea and thiourea units. This folding is maintained intact when forming catalytically relevant salts with larger anions that mimic the dialkyl malonate substrates. In contrast, with smaller halide anions it folds around the halide anion (anion receptor folding) and the intramolecular hydrogen bonds are disrupted. Interestingly, the catalyst dynamic refolding from the native to the anion receptor form was possible.

Bobal documented an ease to prepare *C*2-symmetric diamine-tethered bis(thiourea) organocatalyst **C63** for the asymmetric Henry reaction of nitroalkanes **4** and aromatic aldehydes (Scheme 47).[89] Products **153** were obtained with very high yields along with high selectivities. Not surprisingly, the reactions with superior nitroalkanes took considerably longer times for completion and afforded products **154** with diminished selectivity. Control experiments using as catalyst the parent "monomeric" amine-thiourea **C64** led to only marginal activity and selectivity. Another interesting feature of catalyst **C63** is that it can be recovered by precipitation of the oxalate salt upon addition of an ethereal solution of anhydrous oxalic acid to the reaction mixture and filtration.

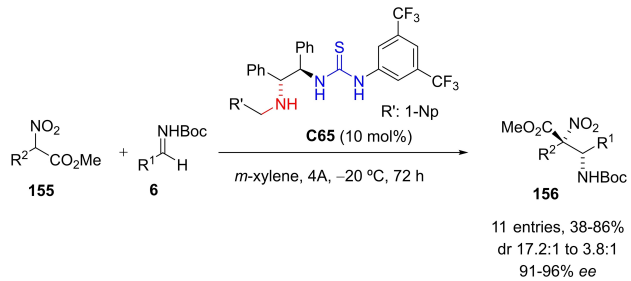


Scheme 47. Asymmetric reaction between nitroalkanes and aromatic aldehydes catalyzed by C2-symmetric bis-thiourea BBs. Bobal, 2017.[89]

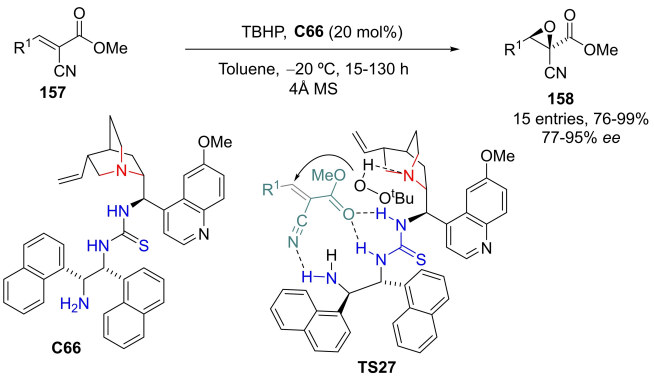
2.6. Thiourea-amine systems

Li and Chen have found that thiourea-tertiary amine bifunctional catalysts that are fruitful in various 1,2- and 1,4-addition reactions performed suboptimal in the nitro-Mannich reaction of α-substituted nitroacetates **155** and *N*-Boc aldimines **6**. Much to their surprise, they found that the corresponding secondary amine-thiourea analogs like **C65** performed comparatively superior.[90] Based on this observation, they concluded that the catalysts secondary amine unit plays a crucial role in the reaction transition-state other than merely acting as a Brønsted base. Upon optimization of the catalysts derived from 1,2-diphenylethanediamine, those bearing an $ArCH_2$ group attached to nitrogen (1-naphthylCH_2 was the best) led to consistently higher selectivity than catalysts with alkylCH_2 groups attached. Under optimal conditions, adducts **156**, bearing a tetrasubstituted carbon, were obtained in high diastereo-and enantioselectivity (Scheme 48).

In an unrelated development, Lattanzi and coworkers have showed that epoxidation reactions of challenging β-substituted α,β-unsaturated esters **157** with TBHP is promoted by thiourea-tertiary/primary diamine catalysts, affording epoxy adducts **158** as essentially single diastereomers and high enantioselectivity (Scheme 49).[91] Simple thiourea-tertiary amine catalysts could also promote the reaction but provided low enantioselectivity. Thus far, replacing the primary amine in the catalyst structure with a secondary amine or a hydroxyl group as alternative H-



Scheme 48. Thiourea-secondary amine combining catalyst **C65** for the nitro-Mannich reaction. Li & Chen, 2008.[90]



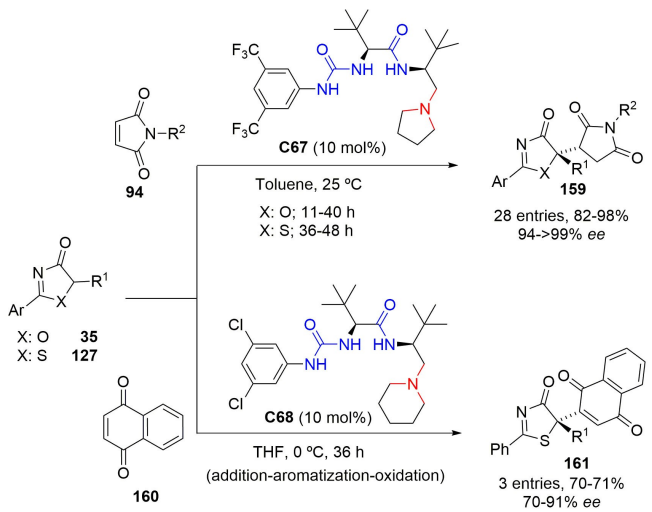
Scheme 49. Enantioselective epoxidaton of β-substituted α,β-unsaturated esters **157** promoted by thiourea BBs bearing a primary amine. Lattanzi, 2017.[91]

bonding sites dramatically depressed the efficiency and enantiocontrol through a complete loss of activity. The crucial importance of the NH_2 and the thiourea units in tuning the enantioselectivity was ascribed to cooperative H-bonding engagement with the cyano and ester groups, as shown in the scheme (**TS27**). While the method tolerated a broad range of differently substituted α-cyanocinnamates, the asymmetric induction appears to be highly dependent on the nature of the β-substituent and the ester groups.

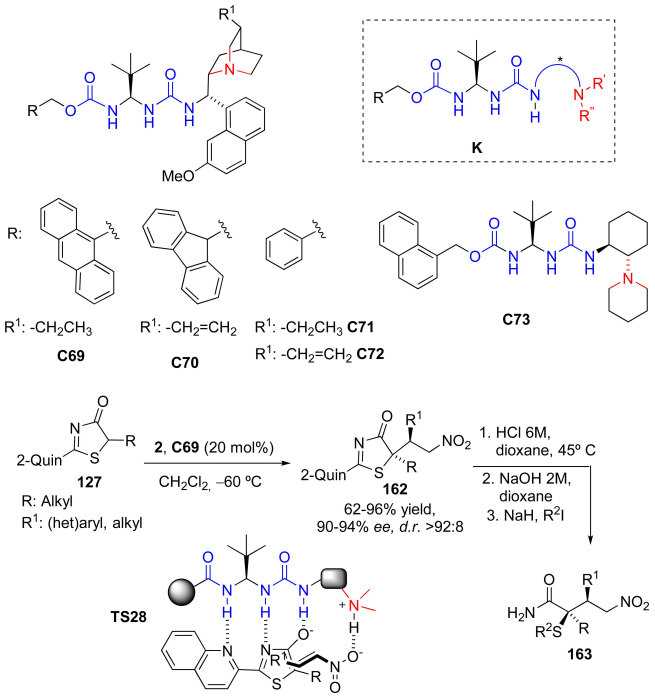
3. Urea-based Multifunctional Brønsted Base Catalysts

In comparison with multifunctional organobase catalysts based on thiourea unit, the urea analogs have been developed to a lesser extent, in part because the thiourea congeners provide superior efficiency and selectivity usually. However, this trend is not universal. Lee Liu, Jiang and co-workers documented organobase catalysts comprised of a urea-amide moiety as multiple H-bond donor system for triggering the asymmetric conjugate additions of 5*H*-oxazol-4-ones **35** or 5*H*-thiazol-4-ones **127** to maleimides **94**. These authors reported that the parent urea **C67** behaved as superior catalyst as compared with the corresponding thiourea congener, affording adducts **159** in excellent yield and selectivity (Scheme 50).[92] Further substrate exploration led to the finding that naphthoquinone **160** was also a competent substrate in the urea-amide-catalyzed addition-aromatization-oxidation cascade promoted by the analogous **C68** catalyst to yield adducts **161** in good yields and enantioselectivity.

The Palomo group developed urea-carbamate systems of general structure **K** as new bifunctional catalysts capable to interact to the reaction substrates through multiple H-bonds (Scheme 51). The new catalysts are easily tunable and prepared



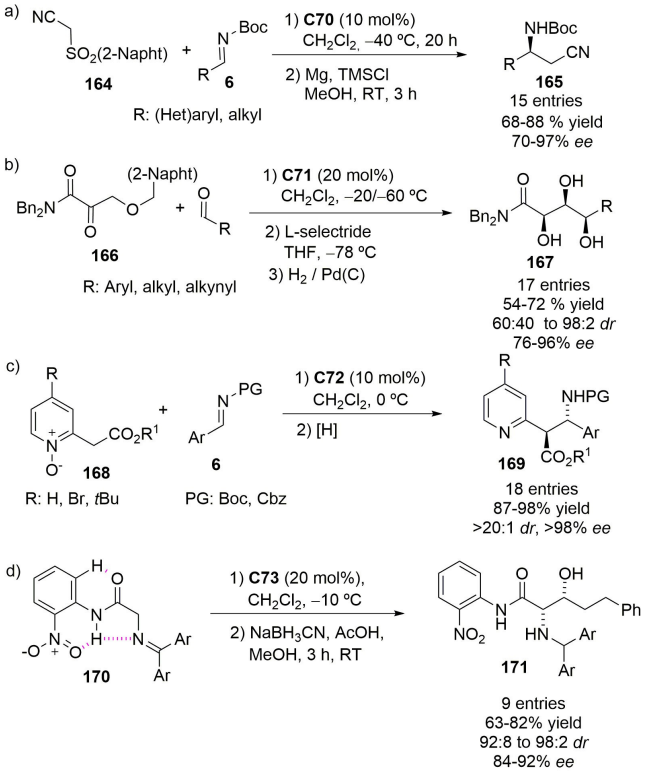
Scheme 50. Urea-amide bases employed to promote various Michael additions. Liu & Jiang, 2016.[92]



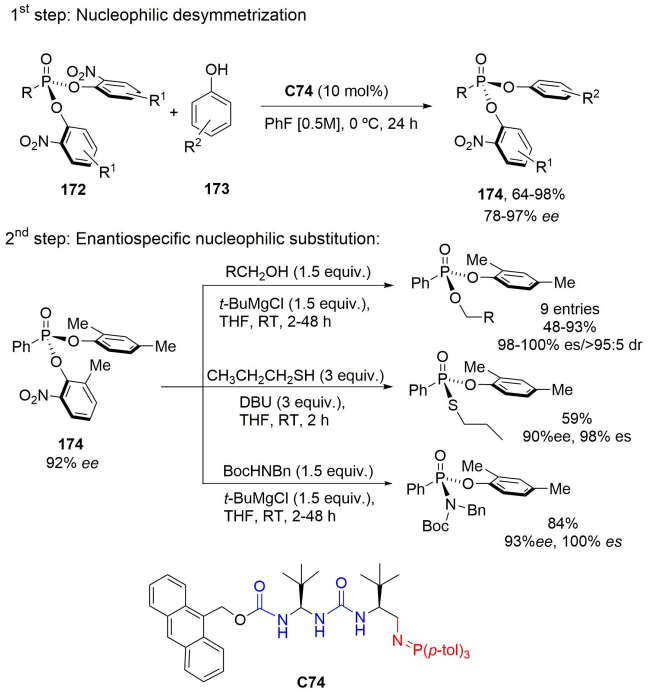
Scheme 51. First ureidopeptide-like BB catalysts described and the proposed four point-contact transition state for the addition of **127** to nitroolefins. Palomo, 2013.[93]

from the coupling of the corresponding cinchona alkaloid-derived amine (or related chiral amine) and α-amino acid-derived isocyanate, and have proven to be successful in promoting several carbon-carbon bond-forming reactions. The first successful application of this catalyst type is represented by **C69**, which demonstrated to be very efficient for the conjugate addition of thiazol-4-ones **127** to nitroalkenes **2**, which proceeded with high yields (lower for β-alkyl nitroolefins) and very high stereoselectivity. Ulterior elaboration of adducts **162** thus provides a new enantioselective route to otherwise difficult to prepare tertiary thiols and sulfides, as **163**.[93] The authors proposed a Pápai-type transition state **TS28** with the urea and carbamate three NH groups of the catalyst simultaneously H-bonded to the multidentate quinoline-thiazolone substrate, while the protonated quinuclidine nitrogen coordinates to the acceptor reagent.

As shown in Scheme 52, these type of catalysts performed exceedingly in several other addition reactions that involve donor substrates capable of bidentate H-bonding to the catalyst. These include the Mannich reaction of sulfonyl acetonitriles (Scheme 52a),[94] the aldol reaction of α-ketoamides with aldehydes (Scheme 52b)[95] and the Mannich reaction of pyridyl *N*-oxide acetates and aromatic imines (Scheme 52c).[96] More recently it has been found that this catalyst type are also efficient for the aldol reaction of Schiff bases of glycine o-nitroanilide and aldehydes (Scheme 52d).[97] In this case cyclohexyldiamine derived **C73** provided very good results thus demonstrating that fine tune of these structures can be easily accomplished. Control experiments using conventional bifunc-



Scheme 52. Described asymmetric reactions employing multiple H-bond donating ureidopeptide-like catalysts **C70**-**C73**. a,b,c) Palomo 2014–2017.[94–96] d) Mielgo & Palomo 2021.[97]



Scheme 53. Catalytic enantioselective desymmetrisation reaction of phosphonate esters promoted by the ureidopeptide-like BIMP catalyst **C74** and subsequent enantiospecific derivatization. Dixon, 2021.[98]

tional thiourea and squaramide bifunctional catalysts in the aforementioned transformations usually led to lower reactivity and/or stereoselectivity, thus indicating the importance of the additional H-bond donating group in catalysts of type **K**.

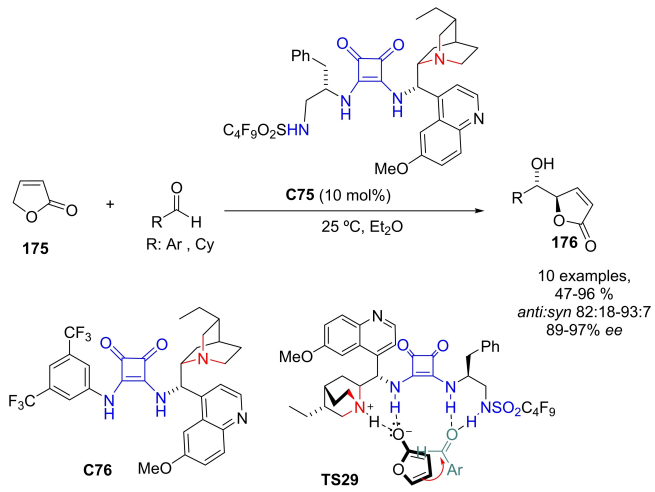
More recently Dixon described a novel two-stage strategy for the synthesis of stereogenic phosphorous (V) compounds through an unprecedented enantioselective nucleophilic desymmetrisation reaction and subsequent enantiospecific derivatization.[98] A novel bifunctional iminophosphorane (BIMP) catalyst bearing an urea-carbamate H-bond donor moiety (**C74**, Scheme 53) provided a unique chiral environment and sufficient pronucleophile activation to allow the desymmetrisation of derivatives **172** through reaction with phenols to proceed with excellent yield and enantioselectivity. Subsequent enantiospecific reaction of products **174** through S_N2 displacement of the nitrophenol leaving group with alcohols, thiols and amines as the nucleophiles affords different phosphorous derivatives in excellent enantiospecifity /diastereoselectivity. DFT studies on the desymmetrization step showed HB interactions between the three NH groups of the ureidoaminal catalyst and the substrate both P=O and nitro groups, thus revealing again the significant role of the additional H bond donor in the catalyst.

4. Squaramide-based Multifunctional Brønsted Base Catalysts

Since the first report by Rawal demonstrating the capability of squaramide unit to act as dual H-bond donor in bifunctional BB catalysis, many examples illustrating the often superior performance of this unit as compared to related H-bonding units, inter alia urea and thiourea, have appeared.[11] No surprisingly, catalysts comprised of a squaramide unit, a BB unit and additional H-bond donor function have been successfully developed. Main advances based on such multifunctional catalyst development are summarized below, the various examples being organized according to the nature of the additional HB donor group (sulfonamide, alcohol, amide).

4.1. Squaramide-sulfonamide systems

Bifunctional amine/squaramide catalysts bearing an additional sulfonamide group can also be useful for asymmetric catalysis. In this context in 2017 Hirashima and Miura introduced catalyst **C75** for the asymmetric vinylogous aldol reaction of furan-2-(*5H*)-one **175** with aldehydes to afford the corresponding aldol products **176** in high to excellent enantioselectivities (Scheme 54).[99] The stereoselectivity was significantly lower when the reaction was ran in the presence of catalyst **C76** lacking the sulfonamide moiety. The authors proposed a plausible transition state (**TS29**) wherein one of the NH groups of the squaramide together with the sulfonamide NH activate

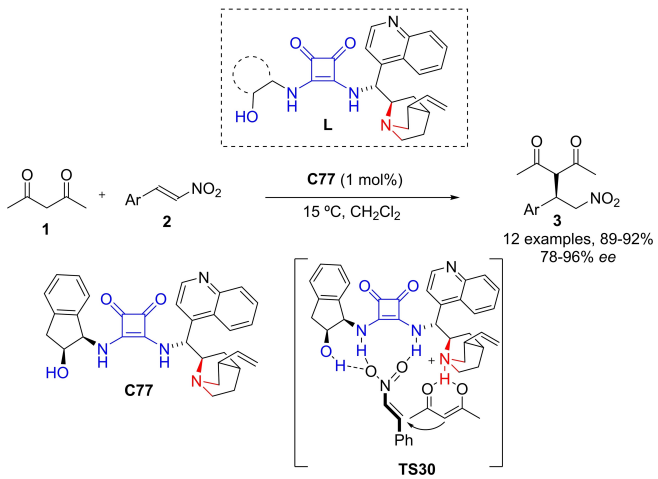


Scheme 54. Squaramide-sulfonamide BB catalyst for the direct vinylogous aldol reaction of furan-2-(*5H*)-one with aldehydes. Hirashima & Miura, 2017.[99]

the aldehyde and the protonated tertiary amine and the other NH group of the squaramide coordinate to the oxygen of the deprotonated furan-2-(*5H*)-one.

4.2. Squaramide-alcohol systems

In 2012 Dong described for the first time the synthesis of a series of new chiral bifunctional squaramide multiple H-bond organocatalysts by merging chiral privileged scaffolds of β-amino alcohols and cinchona alkaloids, as represented by **L** (Scheme 55).[100] The resulting catalysts incorporate a hydroxy functionality as an additional potential coordinating point for the substrates activation. The authors investigated these new structures in the Michael addition of acetylacetone to nitroolefins and, among all the tested derivatives and chirality

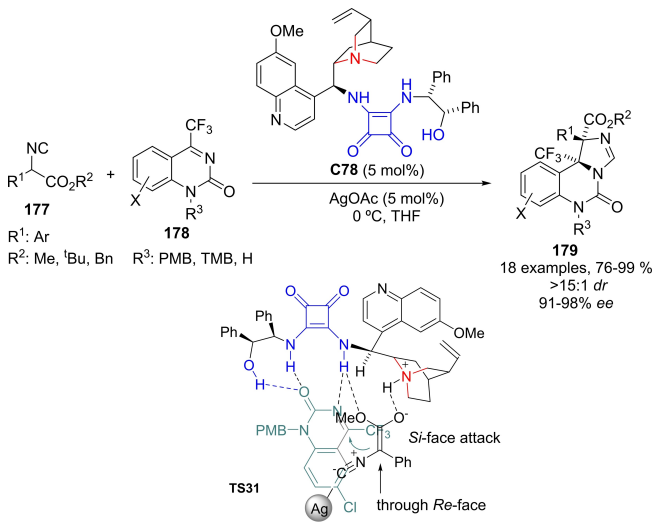


Scheme 55. Michael addition to nitroolefins promoted by a squaramide-aminoindanol derived BB. Dong, 2012.[100]

sources, 2-aminoindanol-derived squaramide-alcohol **C77** was found the optimum catalyst as the corresponding adducts **3** were afforded in excellent yields and *ee* values with only 1 mol% catalyst loading (Scheme 55). Heterocyclic olefins such as 2-furyl and 2-thienyl-nitroolefins were also tolerated, but gave inferior *ee* values (77% and 78%, respectively). In addition, 1,3-dicarbonyl compounds other than 1,3-diketones (i.e. β-ketoesters) were also employed as nucleophiles. Excellent yields and *ee* values and moderate diastereomeric ratios were observed in these latter cases. In the proposed TS by the authors (**TS30**) the squaramide N–Hs and the indanol O–H both activate the nitroolefin, whilst the protonated tertiary amine of the cinchona alkaloid coordinates to the 1,3-dicarbonyl substrate. The OH group in catalyst **C77** is key for attaining high stereoselectivity as the reaction using the *O*-Me analog instead proceeded in significantly lower *ee* (24% *ee*).

Inspired by the same general structure **L**, Zhao and Shi developed a cinchona alkaloid squaramide/AgOAc cooperatively catalyzed diastereo- and enantioselective Mannich/cyclization cascade reaction of isocyanoacetates **177** and cyclic trifluoromethyl ketimines **178** to afford optically active trifluoromethyl-substituted tetrahydroimidazo[1,5-c]quinazoline derivatives **179** in good yields, good diastereoselectivities and excellent enantioselectivities[101] (Scheme 56). The Ag (I) salt seems to be essential in the cooperative catalytic process to facilitate deprotonation of the isocyanoacetate through chelation. The incorporation of the OH functionality into the BB catalyst **C78** provides enantioselectivity improvement (Δ*ee* 11%) when compared with the analogous catalyst lacking this motif. The authors proposed transition state model **TS31** that accounts for the experimentally encountered stereoselectivity.

Catalysts that follow the general structure **L** but show a *trans*-cyclohexane-1,2-diamine basic unit instead of the cinchona fragment, have also been developed. In this context the squaramide-linked chloramphenicol based catalyst **C79** was

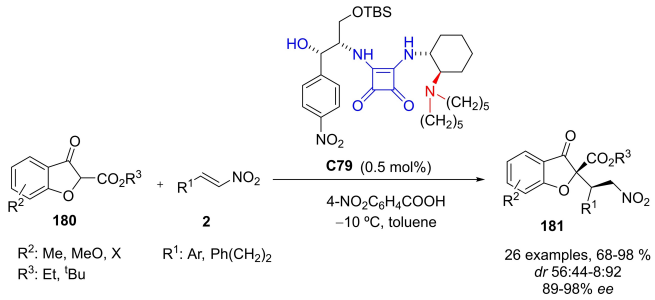


Scheme 56. Squaramide-alcohol cinchona derived BB/AgOAc cooperatively catalyzed Mannich/cyclization cascade reaction of isocyanoacetates and cyclic trifluoromethyl ketimines. Zhao and Shi, 2014.[101]

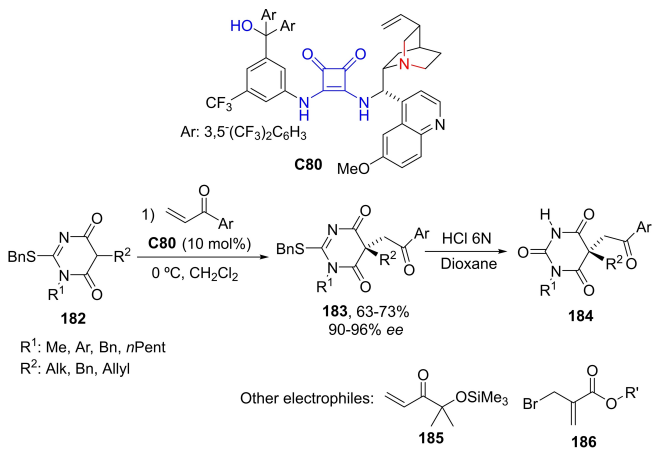
demonstrated effective in promoting the Michael addition of 2,3-dihydrobenzofuran-2-carboxylates **180** to nitroolefins.[102] Control experiments suggested that this catalyst was more efficient than the bifunctional catalysts lacking the amino-alcohol scaffold and that matching chirality between the two chiral scaffolds, namely the chloramphenicol and the 1,2-diamine, was key for having good reactivity and high stereoselectivity. Only 0.5 mol% catalyst loading was enough to produce 2,3-dihydrobenzofuran-2-carboxylate derivatives with a broad scope and in good yields, moderate to low diastereoselectivities and good to excellent enantioselectivities (Scheme 57).

Palomo's group has shown that a bifunctional squaramide multiple H-bond organocatalyst bearing a bulkier carbinol functionality (**C80**) is optimal for the enantioselective addition of barbiturate equivalents **182** to enones, giving rise, upon subsequent acidic hydrolysis, chiral barbiturates **184** with an in-ring quaternary stereogenic center (Scheme 58).[103] In contrast to the previously showed squaramide-alcohol catalysts, the only chirality source in catalyst **C80** comes from the cinchona moiety. Catalyst **C80** is also able to promote other highly enantioselective reactions of templates **182**, including their addition to the acrylate equivalent **185** and their S_N2' substitution reaction with the Morita-Baylis-Hillman-type bromides **186**. Control experiments using the *O*-TMS analog of **C80** led to reaction adducts with decreased enantioselectivity (Δee aprox. −20%), an observation in support of the relevant role played by the free OH group in the transition state.

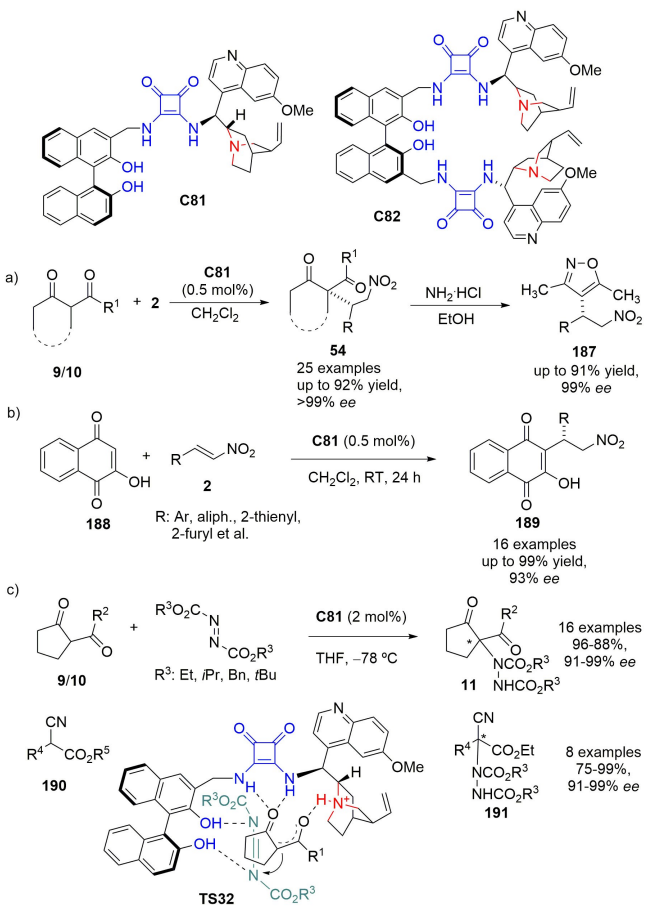
In the same context Dong's group developed a BINOL derived squaramide catalyst exemplified by **C81** that could function as multiple hydrogen bond donor. This catalyst is able to promote the Michael addition of 1,3-dicarbonyl compounds **9**/**10** to nitroolefins efficiently to afford adducts **54** in very good yields and excellent diastereo- and enantioselectivity (Scheme 59a).[104] Importantly, the BINOL catalyst performed well at only 0.5 mol% catalyst loading. The adducts **54** were transformed aftermaths into optically active isoxazole derivatives in high yield and with high enantioselectivity. The same catalyst **C81** was later screened in the Michael addition of 2-hydroxy-1,4-naphthoquinones **188** to nitroalkenes to afford products **189** in excellent yields and stereoselectivity at, again, low catalyst loading of 0.5 mol% (Scheme 59b).[105] Dong's group has also demonstrated the efficiency of catalyst **C81** for the α-amination of 1,3-dicarbonyl compounds **9**/**10** and α-cyanoacetates **190** with azodicarboxylates to obtain chiral α-amino acid precursors **11** and **191** respectively, the absolute configuration of which was not reported (Scheme 59c).[106] The



Scheme 57. Squaramide-linked chloramphenicol based hybrid catalyst in the Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins. Peng and Chen, 2018.[102]



Scheme 58. α-Functionalization of 2-alkylthio 4,6-dioxo pyrimidines catalyzed by a bulkier carbinol containing squaramide BB. Oiarbide and Palomo, 2017.[103]



Scheme 59. Enantioselective reactions promoted by BINOL containing squaramide-alcohol BBs **C81** and **C82**. Dong 2013–2015.[104–107]

catalyst can be recovered and reuse for four cycles without loss of activity and enantioselectivity. To explain the excellent enantioselectivity the authors propose the transition state **TS32** wherein the catalyst squaramide and cinchonine NH groups interact through three H-bonds with the 1,3-dicarbonyl moiety, while the two binaphthol OH groups activate through H-bonding the azodicarboxylate. Similar reactivity was observed when using the C_2-symmetrical catalyst **C82** instead, although enantioselectivities were slightly lower.[107]

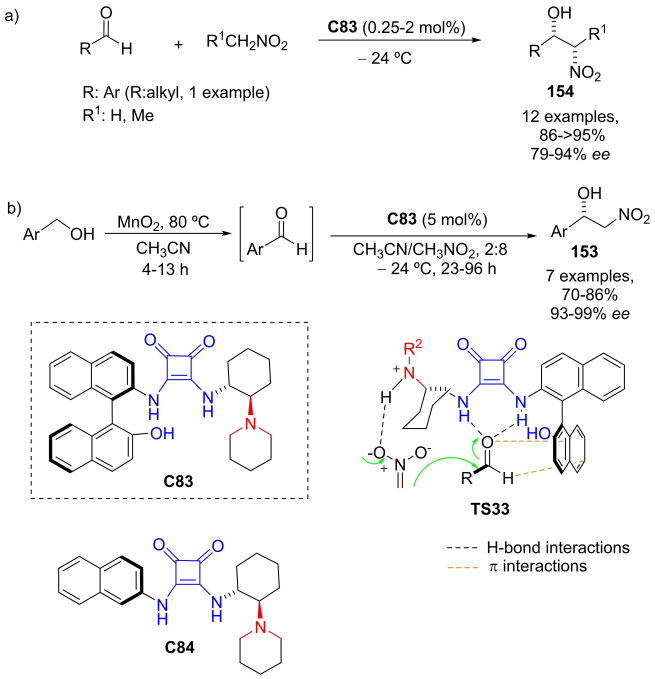
Catalyst **C83**, derived from 2′-amino-[1,1′-binaphthalen]-2-ol and *trans*-1,2-diaminocyclohexane was found by Herrera's group to promote the Henry reaction between nitromethane (or nitroethane) and aromatic aldehydes efficiently (Scheme 60a).[108] The reaction affords the corresponding aldols **154** in good yields and usually very good enantioselectivities in the presence of only 0.25 mol% of the catalyst, which represented at that moment one of the lowest catalyst loading used for this reaction. DFT calculations predicted the aldehyde gets activated by H-bonding to the squaramide NH groups and, at the same time, by π-interactions with the naphthyl moiety. Additionally, nitromethane gets activated through H-bonding to the protonated amine moiety (**TS33**). Curiously, no direct involvement of the catalyst OH group is predicted for this reaction.[109] When the same reaction was carried out in the presence of catalyst **C84**, the reaction proceeded more slowly and with lower selectivity too, presumably because of the inability of **C84** to display effective π-interactions. Later on, the authors implemented a one-pot alcohol oxidation/Henry reaction sequence starting from the corresponding alcohols and with MnO_2 as the oxidant (Scheme 60b).[110]

In 2016 Durmaz reported **C85** as a new class of multifunctional catalyst comprised of a chiral calix[4]arene and two squaramide/amine residues through an ether bond thus leaving two free hydroxyl groups available. This catalyst is able to trigger the enantioselective conjugate addition of acetylacetone to various nitroolefins **2** at room temperature to give the Michael adducts in moderate to excellent yields with good enantioselectivities (Scheme 61).[111] Control experiments confirmed the cooperative effect and special role of the calixarene moiety on the degree of enantioinduction.

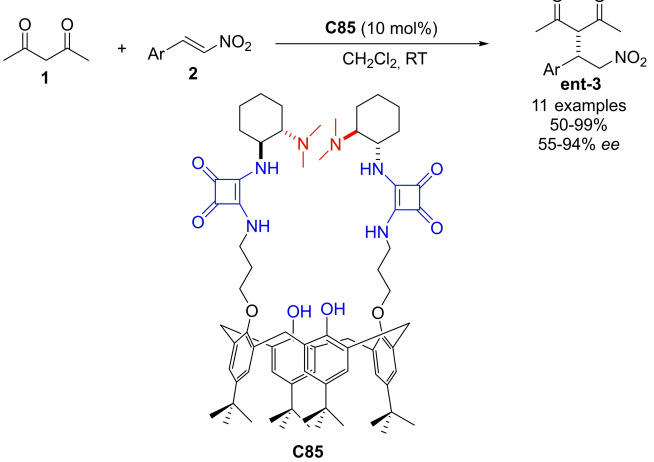
4.3. Squaramide-amide systems

α-Amino acids have also shown to be useful building-blocks for the construction of squaramide catalysts with multiple H-bonding sites. The incorporation of the amino acid unit onto the catalyst structure via amide bond results in various possible arrangements as illustrated in Figure 3. In 2019 Yan introduced catalyst **C86**, which incorporates a valine unit between the cinchona fragment and the squaramide motif (topology **II**).[112] This catalyst performed. well in the Michael addition reaction of α-amido sulfones **192** to ynones **193** to access axially chiral styrenes **194** (Scheme 62a). The products were obtained with moderate to good yields (44–99%), excellent enantioselectivity and almost complete *E/Z* selectivity (up to 97% *ee*, >20:1 *E/Z*). Catalyst **C86** was slightly superior in terms of enantioselectivity than the analogous catalyst carrying a thiourea motif instead the squaramide. Also important, conventional cinchona-thiourea based bifunctional catalysts lacking any additional amide NH behaved significantly worse.

Other amide-containing squaramide-organobase systems that follow topology **I** have also been developed, as illustrated in the next examples. For instance, in 2019 Zhao reported that *L-tert*-leucine derived catalyst **C87**, structurally related to **C86**, but changing the position of the amino acid unit was efficient in promoting the three-component reaction between γ-aryl-



Scheme 60. Henry reaction between nitromethane and aldehydes in the presence of BINOL-squaramide BB **C83**. Herrera, 2016–2018.[108–110]



Scheme 61. Calix[4]arene bis-squaramide **C85** promoted Michael addition of acetylacetone to nitroolefins. Durmaz, 2016.[111]

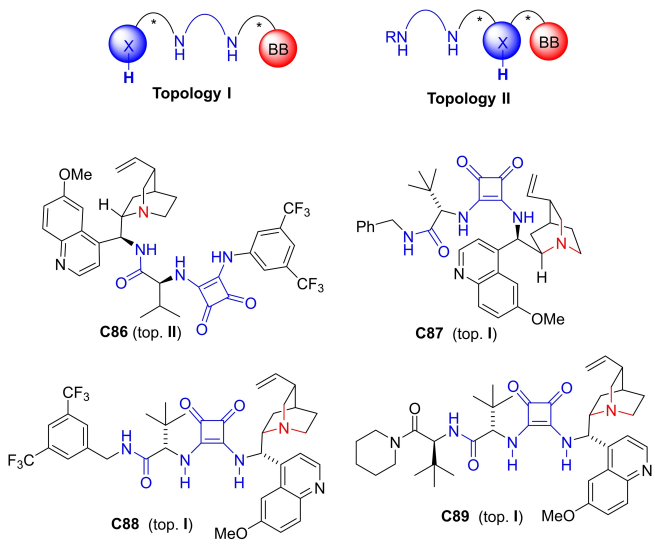
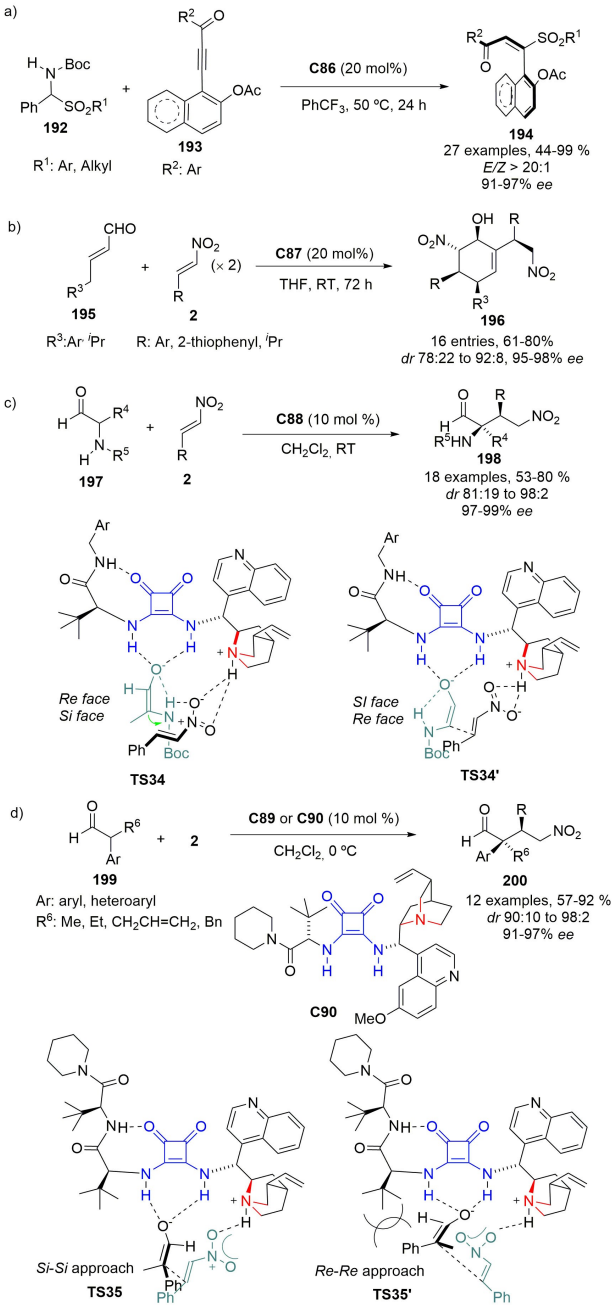


Figure 3. Arrangements for amide-containing squaramide-organobase catalysts and representative examples.

substituted α,β-unsaturated aldehydes **195** and nitroalkenes via the aldehyde dienolate intermediate (Scheme 62b).[113] The unprecedented 1,3 and 1,5-reactivity of the dienolates led to the formation of cyclohexenol derivatives with four contiguous stereogenic centers with good diastereoselectivities and high *ee* values. The incorporation of the amino acid unit in **C87** provided better stereoselectivity than that afforded by the analogous catalyst lacking such a unit.

In another recent example, Palomo laboratory has reported **C88** as efficient catalyst for the addition reaction of *N*-acyl α-aminoaldehydes **197** to nitroolefins to yield the corresponding quaternary α-amino aldehydes **198** with very good enantio- and diastereoselectivity (Scheme 62c).[114] As shown in **TS34** DFT calculations predict a strong intramolecular H-bonding interaction between the amide NH and the squaramide carbonyl in the catalyst which probably enhances the H-bonding capability of the squaramide. This intramolecular interaction may also be responsible for catalyst conformational rigidification and hence improved facial selectivity through steric shielding imparted by the *tert*-butyl group. The least energetic **TS34** shows the α-amino enolate adopting a *Z*-configuration (fixed by an intramolecular H-bonding interaction between the enolate carbonyl oxygen atom and the NH), and an additional H-bond between the enolate NH and the nitro group of the electrophile. This TS (Pápai's model) correctly predicts the preferential formation of isomer **198** from a $Si_{enolate}/Re_{nitroolefin}$ approach. The alternative $Re_{enolate}/Si_{nitroolefin}$ approach that would lead to minor **ent-198** product lies 3.1 kcal/mol higher in energy, as happens with the $Re_{enolate}$ /$Re_{nitroolefin}$ approach leading to the syn diastereomer of **198** (5.2 kcal/mol higher in energy). As shown in Scheme 62d, the same group also demonstrated that related catalysts **C89** and **C90** are capable of efficiently promoting the Michael addition of α-branched aryl acetaldehydes **199**.[115] More specifically α-methyl arylacetaldehydes react efficiently with β-(hetero)aromatic and β-alkyl nitroolefins **2** to provide 1,2,3-



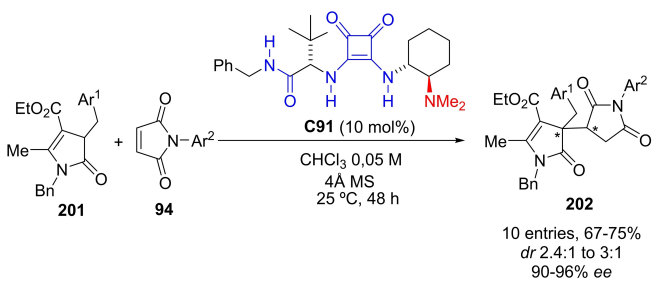
Scheme 62. Stereoselective reactions promoted by amide-squaramide BBs **C86**-**C90**. a) Yan, 2019;[112] b) Zhao, 2019[113] and c,d) Mielgo and Palomo, 2021.[114,115]

trisubstituted *syn* γ-nitroaldehydes **200** in high enantio- and *syn*-selectivity. In this case DFT calculations predict the reaction to occur through the intermediacy of the *E*-enolate. While both catalysts, **C89** and **C90** provided very good stereoselectivity, **C89** turned out to be more active, presumably because of the intramolecular H-bonding interaction described above. In fact, the least energetic TSs **TS35** and **TS35'** once again show an intramolecular NH–O=C interaction in the catalyst structure. The calculated energy difference between **TS35** (major product **200**) and **TS35'** (**ent-200**) was 8.0 kcal/mol. This was attributed

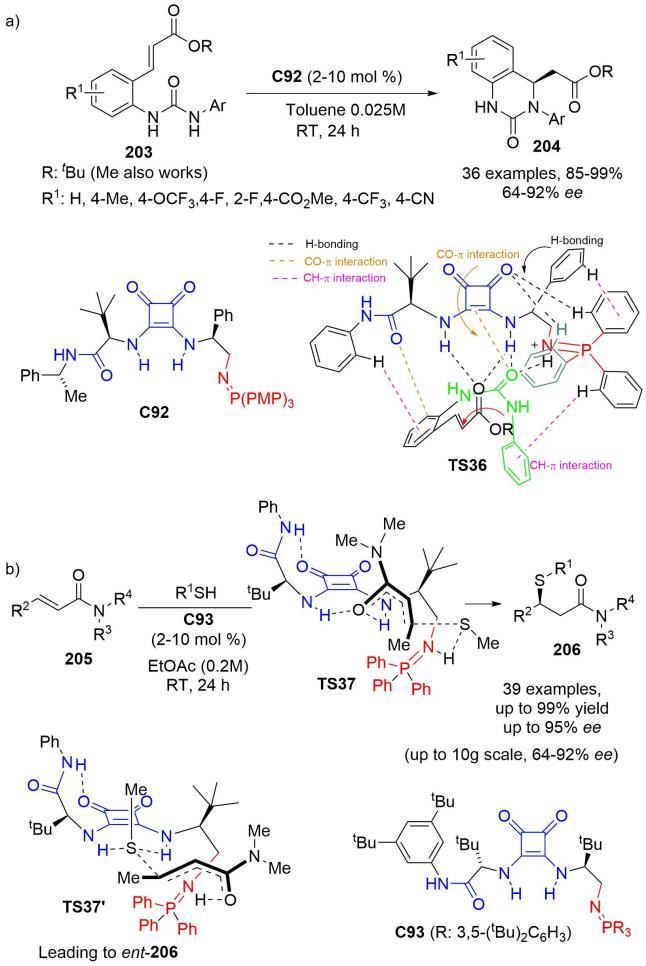
to a larger steric congestion between the *tert*-butyl group of one of the *tert*-Leucines and the phenyl group of the enolate in **TS35′**. The calculated energy for the TS affording the minor *syn* diastereomer of **200** was found to be 6.3 kcal/mol higher in energy. It is worth of mention that arylacetaldehydes **199** with α-substituents larger than methyl were also tolerated, although stereoselectivity was moderate.

Similar multifunctional squaramide-amide catalysts derived from basic structures other than cinchona alkaloid derivatives have also been developed. This is the case of 1,2-cyclohexyldiamine derived catalyst **C91**, reported by Mukherjee in 2019, which is capable to promote the addition reaction of deconjugated butyrolactams **201** to *N*-arylmaleimides **94** to furnish the α-addition products **202** exclusively (absolute configuration not determined). These adducts exhibit consecutive tertiary and all-carbon quaternary steroecenters and are obtained in good yield, moderate diastereoselectivity and good to excellent enantioselectivity (Scheme 63).[116] However, *N*-alkyl maleimides and *ortho*-substituted *N*-aryl maleimides were completely unreactive under these conditions.

In 2021 Dixon reported his third generation iminophosphorane catalysts represented by **C92**, in which the *tert*-Leucine-squaramide moiety provides multiple sites for HB interactions. In particular, **C92** is able to promote the synthesis of hydroquinazolines **204** via intramolecular aza-Michael reaction of urea linked α,β-unsaturated esters **203** (Scheme 64a).[117] The protocol tolerates various functional groups on both aromatic rings on the starting substrates **203**. The reaction adducts are obtained in very good yields and diastereoselectivities, and excellent enantioselectivity. Additionally, multi-gram scale synthesis is suitable using catalyst loading as low as 2 mol%. DFT studies predicted that the optimal catalyst conformation (**TS36**) creates a pocket-like binding site for the substrates to impart enantiofacial selectivity, whilst the squaramide motif demonstrates advantages over urea and thiourea H-bond donor groups on decreasing the destabilizing Pauli repulsion between the reactants. This prediction is in agreement with experimental results which showed that the reaction in the presence of the parent thiourea derivative **C45** (Scheme 30) and related ones provided products in poorer enantioselectivity. **TS36** that has a catalyst conformation and coordination mode to the substrate that both reduces steric repulsion and maximizes interactions, is energetically preferred in this reaction. As shown in the scheme, this TS features several stabilizing interactions, including H-bonding, CO-π and CH-π interactions and was found to be 1.2 kcal/mol more stable than the TS leading to **ent-204**.



Scheme 63. Michael addition reaction of deconjugated butyrolactams to *N*-arylmaleimides, Mukherjee, 2019.[116]



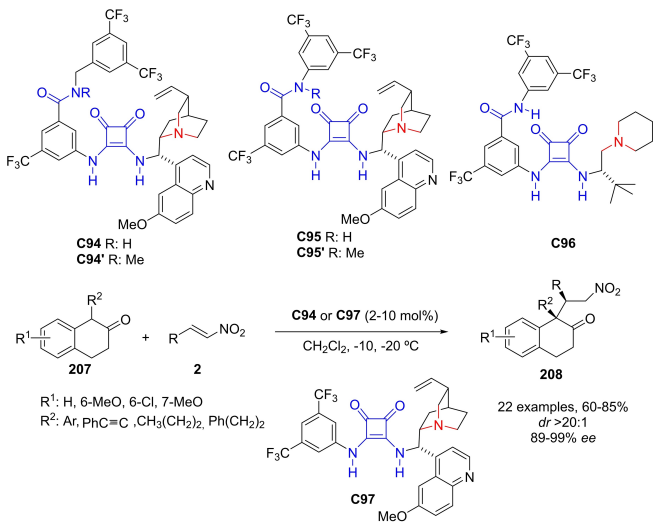
Scheme 64. Amide-squaramide iminophosphorane BBs **C92** and **C93** as promoters of: a) Intramolecular aza-Michael reaction of urea linked α,β-unsaturated esters. Dixon, 2021.[117] b) Sulfa Michael addition (SMA) of alkyl thiols to unactivated α,β-unsaturated amides. Hamlin and Dixon, 2022.[118]

More recently, Hamlin and Dixon found catalyst **C93** is optimal for the first metal-free catalytic intermolecular sulfa-Michael addition of alkyl thiols to unactivated α,β-unsaturated amides **205**, recalcitrant Michael acceptors (Scheme 64b).[118] A wide range of sulfa Michael products, including heterocyclic derivatives, were produced in high yield and enantioselectivity with the process being scalable to decagrams using as low as 2 mol% catalyst loading. The catalytic transformation was thoroughly investigated computationally and the conjugate-addition step was found to be the stereoselectivity-determining one. All the possible TSs including Takemoto's and Pápai's coordination modes were computed. The results revealed **TS37**, as the least energetic TS leading to the experimentally found major enantiomer. In this TS an intramolecular H-bonding interaction between the amide NH and the squaramide oxygen fixes the conformation on one of the arms of the catalyst, creating a three-dimensionally defined pocket within which the α,β-unsaturated amide can fit without considerable steric

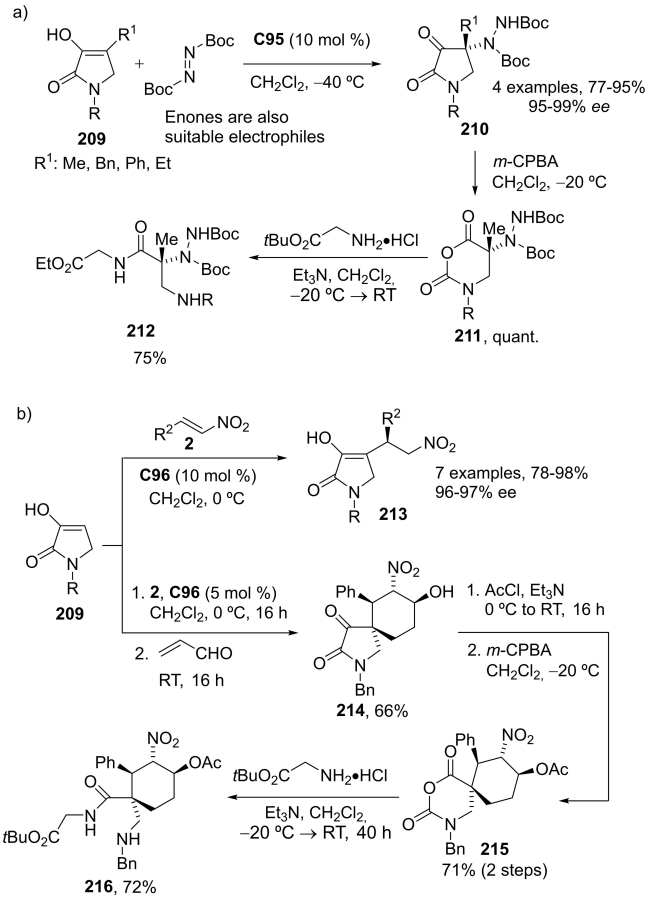
repulsion during the C–S bond-forming event. The stereoselectivity for this transformation originates from the **TS37** transition state that benefits from multiple inter- and intramolecular stabilizing interactions, including hydrogen bonding, CH$-\pi$, and $\pi-\pi$ interactions. These stabilizing features are enhanced in **TS37** in relation to the lowest energetic **TS37′** leading to **ent-206** ($\Delta\Delta G^{\neq} = 4.1$ Kcal/mol).

Amide-containing squaramide-organobase systems that do not incorporate α-amino acid units have also been reported. In this context, Palomo group described a new subclass of cinchona-alkaloid-derived bifunctional catalysts **C94**-**C96** bearing a carboxamide group as an additional moiety for catalyst fine tuning (Scheme 65). On the one hand, catalyst **C94** was found to promote the regio-, diastereo-, and enantioselective C_α-alkylation of β-tetralones **207** and related aromatic-ring-fused cycloalkanones via Michael addition to nitroolefins (Scheme 65).[119] Both, α-substituted and α-unsubstituted tetralones reacted under the optimized conditions affording products **208** in excellent stereoselectivity. For α-unsubstituted substrates **207** ($R^2 \neq H$) the amide lacking catalyst **C97** was found to be equally effective at 2 mol% loading. However, for the α-substituted congeners **207**, this latter catalyst was inferior. Control experiments using the *N*-methylated catalyst **C94′** led to addition products with a moderate 60% *ee*, thus indicating the amide NH in catalyst **C94** is important.

On the other hand, carboxamide derived catalysts **C95** enabled the highly enantioselective addition of C_4-substituted pyrrolidin-2,3-diones **209** to *tert*-butyl azodicarboxylate to produce the corresponding α-hydrazination adducts **210** in very good yields and enantioselectivities (Scheme 66a).[120] In the presence of either catalyst **C95** or the *N*-methyl analog **C95′**, the reaction could be extended to some other electrophilic reaction partners such as α,β-unsaturated ketones. Significantly, catalysts lacking the carboxamide motif afforded the reaction adducts in lower enantioselectivities. Interestingly, adducts **210**



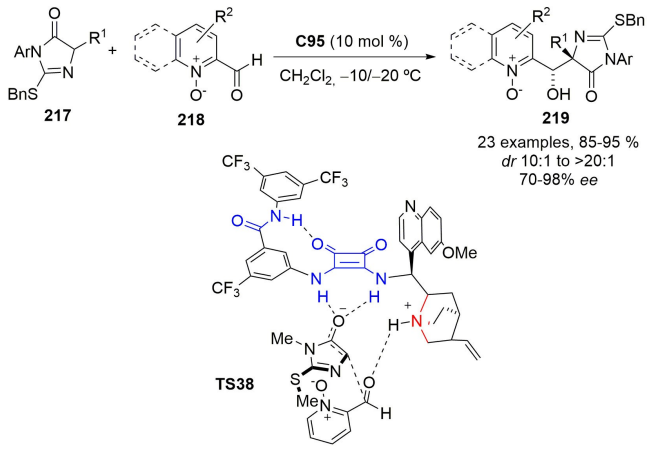
Scheme 65. Amide-containing squaramide-organobase new subfamily catalysts and first example of a Michael addition of tetralones to nitroolefins promoted by this catalyst type. Palomo, 2017.[119]



Scheme 66. C4-Functionalization of pyrrolidin-2,3-diones promoted by amide-containing squaramide-organobases **C95** and **C96** and development of an efficient route to $\beta^{2,2}$-amino acid derivatives. Palomo, 2017.[120]

could aftermaths be transformed into $\beta^{2,2}$-amino acids **212** via oxidative ring-expansion to *N*-carboxyanhydrides (NCA's) **211** and subsequent coupling with nucleophiles. In a variation involving the C_4-unsusbstituted pyrrolidin-2,3-diones **209** to provide adducts **213**, among the catalysts tested **C96** provided the best results (Scheme 66b). Interestingly, a **C96** catalyzed two-step, one-pot process that involves nitroolefins and acrylaldehyde as the consecutive Michael acceptors, worked nicely to furnish spirocompound **214** with four consecutive stereocenters as essentially single stereoisomer. Further oxidative ring expansion to NCA's **215** and treatment with an amine provided access to highly functionalized α,β-amino acid dipeptide hybrid **216**.

In another example, catalyst **C95** was able to promote the aldol reaction between α-hydantoin surrogates **217** and azaarene 2-carbaldehyde *N*-oxides **218** to provide adducts **219** bearing two vicinal tertiary/quaternary carbons in excellent diastereo- and enantioselectivity (Scheme 67).[121] The use of the *N*-oxide derivatives instead of the parent azaarene carbaldehydes was key for attaining reactivity, as is the nature of catalyst **C95** for reaching high stereoselectivity. DFT studies of the potential energy surface of the reaction correlate the activity of the catalysts and support an intramolecular hydrogen-bond-



Scheme 67. Reaction between α-hydantoin surrogates and azaarene 2-carbaldehyde *N*-oxides promoted by amide-squaramide catalysts **C95**. Dinér, Oiarbide & Palomo, 2019.[121]

assisted activation of the squaramide moiety in the transition state of the catalytic reaction (**TS38**). The relevance of the amide NH group in this new catalyst subclass was supported by the fact that the above reactions proceeded with notably lower enantioselectivity (45% *ee*) when the *N*-methyl derivative **C95′** was employed as catalyst instead.

5. Summary and Outlook

In this review we showcase the progress on thiourea-, urea-, and squaramide-based Brønsted base/H-bonding (BB/HB) bifunctional catalysts featuring an additional H-bond donor functionality (catalysts with multiple H-bond donor capability). After first reports dealing with these type of catalysts about 15 years ago, in recent years the use of, mainly, thiourea- and squaramide-based organobase catalysts with multiple H-bond capability has grown steadily. New catalysts incorporating alcohol, sulfonamide, amide, amidine, amine and thiourea groups as additional H-bonding unit (HB2) have been developed. Out of them, (sulfon)amides and alcohols are prevalent by far. The order in which the three nominal active sites (HB1, BB, HB2) are located on the catalyst covalent backbone follows various patterns, which we defined as topologies **I**–**IV**, respectively. Successful examples of each topology **I**–**IV** have been documented, although topology **I** (namely, HB2-HB1-BB connectivity pattern) is dominant. As control experiments in many cases show, the resulting multifunctional catalysts are comparatively more active and selective than the conventional BB/HB bifunctional catalysts or the analogs of the actual catalysts featuring a blocked HB2 site, enabling reduction of the threshold catalyst loading for attaining practical conversion. Also, incorporation of the second H-bonding unit (HB2) on catalyst structure is often concomitant to an additional stereogenic unit, which provides further element for catalyst fine tuning. Since these multifunctional catalysts have been applied to a wide variety of reaction categories, including carbon-carbon, -oxygen, -nitrogen, and -halogen bond formations, as well as isomerizations and tandem/cycloaddition processes, there is no universally accepted mechanism of catalyst mode of action. However, two prototypical functions are most often ascribed to the HB2 unit in the transition state (TS) of the key bond-forming step: (i) it H-bonds to one or both the reactants (the actual nucleophilic and electrophilic species), or (ii) it internally H-bonds to the carbonyl group of the catalyst primary HB site, that is, the (thio)urea or squaramide. In either case, the additional H-bond would help in stabilizing TS while facilitating catalyst preorganization and/or TS rigidification. Multifunctional catalysts comprised of a thiourea, a tertiary amine and a boronic acid are unique in that the boronic acid residue is presumed to participate by formation of mixed anhydrides with the substrate carboxylic acid, rather than solely participating in H-bonding. Most of the catalysts in the above developments are based on tertiary amines as the base unit. Few examples incorporating stronger Brønsted bases such as guanidines and iminophosphoranes have also appeared which set the principle of mutual compatibility between the various basic and acidic sites within the same catalyst structure and suggests further expansion of the substrate scope in the area is to come. While these multifunctional catalysts are usually more active than common bifunctional catalysts, the effective catalyst loading remains relatively high yet and even more active catalysts are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] R. A. Copeland, *Enzymes: A Practical Introduction to Structure, Mechanism, and Data Analysis*, Wiley-VCH, 2nd Edition, **2000**.
[2] Selected reviews on bi(multi)functional asymmetric catalysis: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2209; b) M. Shibasaki, S. Matsunaga, N. Kumagai, *Synlett* **2008**, 1583–1602; c) J.-S. Yu, J. Zhou, *Asymmetric Multifunctional Catalysis. In Multicatalyst System in Asymmetric Catalysis* (Ed.: J. Zhou), Wiley, **2015**, 159–289.
[3] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430.
[4] Selected reviews on chiral Brønsted base/hydrogen-bonding catalysis: a) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; b) C. Nájera, J. M. Sansano, J. M. Saá, *Eur. J. Org. Chem.* **2009**, 2385–2400; c) W.-Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298–1310; d) F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, *6*, 645–667; e) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281.
[5] Selected reviews on asymmetric Brønsted base catalysis: a) S.-K Tian, Y. Chen, Y. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*,

632–653; c) T. Marcelli, H. Hiemstra, *Synthesis* **2010**,, 1229–1279; d) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200; e) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis and Additional Topics*, Ed.: K. Maruoka; Thieme, Stuttgart, **2012**; f) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197; g) S. Dong, X. Feng, X. Liu, *Chem. Soc. Rev.* **2018**, *47*, 8525–8540; h) H.-C. Chou, D. Leow, C.-H. Tan, *Chem. Asian J.* **2019**, *14*, 3803–3822; i) Y.-H. Wang, Z.-Y. Cao, Q.-H. Li, G.-Q. Lin, J. Zhou, P. Tian, *Angew. Chem.* **2020**, *132*, 8080–8090; *Angew. Chem. Int. Ed.* **2020**, *59*, 8004–8014; j) M. Formica, D. Rozsar, G. Su, A. J. M. Farley, D. J. Dixon, *Acc. Chem. Res.* **2020**, *53*, 2235–2247.

[6] a) S. J. Connon, *Synlett* **2009**, 354–376; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; c) A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799; d) F. Steppeler, D. Iwan, E. Wojaczýnska, J. Wojaczýnski, *Molecules* **2020**, *25*, 401–456.

[7] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; b) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870; c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; d) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

[8] a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220; b) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414.

[9] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[10] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[11] J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899.

[12] S. Gandhi, V. Sivadas, B. Baire, *Eur. J. Org. Chem.* **2021**, 220–234.

[13] C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433.

[14] X.-Q. Dong, H.-L. Teng, C.-J. Wang, *Org. Lett.* **2009**, *11*, 1265–1268.

[15] X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 6840–6842.

[16] C.-J. Wang, X.-Q. Dong, Z.-H. Zhang, Z.-Y. Xue, H.-L. Teng, *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607.

[17] Z.-H. Zhang, X.-Q. Dong, H.-Y. Tao, C.-J. Wang, *Arkivoc* **2011**, 137–150.

[18] W. Liu, L. Zou, B. Fu, X. Wang, K. Wang, Z. Sun, F. Peng, W. Wang, Z. Shao, *J. Org. Chem.* **2016**, *81*, 8296–8305.

[19] X.-Q. Dong, X. Fang, C.-J. Wang, *Org. Lett.* **2011**, *13*, 4426–4429.

[20] X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou, C.-J. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1141–1147.

[21] X. Fang, J. Li, C.-J. Wang, *Org. Lett.* **2013**, *15*, 3448–3451.

[22] L. Yao, K. Liu, H.-Y. Tao, G.-F. Qiu, X. Zhou, C.-J. Wang, *Chem. Commun.* **2013**, *49*, 6078–6080.

[23] X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2010**, *122*, 8557–8561; *Angew. Chem. Int. Ed.* **2010**, *49*, 8379–8383.

[24] X.-F. Wang, L. Peng, J. An, C. Li, Q.-Q. Yang, L.-Q. Lu, F.-L. Gu, W.-J. Xiao, *Chem. Eur. J.* **2011**, *17*, 6484–6491.

[25] S. Wang, Z. Guo, S. Chen, Y. Jiang, F. Zhang, X. Liu, W. Chen, C. Sheng, *Chem. Eur. J.* **2018**, *24*, 62–66.

[26] W. Hou, B. Zheng, J. Chen, Y. Peng, *Org. Lett.* **2012**, *14*, 2378–2381.

[27] H. J. Lee, S. B. Woo, D. Y. Kim, *Tetrahedron Lett.* **2012**, *53*, 3374–3377.

[28] H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461–463.

[29] W. Li, W. Wu, F. Yu, H. Huang, X. Liang, J. Ye, *Org. Biomol. Chem.* **2011**, *9*, 2505–2511.

[30] M.-X. Zhao, W.-H. Tang, M.-X. Chen, D.-K. Wei, T.-L. Dai, M. Shi, *Eur. J. Org. Chem.* **2011**, 6078–6084.

[31] M.-X. Zhao, H. Zhou, W.-H. Tang, W.-S. Qu, M. Shi, *Adv. Synth. Catal.* **2013**, *355*, 1277–1283.

[32] T.-Z. Li, X.-B. Wang, F. Sha, X.-Y. Wu, *J. Org. Chem.* **2014**, *79*, 4332–4339.

[33] J. Xie, W.-L. Xing, F. Sha, X.-Y. Wu, *Eur. J. Org. Chem.* **2016**, 3983–3992.

[34] A. Ansari, P. Patel, G. Kumarab, N. H. Khan, *New J. Chem.* **2019**, *43*, 14511–14517.

[35] Z.-H. Zhang, X.-Q. Dong, D. Chen, C.-J. Wang, *Chem. Eur. J.* **2008**, *14*, 8780–8783.

[36] X. Fang, X.-Q. Dong, Y.-Y. Liu, C.-J. Wang, *Tetrahedron Lett.* **2013**, *54*, 4509–4511.

[37] O. Bassas, J. Huuskonen, K. Rissanen, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2009**,, 1340–1351.

[38] Q. Zhu, Y. Lu, *Org. Lett.* **2009**, *11*, 1721–1724.

[39] X. Liu, Y. Lu, *Org. Biomol. Chem.* **2010**, *8*, 4063–4065.

[40] J.-K. Xie, Y. Wang, J.-B. Lin, X.-R Ren, P.-F Xu, *Chem. Eur. J.* **2017**, *23*, 6752–6756.

[41] P.-F. Zheng, R. Zeng, K. Jiang, H.-W. Li, Y. Ye, C. Mu, L. Shuai, Q. Ouyang, Y.-C. Chen, *Org. Lett.* **2019**, *21*, 10052–10056.

[42] X. Shi, W. He, H. Li, X. Zhang, S. Zhang, *Tetrahedron Lett.* **2011**, *52*, 3204–3207.

[43] H. Li, X. Zhang, X. Shi, N. Ji, W. He, S. Zhang, B. Zhang, *Adv. Synth. Catal.* **2012**, *354*, 2264–2274.

[44] J. Wang, Y. Liu, Z. Wei, J. Cao, D. Liang, Y. Lin, H.-f. Duan, *ACS Omega* **2021**, *6*, 5812–5824.

[45] Y. Liu, X. Wang, X. Wang, W. He, *Org. Biomol. Chem.* **2014**, *12*, 3163–3166.

[46] N.-K. Li, Z.-M. Liu, X.-F. Huang, J.-X. Zhang, X. Chen, Y. Wang, X.-W. Wang, *RSC Adv.* **2013**, *3*, 9154–9157.

[47] S. Meninno, A. Vidal-Albalat, A. Lattanzi, *Org. Lett.* **2015**, *17*, 4348–4351.

[48] L.-M. Shi, W.-W. Dong, H.-Y. Tao, X.-Q. Dong, C.-J. Wang, *Org. Lett.* **2017**, *19*, 4532–4535.

[49] H. Ma, K. Matsuzaki, Y.-D. Yang, E. Tokunaga, D. Nakane, T. Ozawa, H. Masuda, N. Shibata, *Chem. Commun.* **2013**, *49*, 11206–11208.

[50] X. Ren, C. He, Y. Feng, Y. Chai, W. Yao, W. Chen, S. Zhang, *Org. Biomol. Chem.* **2015**, *13*, 5054–5060.

[51] H. N. Genc, A. Sirit, *Tetrahedron: Asymmetry* **2016**, *27*, 201–207.

[52] H. N. Genc, A. Sirit, *J. Inclusion Phenom. Macrocyclic Chem.* **2018**, *90*, 39–49.

[53] D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.

[54] S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883.

[55] J. A. Bull, E. P. Balskus, R. A. J. Horan, M. Langner, S. V. Ley, *Chem. Eur. J.* **2007**, *13*, 5515–5538.

[56] J. S. Eun, S.-Y. Seo, *Arch. Pharmacal Res.* **2009**, *32*, 1673–1679.

[57] A. Berkessel, S. Mukherjee, T. N. Müller, F. Cleemann, K. Roland, M. Brandenburg, J.-M. Neudörfl, J. Lex, *Org. Biomol. Chem.* **2006**, *4*, 4319–4330.

[58] J.-L. Wu, B.-X. Du, Y.-C. Zhang, Y.-Y. He, J.-Y. Wang, P. Wu, F. Shi, *Adv. Synth. Catal.* **2016**, *358*, 2777–2790.

[59] a) M. S. Manna, S. Mukherjee, *Chem. Eur. J.* **2012**, *18*, 15277–15282; b) M. S. Manna, S. Mukherjee, *Chem. Sci.* **2014**, *5*, 1627–1633; c) M. S. Manna, R. Sarkar, S. Mukherjee, *Chem. Eur. J.* **2016**, *22*, 14912–14919; d) A. K. Simlandy, S. Mukherjee, *Org. Biomol. Chem.* **2016**, *14*, 5659–5664.

[60] Z.-H. You, Y.-H. Chen, Y. Tang, Y.-K. Liu, *Org. Lett.* **2019**, *21*, 8358–8363.

[61] B. A. F. L. Bailly, L. Byrne, J. Clayden, *Angew. Chem.* **2016**, *125*, 2172–2176; *Angew. Chem. Int. Ed.* **2016**, *55*, 2132–2136.

[62] J. Yang, A. J. M. Farley, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 606–610.

[63] M. Formica, G. Sorin, A. J. M. Farley, J. Diaz, R. S. Paton, D. J. Dixon, *Chem. Sci.* **2018**, *9*, 6969–6974.

[64] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

[65] A. Hamza, G. Schubert, T. Sóos, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[66] Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756.

[67] X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315–8319.

[68] J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L.-W. Xu, Y. Lu, *Chem. Commun.* **2013**, *49*, 5775–5777.

[69] N.-j. Zhong, L. Liu, D. Wang, Y.-J. Chen, *Chem. Commun.* **2013**, *49*, 3697–3699.

[70] D.-F. Yue, J.-Q. Zhao, X.-Z. Chen, Y. Zhou, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan, *Org. Lett.* **2017**, *19*, 4508–4511.

[71] Z.-Z. Ge, L. Yang, Y. You, Z.-H. Wang, K.-X. Xie, M.-Q. Zhou, J.-Q. Zhao, W.-C. Yuan, *Chem. Commun.* **2020**, *56*, 2586–2589.

[72] Q. Wei, W. Hou, N. Liao, Y. Peng, *Adv. Synth. Catal.* **2017**, *359*, 2364–2368.

[73] B. Zhu, S. Qiu, J. Li, M. L. Coote, R. Lee, Z. Jiang, *Chem. Sci.* **2016**, *7*, 6060–6067.

[74] X. Yang, Y.-H. Zhou, H. Yang, S.-S. Wang, Q. Ouyang, Q.-L. Luo, Q.-X. Guo, *Org. Lett.* **2019**, *21*, 1161–1164.

[75] L. Yang, J.-Q. Zhao, Y. You, Z.-H. Wang, W.-C. Yuan, *Chem. Commun.* **2020**, *56*, 12363–12366.

[76] N. Hayama, T. Azuma, Y. Kobayashi, Y. Takemoto, *Chem. Pharm. Bull.* **2016**, *64*, 704–717.

[77] T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma, Y. Takemoto, *Org. Lett.* **2014**, *16*, 4256–4259.

[78] N. Hayama, R. Kuramoto, T. Földes, K. Nishibayashi, Y. Kobayashi, I. Pápai, Y. Takemoto, *J. Am. Chem. Soc.* **2018**, *140*, 12216–12225.

[79] K. Michigami, H. Murakami, T. Nakamura, N. Hayama, Y. Takemoto, *Org. Biomol. Chem.* **2019**, *17*, 2331–2335.
[80] N. Hayama, Y. Kobayashi, E. Sekimoto, A. Miyazaki, K. Inamoto, T. Kimachi, Y. Takemoto, *Chem. Sci.* **2020**, *11*, 5572–5576.
[81] H. Murakami, A. Yamada, K. Michigami, Y. Takemoto, *Asian J. Org. Chem.* **2021**, *10*, 1097–1101.
[82] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5592.
[83] a) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; b) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894–2897; c) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150–1160.
[84] Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 7457–7461; *Angew. Chem. Int. Ed.* **2010**, *49*, 7299–7303.
[85] Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 9440–9443; *Angew. Chem. Int. Ed.* **2010**, *49*, 9254–9257.
[86] Y. Sohtome, T. Yamaguchi, S. Tanaka, K. Nagasawa, *Org. Biomol. Chem.* **2013**, *11*, 2780–2786.
[87] N. Probst, A. Madarász, A. Valkonen, I. Pápai, K. Rissanen, A. Neuvonen, P. M. Pihko, *Angew. Chem.* **2012**, *124*, 8623–8627; *Angew. Chem. Int. Ed.* **2012**, *51*, 8495–8499.
[88] A. J. Neuvonen, D. Noutsias, F. Topić, K. Rissanen, T. Földes, I. Pápai, P. M. Pihko, *J. Org. Chem.* **2019**, *84*, 15009–15019.
[89] J. Otevrel, P. Bobal, *J. Org. Chem.* **2017**, *82*, 8342–8358.
[90] B. Han, Q.-P. Liu, R. Li, X. Tian, X.-F. Xiong, J.-G. Deng, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 8094–8097.
[91] S. Meninno, L. Zullo, J. Overgaard, A. Lattanzi, *Adv. Synth. Catal.* **2017**, *359*, 913–918.
[92] J. Li, S. Qiu, X. Ye, B. Zhu, H. Liu, Z. Jiang, *J. Org. Chem.* **2016**, *81*, 11916–11923.
[93] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem.* **2013**, *125*, 12062–12067; *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.
[94] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.
[95] H. Echave, R. López, C. Palomo, *Angew. Chem.* **2016**, *128*, 3425–3429; *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.
[96] I. Bastida, M. San Segundo, R. López, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 13332–13336.
[97] S. Vera, A. Vázquez, R. Rodriguez, S. Del Pozo, I. Urruzuno, A. De Cózar, A. Mielgo, C. Palomo, *J. Org. Chem.* **2021**, *86*, 7757–7772.
[98] M. Formica, T. Rogova, H. Shi, N. Sahara, A. J. M. Farley, K. E. Christensen, F. Duarte, D. J. Dixon, **2021**, http://doi.org/10.26434/chemrxiv-2021-5714 s-v2.
[99] T. Sakai, S.-i. Hirashima, Y. Yamashita, R. Arai, K. Nakashima, A. Yoshida, Y. Koseki, T. Miura, *J. Org. Chem.* **2017**, *82*, 4661–4667.
[100] Z. Dong, G. Qiu, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2012**, *23*, 1550–1556.
[101] M.-X. Zhao, H.-L. Bi, R.-H. Jiang, X.-W. Xu, M. Shi, *Org. Lett.* **2014**, *16*, 4566–4569.
[102] L. Yan, G. Huang, H. Wang, F. Xiong, H. Peng, F. Chen, *Eur. J. Org. Chem.* **2018**, *2018*, 99–103.
[103] S. del Pozo, S. Vera, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2017**, *139*, 15308–15311.
[104] B. Liu, X. Hang, Z. Dong, H. Lv, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2013**, *24*, 1276–1280.
[105] E. Zhou, B. Liu, C. Dong, *Tetrahedron: Asymmetry* **2014**, *25*, 181–186.
[106] Y. Gao, B. Liu, H.-B. Zhou, W. Wang, C. Dong, *RSC Adv.* **2015**, *5*, 24392–24398.
[107] S. Tang, Z.-Y. Wang, B. Liu, C.-E. Dong, *Chin. Chem. Lett.* **2015**, *26*, 744–748.
[108] J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2016**, *358*, 1801–1809.
[109] J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *ACS Catal.* **2017**, *7*, 6430–6439.
[110] J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2018**, *360*, 124–129.
[111] U. Vural, M. Durmaz, A. Sirit, *Org. Chem. Front.* **2016**, *3*, 730–736.
[112] N. Zhang, T. He, Y. Liu, S. Li, Y. Tan, L. Peng, D. Li, C. Shan, H. Yan, *Org. Chem. Front.* **2019**, *6*, 451–455.
[113] D. Majee, S. Jakkampudi, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2019**, *21*, 9166–9170.
[114] A. García-Urricelqui, A. de Cózar, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2021**, *27*, 2483–2492.
[115] A. Garcia-Urricelqui, A. de Cózar, T. E. Campano, A. Mielgo, C. Palomo, *Eur. J. Org. Chem.* **2021**, 3604–3612.
[116] B. Ray, S. Mukherjee, *Tetrahedron* **2019**, *75*, 3292–3298.
[117] G. Su, C. J. Thomson, K. Yamazaki, D. Rozsar, K. E. Christensen, T. A. Hamlin, D. J. Dixon, *Chem. Sci.* **2021**, *12*, 6064–6072.
[118] D. Rozsar, M. Formica, K. Yamazaki, T. A. Hamlin, D. J. Dixon, *J. Am. Chem. Soc.* **2022**, *144*, 1006–1015.
[119] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem.* **2017**, *129*, 2091–2095; *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.
[120] E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185–8195.
[121] J. Izquierdo, N. Demurget, A. Landa, T. Brinck, J. M. Mercero, P. Dinér, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, *25*, 12431–12438.

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