ORGANIC CHEMISTRY FRONTIERS

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Org. Chem. Front.*, 2025, **12**, 4126

Recent advances in organocatalytic asymmetric multicomponent reactions

Peng-Ying Jiang,[a,b] San Wu,[a] Jun (Joelle) Wang, *[b] Shao-Hua Xiang [a] and Bin Tan *[a]

Received 19th February 2025, Accepted 25th March 2025

DOI: 10.1039/d5qo00347d

rsc.li/frontiers-organic

Multicomponent reactions enable the simultaneous formation of multiple chemical bonds in a single synthetic operation, efficiently combining three or more reactants to access structurally complex molecules. The integration of chiral catalysts into such processes establishes a well-defined asymmetric environment, facilitating precise stereochemical control and delivering enantioenriched products containing stereogenic elements. In recent years, environmentally benign organocatalytic strategies have emerged as a powerful platform for asymmetric multicomponent reactions, demonstrating remarkable versatility in constructing diverse molecular architectures with high enantioselectivity. This review systematically categorizes recent advances in this field based on organocatalyst types, with a focus on their roles in distinct reaction mechanisms, key intermediates, and substrate activation modes. Representative transformations are discussed to illustrate design principles and challenges in achieving stereocontrol within multicomponent systems.

10th anniversary statement

As an organic chemistry researcher, I feel deeply honored to contribute a review on advances in organocatalytic asymmetric multicomponent reactions to the 10th anniversary collection of Organic Chemistry Frontiers (OCF). In early 2016, my collaborators and I published our first paper in OCF, and five years later, it was instrumental as one of the five representative works we presented in our successful application for the Guangdong Provincial Natural Science Award. Undoubtedly, this emerging journal has played an important role in the growth of many young domestic researchers like me. Over the past decade, OCF has become an indispensable force in disseminating the development of organic chemistry in China. On this momentous occasion, I wish that this journal will continue to provide a timely window for many researchers to showcase original research results and also provide an excellent platform for young people to learn and exchange ideas.

1. Introduction

Multicomponent reactions (MCRs) offer a unique opportunity to combine simple, readily available raw materials into intricate, structurally complex molecules through a single, streamlined process.[1] These transformations exhibit remarkable potential across a broad spectrum of fields, including drug discovery and natural product synthesis,[2–8] due to their high convergence, atom economy, and skeletal diversity.[9–12] In fact, with the prevalence of chiral molecules in the current drug market, the development of enantioselective multicomponent reactions has garnered significant attention in recent years. However, the complexity of these reactions, which often involve three or more components simultaneously, makes the system extremely intricate. The challenge lies in the inherent side reactions and background reactions that make chemo-, regio-, and stereoselectivity control in asymmetric multicomponent reactions (AMCRs) a substantial obstacle to overcome.

Asymmetric catalysis stands as the most effective method for obtaining a single stereoisomer. By introducing a chiral catalytic system, it not only creates an asymmetric environment for enantioinduction but also enables the amplification of the desired reactivity, ultimately providing an efficient means to control stereoselective MCRs (Fig. 1).

The past decades have witnessed asymmetric catalysis at the forefront of the synthetic chemistry area, driven by the exploitation of diverse catalytic systems and activation modes,[13–18] especially enantioselective organocatalysis. In comparison with transition metal catalysis, this emerging catalytic platform features relatively high catalyst stability, excellent functional group tolerance, and environmental sustainability, along with the crucial advantage of avoiding metal residues in the products, making it highly appealing in chiral drug

[a]Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology, Shenzhen, 518055, China. E-mail: tanb@sustech.edu.cn
[b]Department of Chemistry, Hong Kong Baptist University, Kowloon, Hong Kong, China. E-mail: junwang@hkbu.edu.hk

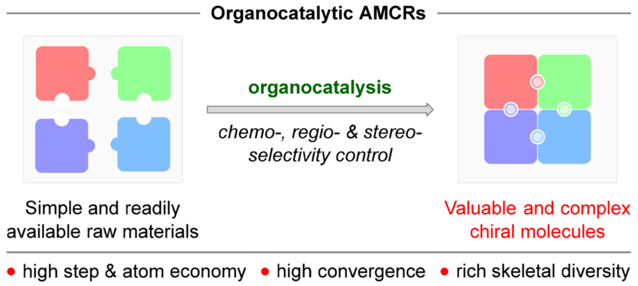


Fig. 1 Asymmetric multicomponent reactions.

research and development.[19–21] Asymmetric organocatalysis has exhibited great potential in AMCRs, successfully revitalizing a wide range of time-honoured yet highly valuable MCRs, including the Biginelli reaction, the Passerini reaction, the Ugi reaction, *etc*. In the early years, several elegant reviews had been published, which summarized the research status in this field in great detail.[22–25] This review mainly focuses on summarizing and analysing the significant achievements within the last ten years, specifically examining the utilization of different chiral organocatalysts such as amines, thioureas and Brønsted acids. The representative substrate coverage under different chiral catalytic systems will be pointed out in detail, and discussions will be carried out around the mechanisms, activation and stereocontrol modes and proposed transition states.

2. Chiral Brønsted acid catalysis

2.1 Asymmetric three-component reaction

The Biginelli reaction is one of the earliest discovered multi-component reactions, dating back to 1893. It typically involves the reaction of an aldehyde (**1**), a (thio)urea (**2**), and a β-ketoester (**3**) in the presence of an acidic catalyst to form a dihydropyrimidinone (DHPM, **4**) product. In recent decades, chiral Brønsted acids[26–28] have emerged as powerful organocatalysts for asymmetric imine activation.[29–31] Mechanistic studies of the Biginelli reaction have suggested that chiral phosphoric acids (CPAs)[32–34] hold great promise as catalysts for controlling enantioselectivity. This hypothesis was validated in 2006 when the Gong group reported the first asymmetric Biginelli reaction, using an H_8-BINOL-derived (*R*)-**C1** catalyst. This pioneering work enabled the synthesis of a broad range of DHPMs with high enantiopurity (88–97% ee).[35] In 2009, they expanded the range of substrates through the regulation of (*R*)-**C2**, enabling the accommodation of cyclic and linear alkyl ketones (**5**) with inferior reactivity (Biginelli-like reaction). However, both the yield and enantiocontrol were visibly decreased when aromatic ketones were employed. The effect of the 3,3′-substituents of CPAs on the stereochemical control was also theoretically rationalized.[36] In 2017 and 2020, Hu and co-workers disclosed the applicability of another class of CPAs (**C3**, **C4**) in the asymmetric Biginelli reaction. These chiral catalysts with tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) as the core skeleton had previously been reported to facilitate the asymmetric Mannich reaction.[37] Control experiments verified that the hydrogen atoms of both hydroxyl groups on the catalyst are of crucial importance.[38,39] However, centrally chiral catalysts exhibited lower enantiocontrol and narrower substrate generality compared to those with axially chiral skeletons (Fig. 2). After that, Zou,[40] Xiao[41] and Silvani[42] independently made certain contributions to this transformation, paving a convenient avenue towards several pharmaceutical intermediates.

Besides the canonical Biginelli reaction, CPA catalysts also displayed remarkable enantiocontrol ability in the trapping of imines with other substrates *via* hydrogen-bonding activation. In 2008, an asymmetric three-component reaction of α,β-unsaturated aromatic aldehydes (**6**), amines (**7**) and

Peng-Ying Jiang

Peng-Ying Jiang was born in Guangxi, China, in 1996. She received her B.S. in pharmacy from Sichuan University in 2018. Then she received her Ph.D. in energy and environmental protection in 2024 under the supervision of Prof. Bin Tan from Harbin Institute of Technology. In the same year, she joined Prof. Tan's group and is currently working as a postdoctoral researcher. Her research interest focuses on the asymmetric construction of axially chiral aryl isoquinolines.

San Wu

San Wu was born in Anhui, China, in 1991. He received his B.S. in 2013 and M.S. in 2016 in chemistry under the supervision of Prof. Songlin Zhang from Soochow University. Then he received his Ph.D. under the supervision of Prof. Bin Tan from Harbin Institute of Technology in 2022. After graduation, he continued his work in Prof. Tan's research group as a postdoctoral researcher and is currently a Research Assistant Professor. His research interest focuses on the organocatalytic asymmetric synthesis of axially chiral compounds and heteroatom-chirogenic compounds.

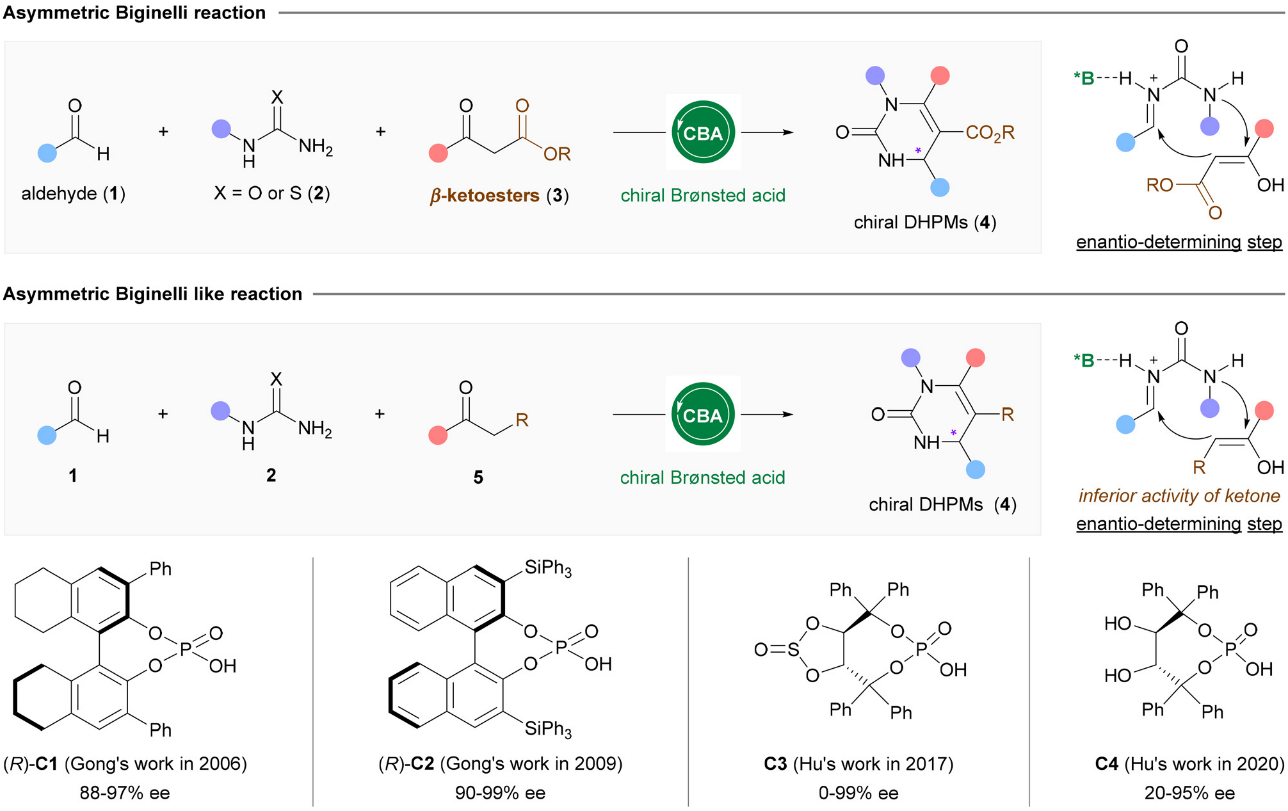


Fig. 2 Asymmetric Biginelli reaction catalyzed by CPA catalysts.

β-ketoesters with (*R*)-**C5** was developed by Gong's group, producing dihydropyridines (**8**) with high enantioselectivities. In this reaction, α,β-unsaturated iminium is generated from α,β-unsaturated aldehyde and primary amine under CPA catalysis. Subsequent asymmetric conjugate addition and cyclization lead to the target product (Fig. 3a).[43] Similarly, Sun reported an asymmetric aza-Diels–Alder reaction between *in situ*-formed imines and indoles (**10**) in the presence of 1,1-spirobiindane-7,7′-diol-based (*R*)-**C6**. The subsequent intramolecular ring-opening of oxetanes oriented at the *ortho*-posi-

Jun (Joelle) Wang

Jun (Joelle) Wang received her B.S. from Lanzhou University, M. Phil. from Shanghai Institute of Organic Chemistry (SIOC), and Ph.D. from Hong Kong Polytechnic University in 2009. Following her doctoral studies, she conducted post-doctoral research at the University of Texas Southwestern Medical Center (UTSW). From 2012 to 2020, Prof. Wang held positions as assistant professor and tenured associate professor at Southern University of Science and Technology (SUSTech). In 2020, she relocated her research program to Hong Kong Baptist University (HKBU), where she currently serves as a full professor. Her research interests include asymmetric catalysis, synthetic methodology, and green chemistry.

Shao-Hua Xiang

Shao-Hua Xiang was born in Hubei, China, in 1984. He obtained his B.S. in chemistry in 2006 and M.S. in organic chemistry in 2009 under the supervision of Prof. Pei-Qiang Huang from Xiamen University. In 2015, he received his Ph.D. from Nanyang Technological University, Singapore, under the direction of Prof. Xue-Wei Liu. Currently, he is a Research Associate Professor at SUSTech. His research interest focuses on the asymmetric construction of atropisomers.

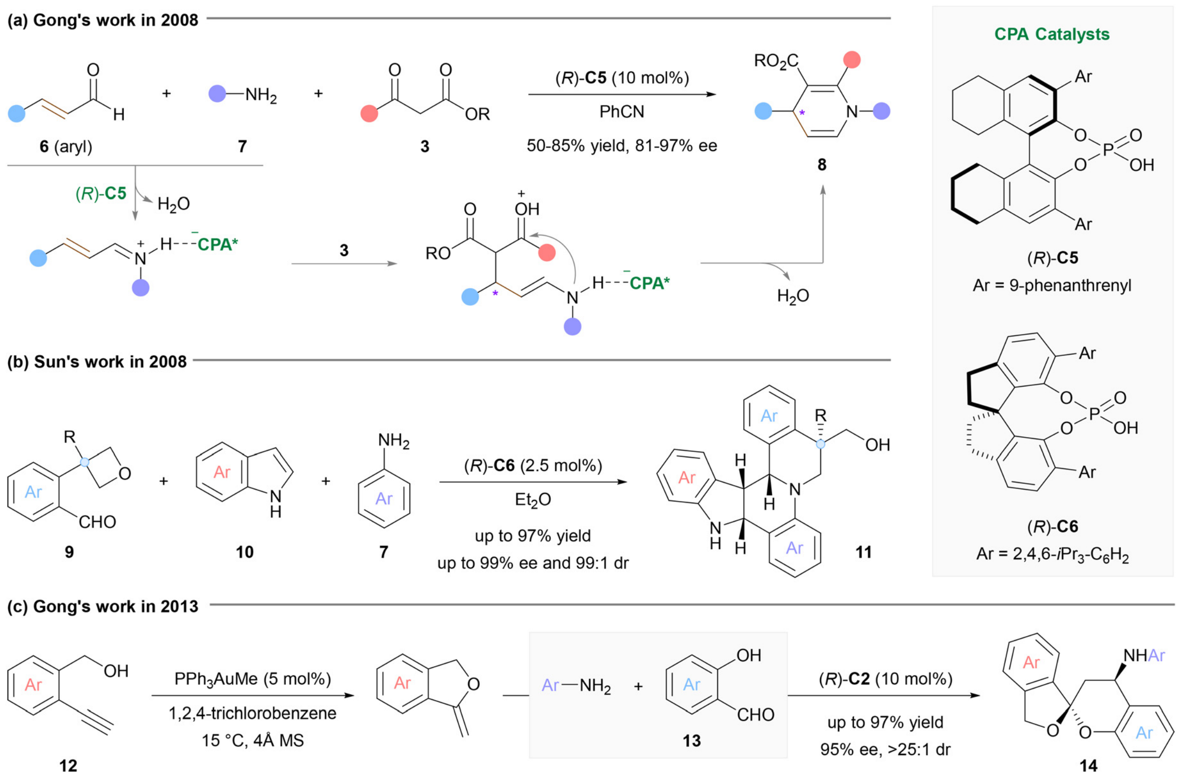
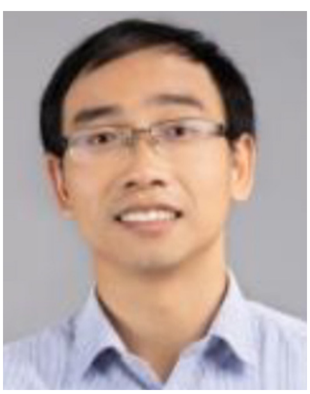


Fig. 3 Other variants of the asymmetric Biginelli reaction catalyzed by CPA.

tion of aromatic aldehydes (**9**) from the cyclized amines afforded structurally complex molecules (**11**) containing indoline, tetrahydroquinoline, and tetrahydroisoquinoline moieties. These products exhibited excellent diastereomeric ratios (dr) and ee values (Fig. 3b).[44] Additionally, nucleophilic TMSCN was amenable and the CPA-promoted asymmetric three-component Strecker reaction provided α-aminonitriles with excellent efficiency but low enantiocontrol.[45] In 2013, the enantioselective interruption of imines with (2-ethynylphenyl) methanol and its analogs (**12**) was realized by Gong. The relay three-component reaction enabled by the synergistic Au(I)/(*R*)-**C2** catalysis offered an expeditious route towards the synthesis of highly enantioenriched spiroacetals (Fig. 3c).[46] In the same year, Lin and co-workers disclosed an asymmetric three-component Povarov reaction to generate benzo[*e*]indolizidines with excellent yield and stereocontrol.[47]

The Passerini reaction is a classic isocyanide-based three-component reaction. It offers a rapid route for the assembly of α-acyloxyamides (**17**) *via* a one-pot reaction of a carboxylic acid (**15**), an aldehyde (**1**) and an isocyanide (**16**). Since one stereogenic center is generated, great efforts have been devoted to control the stereochemistry to expand the synthetic utility of this reaction. Attempts have primarily focused on chiral Lewis acid systems until Tan's work in 2015. In this reaction, the organocatalyst (*R*)-**C7** and carboxylic acid **15** form a heterodimer, which serves as a bifunctional catalyst to activate both the aldehyde (**1**) and isocyanide (**16**). The CPA dictates the stereochemical information to the nitrilium intermediate. The formation of the heterodimer may simultaneously enhance the acidity of the CPA and the nucleophilicity of the carboxylic acid, rendering the addition of the carboxylic acid to the nitrilium intermediate easier. This strategy not only delivered α-acyloxyamides with excellent enantiocontrol, but also demonstrated remarkable substrate generality, particularly for the aldehyde component. Both aryl and alkyl aldehydes, even



Bin Tan

Bin Tan was born in Hunan, China, in 1978. He received his B.S. from Hunan University of Science and Technology in 2001 and M.S. from Xiamen University in 2005. He obtained his Ph.D. from Nanyang Technological University, Singapore, under the direction of Prof. Guofu Zhong in 2010. From 2010 to 2012, he was a postdoctoral fellow with Prof. Carlos F. Barbas III at The Scripps Research Institute, USA. He became an associate professor at SUSTech in 2012 and then a full professor in 2018. His research currently focuses on the asymmetric synthesis and application of axially chiral molecules.

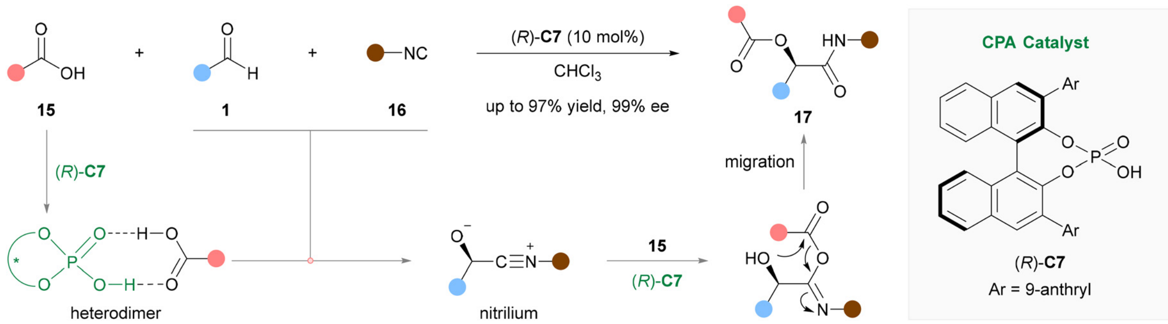


Fig. 4 Asymmetric Passerini reaction catalyzed by CPA.

sterically hindered pivalaldehyde, could be efficiently converted to the corresponding α-acyloxyamides (Fig. 4).[48]

In 1959, Ugi and co-workers subtly included another component, amine, in the Passerini reaction, and the resulting Ugi four-component reaction gave α-acylamino amides as the product with water as the only by-product. The introduction of an additional component notably enhances the flexibility of this reaction and greatly expands the structural diversity of the products. As a result, it has been widely employed in the construction of a vast array of heterocyclic and macrocyclic structures.[49] However, the increased complexity of the reaction system also presents a significant challenge in achieving effective stereoinduction.[50] Considering that the introduction of carboxylic acid not only adds complexity to the reaction but also leads to undesired background reactions, Zhu and co-workers conducted pioneering research on the catalytic asymmetric three-component reactions of aldehydes, anilines, and α-isocyanoacetamides (**18**). Through the facilitation of the CPA (*R*)-**C8**, this reaction successfully afforded 5-(1-aminoalkyl)-5-aminooxazoles **19** in excellent yields with moderate to good enantioselectivities (Fig. 5a).[51] This work laid the foundation for their development of a streamlined variant of the catalytic asymmetric Ugi four-component reaction, in which the carboxylic acid and aldehyde components were ingeniously integrated into a single compound **20**. Nonetheless, this Ugi four-center three-component reaction only accommodated six sub-

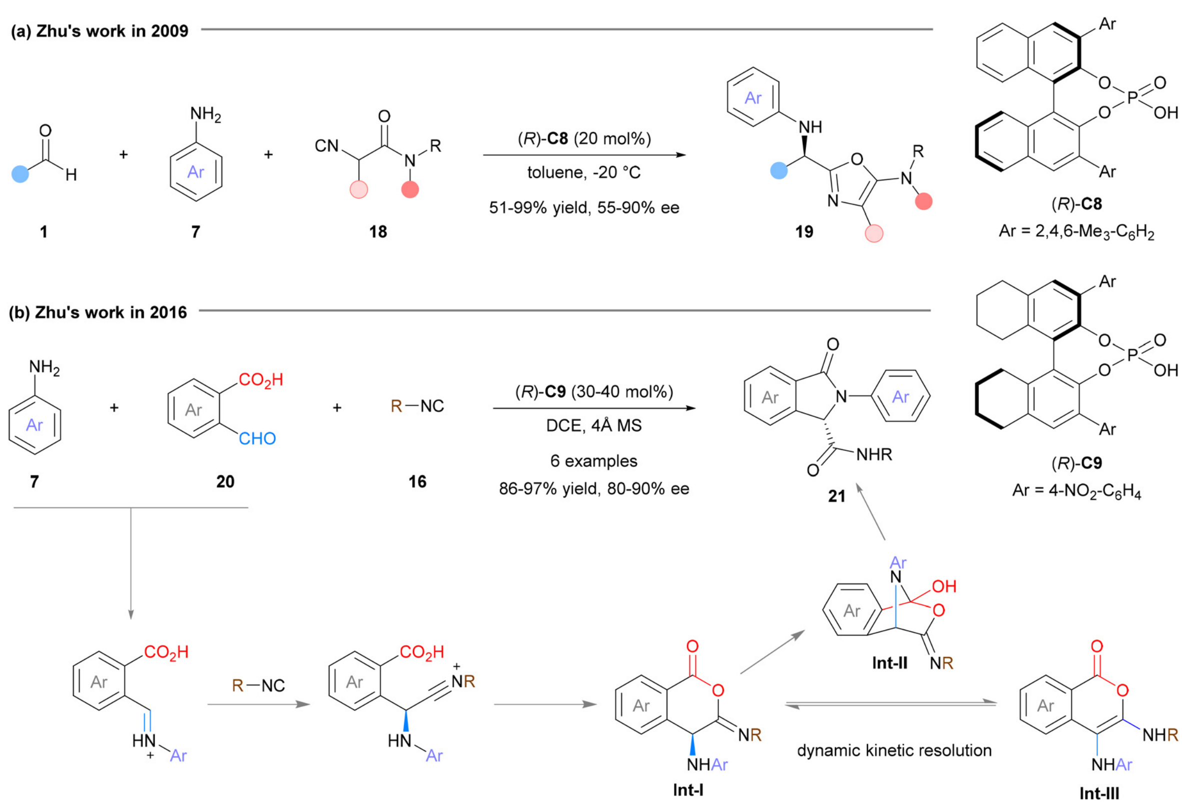


Fig. 5 Initial attempts on enantioselective Ugi-type three-component reactions.

strates and necessitated 30–40 mol% loading of (*R*)-**C9** to give satisfactory ee values for the 3-oxo-2-arylisoindoline-1-carboxamide products **21** (Fig. 5b).[52] Mechanistic investigations indicate that the enantiocontrol is contributed to the dynamic kinetic resolution of achiral **Int-III** generated from imine–enamine isomerization of chiral **Int-I** rather than the C–C bond-forming process. It should be mentioned that the utilization of secondary amides instead of primary amines in a one-pot reductive Ugi-type three-component reaction was established by the Huang group *via* direct activation and transformation of amides. This reaction provided rapid access to a series of α-acetamidoamides with carboxylic acid and isocyanide as the other two components.[53]

Optically active aziridines hold significant potential across diverse research fields, particularly as versatile synthons in synthetic chemistry. The pioneering achievement of asymmetric multicomponent reactions in the synthesis of such compounds (**24**) was realized in 2009 by the Akiyama group through CPA-catalyzed asymmetric cycloaddition of imines and diazoacetate **23a**. However, this enantioselective aza-Darzens reaction was confined to benzoyl-substituted aldehydes (**22**), limiting its further application (Fig. 6a).[54]

In 2017, Bew and co-workers established a relatively broad asymmetric three-component aza-Darzens reaction. The key to this transformation was the judicious choice of a CPA-derived Brønsted acid catalyst (*S*)-**11**, which possesses stronger acidity. This enabled the reaction to accommodate a wide range of commonly used (hetero)aryl aldehydes. Additionally, the presence of a *tert*-butoxy group at the *ortho*-position of the aromatic amines played a crucial role in achieving high stereochemical induction of aziridines (**25**). This effect was facilitated through both hydrogen bonding interactions and steric influences (Fig. 6b).[55]

In 2019, Studer and co-workers reported an enantioselective three-component Minisci reaction, providing a valuable synthetic route to pharmaceutically relevant γ-amino acid derivatives (**29**). This cascade reaction, initiated from α-bromocarbonyl compounds (**26**), enamides (**27**), and quinolines or pyridines (**28**), proceeded with high levels of chemoselectivity, regioselectivity, and enantioselectivity under mild conditions. The dual catalysis by photoredox and CPA was crucial to achieving these selective outcomes. The mechanism involves the initial single-electron transfer in α-bromocarbonyls (**26**), which generates an alkyl radical. This radical subsequently reacts with the electron-rich enamine, resulting in the formation of a nucleophilic radical. Driven by the bifunctional activation of the catalyst (*R*)-**12**, which involves both quinoline/pyridine and the resulting radical species, the enantioselective nucleophilic addition of iminium takes place, ultimately yielding the desired γ-amino acid derivatives (**29**). Chiral 1,2-diamine (**30**) derivatives could also be achieved with the same strategy (Fig. 7).[56]

Aside from central chirality, AMCRs have also been successfully applied in the construction of axially and helically chiral architectures. In 2015, Doyle reported a three-component cascade reaction of *in situ*-formed enamines with 2,3-diketoesters (**31**) under Brønsted acid catalysis to afford 5-vinyl-pyrrole and 4-hydroxy-indole derivatives in generally moderate to good yields *via* successive aldol/cyclization/aromatization.[57] Inspired by this pioneering work, an asymmetric variant was realized by Lin and co-workers using aryl amines bearing sterically hindered groups at the *ortho*-position. This reaction furnished various atropisomeric *N*-arylindole compounds (**33**) in good yields with excellent enantioselectivities. Experimental results revealed that the catalyst (*R*)-**13** derived from the 3,3,3′,3′-tetramethyl-1,1′-spirobiindane-7,7′-diol (TM-SPINOL) skeleton exhibited better stereoinduction ability than those derived from commonly used cores, including BINOL and SPINOL (Fig. 8a).[58]

In 2023, AMCR was effectively harnessed by Yang and co-workers in the synthesis of chiral azahelicenes (**36**) *via* a one-

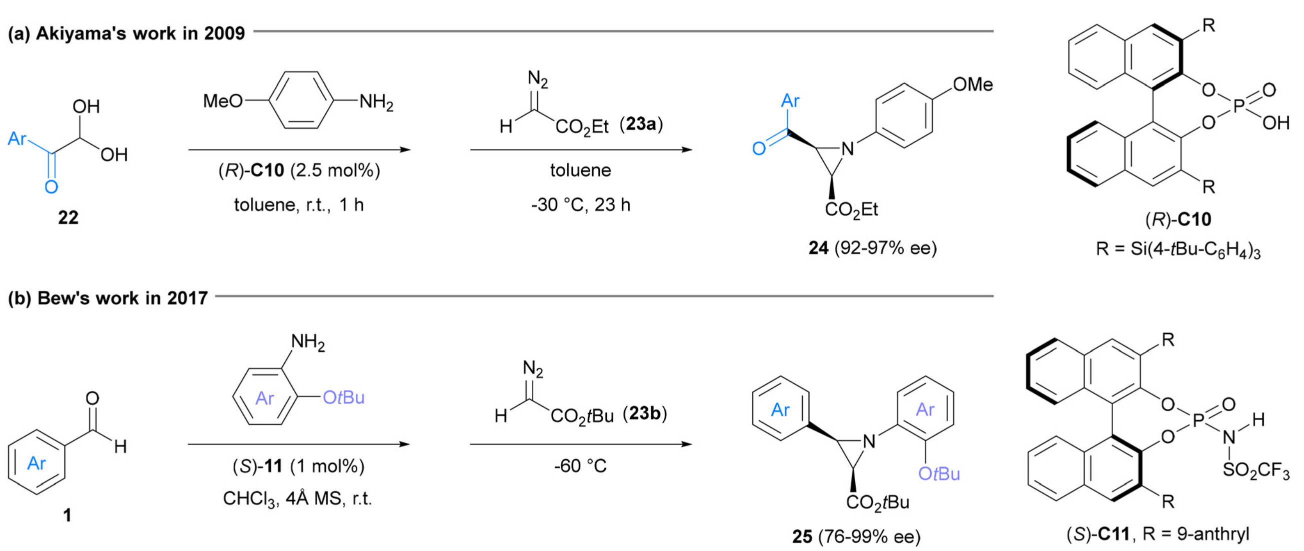


Fig. 6 Asymmetric Brønsted acid-catalyzed three-component aza-Darzens reactions.

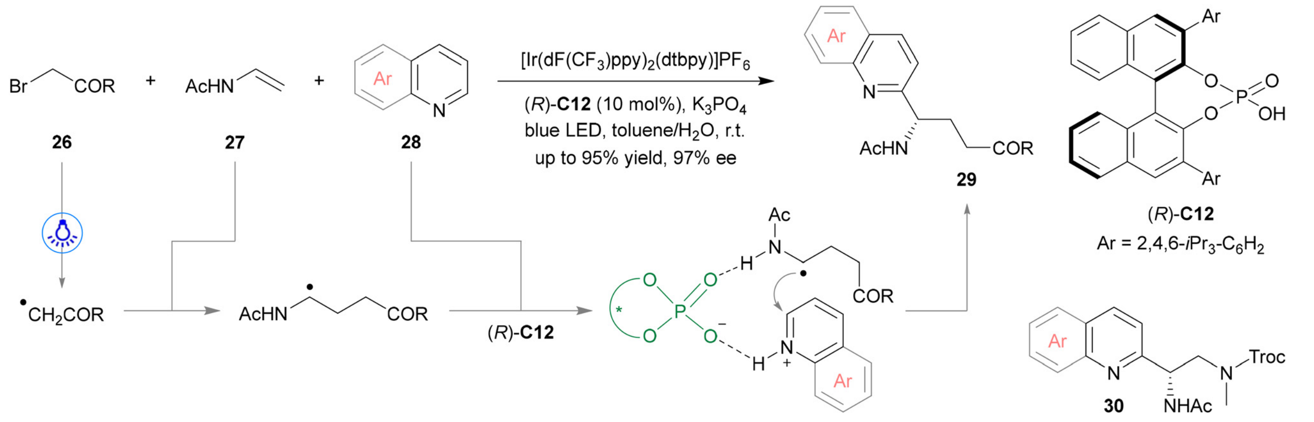


Fig. 7 Enantioselective three-component Minisci reaction catalyzed by CPA.

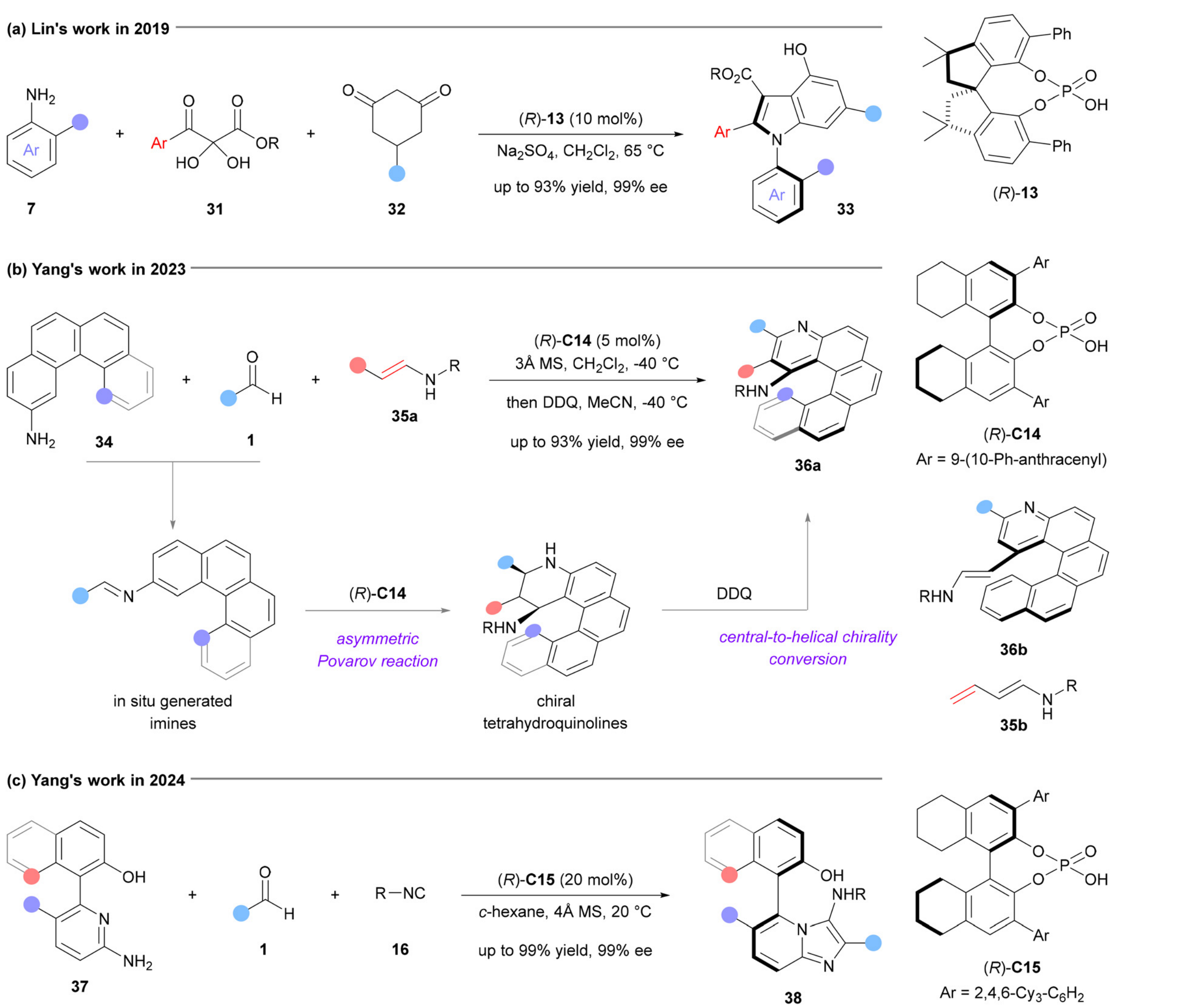


Fig. 8 Synthesis of atropisomers and helicenes *via* CPA-catalyzed AMCRs.

pot reaction involving polycyclic aryl amines (**34**), aldehydes (**1**), and amides (**35a**). This transformation comprises two sequential processes. The first is the asymmetric Povarov reaction, where imines are intercepted by electron-rich olefins in the presence of (*R*)-**14**. Subsequently, the resulting chiral tetrahydroquinolines are oxidized to yield the final azahelicene products (**36a**) through an aromatization-enabled central-to-helical chirality conversion. When diene substrates **35b** were utilized, the asymmetric cyclization of the terminal alkene with the imine takes place to give **36b** as products. These compounds were found to possess unique acid/base-triggered switching of photophysical properties (Fig. 8b).[59] More recently, the same group realized the enantioselective Groebke–Blackburn–Bienaymé reaction by means of organocatalysis. Using the catalyst (*R*)-**15**, various 6-aryl-2-aminopyridines (**37**), aldehydes (**1**), and isocyanides (**16**) were efficiently converted to structurally diverse imidazo[1,2-*a*]pyridine atropisomers (**38**) in high to excellent yields with excellent enantiopurities. Control experiments demonstrated that the remote hydrogen bonding donor on the substrate plays a crucial role in achieving high stereoselectivity in the reaction (Fig. 8c).[60]

Besides CPA, other chiral Brønsted acid catalysts have also been used in AMCRs. In 2012, Maruoka reported an asymmetric Ugi-type reaction using hydrazides (**39**) instead of traditional amines. In this reaction, the BINOL-embedded axially chiral dicarboxylic acid catalyst (*R*)-**16** was utilized to facilitate the asymmetric addition of isocyanides (**16**) to the *in situ* generated acyclic azomethine imines. The intramolecular trapping of the resulting nitrilium ion intermediates with the oxygen atoms of hydrazides generates a series of chiral heterocyclic compounds (**40**). Notably, the 2-benzoyl group of the isocyanides can be efficiently removed to afford benzoxazole derivatives (**41**) with excellent efficiency and enantiocontrol. This transformation is achieved through a one-pot treatment of the Ugi-type reaction mixture with K_2CO_3 in CF_3CH_2OH (Fig. 9a).[61] In 2016, axially chiral disulfonimide (*R*)-**17** was elegantly adopted by Rodríguez and co-workers to promote the enantioselective three-component reaction of aldehydes (**1**), aromatic amines (**7**) and enol ethers (**42**). Compared with the traditional CPAs, this type of Brønsted acid catalyst harbors one more basic site. It was found that the installation of substituents at the 3,3′-positions of (*R*)-**17** gave rise to the configurational inversion of pyrrolo[1,2-*a*]indole derivatives (**43**) and computational studies were performed to explain this unusual enantioinversion phenomenon (Fig. 9b).[62]

In addition, a chiral task-specific ionic liquid, merging a chiral phosphate anion and a nonchiral Brønsted acid-appended imidazolium cation, was effectively employed to catalyze the asymmetric three-component Biginelli reaction by the Neto group in 2018.[63] On the other hand, Peng and co-workers combined CPA and silver carbonate to catalyze a cyclization/Mannich tandem reaction of 2-alkynylbenzaldehydes, aromatic amines, and dimethylphosphonate in 2020. Good stereoinduction was observed in the desired cyclic α-aminophosphonate products.[64]

2.2 Asymmetric four-component reaction

As previously stated, the typical Ugi reaction involves four distinct components: a carbonyl compound, an amine, an acid, and an isocyanide. Due to the complexity of its reaction mechanism, research on asymmetric variations of this well-established reaction has primarily focused on three-com-

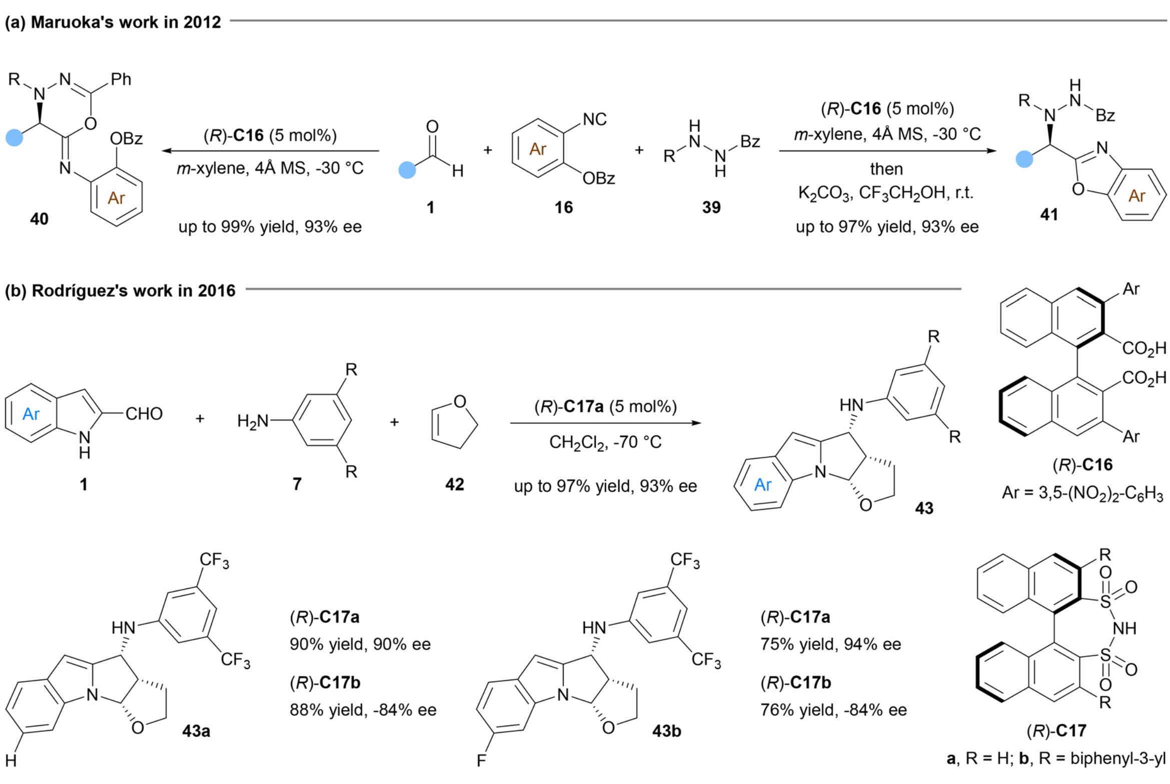


Fig. 9 AMCRs catalyzed by other chiral Brønsted acids.

ponent reactions with simplified systems. Despite numerous attempts, the four-component Ugi reaction remained elusive until Tan's groundbreaking work in 2018. In this study, CPAs were utilized as the most effective catalysts. It was hypothesized that the greater acidity of CPA compared to carboxylic acid facilitates the acceleration of the target reaction's kinetics and surpasses the background reactions. Furthermore, the self-assembled heterodimerization between CPA and carboxylic acid results in an enhancement of acidity of the catalyst and an increase in the nucleophilicity of the carboxylic acid, effectively realizing catalytic asymmetric control. Simultaneously, the rapid formation of imines and the preferential activation of carbonyl groups under CPA catalysis can effectively suppress the Passerini reaction and other undesired side reactions. The developed reaction exhibited broad substrate generality. Both aliphatic and aromatic aldehydes were accommodated through slight modification of the CPA catalyst, offering a library of more than 80 α-acylamino amides (**44**) in generally good yields with excellent enantioselectivities. Further elaboration of the highly enantioenriched products *via* post-condensation enabled a rapid approach for synthesizing pharmaceutically relevant molecules. DFT calculations were performed by Houk and co-workers to demonstrate the reaction mechanism and origins of stereoselectivity (Fig. 10a).[65] In 2020, the Tan group applied this catalytic system to the asymmetric Ugi reaction with H_2O *in situ* generated along with the formation of imines instead of carboxylic acids to provide the α-amino amides with high enantiocontrol.[66]

Three years later, access to β-amino acids and their derivatives (**46**) was achieved through the re-design of the catalytic asymmetric four-component Ugi reaction. In this work, the C1-synthon isocyanide component was replaced with the ambiphilic C2-synthon ynamide (**45**). The employment of CPA-derived *N*-triflylphosphoramide derivatives with stronger acidity as catalysts is crucial to facilitate this transformation. Three classes of β-amino amides bearing one or two contiguous carbon stereocenters, totaling over one hundred, were accessible through altering ynamides or oxygen nucleophiles. Notably, this approach can be utilized in the late-stage modification of drugs (Fig. 10b),[67] demonstrating its practicality and flexibility in synthetic chemistry.

Besides the classic examples shown above, chiral Brønsted acids have also been used in some other AMCRs in the synthesis of chiral heterocyclic compounds.[68] In these reactions, the initial step is usually the formation of imines or their derivatives. Through hydrogen-bonding activation of chiral

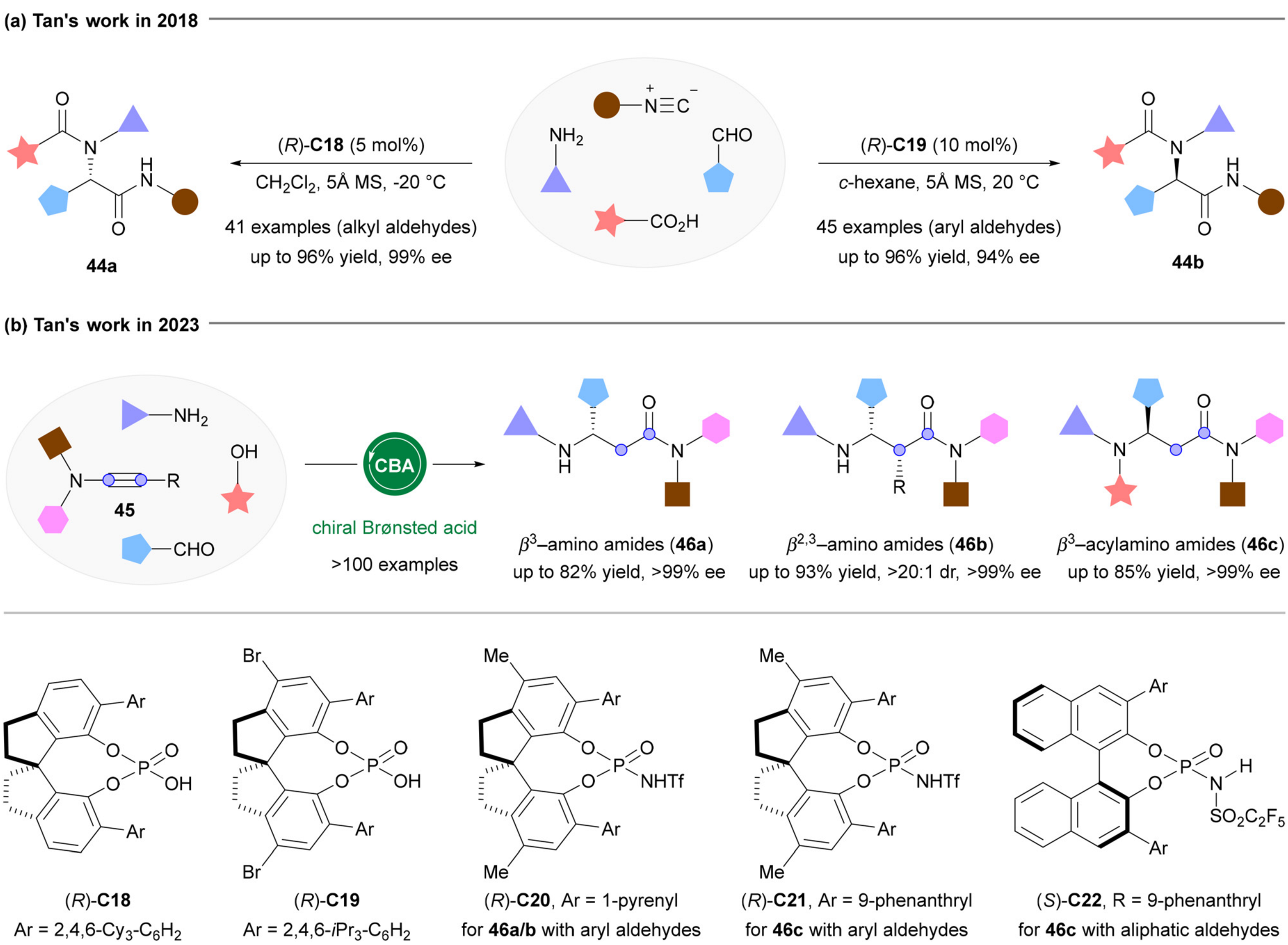


Fig. 10 Asymmetric four-component Ugi-type reactions.

Brønsted acids, imines or their tautomers undergo asymmetric cycloaddition with the other component to afford the desired products. As for the construction of spiro structures, which was comprehensively summarized by Franz and co-workers[69] in 2021, we will not delve into further details here.

3. Chiral amine catalysis

Amines react with carbonyl compounds to form imines or enamines as transient intermediates. These reactive species can undergo subsequent transformations with diverse coupling partners, while the amine catalyst is regenerated under mild work-up conditions. To harness this reactivity for asymmetric synthesis, chiral amine catalysts, particularly secondary amines, have been strategically designed to activate carbonyl substrates and orchestrate enantioselective bond-forming processes. The structural tunability of these chiral catalysts, achieved through modular substitution patterns on their frameworks, enables precise stereochemical induction across a broad spectrum of transformations.[70] Notably, such amine-based catalytic systems have been successfully implemented in AMCRs, demonstrating their versatility in constructing complex molecular architectures with high stereocontrol.

As early as 2000, List reported the first example of the asymmetric three-component Mannich reaction of aldehydes, acetone and *p*-anisidine employing proline **C23** as the catalyst, providing a rapid access towards chiral β-amino ketones **47** through the nucleophilic addition of enamine which was generated by activating acetone to form imine intermediates. Generally, relatively high enantioselectivities and poor yields were obtained for aromatic aldehydes, while aliphatic aldehyde substrates resulted in compromised enantiocontrol but improved efficiency (Fig. 11a).[71] Subsequently, in 2005, Jørgensen and co-workers reported the discovery of a chiral amine **C24**-catalyzed AMCR of α,β-unsaturated aldehydes. This reaction combines iminium and enamine activation to generate active iminium ion intermediates, which then lead to a highly enantioselective addition of thiols (**48**) at the β-carbon center. The resulting enamines are trapped by azodicarboxylates (**49**), acting as the electrophiles. Upon treatment with $NaBH_4$, cyclization products **50** bearing two stereogenic centers were formed with generally good to high diastereocontrol and remarkable enantiocontrol (Fig. 11b).[72] Apart from thiols, succinimide was also an amenable nucleophile for this

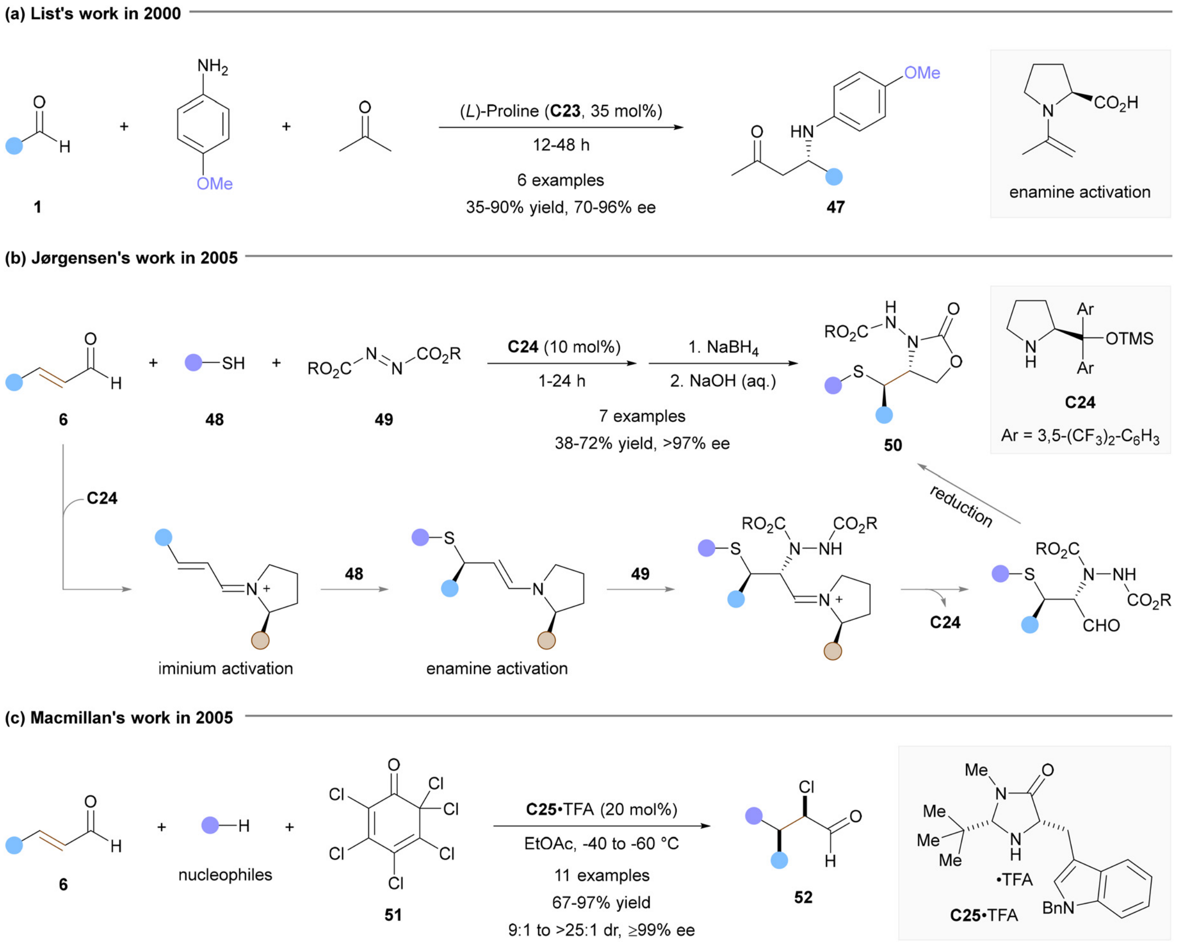


Fig. 11 Pioneering AMCRs catalyzed by chiral secondary amines.

protocol to give the corresponding products stereoselectively.[73] Utilizing the same tactic, Macmillan and co-workers realized the asymmetric chlorofunctionalization of α,β-unsaturated aldehydes with chlorinated quinone **51** as the electrophilic chlorine source (Fig. 11c).[74] Notably, structurally novel bridged benzoxazocines could be formed through a γ-selective Mannich-initiated one-pot cascade reaction when electron-rich aromatic amines and electron-deficient salicylaldehydes were incorporated into this type of transformation.[75]

In 2006, a chiral amine **C26** catalytic enamine–iminium–enamine triple activation sequence was realized by the Enders group, employing aldehydes, α,β-unsaturated aldehydes and nitroolefins (**53**) as starting materials. This AMCR furnished *tetra*-substituted cyclohexene derivatives (**54**) possessing four contiguous stereogenic centers with complete enantiocontrol *via* successive Michael, Michael, and aldol reactions. Despite modest chemical yields and only moderate dr values in most cases, this three-component multistep reaction demonstrated exceptional versatility in constructing a broad array of multi-functionalized cyclohexene derivatives. These derivatives are highly valuable as versatile chiral building blocks in organic synthesis (Fig. 12a).[76] Afterwards, the same group further expanded the range of the developed AMCR and a variety of complex chiral molecules **55–60** were readily accessed (Fig. 12b).[77–81] Additionally, the Jørgensen group disclosed an enantioselective three-component reaction involving two different α,β-unsaturated aldehydes and malononitrile in 2007, utilizing a similar strategy. Through consecutive iminium–iminium–enamine activation, two stereogenic centers were formed in the cyclohexene products **61** under the catalysis of **C24** (Fig. 12c).[82]

Aside from Michael-type addition, chiral amine catalysts were also engaged in asymmetric 1,3-dipolar cycloaddition reactions. In 2007, inspired by the two-component reaction between nitrones and α,β-unsaturated aldehydes for the synthesis of isoxazolidines reported by MacMillan and co-workers,[83] and by virtue of chiral amine-enabled iminium activation, Córdova's group proposed an asymmetric three-

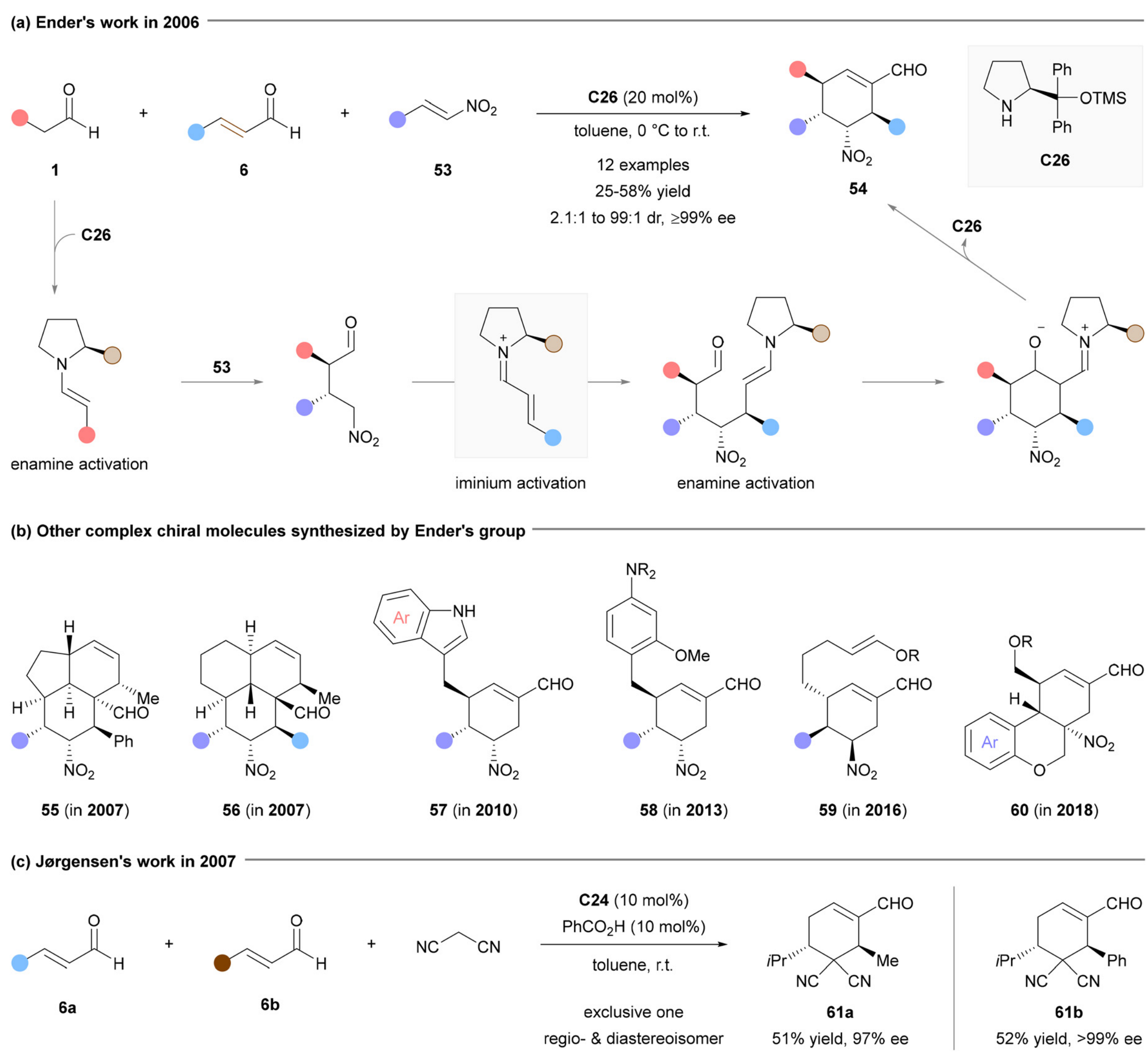


Fig. 12 Chiral amine-catalyzed AMCRs involving multiple activation sequences.

component variant through the *in situ* generation of nitrones (**63**) from hydroxylamines (**62**) and aldehydes (**1**). Considering the slight epimerization of the resulting aldehyde products (**65**) upon silica-gel column chromatography, reduction with $NaBH_4$ was performed to give the chiral alcohols (**64**) as the final products (Fig. 13a).[84] In the same year, they performed a similar reaction by substituting hydroxylamine with 2-aminomalonate. Through the 1,3-dipolar cycloaddition of *in situ*-generated imines with chiral amine-activated iminium intermediates, highly functionalized pyrrolidine derivatives were readily obtained with enantioselectivities exceeding 90%.[85] In 2020, Liu and co-workers reported a chiral amine-catalyzed asymmetric multicomponent reaction (AMCR) involving hydroxylamine, acrylaldehyde, and acetal-containing enones (**66**). The reaction began with the formation of cyclic hemiacetals (**67**) through an aza-Michael reaction, facilitated by iminium activation. Subsequent enamine activation of these cyclic hemiacetals enabled a Michael addition with the acetal-containing enones, yielding highly functionalized hemiacetals (**68**). To simplify the reaction system, (±)-camphorsulfonic acid (CSA) was added to give bisacetal-containing bicyclic isoxazolidines with four continuous stereocenters (**69**) as the final products for analysis (Fig. 13b).[86]

Chiral amines have also participated in the asymmetric Biginelli reaction as co-catalysts. In 2008, Feng and co-workers reported their success through the combination of a chiral amine (**C27**) and an achiral Brønsted acid. Two independent activation modes were involved in this reaction. Imines were *in situ* generated from aldehydes and urea under Brønsted acid catalysis, while the chiral amine catalyst promoted the formation of enamine intermediates from β-ketoesters. Aromatic, heteroaromatic, and fused-ring aldehydes were all found to be suitable substrates for this transformation and afforded dihydropyrimidines with good to excellent enantiocontrol but poor yields (Fig. 14a).[87] Given the specific activation ability and unique activation mode of chiral secondary amine catalysts towards aldehydes or ketones, structurally novel molecules may be readily accessed through rational introduction of other components. In 2021, harnessing the high reactivity of aromatic isobenzopyrylium ions, Jørgensen and co-workers realized the asymmetric synthesis of chiral tetrahydronaphthols (**72**) containing four contiguous stereocenters from the reaction of isochromenes (**71**), α,β-unsaturated aldehydes and H_2O *via* dienamine catalysis. In this transformation, a catalytic amount of Brønsted acid HCl was added to release the reactive isobenzopyrylium intermediates. Notably, the resulting product was efficiently utilized in the con-

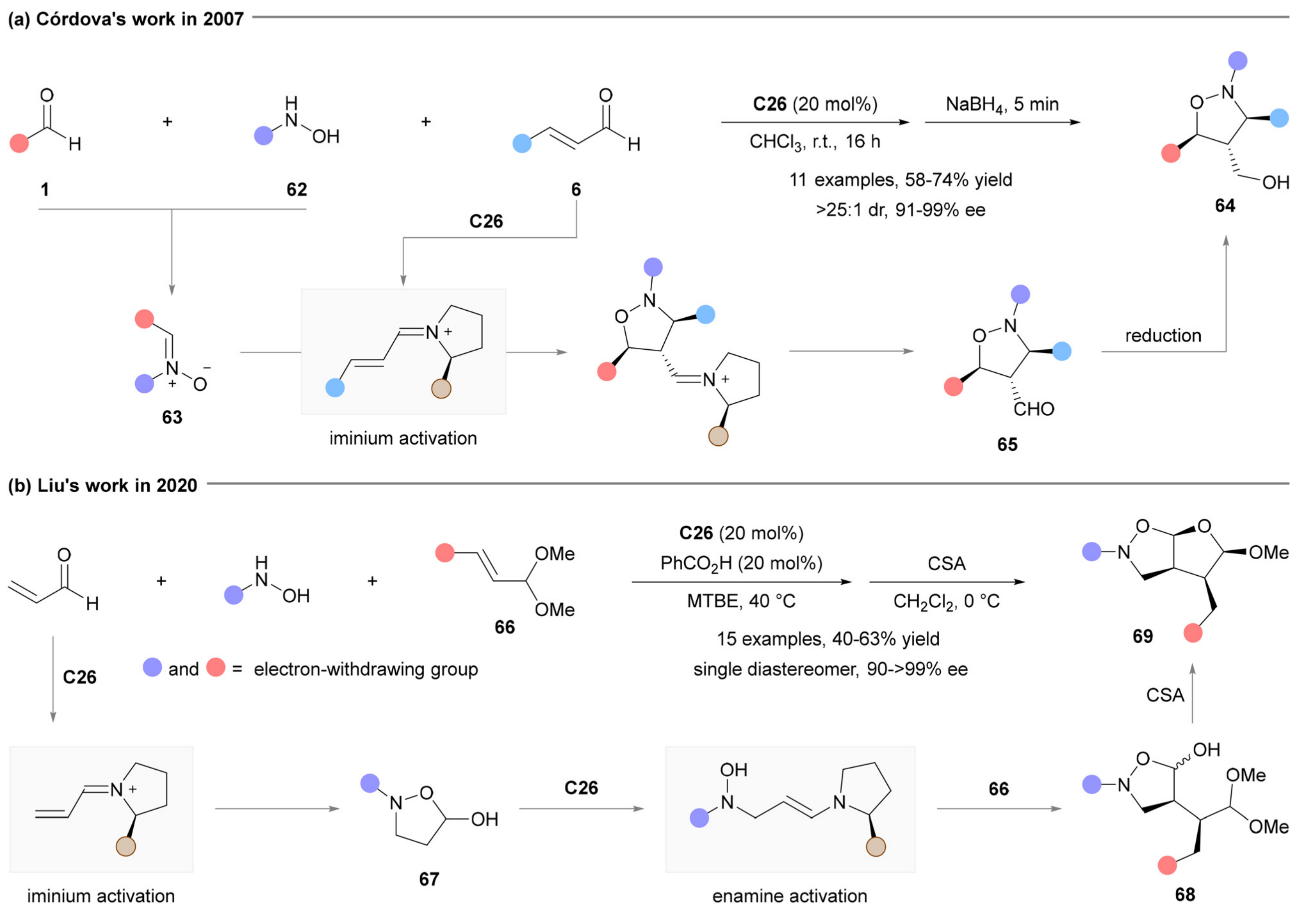


Fig. 13 Chiral amine-catalyzed AMCRs involving a hydroxylamine component.

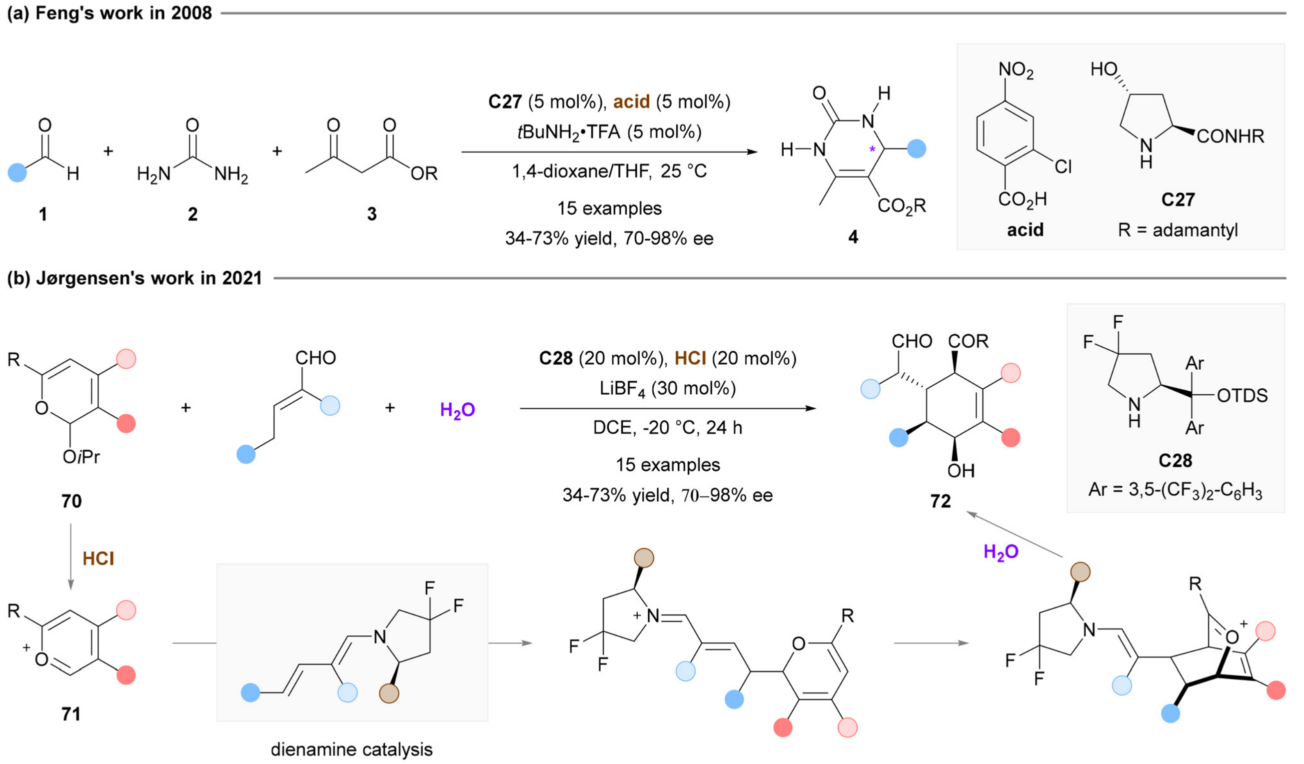


Fig. 14 AMCRs with chiral secondary amines as co-catalysts.

struction of octahydrobenzo[*h*]isoquinoline and [2.2.2]octane skeletons (Fig. 14b).[88]

In addition to secondary amines, chiral primary amines derived from enantiopure cinchona alkaloids have also demonstrated remarkable capabilities in catalyzing organic reactions. Unlike secondary amines, primary amine catalysis provides unique opportunities to address substrates with significant steric hindrance, such as ketones and α,α-disubstituted aldehydes. For its application in AMCR, a pioneering work was reported by the Melchiorre group in 2009. They demonstrated the activation of α,β-disubstituted enals by **C29** through a well-defined iminium/enamine tandem sequence. This approach enabled the stereoselective synthesis of various valuable precursors of α-amino acids (**73**), which feature two adjacent stereogenic centers. Azodicarboxylates (**49**) were employed as electrophiles, while indoles and thiols served as nucleophiles (Fig. 15a).[89] In 2018, Chen and co-workers developed an AMCR involving aldehydes, isoxazol-5(4*H*)-ones (**74**), and 3-substituted 2-cyclopentenones (**75**). This reaction, catalyzed by primary amine **C30**, enabled the rapid construction of highly enantioenriched spirocyclic frameworks (**76**) through the presented mechanistic pathway (Fig. 15b).[90]

4. Chiral thiourea-derived organocatalysts

Bifunctional chiral thiourea-amine organocatalysts have garnered significant attention in asymmetric synthesis due to their unique ability to simultaneously activate both electrophilic and nucleophilic reactants. This dual activation mode is highly advantageous for enhancing reaction rates and achieving superior enantiocontrol. The application of such catalysts in AMCRs has been extensively explored.[91] In this context, we will highlight several representative research findings.

The asymmetric Strecker reaction is a powerful strategy for the enantioselective synthesis of α-amino acid derivatives. However, one major limitation of the traditional Strecker reaction is the use of toxic hydrogen cyanide (HCN). To address this challenge, a modified three-component acyl-Strecker reaction has been developed, employing acyl cyanides as an alternative source of cyanide ions (CN^-). In 2007, the first organocatalytic asymmetric variant of this AMCR was realized by the List group where various α-aminonitriles (**78**) were assembled with excellent yields and enantioselectivities from aldehydes, amines and acyl cyanides (**77**) in the presence of the chiral thiourea-based organocatalyst **C31**. Both aryl and aliphatic aldehydes were amenable for this reaction; however, compromised enantiocontrol was obtained when simple alkylamines were evaluated (Fig. 16).[92]

The Petasis reaction is also a very famous multicomponent reaction and has a lot of applications in organic synthesis. In 2007, the Takemoto group reported that a newly designed chiral thiourea catalyst **C32** could activate organoboric acids and facilitate the enantioselective variant of the Petasis-type transformation of quinoline compounds even at low temperatures. A high degree of enantiocontrol was achieved in the

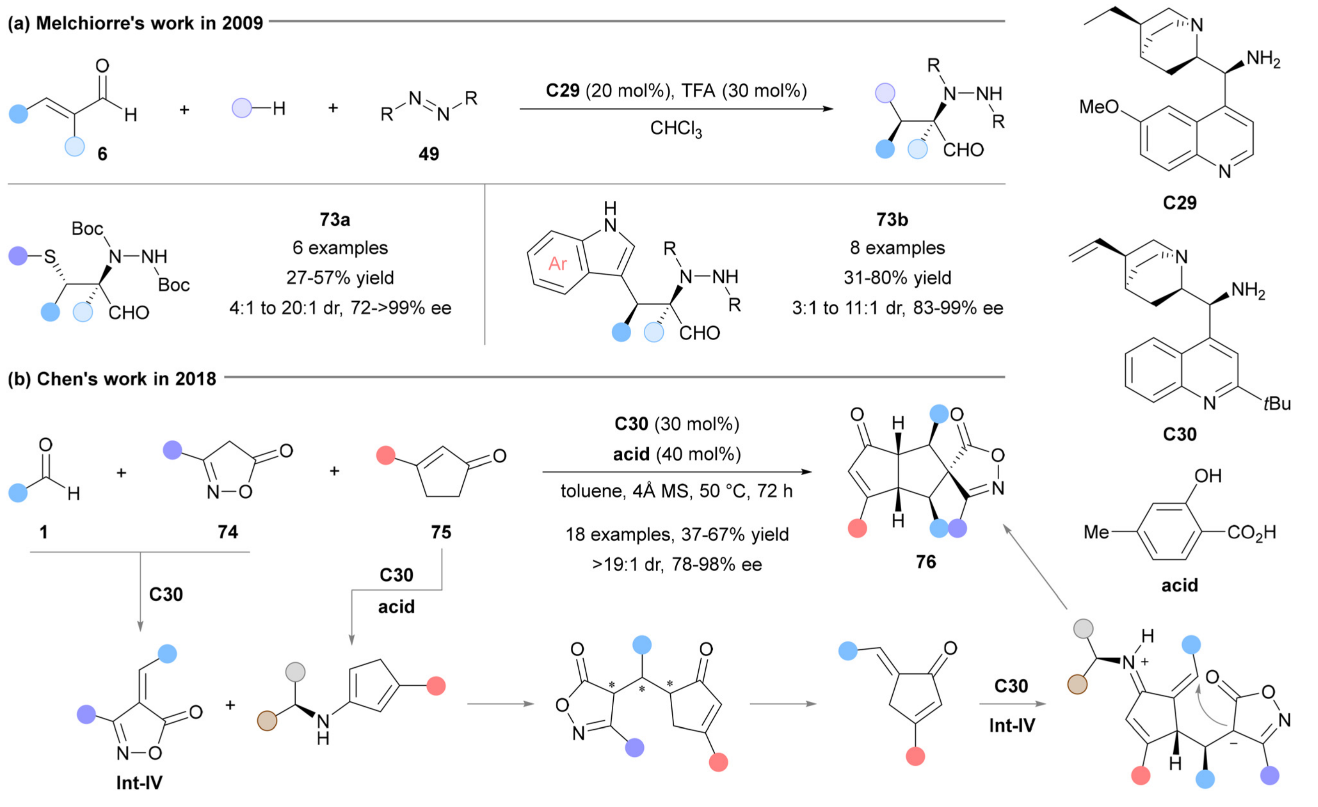


Fig. 15 AMCRs catalyzed by chiral primary amines.

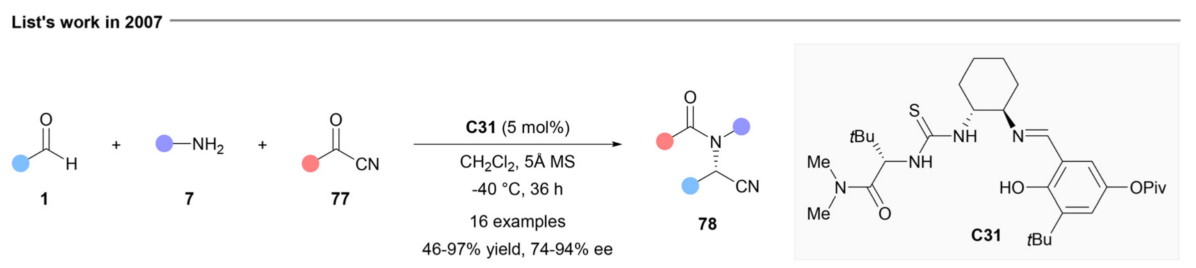


Fig. 16 Asymmetric multi-component Strecker reaction catalyzed by chiral thiourea.

reaction of various quinoline compounds (**79**) and alkenyl boronic acids (**80**). It was proposed that the 1,2-amino alcohol moiety on the catalyst activated the boronate nucleophile while thiourea activated the electrophilic *N*-acylated quinolinium salt *via* hydrogen bonds (Fig. 17a).[93] In 2012, Yuan and co-workers realized a catalytic enantioselective three-component Petasis reaction among salicylaldehydes, amines, and organoboronic acids with a chiral thiourea catalyst **C33** bearing both central and axial chirality elements. This reaction gave a wide range of alkylaminophenols (**81**) with generally good yields and high enantioselectivities. It should be mentioned that a cyclic binaphthyl-derived boronate ester fragment is proposed through the diol exchange of the BINOL moiety in the catalyst with the boronic acid reactant (Fig. 17b).[94]

The application of chiral thiourea-amine bifunctional catalysts in the asymmetric Biginelli reaction was introduced in 2011 by the Chen group. The identification of a sugar-glycosylated chiral phase-transfer catalyst **C34**·TfOH is essential for high enantiocontrol. It is suggested that the thiourea entity activates the condensed α,β-unsaturated imine through hydrogen bonding interaction, and the primary amine functionality enables the generation of an active enamine from β-ketoester for the subsequent nucleophilic addition event (Fig. 18a).[95] Soon after, Bolm and co-workers attempted this reaction with chiral sulfoximine-derived bifunctional thiourea catalysts. However, none of the evaluated chiral catalysts provided satisfactory stereoinduction in the desired DHPM products.[96] In 2016, Han and co-workers developed an organocatalyst **C35** which was self-assembled from a cinchona alkaloid-based thiourea and an L-proline derivative for promoting the asymmetric Biginelli reaction with excellent efficiency and enantiocontrol. When the two catalysts were used separately, both the yield and enantioselectivity were significantly decreased (Fig. 18b).[97] Moreover, diverse variants of the asymmetric

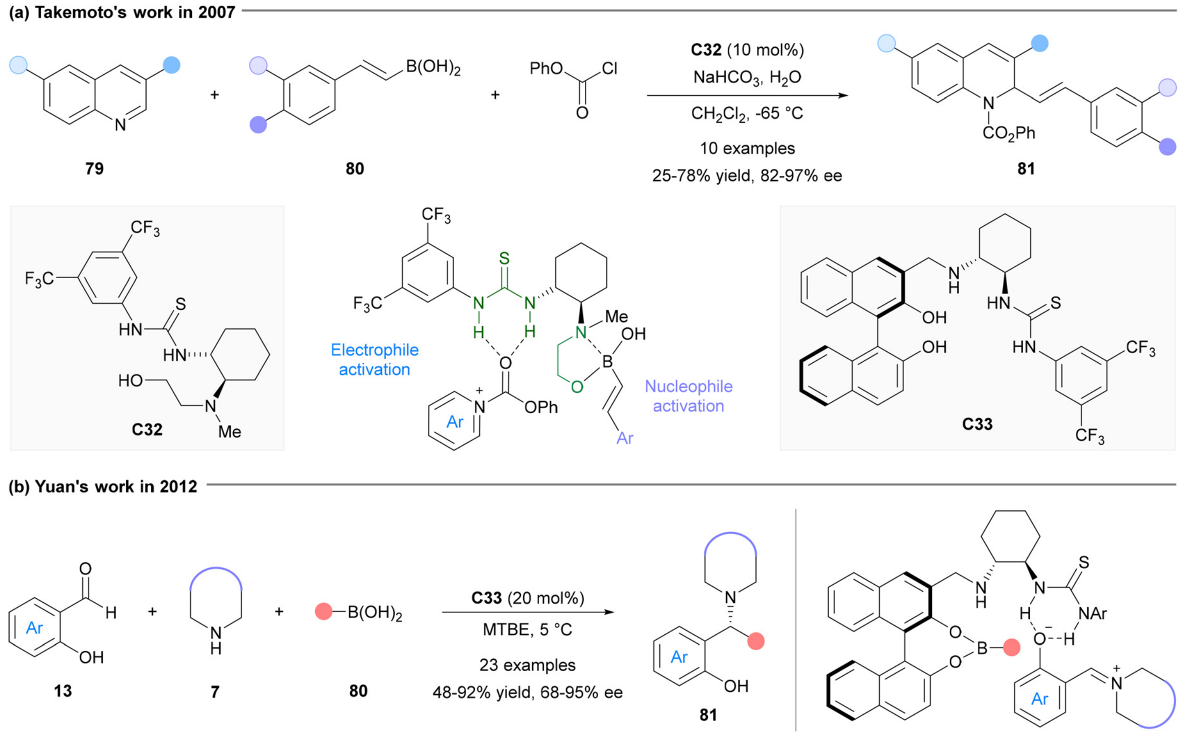


Fig. 17 Asymmetric multi-component Petasis-type reaction catalyzed by chiral thiourea.

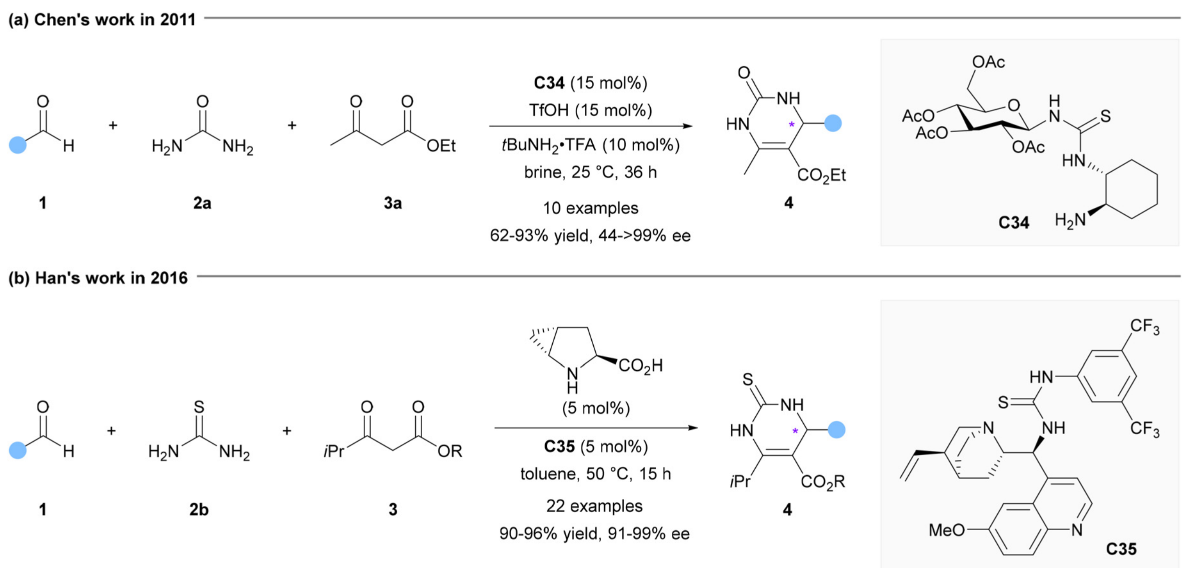


Fig. 18 Asymmetric multi-component Biginelli reaction catalyzed by chiral thiourea.

Biginelli reaction with aldehydes and amines as substrates were achieved using this type of catalyst by means of hydrogen bonding interaction between thiourea and imine, which directed enantioselective Mannich-type reactions.[98–103]

Besides, chiral thiourea-based bifunctional catalysis has also been applied in some other types of transformations. For instance, Xu, Dixon and co-workers reported a highly enantioselective protocol for the preparation of cyclohexanes (**83**) with multiple stereogenic centers *via* synergistic catalysis of a thiourea-amine and a cyclic secondary amine using asymmetric Michael addition as one of the key steps. In the reaction pathway, the thiourea-amine promotes the Michael addition between malonate esters (**82**) and nitroalkenes *via* bifunctional activation. After that, secondary Michael addition occurs from the resulting chiral adducts to iminiums generated from the cyclic secondary amine and α,β-unsaturated aldehydes.

Subsequent cyclization gives chiral cyclohexanes as the final products. By altering the stereochemical configurations of the proline catalysts used in this reaction, different diastereomers could be rapidly accessed with high enantiocontrol (Fig. 19a).[104] In 2010, they expanded this chemistry to AMCRs of aldehydes, nitroalkenes and imines (**84**). In contrast, enamine activation of aldehydes by the chiral amine catalyst was involved in this reaction, and fully substituted cyclic hemiaminals (**85**) were synthesized with nearly complete enantiocontrol (Fig. 19b).[105] Apart from synergistic catalysis, the introduction of a chiral amine into chiral thiourea catalysts also demonstrated good stereoinduction ability in the construction of cyclic structures involving enantioselective Michael addition.[106–109]

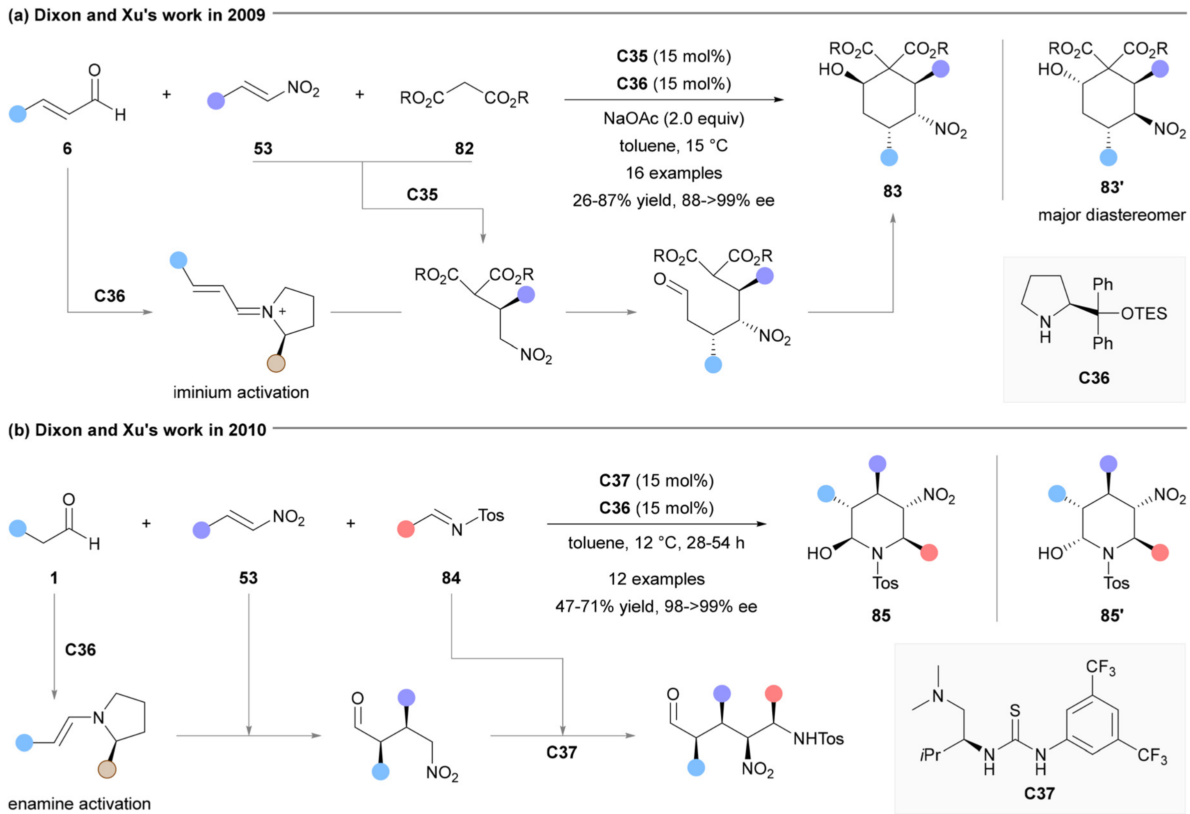


Fig. 19 AMCRs towards substituted six-membered cycles catalyzed by chiral thiourea.

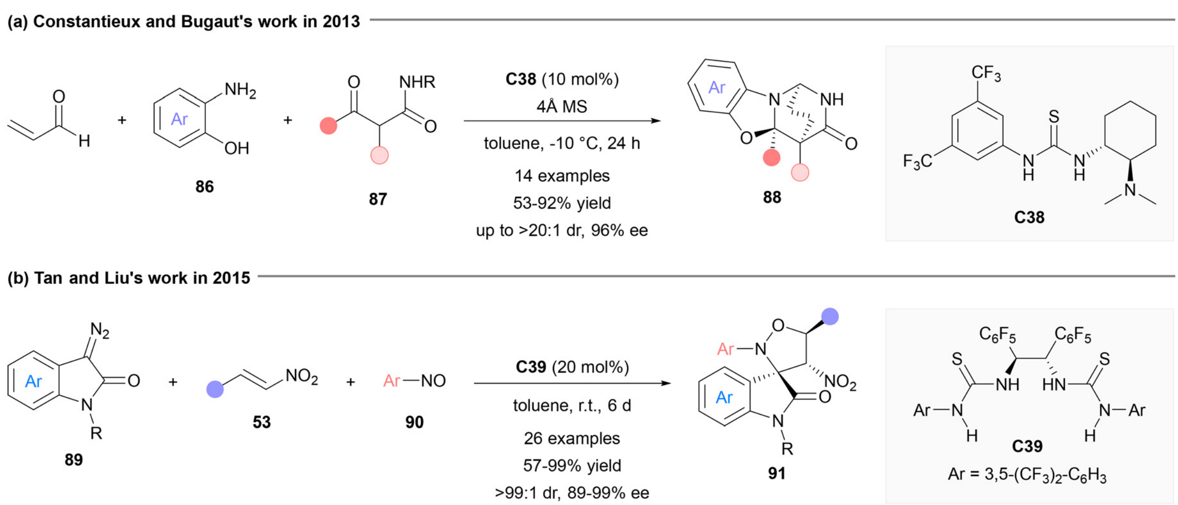


Fig. 20 AMCRs for the construction of other complex structures catalyzed by chiral thiourea.

Furthermore, AMCRs under bifunctional chiral thiourea catalysis have also provided efficient synthetic routes towards more complex structures. For instance, in 2013, functionalized 2,6-diazabicyclo-[2.2.2]octanone structures (**88**) were assembled by Constantieux, Bugaut and co-workers from aminophenols (**86**), β-ketoamides (**87**), and acrolein using catalyst **C38**. Generally, moderate to good stereocontrol could be obtained for the probed substrates (Fig. 20a).[110] On the other hand, Tan, Liu and co-workers realized the construction of highly enantioenriched spirocycles employing chiral thiourea catalytic AMCR in 2015. With diazooxindoles (**89**), nitroalkenes and nitrosoarenes (**90**) as starting materials, a series of spirooxindole derivatives were synthesized in a highly diastereoselective and enantioselective manner by using bis-thiourea catalyst **C39**. They proposed that the nitroalkene and nitroso components were successively activated by the catalyst for nucleophilic additions (Fig. 20b).[111] This strategy was also effectively utilized in forging other novel spirocyclic frameworks with multiple stereogenic centers.[112–118] Noteworthily, when the thiourea moiety was substituted by a squaramide bearing two hydrogen-bonding sites, the resulting squaramide-amine catalysts were also able to catalyze various AMCRs with similar catalytic modes.[119–121]

Additionally, an asymmetric three-component reductive coupling reaction facilitated by a chiral thiourea catalyst was developed by Johnson's group in 2016, starting from dimethyl

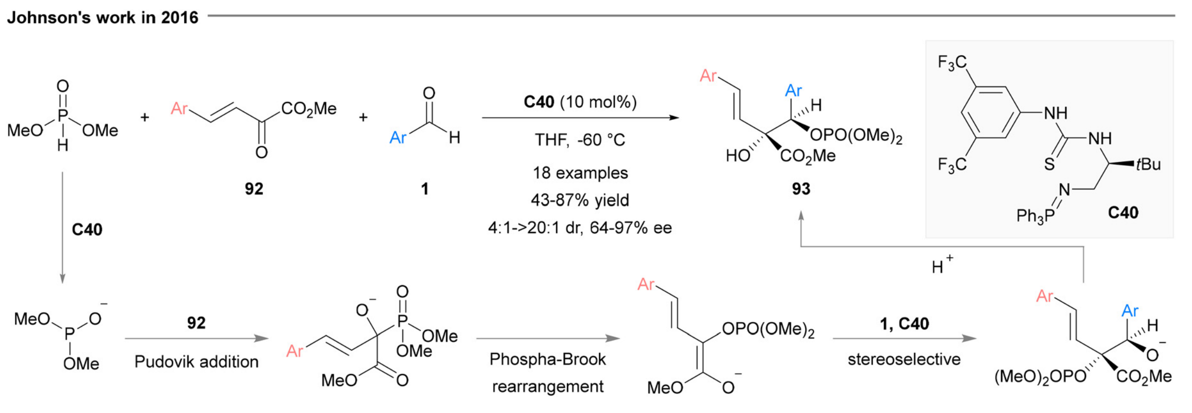


Fig. 21 Asymmetric reductive coupling reactions catalyzed by chiral thiourea.

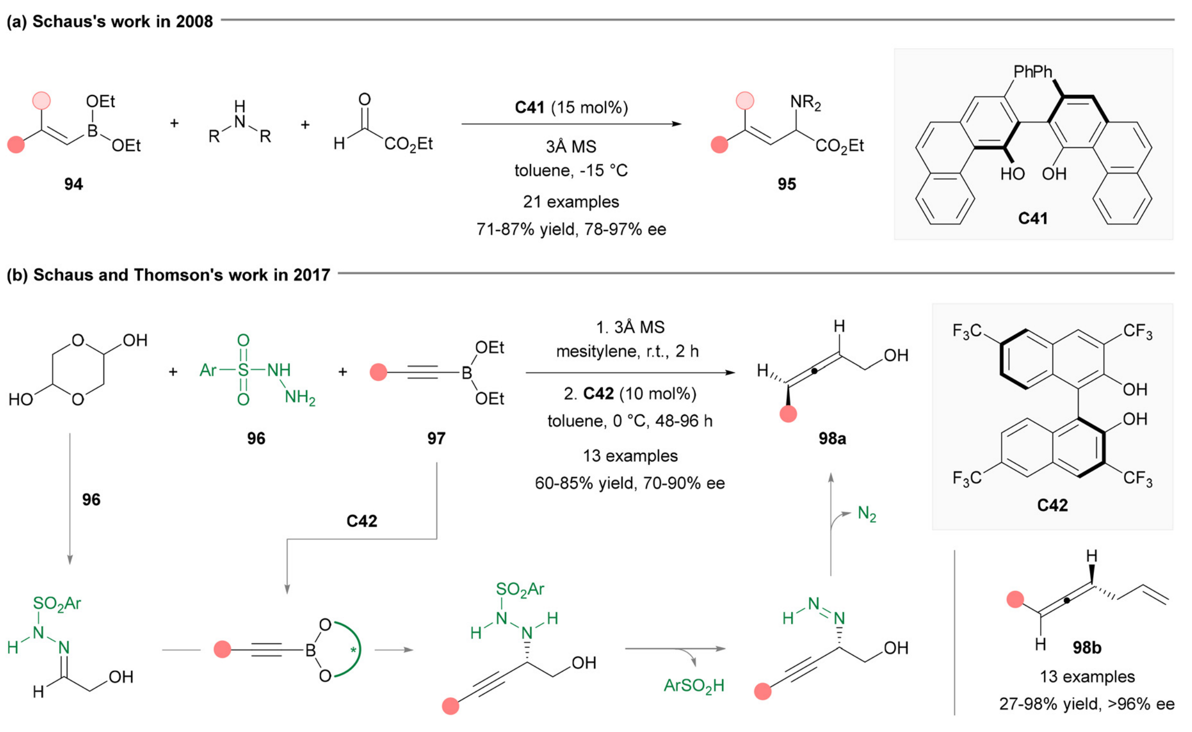


Fig. 22 Asymmetric Petasis and traceless Petasis reactions catalyzed by chiral diols.

phosphite, benzylidene pyruvates (**92**) and aldehydes. The triaryliminophosphorane functionality on **C40** is essential for the high stereoinduction of the vicinal polyfunctionalized stereocenters in product **93**. In the proposed mechanistic pathway, the reaction is initiated by a Pudovik addition, in which the deprotonated dimethyl phosphite reacts with compound **92**. This step is followed by a phospha-Brook rearrangement, generating an enolate intermediate that can be stereoselectively trapped by aldehydes to yield the desired products (Fig. 21).[122]

5. Other chiral catalysts

CPA and its derivatives have emerged as a privileged class of Brønsted acids in catalytic asymmetric synthesis. Their chiral diol cores have consistently demonstrated remarkable performance in a variety of enantioselective transformations. In a previous study, it was shown that incorporating an alcohol moiety into the chiral catalyst can lead to interaction with boronic acids, thereby directing stereochemical induction during the addition to activated quinolines.[93] Meanwhile, chiral diols can activate achiral boronates *via* transesterification, thereby generating chiral boronates that subsequently enable asymmetric alkynylation[123] and allylation[124] reactions.

Motivated by these achievements, the Schaus group realized the enantioselective three-component Petasis reaction of alkenyl boronates (**94**), secondary amines, and ethyl glyoxylate to synthesize chiral α-amino acid esters (**95**) under the catalysis of chiral biphenol **C41** (Fig. 22a).[125] Subsequently, several variants of this reaction were reported, successively exploiting a similar strategy.[126–128] In 2012, Thomson and co-workers proposed that by utilizing sulfonylhydrazide as the initiator, a Petasis-type coupling reaction could occur between α-hydroxyaldehydes and alkynyl trifluoroborate salts to afford allene structures in the presence of a Lewis acid. This reaction is also known as the traceless Petasis reaction.[129] In 2017, a catalytic asymmetric version of the traceless Petasis reaction was reported by the groups of Schaus and Thomson with 1,1′-bi-2-naphthol (BINOL)-derived chiral diols as catalysts. Starting from the glycolaldehyde dimer, the hydrazone species is formed through the reaction with sulfonylhydrazide (**96**). This intermediate can react with chiral alkynyl boronates which are generated *in situ* from catalyst **C42** with achiral alkynyl boronates (**97**) to afford propargyl hydrazides. After the loss of sulfinic acid and the extrusion of nitrogen, chiral allenes **98a** were delivered. This protocol was also applicable to the synthesis of chiral allenes **98b** utilizing alkynyl aldehydes and allyl boronates as reactants (Fig. 22b).[130] Moreover, by utilizing the interaction between the hydroxyl group and boron, in 2014, Wulff and co-workers synthesized a group of chiral catalysts with boroxine as the core skeleton by subjecting various chiral biaryl ligands to an amine, water, $BH_3·SMe_2$ and a phenol. The *in situ*-formed catalysts possess compelling

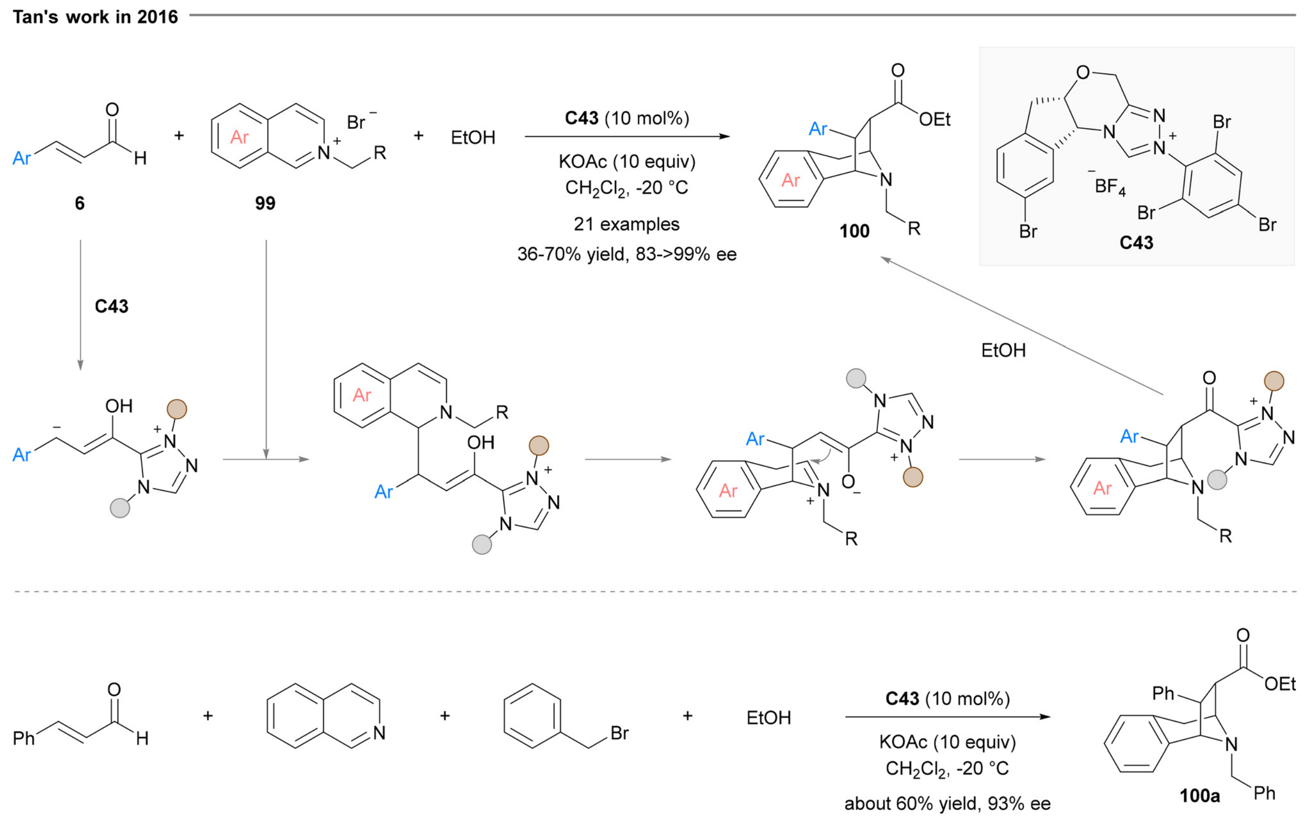


Fig. 23 NHC-catalyzed AMCR for the synthesis of chiral benztropines.

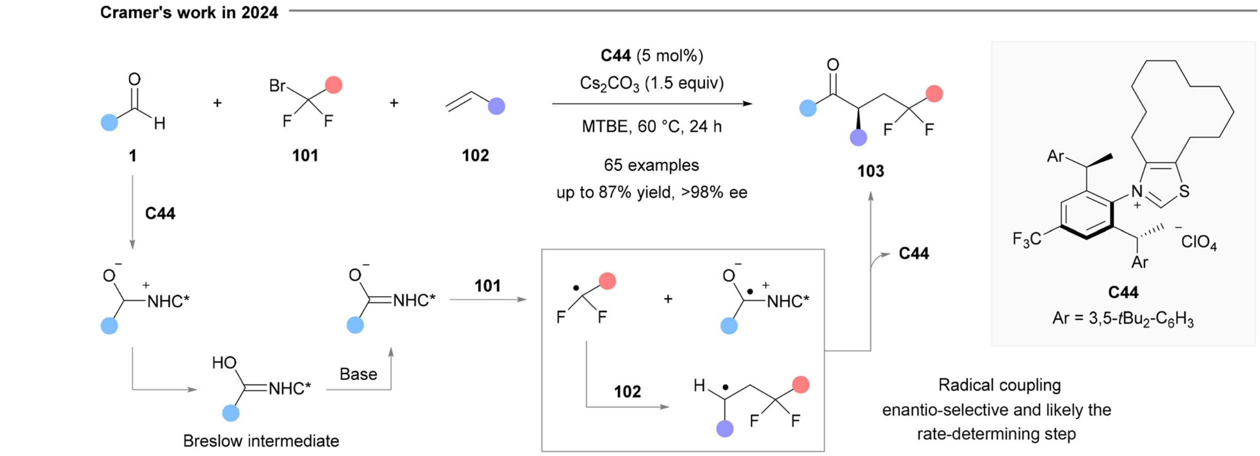


Fig. 24 NHC-catalyzed AMCR involving a radical course.

potential to enhance the asymmetric three-component Ugi reaction, involving an aldehyde, a secondary amine, and an isonitrile.[131] To gain a comprehensive understanding of the recent advancements in the Petasis reaction, it is advisable to refer recent reviews[132,133] for additional details.

As is well known, α,β-unsaturated aldehydes can act as nucleophiles bearing two nucleophilic centers and undergo enantioselective cyclization reactions through polarity inversion under the catalysis of chiral N-heterocyclic carbenes (NHCs). Exploiting this unique reactivity, Tan's group accomplished an NHC **C43**-catalyzed AMCR of an α,β-unsaturated aldehyde, an isoquinolinium (**99**) and an alcohol. Substituted benztropines (**100**) with four contiguous stereocenters were produced in a highly diastereo- and enantioselective manner through a double Mannich reaction of isoquinolines that were activated by benzyl-type bromide. Notably, a four-component reaction was also viable under the developed catalytic system (Fig. 23).[134]

More recently, Cramer *et al.* designed a class of chiral thiazole-based carbenes with three highly tunable sites. Through subtle elaboration of the NHC catalyst, an asymmetric three-component radical dicarbofunctionalization reaction was developed. Unlike the classic NHC catalysis, the Breslow intermediate formed by the reaction of **C44** with an aldehyde undergoes a single-electron transfer with difluoroalkyl bromides (**101**), generating a reactive difluoroalkyl radical and a persistent ketyl radical intermediate *via* a Breslow enolate. After that, a radical addition of the difluoroalkyl radical to olefins (**102**) occurs to give a new radical species. Subsequent radical coupling of the adduct to the olefins (**102**) affords the highly enantioenriched β-difluoroalkylated α-chiral ketones (**103**), and the control of enantioselectivity is achieved during this process (Fig. 24).[135–137]

6. Conclusions

In this review, we present a concise summary of recent advances in organocatalytic AMCRs. Undoubtedly, the rapid evolution of asymmetric organocatalysis has led to the emergence of diverse catalytic systems and novel activation modes, enabling precise stereochemical control over challenging multicomponent transformations. These breakthroughs have created unprecedented opportunities for the efficient and divergent assembly of structurally complex frameworks containing multiple stereogenic centers, thereby establishing valuable platforms for developing chiral pharmaceutical candidates. However, current methodologies predominantly rely on stereoselective additions to imines or employ odorous isocyanide components, resulting in limited substrate generality and mechanistically constrained pathways. Furthermore, practical implementations remain underdeveloped. To address these challenges, future research could exploit photochemical or electrochemical strategies to activate inert substrates, design innovative organocatalysts with tailored activation modes, and develop customized AMCR protocols targeting privileged chiral scaffolds in medicinal chemistry. Particular emphasis should be placed on expanding reaction diversity while maintaining stereochemical fidelity, ultimately bridging the gap between methodological innovation and practical synthetic applications.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This work was financially supported by the National Key R&D Program of China (2022YFA1503703), the National Natural

Science Foundation of China (22425011, 22231004, and 22271135), the Guangdong Innovative Program (2019BT02Y335), the Guangdong Basic and Applied Basic Research Foundation (2024B1515020055), the New Cornerstone Science Foundation through the Xplorer Prize, the Hong Kong Scholars Program (XJ2024-007), the Shenzhen Science and Technology Program (JCYJ20210324120205016 and KQTD20210811090112004) and high-level special funds (G03050K003). The authors appreciate the assistance of SUSTech Core Research Facilities.

References

1 A. Dömling, W. Wang and K. Wang, Chemistry and Biology of Multicomponent Reactions, *Chem. Rev.*, 2012, **112**, 3083–3135.

2 B. B. Touré and D. G. Hall, Natural Product Synthesis Using Multicomponent Reaction Strategies, *Chem. Rev.*, 2009, **109**, 4439–4486.

3 D. Wang, F. Xiao, F. Zhang and G.-J. Deng, Three-Component Synthesis of 2-Heteroaryl-3-hydroxybenzo[b]-thiophenes under Transition-Metal-Free Conditions, *Chin. J. Chem.*, 2021, **39**, 2483–2488.

4 P. Jiang, Z. Shan, S. Chen, Q. Wang, S. Jiang, H. Zheng and G.-J. Deng, Metal-Free Synthesis of Benzo[a]phenanthridines from Aromatic Aldehydes, Cyclohexanones, and Aromatic Amines, *Chin. J. Chem.*, 2022, **40**, 365–370.

5 W. Zuo, Y. Cheng, Z. Zhu, L. Zuo, X. Geng, Z. Li and L. Wang, Visible-Light-Induced Domino Cyclization to Access Pyrido[2,3-d]pyrimidine-2,4-diones via a Radical-Polar Crossover Reaction, *Chin. J. Chem.*, 2024, **42**, 2346–2350.

6 X.-B. Wu, J.-X. Shi, Y.-M. Ou, H.-J. Jiang, Y.-J. Fang, Q.-M. Wang, Q. Gao and J. Yu, Sequential Enantioselective Ugi-4CR/post-Ugi Transformation Strategy: A Precise Construction of Structurally Diverse Azaspiro Polycyclic Scaffolds, *Sci. China: Chem.*, 2024, **67**, 576–586.

7 L. Tang, G. Lv, T. Wu, L. Zhang, X. Wang, F. Jia, Q. Zhou and G. Zou, Photoredox-Catalyzed Three-Component Carbotrifluoromethylation of Alkenes via Radical–Radical Cross-Coupling, *Org. Chem. Front.*, 2024, **11**, 4708–4715.

8 H. Chen, X. Shang, N. Jiang, Q. Zhou, K.-W. Tang, L.-J. Zhong and Y. Liu, Photoinduced Copper-Catalyzed Three-Component Alkylarylation of Alkenes Involving C–S Bond Cleavage of Sulfonium Salts, *Org. Chem. Front.*, 2025, **12**, 1498–1505.

9 Y. Zhou and B. Liu, Metal-Free Visible-Light-Induced Borylative/Silylative Pyridylation of Vinylarenes, *Org. Chem. Front.*, 2025, **12**, 142–147.

10 L. Ding, G. Yang, L. Luo, Y. Ma, J. Shi, D. Liang and Y. Li, DABCO-Mediated Photoelectrochemical Three-Component Sulfonocyclization of 3-Aza-1,5-dienes, *Chin. J. Chem.*, 2025, **43**, 491–500.

11 T. Li, W. Wang, M. Dong, Z. Zhang, S. Yu, Z. Chen, S. Wei and D. Yi, Synergistic Brønsted Base/Photoredox-Catalyzed Three-Component Coupling with Malonates to Synthesize δ-Hydroxy Esters and δ-Keto Esters, *Chin. J. Chem.*, 2024, **42**, 957–962.

12 E. Koranteng, Z.-C. Shu, Y.-Y. Liu, Q. Yang, B. Shi, Q.-X. Wu, F. Tan, L.-Q. Lu and W.-J. Xiao, Metallaphotoredox-Catalyzed Three-Component Couplings for Practical Synthesis of Ureas and Carbamates, *Chin. J. Chem.*, 2024, **42**, 264–270.

13 M. Belal, Z. Li, X. Lu and G. Yin, Recent Advances in the Synthesis of 1,1-Diarylalkanes by Transition-Metal Catalysis, *Sci. China: Chem.*, 2021, **64**, 513–533.

14 B. Xiao, T.-Y. Sun, J. Zhang and Y.-D. Wu, Theoretical Insight Into the Activity and Selectivity in Palladium/Ming-Phos-Catalyzed Three-Component Asymmetric Synthesis of Gem-Diarylmethine Silanes, *Sci. China: Chem.*, 2023, **66**, 2817–2827.

15 J.-B. Lin, D.-S. Ji and P.-F. Xu, Catalytically Generated Noncovalent Ammonium Dienolate: A Versatile Platform for the Development of Organocatalytic Asymmetric Cascade Reactions, *Sci. China: Chem.*, 2024, **67**, 2524–2546.

16 J. Wang and X. Li, Rhodium-Catalyzed Enantio- and Diastereoselective Carboamidation of Bicyclic Olefins toward Construction of Remote Chiral Centers and Axis, *Sci. China: Chem.*, 2023, **66**, 2046–2052.

17 Y. Zhang, J. Wu, L. Ning, Q. Chen, X. Feng and X. Liu, Enantioselective Synthesis of Tetrasubstituted Allenes via Addition/Arylation Tandem Reaction of 2-Activated 1,3-Enynes, *Sci. China: Chem.*, 2023, **66**, 526–533.

18 X. He, F. Zhou, Q. Wang, X. Wang, Z. Chang, X. Zhang and Z. Lian, Enantioselective Synthesis of α-Chiral Sulfonates through Palladium-Catalyzed Tsuji–Trost Sulfonylation with Sulfur Dioxide, *Org. Chem. Front.*, 2025, **12**, 1274–1283.

19 J. Alemán and S. Cabrera, Applications of Asymmetric Organocatalysis in Medicinal Chemistry, *Chem. Soc. Rev.*, 2013, **42**, 774–793.

20 N. Brodt and J. Niemeyer, Chiral Organophosphates as Ligands in Asymmetric Metal Catalysis, *Org. Chem. Front.*, 2023, **10**, 3080–3109.

21 X.-L. Liu, M.-L. Gong, X. Yang, P. Tian and Q.-H. Li, Recent Progress in Asymmetric Rearrangement Reactions Mediated by Chiral Brønsted Acids, *Org. Chem. Front.*, 2024, **11**, 4934–4953.

22 D. J. Ramón and M. Yus, Asymmetric Multicomponent Reactions (AMCRs): The New Frontier, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602–1634.

23 C. de Graaff, E. Ruijter and R. V. A. Orru, Recent Developments in Asymmetric Multicomponent Reactions, *Chem. Soc. Rev.*, 2012, **41**, 3969–4009.

24 C. M. R. Volla, I. Atodiresei and M. Rueping, Catalytic C–C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis, *Chem. Rev.*, 2014, **114**, 2390–2431.

25 P. S. G. Nunes, H. D. A. Vidal and A. G. Corrêa, Recent Advances in Catalytic Enantioselective Multicomponent Reactions, *Org. Biomol. Chem.*, 2020, **18**, 7751–7773.

26 T. Akiyama, Strong Brønsted Acids, *Chem. Rev.*, 2007, **107**, 5744–5758.

27 D. Kampen, C. M. Reisinger and B. List, Chiral Brønsted Acids for Asymmetric Organocatalysis, *Top. Curr. Chem.*, 2010, **291**, 395–456.

28 X.-L. Liu, M.-L. Gong, X. Yang, P. Tian and Q.-H. Li, Recent Progress in Asymmetric Rearrangement Reactions Mediated by Chiral Brønsted Acids, *Org. Chem. Front.*, 2024, **11**, 4934–4953.

29 T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568.

30 D. Uraguchi and M. Terada, Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions *via* Electrophilic Activation, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357.

31 A. Ting and S. E. Schaus, Organocatalytic Asymmetric Mannich Reactions: New Methodology, Catalyst Design, and Synthetic Applications, *Eur. J. Org. Chem.*, 2007, 5797–5815.

32 D. Parmar, E. Sugiono, S. Raja and M. Rueping, Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates, *Chem. Rev.*, 2014, **114**, 9047–9153.

33 R. Maji, S. C. Mallojjala and S. E. Wheeler, Chiral Phosphoric Acid Catalysis: from Numbers to Insights, *Chem. Soc. Rev.*, 2018, **47**, 1142–1158.

34 X. del Corte, E. M. de Marigrta, F. Palacios, J. Vicario and A. Maestro, An Overview of the Applications of Chiral Phosphoric Acid Organocatalysts in Enantioselective Additions to C=O and C=N bonds, *Org. Chem. Front.*, 2022, **9**, 6331–6399.

35 X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, Highly Enantioselective Organocatalytic Biginelli Reaction, *J. Am. Chem. Soc.*, 2006, **128**, 14802–14803.

36 N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan and L.-Z. Gong, Highly Enantioselective Organocatalytic Biginelli and Biginelli-Like Condensations: Reversal of the Stereochemistry by Tuning the 3,3′-Disubstituents of Phosphoric Acids, *J. Am. Chem. Soc.*, 2009, **131**, 15301–15310.

37 T. Akiyama, Y. Saitoh, H. Morita and K. Fuchibe, Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid Derived from TADDOL, *Adv. Synth. Catal.*, 2005, **347**, 1523–1526.

38 X. Hu, R. Zhang, J. Xie, Z. Zhou and Z. Shan, Synthesis of a Novel Sterically Hindered Chiral Cyclic Phosphoric Acid Derived from *L*-Tartaric Acid and Application to the Asymmetric Catalytic Biginelli Reaction, *Tetrahedron: Asymmetry*, 2017, **28**, 69–74.

39 X. Hu, J. Guo, C. Wang, R. Zhang and V. Borovkov, Stereoselective Biginelli-Like Reaction Catalyzed by a Chiral Phosphoric Acid Bearing Two Hydroxy Groups, *Beilstein J. Org. Chem.*, 2020, **16**, 1875–1880.

40 Y. Guo, Z. Gao, X. Meng, G. Huang, H. Zhong, H. Yu, X. Ding, H. Tang and C. Zou, Highly Enantioselective Biginelli Reaction of Aliphatic Aldehydes Catalyzed by Chiral Phosphoric Acids, *Synlett*, 2017, 2041–2045.

41 Y. Guo, Z. Gao, K. Wang, J. Li, X. Bi, L. Guo, H. Liu, E. Shi and J. Xiao, Chiral Spirocyclic Phosphoric Acid-Catalyzed Synthesis of 4-Alkyl-3,4-dihydropyrimidin-2(1H)-one Derivatives by Asymmetric Biginelli Reactions, *Asian J. Org. Chem.*, 2020, **9**, 626–630.

42 M. Stucchi, G. Lesma, F. Meneghetti, G. Rainoldi, A. Sacchetti and A. Silvani, Organocatalytic Asymmetric Biginelli-Like Reaction Involving Isatin, *J. Org. Chem.*, 2016, **81**, 1877–1884.

43 J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao and L.-Z. Gong, Organocatalytic Asymmetric Three-Component Cyclization of Cinnamaldehydes and Primary Amines with 1,3-Dicarbonyl Compounds: Straightforward Access to Enantiomerically Enriched Dihydropyridines, *Angew. Chem., Int. Ed.*, 2008, **47**, 2458–2462.

44 Z. Chen, B. Wang, Z. Wang, G. Zhu and J. Sun, Complex Bioactive Alkaloid-Type Polycycles through Efficient Catalytic Asymmetric Multicomponent Aza-Diels–Alder Reaction of Indoles with Oxetane as Directing Group, *Angew. Chem., Int. Ed.*, 2013, **52**, 2027–2031.

45 G.-W. Zhang, D.-H. Zheng, J. Nie, T. Wang and J.-A. Ma, Brønsted Acid-Catalyzed Efficient Strecker Reaction of Ketones, Amines and Trimethylsilyl Cyanide, *Org. Biomol. Chem.*, 2010, **8**, 1399–1405.

46 H. Wu, Y.-P. He and L.-Z. Gong, Direct Access to Enantioenriched Spiroacetals through Asymmetric Relay Catalytic Three-Component Reaction, *Org. Lett.*, 2013, **15**, 460–463.

47 D. Huang, F. Xu, T. Chen, Y. Wang and X. Lin, Highly Enantioselective Three-Component Povarov Reaction Catalyzed by SPINOL-Phosphoric Acids, *RSC Adv.*, 2013, **3**, 573–578.

48 J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu and B. Tan, Phosphoric Acid-Catalyzed Asymmetric Classic Passerini Reaction, *J. Am. Chem. Soc.*, 2015, **137**, 14039–14042.

49 L. A. Wessjohann, D. G. Rivera and O. E. Vercillo, Multiple Multicomponent Macrocyclizations (MiBs): A Strategic Development Toward Macrocycle Diversity, *Chem. Rev.*, 2009, **109**, 796–814.

50 J. C. Flores-Reyes, A. Islas-Jácome and E. González-Zamora, The Ugi Three-Component Reaction and Its Variants, *Org. Chem. Front.*, 2021, **8**, 5460–5515.

51 T. Yue, M.-X. Wang, D.-X. Wang, G. Masson and J. Zhu, Brønsted Acid Catalyzed Enantioselective Three-Component Reaction Involving the α-Addition of Isocyanides to Imines, *Angew. Chem., Int. Ed.*, 2009, **48**, 6717–6721.

52 Y. Zhang, Y.-F. Ao, Z.-T. Huang, D.-X. Wang, M.-X. Wang and J. Zhu, Chiral Phosphoric Acid Catalyzed Asymmetric Ugi Reaction by Dynamic Kinetic Resolution of the Primary Multicomponent Adduct, *Angew. Chem., Int. Ed.*, 2016, **55**, 5282–5285.

53 J.-F. Zheng, X.-Y. Qian and P.-Q. Huang, Direct Transformation of Amides: A One-Pot Reductive Ugi-Type Three-Component Reaction of Secondary Amides, *Org. Chem. Front.*, 2015, **2**, 927–935.

54 T. Akiyama, T. Suzuki and K. Mori, Enantioselective Aza-Darzens Reaction Catalyzed by A Chiral Phosphoric Acid, *Org. Lett.*, 2009, **11**, 2445–2447.

55 S. P. Bew, J. Liddle, D. L. Hughes, P. Pesce and S. M. Thurston, Chiral Brønsted Acid-Catalyzed Asymmetric Synthesis of *N*-Aryl-*cis*-Aziridine Carboxylate Esters, *Angew. Chem., Int. Ed.*, 2017, **56**, 5322–5326.

56 D. Zheng and A. Studer, Asymmetric Synthesis of Heterocyclic γ-Amino-Acid and Diamine Derivatives by Three-Component Radical Cascade Reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 15803–15807.

57 Q. Sha, H. Arman and M. P. Doyle, Three-Component Cascade Reactions with 2,3-Diketoesters: A Novel Metal-Free Synthesis of 5-Vinyl-Pyrrole and 4-Hydroxy-Indole Derivatives, *Org. Lett.*, 2015, **17**, 3876–3879.

58 L. Wang, J. Zhong and X. Lin, Atroposelective Phosphoric Acid Catalyzed Three-Component Cascade Reaction: Enantioselective Synthesis of Axially Chiral *N*-Arylindoles, *Angew. Chem., Int. Ed.*, 2019, **58**, 15824–15828.

59 W. Liu, T. Qin, W. Xie, J. Zhou, Z. Ye and X. Yang, Enantioselective Synthesis of Azahelicenes through Organocatalyzed Multicomponent Reactions, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303430.

60 S. Hong, W. Liu, C. Zhang and X. Yang, Atroposelective Synthesis of Axially Chiral Imidazo[1,2-a]pyridines via Asymmetric Multicomponent Reaction, *Sci. Adv.*, 2024, **10**, eadr6135.

61 T. Hashimoto, H. Kimura, Y. Kawamata and K. Maruoka, A Catalytic Asymmetric Ugi-type Reaction With Acyclic Azomethine Imines, *Angew. Chem., Int. Ed.*, 2012, **51**, 7279–7281.

62 A. Galván, A. B. González-Pérez, R. Álvarez, A. R. de Lera, F. J. Fañanás and F. Rodríguez, Exploiting the Multidentate Nature of Chiral Disulfonimides in a Multicomponent Reaction for the Asymmetric Synthesis of Pyrrolo[1,2-a]indoles: A Remarkable Case of Enantioinversion, *Angew. Chem., Int. Ed.*, 2016, **55**, 3428–3432.

63 H. G. O. Alvim, D. L. J. Pinheiro, V. H. Carvalho-Silva, M. Fioramonte, F. C. Gozzo, W. A. da Silva, G. W. Amarante and B. A. D. Neto, Combined Role of the Asymmetric Counteranion-Directed Catalysis (ACDC) and Ionic Liquid Effect for the Enantioselective Biginelli Multicomponent Reaction, *J. Org. Chem.*, 2018, **83**, 12143–12153.

64 L. Zou, J. Huang, N. Liao, Y. Liu, Q. Guo and Y. Peng, Catalytic Asymmetric Three-Component Reaction of 2-Alkynylbenzaldehydes, Amines, and Dimethylphosphonate, *Org. Lett.*, 2020, **22**, 6932–6937.

65 J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk and B. Tan, Asymmetric Phosphoric Acid–Catalyzed Four-Component Ugi Reaction, *Science*, 2018, **361**, eaas8707.

66 J. Zhang, Y.-Y. Wang, H. Sun, S.-Y. Li, S.-H. Xiang and B. Tan, Enantioselective Three-Component Ugi Reaction Catalyzed by Chiral Phosphoric Acid, *Sci. China: Chem.*, 2020, **63**, 47–54.

67 J. Wei, J. Zhang, J. K. Cheng, S.-H. Xiang and B. Tan, Modular Enantioselective Access to β-Amino Amides by Brønsted Acid-Catalysed Multicomponent Reactions, *Nat. Chem.*, 2023, **15**, 647–657.

68 J. Yu, F. Shi and L.-Z. Gong, Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles, *Acc. Chem. Res.*, 2011, **44**, 1156–1171.

69 Y. Wang, A. A. Cobo and A. K. Franz, Recent Advances in Organocatalytic Asymmetric Multicomponent Cascade Reactions for Enantioselective Synthesis of Spirooxindoles, *Org. Chem. Front.*, 2021, **8**, 4315–4348.

70 S. Mukherjee, J.-W. Yang, S. Hoffmann and B. List, Asymmetric Enamine Catalysis, *Chem. Rev.*, 2007, **107**, 5471–5569.

71 B. List, The Direct Catalytic Asymmetric Three-Component Mannich Reaction, *J. Am. Chem. Soc.*, 2000, **122**, 9336–9337.

72 M. Marigo, T. Schulte, J. Franzén and K. A. Jørgensen, Asymmetric Multicomponent Domino Reactions and Highly Enantioselective Conjugated Addition of Thiols to α,β-Unsaturated Aldehydes, *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711.

73 H. Jiang, J. B. Nielsen, M. Nielsen and K. A. Jørgensen, Organocatalysed Asymmetric β-Amination and Multicomponent *syn*-Selective Diamination of α,β-Unsaturated Aldehydes, *Chem. – Eur. J.*, 2007, **13**, 9068–9075.

74 Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. Macmillan, Enantioselective Organo-Cascade Catalysis, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053.

75 L. K. Ransborg, M. Overgaard, J. Hejmanowska, S. Barfüsser, K. A. Jørgensen and Ł. Albrecht, Asymmetric Formation of Bridged Benzoxazocines through an Organocatalytic Multicomponent Dienamine-Mediated One-Pot Cascade, *Org. Lett.*, 2014, **16**, 4182–4185.

76 D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, Control of four stereocentres in a triple cascade organocatalytic reaction, *Nature*, 2006, **441**, 861–863.

77 D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe and B. Wendt, Organocatalytic One-Pot Asymmetric Synthesis of Functionalized Tricyclic Carbon Frameworks from a Triple-Cascade/Diels–Alder Sequence, *Angew. Chem., Int. Ed.*, 2007, **46**, 467–469.

78 D. Enders, C. Wang, M. Mukanova and A. Greb, Organocatalytic Asymmetric Synthesis of Polyfunctionalized 3-(Cyclohexenylmethyl)-Indoles via a Quadruple Domino Friedel–Crafts-Type/Michael/Michael/

Aldol Condensation Reaction, *Chem. Commun.*, 2010, **46**, 2447–2449.

79 N. Erdmann, A. R. Philipps, I. Atodiresei and D. Enders, An Asymmetric Organocatalytic Quadruple Cascade Initiated by a Friedel–Crafts-Type Reaction with Electron-Rich Arenes, *Adv. Synth. Catal.*, 2013, **355**, 847–852.

80 S. Dochain, F. Vetica, R. Puttreddy, K. Rissanen and D. Enders, Combining Organocatalysis and Lanthanide Catalysis: A Sequential One-Pot Quadruple Reaction Sequence/Hetero-Diels–Alder Asymmetric Synthesis of Functionalized Tricycles, *Angew. Chem., Int. Ed.*, 2016, **55**, 16153–16155.

81 M. Kumar, P. Chauhan, S. J. Bailey, E. Jafari, C. von Essen, K. Rissanen and D. Enders, Organocatalytic Oxa-Michael/Michael/Michael/Aldol Condensation Quadruple Domino Sequence: Asymmetric Synthesis of Tricyclic Chromanes, *Org. Lett.*, 2018, **20**, 1232–1235.

82 A. Carlone, S. Cabrera, M. Marigo and K. A. Jørgensen, A New Approach for an Organocatalytic Multicomponent Domino Asymmetric Reaction, *Angew. Chem., Int. Ed.*, 2007, **46**, 1101–1104.

83 W. S. Jen, J. J. M. Wiener and D. W. C. Macmillan, New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition, *J. Am. Chem. Soc.*, 2000, **122**, 9874–9875.

84 R. Rios, I. Ibrahem, J. Vesely, G.-L. Zhao and A. Córdova, A Simple One-Pot, Three-Component, Catalytic, Highly Enantioselective Isoxazolidine Synthesis, *Tetrahedron Lett.*, 2007, **48**, 5701–5705.

85 I. Ibrahem, R. Rios, J. Vesely and A. Córdova, Organocatalytic Asymmetric Multi-Component [C+NC+CC] Synthesis of Highly Functionalized Pyrrolidine Derivatives, *Tetrahedron Lett.*, 2007, **48**, 6252–6257.

86 J.-P. Pei, X.-J. Lv, C.-J. Peng and Y.-K. Liu, Asymmetric Organocatalytic Multicomponent Reactions for Efficient Construction of Bicyclic Compounds Bearing Bisacetal and Isoxazolidine Moieties, *Chem. Commun.*, 2020, **56**, 12765–12768.

87 J. Xin, L. Chang, Z. Hou, D. Shang, X. Liu and X. Feng, An Enantioselective Biginelli Reaction Catalyzed by a Simple Chiral Secondary Amine and Achiral Brønsted Acid by a Dual-Activation Route, *Chem. – Eur. J.*, 2008, **14**, 3177–3181.

88 Y. Liu, J. A. Izzo, D. Mcleod, S. Ričko, E. B. Svenningsen, T. B. Poulsen and K. A. Jørgensen, Organocatalytic Asymmetric Multicomponent Cascade Reaction for the Synthesis of Contiguously Substituted Tetrahydronaphthols, *J. Am. Chem. Soc.*, 2021, **143**, 8208–8220.

89 P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli and P. Melchiorre, Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes, *Angew. Chem., Int. Ed.*, 2009, **48**, 7892–7894.

90 W. Xiao, Z. Zhou, Q.-Q. Yang, W. Du and Y.-C. Chen, Organocatalytic Asymmetric Four-Component [5 + 1 + 1 + 1] Cycloadditions via a Quintuple Cascade Process, *Adv. Synth. Catal.*, 2018, **360**, 3526–3533.

91 T. Parvin, R. Yadav and L. H. Choudhury, Recent Applications of Thiourea-Based Organocatalysts in Asymmetric Multicomponent Reactions (AMCRs), *Org. Biomol. Chem.*, 2020, **18**, 5513–5532.

92 S. C. Pan and B. List, Catalytic Asymmetric Three-Component Acyl-Strecker Reaction, *Org. Lett.*, 2007, **9**, 1149–1151.

93 Y. Yamaoka, H. Miyabe and Y. Takemoto, Catalytic Enantioselective Petasis-Type Reaction of Quinolines Catalyzed by a Newly Designed Thiourea Catalyst, *J. Am. Chem. Soc.*, 2007, **129**, 6686–6687.

94 W.-Y. Han, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, Enantioselective Organocatalytic Three-Component Petasis Reaction among Salicylaldehydes, Amines, and Organoboronic Acids, *Org. Lett.*, 2012, **14**, 976–979.

95 Y. Wang, J. Yu, Z. Miao and R. Chen, Bifunctional Primary Amine-Thiourea–TfOH (BPAT·TfOH) as a Chiral Phase-Transfer Catalyst: the Asymmetric Synthesis of Dihydropyrimidines, *Org. Biomol. Chem.*, 2011, **9**, 3050–3054.

96 M. Frings, I. Thomé and C. Bolm, Synthesis of Chiral Sulfoximine-Based Thioureas and Their Application in Asymmetric Organocatalysis, *Beilstein J. Org. Chem.*, 2012, **8**, 1443–1451.

97 Z. Hang, J. Zhu, X. Lian, P. Xu, H. Yu and S. Han, A Highly Enantioselective Biginelli Reaction Using Self-Assembled Methanoproline–Thiourea Organocatalysts: Asymmetric Synthesis of 6-Isopropyl-3,4-Dihydropyrimidines, *Chem. Commun.*, 2016, **52**, 80–83.

98 X. Li, H. Deng, S. Luo and J.-P. Cheng, Organocatalytic Three-Component Reactions of Pyruvate, Aldehyde and Aniline by Hydrogen-Bonding Catalysts, *Eur. J. Org. Chem.*, 2008, 4350–4356.

99 S. Bai, X. Liang, B. Song, P. S. Bhadury, D. Hu and S. Yang, Asymmetric Mannich Reactions Catalyzed by Cinchona Alkaloid Thiourea: Enantioselective One-Pot Synthesis of Novel β-Amino Ester Derivatives, *Tetrahedron: Asymmetry*, 2011, **22**, 518–523.

100 Q. Guo and J. C.-G. Zhao, Highly Enantioselective Three-Component Direct Mannich Reactions of Unfunctionalized Ketones Catalyzed by Bifunctional Organocatalysts, *Org. Lett.*, 2013, **15**, 508–511.

101 A. S. Demir and S. Basceken, Study of Asymmetric Aldol and Mannich Reactions Catalyzed by Proline–Thiourea Host–Guest Complexes in Nonpolar Solvents, *Tetrahedron: Asymmetry*, 2013, **24**, 515–525.

102 F. Cruz-Acosta, P. de Armas and F. García-Tellado, Water-Compatible Hydrogen-Bond Activation: A Scalable and Organocatalytic Model for the Stereoselective Multicomponent Aza-Henry Reaction, *Chem. – Eur. J.*, 2013, **19**, 16550–16554.

103 S. Bai, S. Liu, Y. Zhu, K. Zhao and Q. Wu, Antiviral Bioactivity of Chiral β-Amino Acid Ester Derivatives

Synthesized through a One-Pot, Solvent-Free Asymmetric Mannich Reaction, *Synlett*, 2018, 1921–1925.

104 Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, Asymmetric Organocatalytic Relay Cascades: Catalyst-Controlled Stereoisomer Selection in the Synthesis of Functionalized Cyclohexanes, *Angew. Chem., Int. Ed.*, 2009, **48**, 9834–9838.

105 Y. Wang, D.-F. Yu, Y.-Z. Liu, H. Wei, Y.-C. Luo, D. J. Dixon and P.-F. Xu, Multiple-Organocatalyst-Promoted Cascade Reaction: A Fast and Efficient Entry into Fully Substituted Piperidines, *Chem. – Eur. J.*, 2010, **16**, 3922–3925.

106 R. Imashiro, H. Uehara and C. F. Barbas III, One-Pot Enantioselective Syntheses of Iminosugar Derivatives Using Organocatalytic anti-Michael–anti-Aza-Henry Reactions, *Org. Lett.*, 2010, **12**, 5250–5253.

107 D. Enders, G. Urbanietz, E. Cassens-Sasse, S. Keeß and G. Raabe, Control of Six Contiguous Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence, *Adv. Synth. Catal.*, 2012, **354**, 1481–1488.

108 H. R. Tan, H. F. Ng, J. Chang and J. Wang, Highly Enantioselective Assembly of Functionalized Tetrahydroquinolines with Creation of an All-Carbon Quaternary Center, *Chem. – Eur. J.*, 2012, **18**, 3865–3870.

109 W. Hou, Q. Wei, G. Liu, J. Chen, J. Guo and Y. Peng, Asymmetric Multicomponent Sulfa-Michael/Mannich Cascade Reaction: Synthetic Access to 1,2-Diamino-3-Organosulfur Compounds and 2-Nitro Allylic Amines, *Org. Lett.*, 2015, **17**, 4870–4873.

110 M. M. Sanchez Duque, O. Baslé, Y. Génisson, J.-C. Plaquevent, X. Bugaut, T. Constantieux and J. Rodriguez, Enantioselective Organocatalytic Multicomponent Synthesis of 2,6-Diazabicyclo[2.2.2]octanones, *Angew. Chem., Int. Ed.*, 2013, **52**, 14143–14146.

111 M.-Y. Wu, W.-W. He, X.-Y. Liu and B. Tan, Asymmetric Construction of Spirooxindoles by Organocatalytic Multicomponent Reactions Using Diazooxindoles, *Angew. Chem., Int. Ed.*, 2015, **54**, 9409–9413.

112 W.-T. Wei, C.-X. Chen, R.-J. Lu, J.-J. Wang, X.-J. Zhang and M. Yan, Enantioselective Synthesis of 3,3′-Dihydropyrryl-Spirooxindoles via an Organocatalytic Three-Component Reaction, *Org. Biomol. Chem.*, 2012, **10**, 5245–5252.

113 B. Zhou, Y. Yang, J. Shi, Z. Luo and Y. Li, Synthesis of Six-Membered Spirocyclic Oxindoles with Five Consecutive Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence, *J. Org. Chem.*, 2013, **78**, 2897–2907.

114 X. Huang, K. Pham, W. Yi, X. Zhang, C. Clamens, J. H. Hyatt, J. P. Jasinsk, U. Tayvah and W. Zhang, Recyclable Organocatalyst-Promoted One-Pot Asymmetric Synthesis of Spirooxindoles Bearing Multiple Stereogenic Centers, *Adv. Synth. Catal.*, 2015, **357**, 3820–3824.

115 X. Huang, M. Liu, K. Pham, X. Zhang, W.-B. Yi, J. P. Jasinski and W. Zhang, Organocatalytic One-Pot Asymmetric Synthesis of Thiolated Spiro-γ-Lactam Oxindoles Bearing Three Stereocenters, *J. Org. Chem.*, 2016, **81**, 5362–5369.

116 L.-L. Zhang, J.-W. Zhang, S.-H. Xiang, Z. Guo and B. Tan, Stereoselective Construction of Complex Spirooxindoles via Bisthiourea Catalyzed Three-Component Reactions, *Chin. J. Chem.*, 2018, **36**, 1182–1186.

117 L.-L. Zhang, J.-W. Zhang, S.-H. Xiang, Z. Guo and B. Tan, Remote Control of Axial Chirality: Synthesis of Spirooxindole–Urazoles via Desymmetrization of ATAD, *Org. Lett.*, 2018, **20**, 6022–6026.

118 L. Zhu, X. Ren, Z. Liao, J. Pan, C. Jiang and T. Wang, Asymmetric Three-Component Cyclizations toward Structurally Spiro Pyrrolidines via Bifunctional Phosphonium Salt Catalysis, *Org. Lett.*, 2019, **21**, 8667–8672.

119 L. Tian, X.-Q. Hu, Y.-H. Li and P.-F. Xu, Organocatalytic Asymmetric Multicomponent Cascade Reaction via 1,3-Proton Shift and [3+2] Cycloaddition: An Efficient Strategy for the Synthesis of Oxindole Derivatives, *Chem. Commun.*, 2013, **49**, 7213–7215.

120 M. Blümel, P. Chauhan, R. Hahn, G. Raabe and D. Enders, Asymmetric Synthesis of Tetrahydropyridines via an Organocatalytic One-Pot Multicomponent Michael/Aza-Henry/Cyclization Triple Domino Reaction, *Org. Lett.*, 2014, **16**, 6012–6015.

121 Y. Zhong, X. Zhao, X. Zhao, D. Zhang, W. Li, S. Wei, F. Liu, J. Yu, G. Li and D. Wang, Multi-Component Syntheses of 2-Pyrrolines and Organocatalytic Asymmetric Syntheses of Functionalized Chiral 2-Pyrrolines, *Org. Chem. Front.*, 2021, **8**, 664–669.

122 M. A. Horwitz, B. P. Zavesky, J. I. Martinez-Alvarado and J. S. Johnson, Asymmetric Organocatalytic Reductive Coupling Reactions between Benzylidene Pyruvates and Aldehydes, *Org. Lett.*, 2016, **18**, 36–39.

123 T. R. Wu and J. M. Chong, Ligand-Catalyzed Asymmetric Alkynylboration of Enones: A New Paradigm for Asymmetric Synthesis Using Organoboranes, *J. Am. Chem. Soc.*, 2005, **127**, 3244–3245.

124 S. Lou, P. N. Moquist and S. E. Schaus, Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols, *J. Am. Chem. Soc.*, 2006, **128**, 12660–12661.

125 S. Lou and S. E. Schaus, Asymmetric Petasis Reactions Catalyzed by Chiral Biphenols, *J. Am. Chem. Soc.*, 2008, **130**, 6922–6923.

126 G. Muncipinto, P. N. Moquist, S. L. Schreiber and S. E. Schaus, Catalytic Diastereoselective Petasis Reactions, *Angew. Chem., Int. Ed.*, 2011, **50**, 8172–8175.

127 X. Shi, W. F. Kiesman, A. Levina and Z. Xin, Catalytic Asymmetric Petasis Reactions of Vinylboronates, *J. Org. Chem.*, 2013, **78**, 9415–9423.

128 C. S. Marques, P. McArdle, A. Erxleben and A. J. Burke, Accessing New 5-α-(3,3-Disubstituted Oxindole)-Benzylamine Derivatives from Isatin: Stereoselective Organocatalytic Three Component Petasis Reaction, *Eur. J. Org. Chem.*, 2020, 3622–3634.

129 D. A. Mundal, K. E. Lutz and R. J. Thomson, A Direct Synthesis of Allenes by a Traceless Petasis Reaction, *J. Am. Chem. Soc.*, 2012, **134**, 5782–5785.
130 Y. Jiang, A. B. Diagne, R. J. Thomson and S. E. Schaus, Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions, *J. Am. Chem. Soc.*, 2017, **139**, 1998–2005.
131 W. Zhao, L. Huang, Y. Guan and W. D. Wulff, Three-Component Asymmetric Catalytic Ugi Reaction—Concinnity from Diversity by Substrate-Mediated Catalyst Assembly, *Angew. Chem., Int. Ed.*, 2014, **53**, 3436–3441.
132 P. Wu, M. Givskov and T. E. Nielsen, Reactivity and Synthetic Applications of Multicomponent Petasis Reactions, *Chem. Rev.*, 2019, **119**, 11245–11290.
133 K. J. Gonzalez, C. Cerione and B. M. Stoltz, Strategies for the Development of Asymmetric and Non-Directed Petasis Reactions, *Chem. – Eur. J.*, 2024, **30**, e202401936.
134 J.-H. Xu, S.-C. Zheng, J.-W. Zhang, X.-Y. Liu and B. Tan, Construction of Tropane Derivatives by the Organocatalytic Asymmetric Dearomatization of Isoquinolines, *Angew. Chem., Int. Ed.*, 2016, **55**, 11834–11839.
135 S. Jana and N. Cramer, Tunable Thiazolium Carbenes for Enantioselective Radical Three-Component Dicarbofunctionalizations, *J. Am. Chem. Soc.*, 2024, **146**, 35199–35207.
136 Z. Lin, G. Lv, J. Liu, J. Tang, B. Mu, J. Chen, T. Huang, Z. Yang and Y. Wu, Cooperative NHC/Photoredox Catalysis: Three-Component Reaction of Aroyl Fluorides, Styrenes and Oxalates, *Chin. J. Chem.*, 2024, **42**, 511–515.
137 A. Jialingbieke, X. Hu, Z. Liu, X. Lin, Y. Yin, J. Li, Y. Huang and D. Du, Organocatalytic Radical Aminoacylation of Alkenes for β-Aminoketone Synthesis, *Sci. China: Chem.*, 2025, **68**, 1002–1008.

