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REVIEW

Recent progress on asymmetric multicomponent reactions via chiral phosphoric acid catalysis

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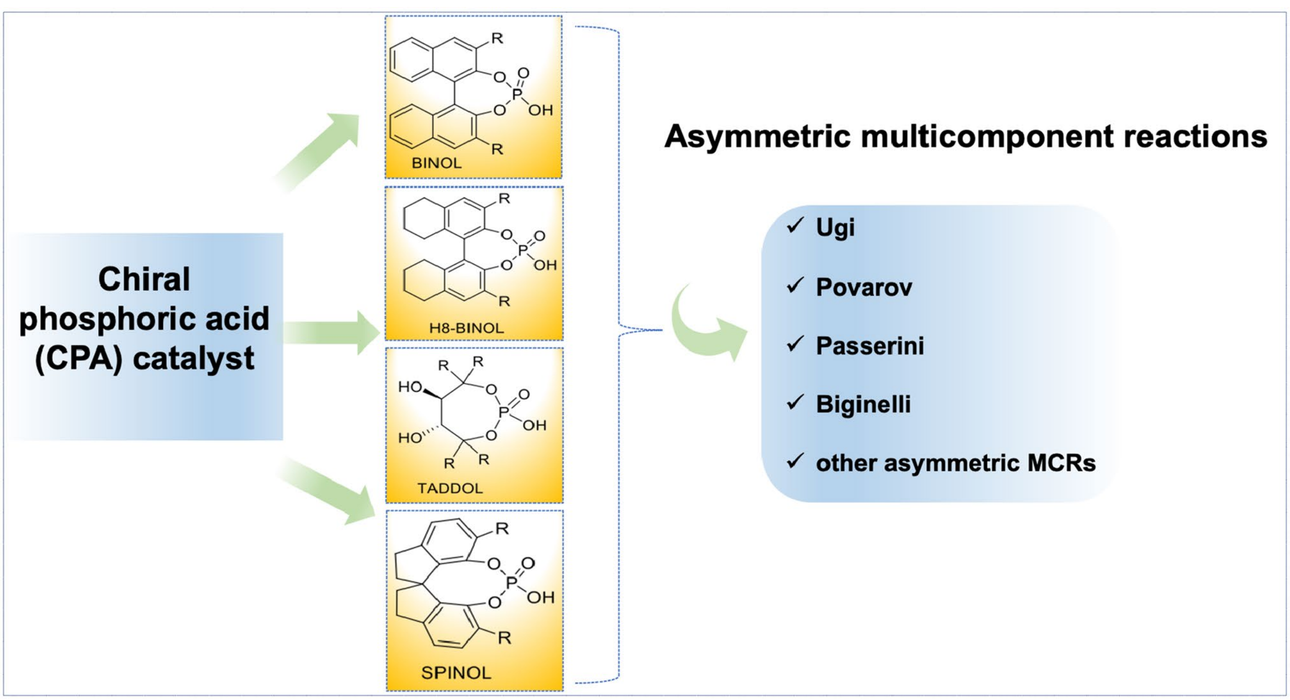
Abstract
Multicomponent reactions (MCRs) are very important to provide enantiomerically enriched compounds with high structural diversity and complexity. These reactions play an important role in the synthesis of natural products, commercial drugs, agrochemicals and catalysts. Currently, CPA-catalyzed enantioselective MCRs are a hot research topic and promising for the discovery of more complex organic compounds. In this article, the chiral phosphoric acid and CPA metal cooperation catalyzed asymmetric multicomponent reactions derived from BINOL, H8-BINOL, SPA and TADDOL such as the Ugi, Passerini, Biginelli, Povarov and other asymmetric MCRs have been reviewed and summarized. Therefore, in this review, we summarize the recent progress in the developments of CPA and its transition metal-cooperative catalyzed enantioselective multicomponent reactions published from 2015 to date.

Graphical abstract



Keywords Chiral phosphoric acid · Multicomponent reaction · Ugi reaction · Passerini reaction · Biginelli reaction

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Introduction

The biological activity of natural products has not only promoted the exploration of efficient approaches to build complex structures, but also stimulated the design of unnatural molecules with different structures and pharmaceutical applications [1]. Among the numerous synthetic approaches, multicomponent reactions (MCRs) are very important to promote their wide application in the synthesis of heterocyclic scaffolds, natural products, macrocycles, polymers [2], pharmaceuticals and agrochemicals [3]. Moreover, the major challenge in organic synthesis is to create molecular diversity and complexity from simple and readily available substrates that have high atom economy [4] and excellent stereoselectivity [5]. Therefore, multicomponent reactions that allow the formation of multiple bonds in a single step are highly desirable. These reactions involve a series of chemical transformations in which the well-defined condensation of three or more units of different reactants or reaction centers occurs in a one-pot fashion without isolation and purification of intermediates [6, 7].

Several research works and reviews on transition metal and organocatalytic multicomponent reactions [8, 9] have been published by researchers. For example, these include transition metal-catalyzed C–H activation/functionalization multicomponent reactions [10, 11], coupling reactions [12, 13], novel dipeptide-based phosphonium salt catalyst MCRs [14], transition metal-free MCRs involving arynes, N-hetero-cycles, isatins [15], etc., are some of them.

Until recently, transition metal-catalyzed and organocatalytic MCRs [5] represented the majority of highly diastereoselective and enantioselective versions of existing and novel MCRs. For example, enantioselective Passerini, Biginelli and Hantzsch MCRs have been described in recent years. In addition, the Ugi reaction is a representative MCR widely used in organic synthesis, polymer engineering and drug discovery [16, 17]. In terms of developing more effective methods, the combination of organocatalytic and MCRs based on the electrophilic trapping of in situ generated active oxonium [18], sulfonium [19] or ammonium ylides [20] derived from diazo compounds, provides a powerful and efficient tool in organic synthesis for the preparation of enantiomerically pure organic compounds [21, 22].

This review describes developments on asymmetric phosphoric acid-catalyzed stereoselective MCRs, which are of great importance for future applications in the pharmaceutical industry and total synthesis of natural products and novel drugs. MCRs and asymmetric transition metal/CPA dual catalysts have experienced rapid growth since 2008 [23]. Today, organocatalysis is one of the most flourishing research areas in contemporary organic synthesis [24] and CPAs are among the most robust organocatalysts that enable a variety of enantioselective bond-forming reactions. Following the discoveries of Akiyama [25] and Tereda [26], CPAs were recognized as novel chiral catalysts and attracted the attention of synthetic organic chemists. The extensive use of phosphoric acids and phosphates as chiral acids, chiral anions and ligands is one of the most important achievements of modern enantioselective catalysis. In this field, the atropochiral derivatives, BINOL, SPINOL, H8-BINOL and TADDOL [27, 28] (Fig. 1), which have axially chiral structures and stereogenic carbons have been developed and used as privileged catalysts to achieve excellent enantioselectivity for multicomponent reactions [29–31]. With respect to their application as chirality-inducing agents, CPAs typically provide hydrogen bonding between a protonated substrate and the chiral conjugated base [32, 33] and form a contact ion pair with electrophilic components [34]. In this review, highlights of recent contributions on stereoselective MCRs catalyzed by CPA and cooperative transition metal/CPA catalysts have been described.

Enantioselective three-component Passerini reaction

Among the oldest MCRs, the Passerini reaction has been found to be valuable for multifunctional α-acyloxyamide synthesis in a practical process with the simultaneous generation of a stereogenic center [35, 36]. In this regard, Tan and co-workers (2015) furnished an efficient enantioselective classic three-component Passerini reaction of aldehyde (**1**), isocyanide (**2**) and carboxylic acid (**3**) in the presence of a chiral phosphoric acid catalyst (**CPA 1**). The reaction is applicable to a wide range of aromatic aldehydes and

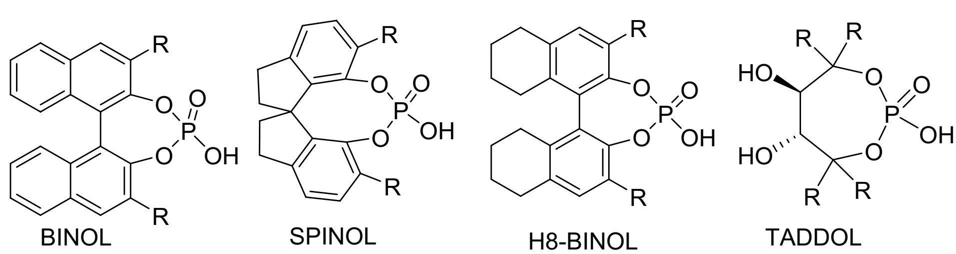
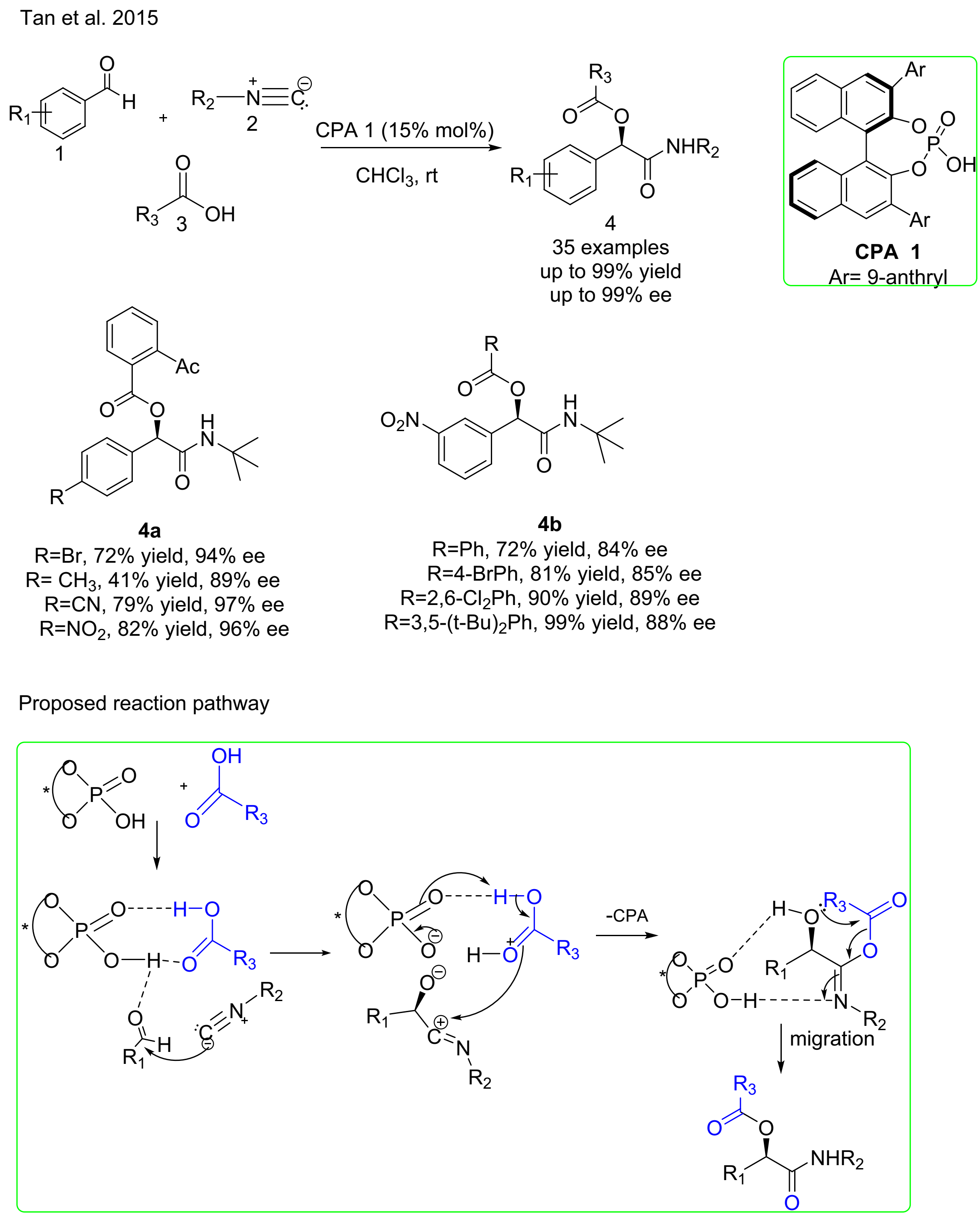


Fig. 1 Chiral phosphoric acid (CPA) scaffolds used in this review



Scheme 1 Enantioselective synthesis of multifunctional α-acyloxyamide and suggested reaction pathway [37]

aliphatic aldehydes including linear aldehydes, α-branched isobutyraldehyde, and cyclohexane-carbaldehyde to afford moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 99%) (Scheme 1). Various aromatic and aliphatic carboxylic acids were also tolerated to provide the corresponding products in high yields with good to excellent enantioselectivities. Besides, if the tert-butyl isocyanide is replaced by cyclohexyl isocyanide or 1,1,3,3-tetramethylbutyl isocyanide, good results were obtained under mild reaction conditions. This reaction was achieved with high yield and enantioselectivity due to the fact that the chiral phosphoric acid is unquestionably a robust organocatalyst to generate a well-defined chiral pocket for the reaction [37].

Enantioselective three- and four-component Ugi reactions

Ugi's reaction combines a carboxylic acid, an amine, an isocyanide, and an aldehyde or ketone, to make an α-acylaminoamide. The prototypical Ugi multicomponent reaction is very important to construct biologically important molecules [38] and natural products bearing peptides, many heterocycles [39–41] and even macrocycles [42]. In 2016, Wang and Zhu group disclosed the first example of chiral phosphoric acid-catalyzed enantioselective Ugi three-component reaction of 2-formylbenzoic acids (**5**), anilines (**5'**), and isonitriles (**2**) for the synthesis of enantioenriched 3-oxoisoindoline-1-carboxamides (**7**) by dynamic kinetic resolution in moderate to high yield and good enantioselectivity [43]. Herein, the authors revealed that as compared to two-component Ugi reactions, the higher catalyst loading is employed in the case of three-component reaction. This reaction is the first example of an enantioselective Ugi reaction in which a carboxylic acid was incorporated as one of the participating functional groups [44]. The possible mechanism of the reaction is the condensation of 2-formylbenzoic acids with anilines affords the iminium salt and intermolecular nucleophilic addition of the divalent carbon atom of isonitriles to iminium salt can provide the nitrilium, which can then be trapped by the tethered carboxylate to provide **A.** Lastly, Mumm rearrangement of **A** via the bridged intermediate **B** occurred and furnished the isoindolinone 7 (Scheme 2).

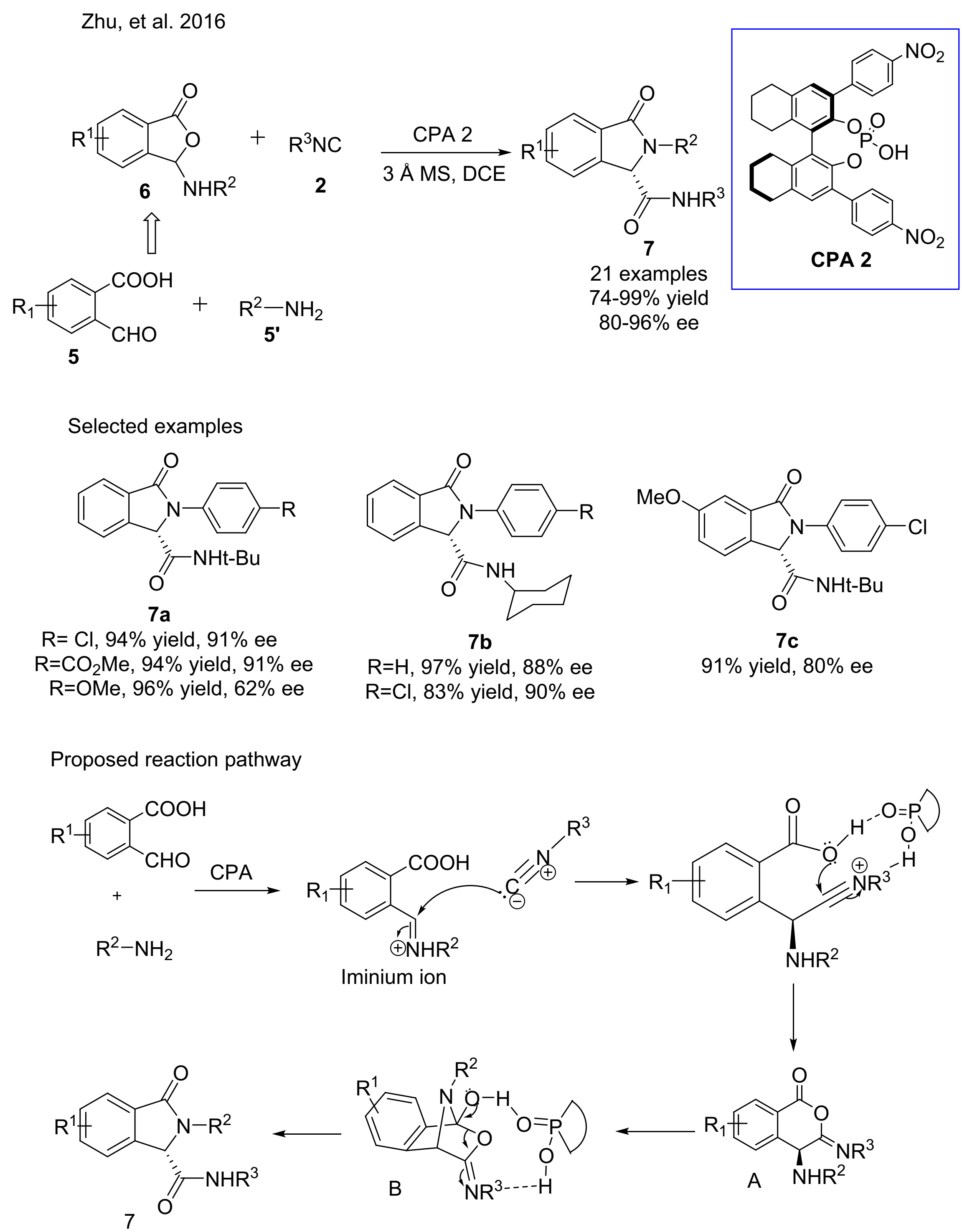
In 2018, Tan and coworkers reported asymmetric phosphoric acid-catalyzed efficient enantioselective construction of α-acylaminoamides from aldehydes (**8**), carboxylic acids (**9**), anilines (**10**) and isocyanides (**2**) through four-component Ugi reaction in good to excellent enantiomeric excess [45]. This research group evaluated both aliphatic and aromatic aldehydes with different amines, carboxylic acids and isocyanides. Accordingly, the reaction was applicable to a wide range of aliphatic and aromatic aldehydes, amines with varied functionalities, linear alkyl carboxylic acids, α-branched isobutyric acid, alkenyl carboxylic acid, and aromatic and hetero-aromatic carboxylic acid with moderate to high yield and good to excellent enantioselectivities. The position and electronic properties of the substituents on the aromatic ring of the aldehydes exerted very limited influence on the stereoselectivity of the process. The origin of stereoselectivity was described by experimental and computational studies (Scheme 3).

The enantioselective three-component Ugi reaction of aniline, aldehydes, and isocyanides, catalyzed by SPINOL-derived phosphoric acid with bulky 2,4,6- tricyclohexylphenyl groups at the 6,6′ positions were developed by Tan and coworkers (2020). The electronic and position of substituents on the aryl ring of the anilines were examined and all substrates reacted to afford α-amino amide derivatives in high yields and excellent enantioselectivities. In addition, this research group assesses a series of aliphatic aldehydes and isocyanides with different steric hindrance and found that all substrates were well-tolerated, leading to the formation of α-amino amides in good to excellent yields (62% to 99%) and enantiocontrol (81% to > 99% ee). However, the use of aromatic aldehydes or aliphatic amines gave the corresponding Ugi products in very low yields. The proposed mechanism of the reaction is well explained by Tan and coworkers [46].

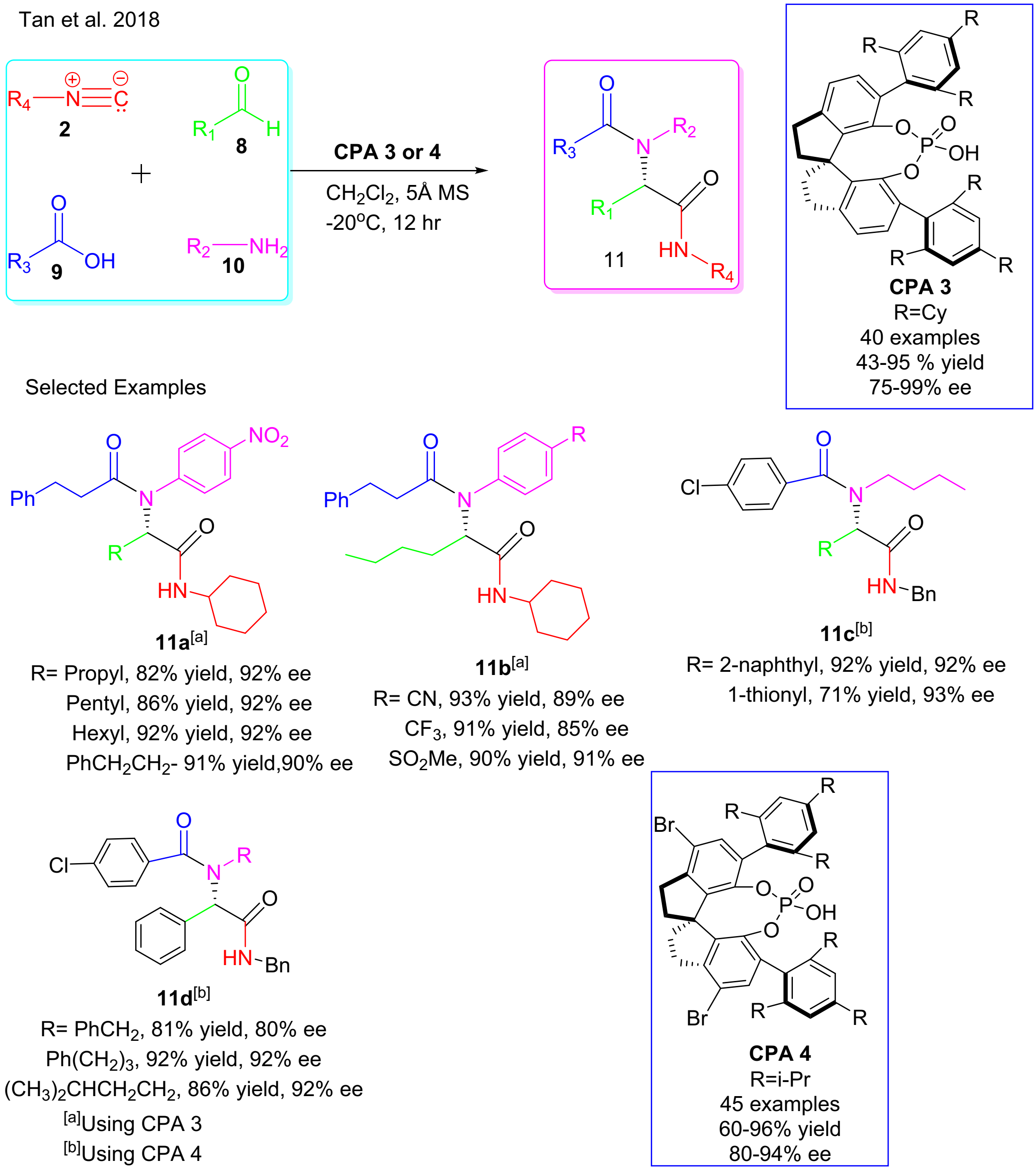
Enantioselective three-component cascade reaction

In organic chemistry, cascade reactions are an emerging technology, which allows the generation of molecular complexity in a single operation and introduces elegance and efficiency to synthetic strategies [47]. In this reaction approach, it is possible to synthesize compounds bearing stereocenters. Herein, the synthesis of indole structure containing molecules through multicomponent cascade reaction is one of the major concerns because indole scaffold is widely found in many natural products, drug, and bioactive molecules [48]. Due to this fact, it is chemists' interest to familiarize axial chirality into the indole skeleton through multicomponent reaction (Scheme 4).

With this context, Lin and co-workers (2019) disclosed synthesis of highly enantioselective axially chiral N-arylindoles via asymmetric three-component cascade reaction of 2,3-diketoesters (**13**), aromatic amines (**14**), and 1,3-cyclohexanediones (**15**) in the presence of chiral phosphoric acid (CPA 5). Different electronic properties and positions of the substituents on the aromatic ring of the substrates were well-tolerated in this transformation. Besides, wide ranges of anilines were tolerated to afford axially chiral N-arylindoles (**16**) in good yields (up to 93%) with good to excellent enantioselectivities (up to 99%). As shown in Scheme 5 with respect to the 1,3-cyclohexanedione substrates, methyl and phenyl group were well tolerated, and N-arylindoles were produced in good yields with high enantioselectivity (up to 94% ee). The formation of a wide range of axially chiral arylindoles in high yields with good to excellent enantioselectivities is due to the chiral spirocyclic



Scheme 2 Synthesis of enantioenriched 3-oxoisoindoline-1-carboxamides

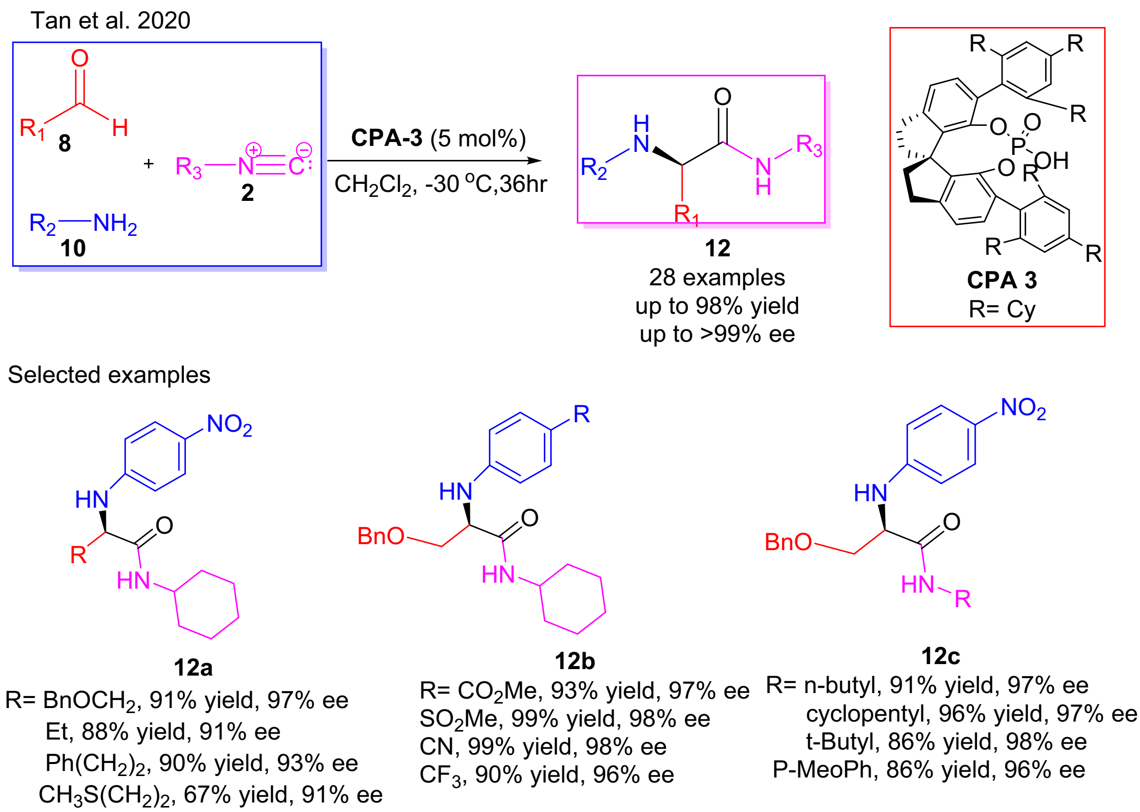


Scheme 3 CPA-catalyzed enantioselective construction of α-acylaminoamides [45]

phosphoric acid catalyst to advance the enantioselectivity in the cascade reaction process [49]. This catalyst can facilitate an aldol reaction to generate a stereocenter which can then be transferred to axial chirality during the aromatization step [50]. The suggested reaction mechanism is clearly elucidated in the review article published by Shi group [51].

Enantioselective three-component Povarov reaction

In 2016, Shi group reported the first chiral phosphoric acid (CPA 6)-catalyzed enantioselective synthesis of indole-derived tetrahydroquinolines via asymmetric Povarov

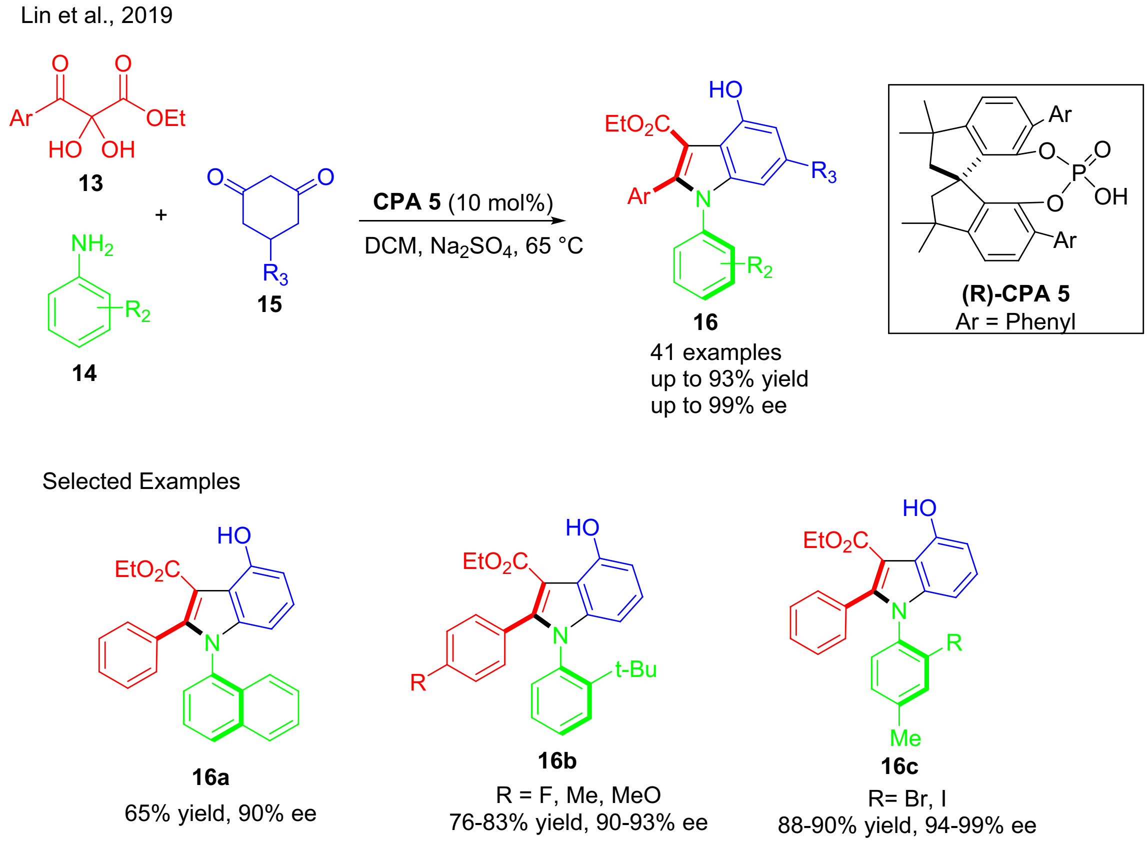


Scheme 4 Enantioselective synthesis of α-amino amide derivatives [46]

three-component reactions of 3-methyl-2-vinylindoles, aldehydes, and anilines. The chiral indole-derived tetrahydroquinolines bearing three contiguous stereogenic centers is obtained in high yields (up to 99%) and excellent diastereo- and enantioselectivities (all > 95:5 dr, up to 96% ee) (Scheme 6). Herein, a range of 3-methyl-2-vinylindoles (**18**) and aromatic aldehydes (**8**) bearing different substituents were tested and applied to the catalytic asymmetric three-component Povarov reaction and delivered enantioenriched indole-derived tetrahydroquinolines (19) with structural diversity. This transformation is very important to enrich the chemistry of the catalytic asymmetric Povarov and multicomponent reaction valuable for diversity-oriented synthesis and related bioassays [52].

Enantioselective three-component Biginelli-like reaction

In 2020, the stereoselective Biginelli-like reaction catalyzed by a new chiral phosphoric acid bearing two free hydroxyl groups was reported by Hu et al. This research group synthesized this new asymmetric phosphoric acid catalyst based on a highly regioselective transformation of chiral 1,1,4,4 tetraphenylbutanetetraol obtained from natural tartaric acid. This catalyst is the type of TADDOL-derived phosphoric acids, which was not comprehensively investigated as catalysts in asymmetric Biginelli and Biginelli-like reactions[53] other than other successful applications in the enantioselective transformation that are reported by Akiyama's group in 2005 [28]. However, Hu et al. tested the catalytic efficacy of this catalyst in the Biginelli-like reactions of three substrates, such as aldehydes, benzylthiourea, and cyclohexanone (Scheme 7), and obtained moderate to good enantioselectivities (up to 95% ee) even though the position of both the electron-donating and electron-withdrawing groups had a dramatic influence on the enantioselectivity of the reaction. As can be seen in the selected examples, substituents at 2-position were unfavorable for the enantioselectivity. According to the control experiments performed, the existence of the two hydroxyl groups of the catalyst was essential for achieving high enantioselectivity for asymmetric Biginelli-like reaction [53].

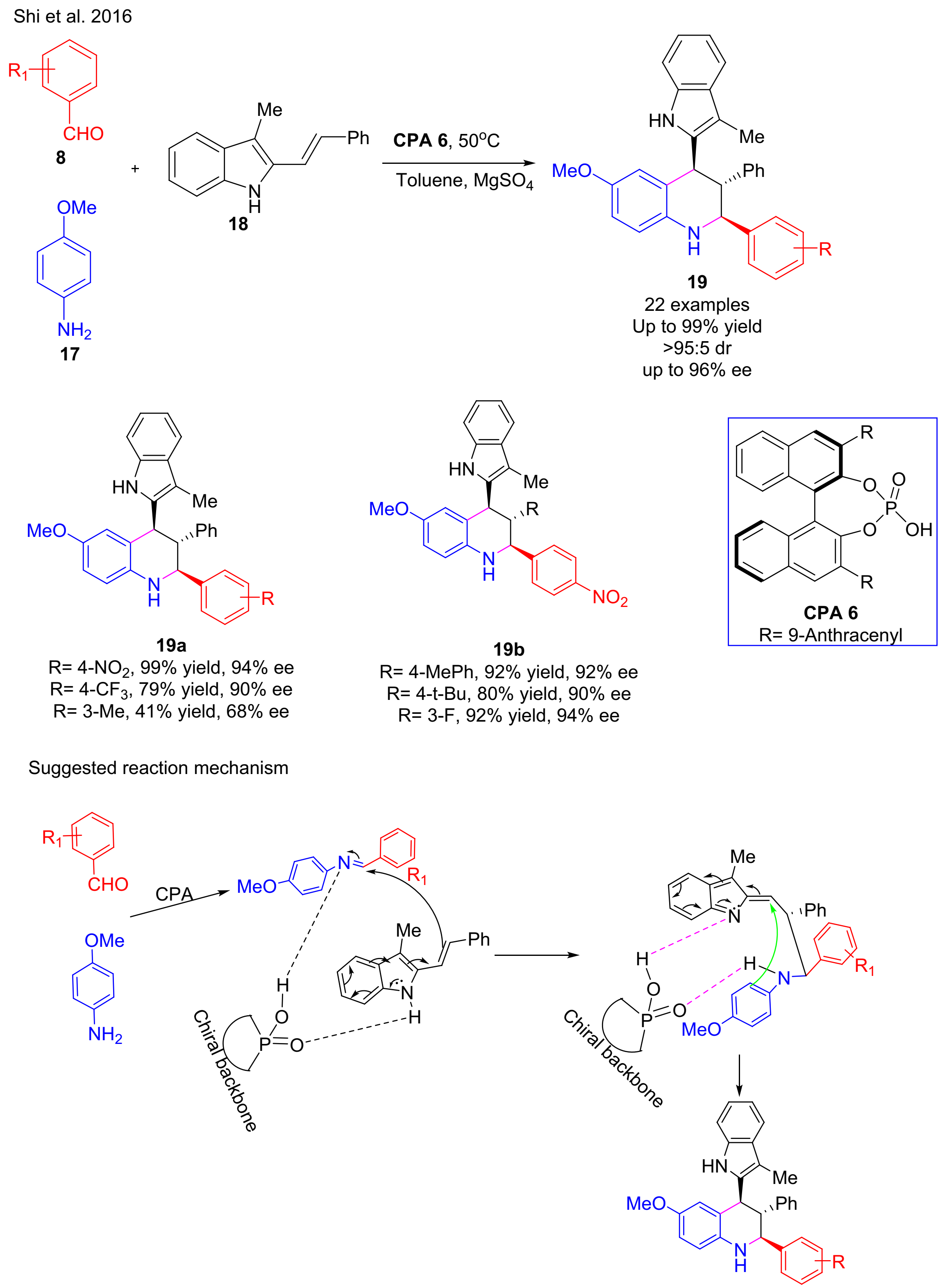


Scheme 5 Enantioselective synthesis of axially chiral N-arylindoles [49]

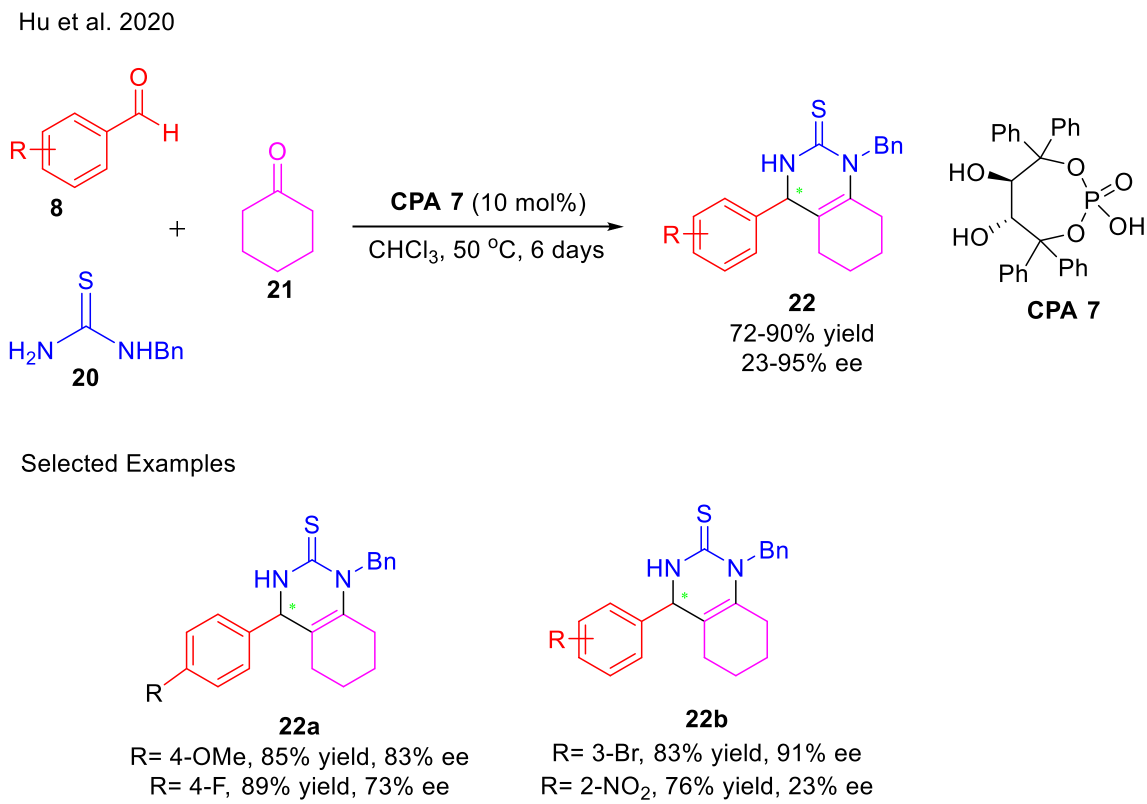
Enantioselective Multi-catalytic Multicomponent reactions

Over many decades, mostly the traditional catalytic strategies, those using a single catalyst to lower the energetic barrier of the subsequent reaction, were in use. However, now a day, multi-catalytic systems have become a powerful synthetic tool in organic chemistry (Scheme 8). On the other hand, multicomponent reactions, where several starting materials react together, have also become a noteworthy concern in the field of organic synthesis [54].

Multicomponent and multi-catalytic reactions are employed to imitate the way the enzymatic machinery converts simple building blocks into complex products [55, 56]. Consequently, the asymmetric synthesis via multicomponent and multi-catalytic reaction approach is crucial. In this regard, very recently, multicomponent and multi-catalytic asymmetric synthesis of furo[2,3-b]pyrrole derivatives from simple 3-butynamines (**23**), glyoxylic acid (**24**) and anilines (**14**) in the presence of a dual catalytic system, formed from a gold complex and a chiral phosphoric acid is reported by Alvarez and Rodriguez (2020). Additionally, these authors took further insights into the mode of action of chiral phosphoric acid catalysts in this reaction [57]. The corresponding furo[2,3-b]pyrrole derivative (**25**) was obtained in very high yield, diastereo- and enantioselectivity (Scheme 9). The furo[2,3-b]pyrrole derivatives bearing three connecting stereocenters were selectively obtained only when the BINOL-derived phosphoric acid catalyst was substituted at 3- and 3'-positions with anthracenyl groups (CPA). The mechanistic study revealed that non-covalent interactions such as the linear geometry of the anthracenyl group of the catalyst, the electron density of the aniline, the electronic complementarity of aromatic rings involved in van der Waals interactions, or the presence of an aryl substituent in 3-butynamine derivative were vital in order to validate the excellent results in terms of yield, diastereo- and enantioselectivity.



Scheme 6 Enantioselective Synthesis of Indole-Derived Tetrahydroquinolines via Povarov reactions [52]

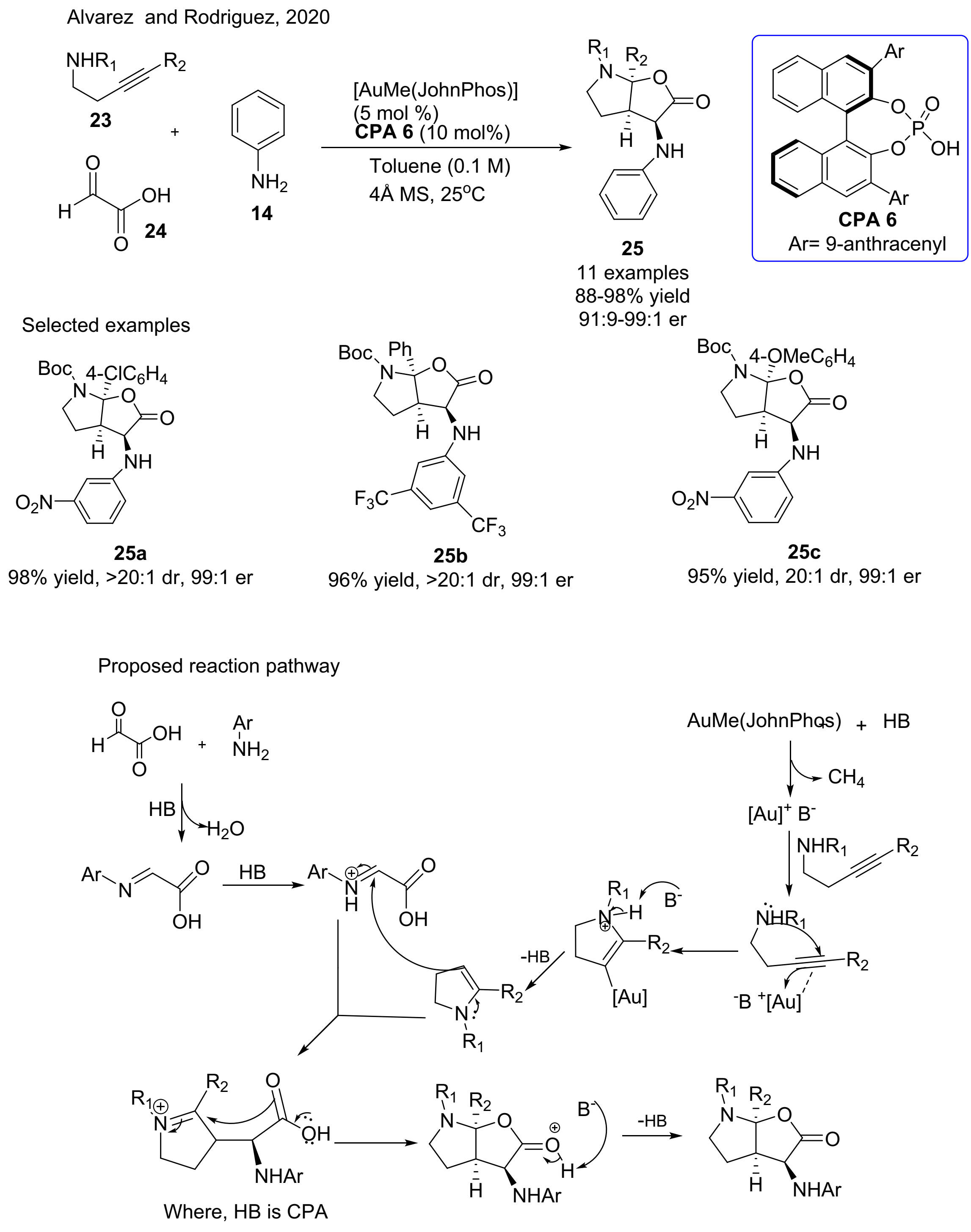


Scheme 7 Stereoselective Biginelli-like reaction catalyzed by a new chiral phosphoric acid

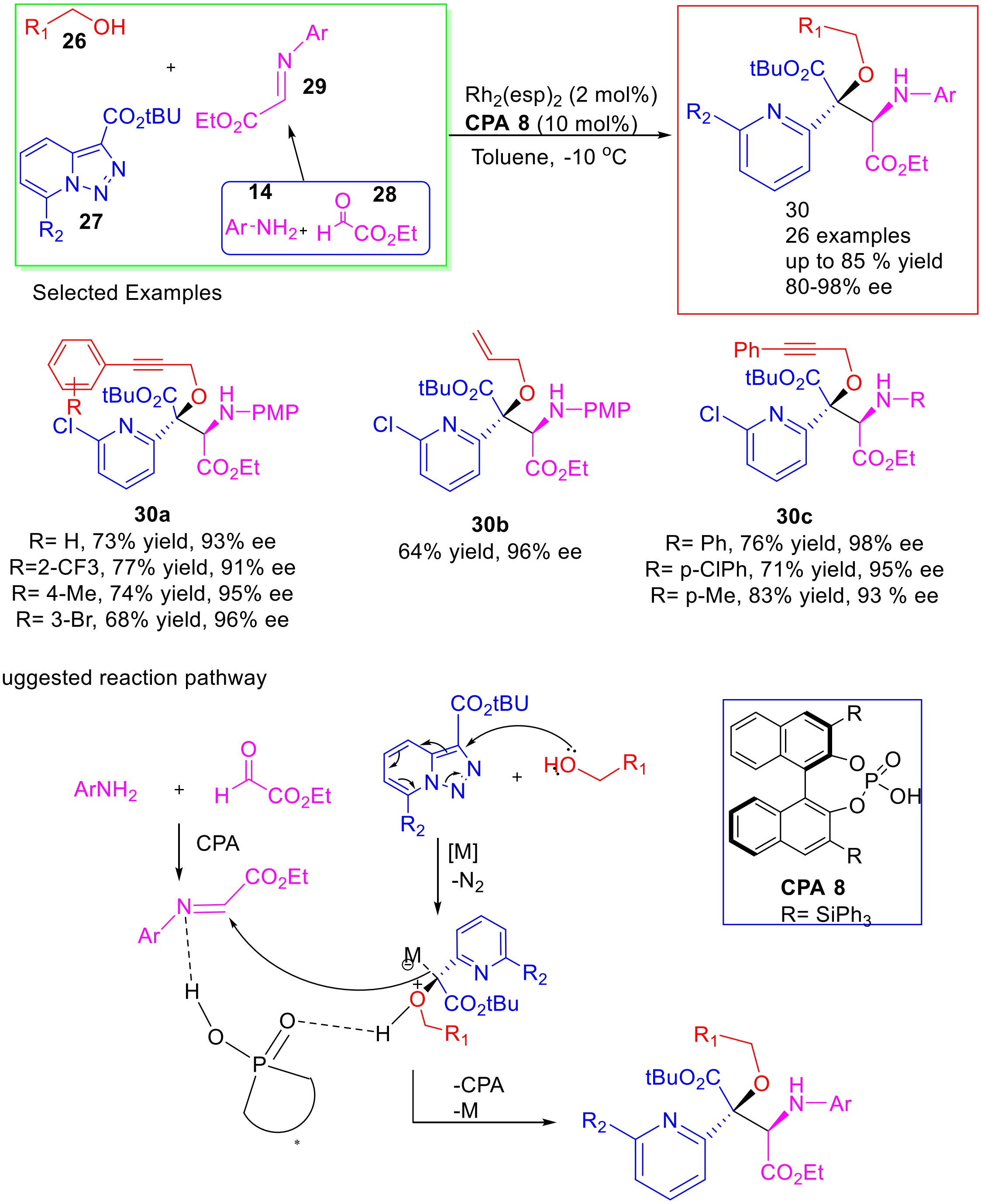
Enantioselective metal/CPA cooperative catalyzed MCRs

Recently, asymmetric **MCRs** involving transition metal complex and chiral organocatalyst such as CPAs attract the attention of chemists. Asymmetric cooperative transition metal complex and chiral organocatalysis are intended to sequentially impart activation on multiple steps by distinct catalysts. Such cooperative catalysis merges the advantages of both metal catalysis and organocatalysis, which plays a pivotal role in step-economy and potential to achieve inaccessible reactivity by a single catalyst [23]. In this regard, in 2020, Hu and coworkers described the asymmetric synthesis of polyfunctionalized chiral succinate derivatives from three- and four-component reaction of pyridotriazoles with propargyl alcohols and imines (or with corresponding aldehydes and amines) in the presence of dual $Rh_2(esp)_2$ and CPA catalyst under mild conditions. This propargyloxylation provides chiral polyfunctionalized succinate derivatives with adjacent quaternary and tertiary stereocenters in good to high yields with excellent enantioselectivities (Scheme 9). The position and electronic nature substituents tested during the reaction are tolerated. Beyond the alkyne motif, pyridyl, alkoxy, amino, and alkenyl species are all tolerated. The propargyl alcohols act as nucleophiles for the formation of corresponding ylide intermediates followed by an enantioselective trapping process with electrophilic reagents under an appropriate catalytic system [58].

Chiral sulfur-containing compounds are found extensively in plenty of pharmaceuticals and natural products [59]. Especially, now a day, sulfur-containing amino acid derivatives get particular interest because of their diverse biological activities [60]. As a result, great effort has been made to synthesize asymmetric sulfur-containing compounds. In this regard, Hu and coworkers (2016) disclosed an enantioselective construction of α-mercapto-β-amino esters through rhodium (II) ($Rh_2(OAc)_4$)/chiral phosphoric acid co-catalyzed three-component reaction of thiols (**31**), imines (**32**), and diazo compounds (**33**). Imines bearing electron-withdrawing groups on aromatic ring afforded the desired three-component products in higher yields and enantioselectivities, whereas imines derived from electron-deficient amines gave relatively lower enantioselectivities. On the other hand, if electron-donating groups present on the aryl ring of aryl diazoacetates, the yield was higher as compared to those bearing electron-withdrawing groups



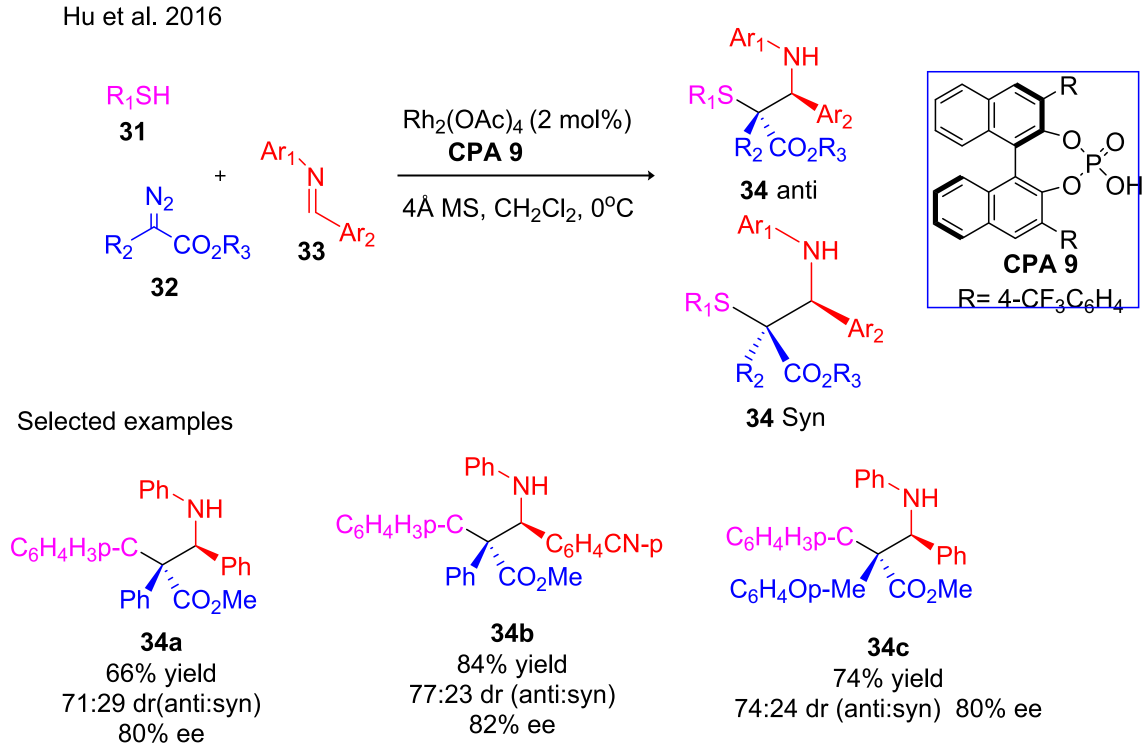
Scheme 8 Multicomponent and multi-catalytic asymmetric synthesis of furo[2,3-b]pyrrole derivatives [57]



Scheme 9 Chiral polyfunctionalized succinate derivatives synthesis and reaction pathway [58]

without affecting stereoselectivity. Generally, a series of α-mercapto-β-amino esters were obtained in good yields with moderate to good stereoselectivities (Scheme 10). The control experiment of this work revealed that $Rh_2(OAc)_4$ is crucial to facilitate the reactivity and the chiral phosphoric acid plays a significant role in both accelerating reactivity and controlling enantioselectivity [19].

Enantiomerically pure homopropargyl amines are very crucial building blocks for the synthesis of many bioactive compounds and natural products [61]. In line with this, Qiu and Hu group (2019) reported the cooperative catalysis of $Rh_2(OAc)_4$ and BINOL-derived chiral phosphoric acid (**CPA 8**) asymmetric three-component reactions of alkynyldiazoacetates (**36**) and imines (**37**), with various nucleophiles such as alcohols, indoles, and N,N-disubstituted anilines (**35**) for



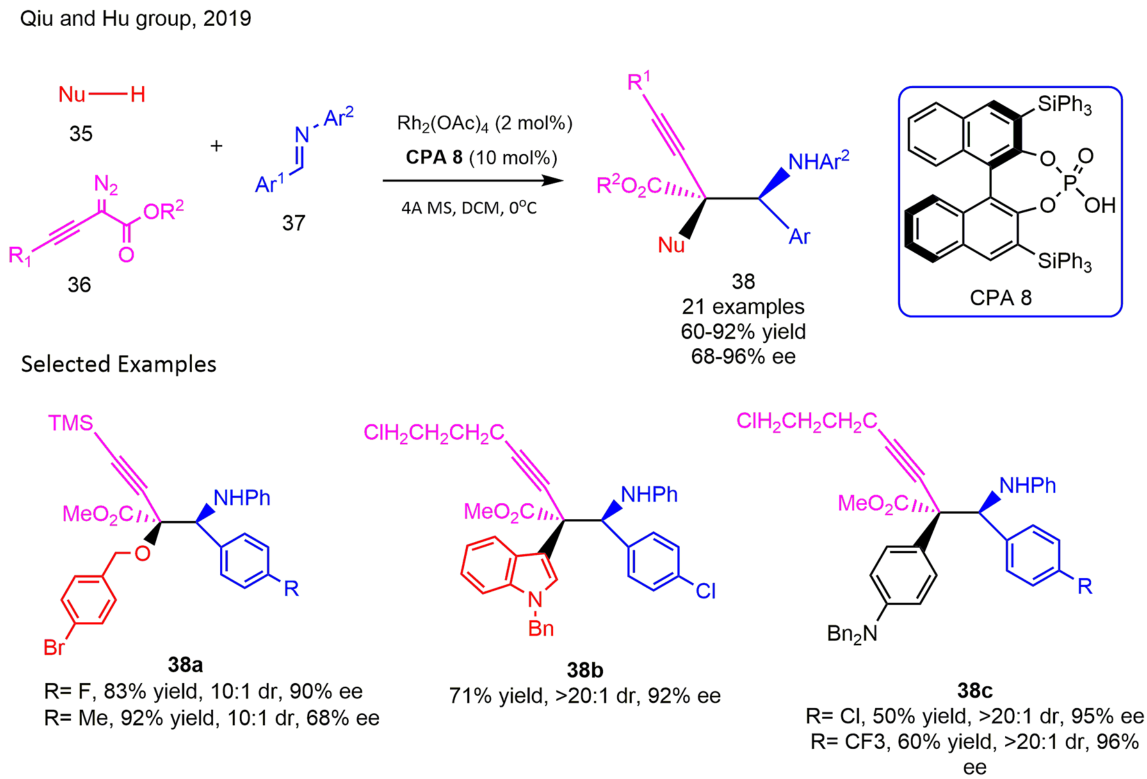
Scheme 10 Enantioselective synthesis of α-Mercapto-β-amino esters [19]

efficient construction of homopropargyl amine carboxylic esters (**38**) (Scheme 11). Substrates bearing different electron-withdrawing and electron-donating groups were tested by this research group and revealed that most of the substituents were well tolerated in this three-component reaction and afforded the corresponding homopropargyl amines containing two vicinal chiral centers in satisfactory to high yields (50–92%) with good to excellent diastereoselectivity (9:1 to > 20:1) and enantioselectivities (68–98%) (Scheme 11). Besides, the reaction shows high functional group tolerance [62].

In 2019, Liu and coworkers reported an asymmetric intermolecular three-component radical-initiated dicarbofunctionalization of 1,1-diarylalkenes (**39**) with diverse carbon-centered radical precursors and electron-rich heteroaromatics, encompassing a direct intermolecular arene C(sp^2)- H functionalization, in the presence of Cu(I)/ chiral phosphoric acid synergetic catalysts. This synthetic strategy provides chiral triarylmethanes (**42**) bearing quaternary all-carbon stereocenters with high efficiency as well as excellent chemo- and enantioselectivity (Scheme 12). The products acquired from this synthetic strategy can be served as practical synthons toward valuable chiral molecular entities in the area of pharmaceuticals, agrochemicals, and functional materials. The mechanistic investigations revealed that the hydrogen bonding and ion–pair interactions between the chiral phosphoric acid catalyst and substrates built the chiral environment and thus led to enantioselective C–C bond formation process [63].

The drug molecules such as Taxol (anticancer) [64], bestatin (treat obesity) [65], metaxalone (relief pain), KNI-227 (anti-HIV) [66] and leuhistin (antibacterial) all contain the norstatine scaffold. Due to the crucial value of norstatine derivatives in pharmaceutical science, their synthesis has been attracting the attention of chemists in the last several decades, even though their chiral phosphoric acid-catalyzed syntheses are rare. Herein, Hu et al. (2019) developed a sustainable enantioselective synthesis of both syn- and anti-norstatine derivatives via CPA-$[Rh(OAc)_2]_2$ dual catalyzed asymmetric multicomponent reaction of diazoacetates and alcohol/water with imines [67]. This beautiful work is a step forward in the sustainable synthesis of more pharmaceutically valuable norstatine derivative-based molecules and hence plays a crucial role in medicinal chemistry. Besides, these molecules are very important for synthesis of interesting building blocks in organic synthesis. In this work, the synthesis of 45 norstatines with moderate to excellent yield (up to 98%) and enantioselectivity (up to > 99%) were reported (Scheme 13). According to the mechanistic study, the synergetic catalysis of CPA and $[Rh(OAc)_2]_2$ plays a pivotal role to maintain the chemoselectivity and enantioselectivity of this asymmetric three-component reaction.

Very recently, Hu and coworkers developed a rhodium/chiral phosphoric acid cooperative catalyzed

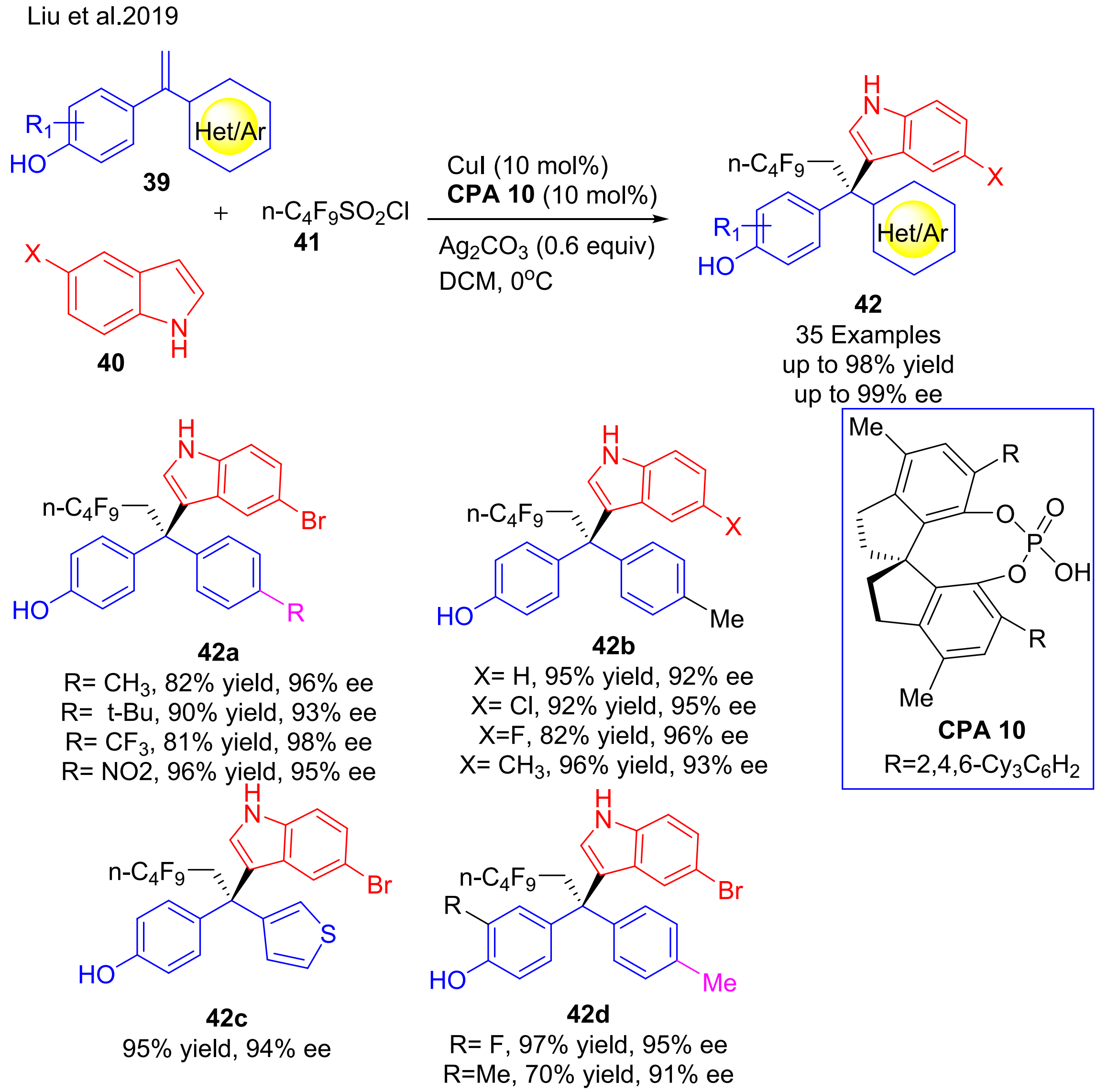


Scheme 11 Asymmetric synthesis of homopropargyl amine carboxylic esters [63]

enantioselective three-component aminomethylation of alcohols (**50**), α-diazo ketones (**51**), and 1,3,5-triaryl-1,3,5-triazines (**52**) to afford chiral β-amino-α-hydroxy ketones (**53**). They screened various CPA and rhodium catalysts and optimized that, CPA 13 and rhodium catalyst, $Rh_2(esp)_2$ were found as appropriate for reactivity and enantioselectivity of this transformation. This reaction offers an efficient electrophile-based asymmetric activation mode of formaldimines for aminomethylation. A very broad scope of alcohols such as aliphatic alcohols, benzyl alcohols, allyl alcohols, propargyl alcohols, and complicated natural alcohols (like geraniol, (2E, 6E)-farnesol, D-menthol, cholesterol) were worked well to furnish the corresponding product in a good efficiency and high enantiocontrol (Scheme 14). However, rather than the electronic properties of benzylic alcohols, their steric effects were also vital for enantioselectivity. On the other hand, the further bulkiness of the groups on alcohol component leads to a decrease the reactivity. The mechanistic studies showed that a dual hydrogen bonding between the chiral phosphoric acid catalyst and two distinct active intermediates was proposed to be crucial for the efficient electrophile-based enantiocontrol [68].

Other CPA-catalyzed MCRs

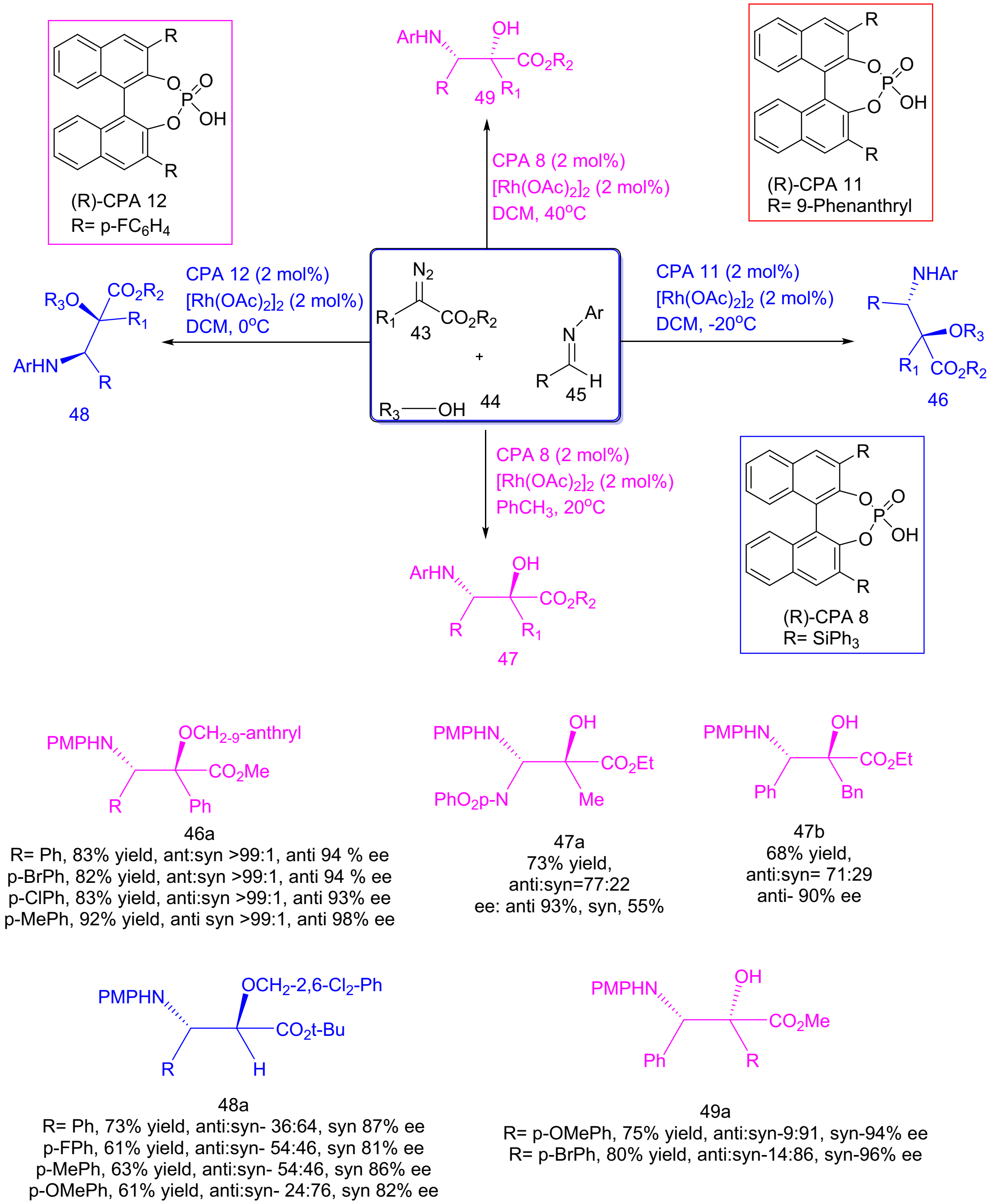
Natural products containing enol-derived 1,5-dihydro -2H-pyrrol-2-ones display a broad range of biological properties such as antitumor, anticancer, antimicrobial, and antiviral activities [69–71]. In addition, 3-amino 1,5-dihydro-2H-pyrrol-2-ones which contain the enamine group in their structure are excellent synthetic tools in organic synthesis [71]. In line with this, Palacios and Vicario's research group (2020) reported a Brönsted acid-catalyzed MCRs between pyruvate derivatives, amines, and aldehydes for the synthesis of phosphorus and fluorine substituted γ-lactam derivatives bearing chiral carbon. These authors performed the construction of enol- or enamine-derived γ-lactams derivatives using racemic phosphoric acids. However, they synthesized five enantioenriched γ-lactam derivatives from ethyl pyruvate (**54**), p-toluidine (55), and phosphorylated aldehyde (**56**) using MCRs (**CPA 8**) at room temperature in the presence of magnesium sulfate. All the tested examples gave good yield with moderate to high enantioselectivity except trifluoroacetaldehyde substrate (Scheme 15). This substrate provided a racemic mixture of lactam may be due to the strong acidity of the proton at the stereogenic carbon arisen from the strong electron-withdrawing effect of trifluoromethyl group [72].



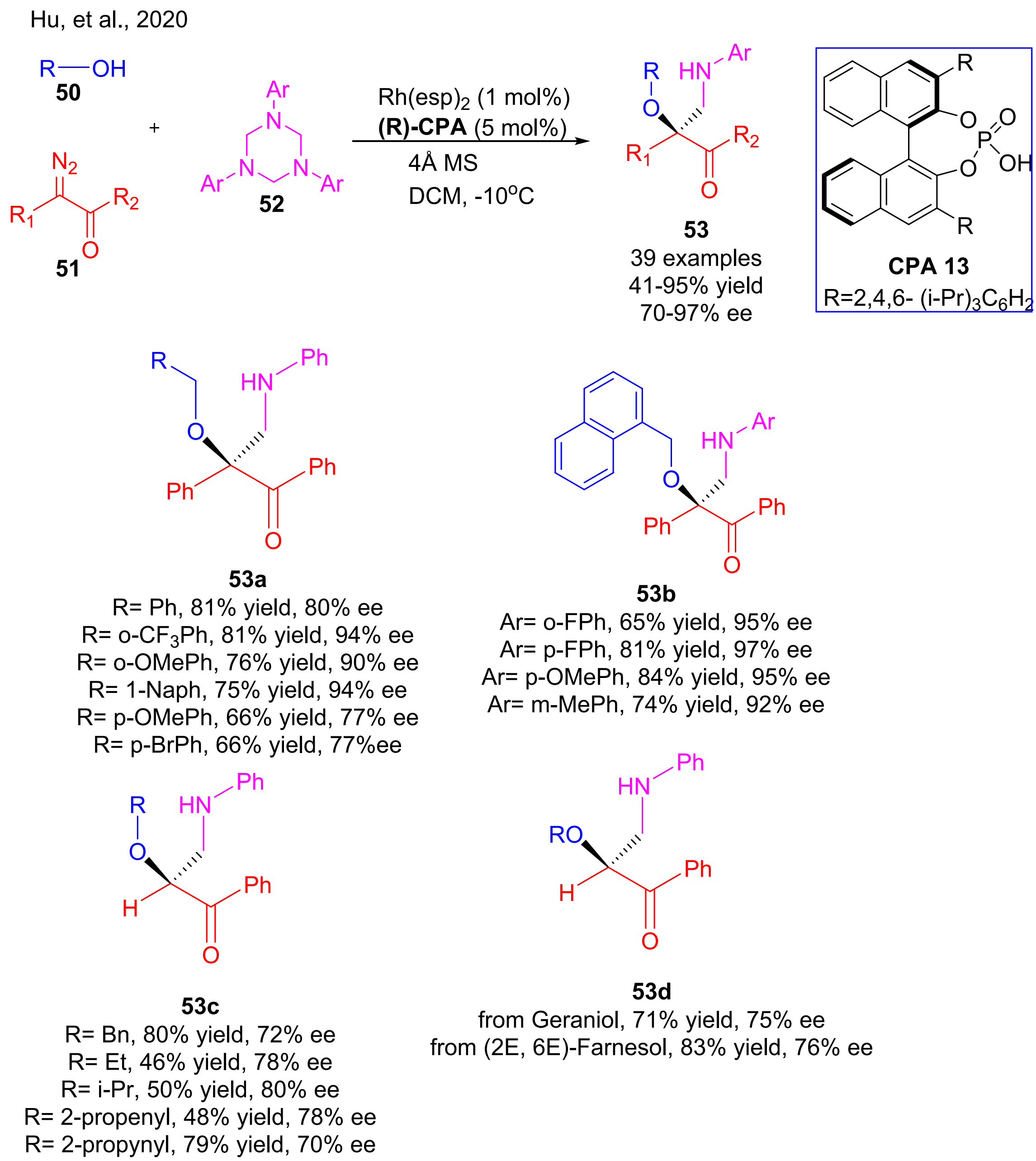
Scheme 12 Asymmetric synthesis of triarylmethanes

Conclusions and outlooks

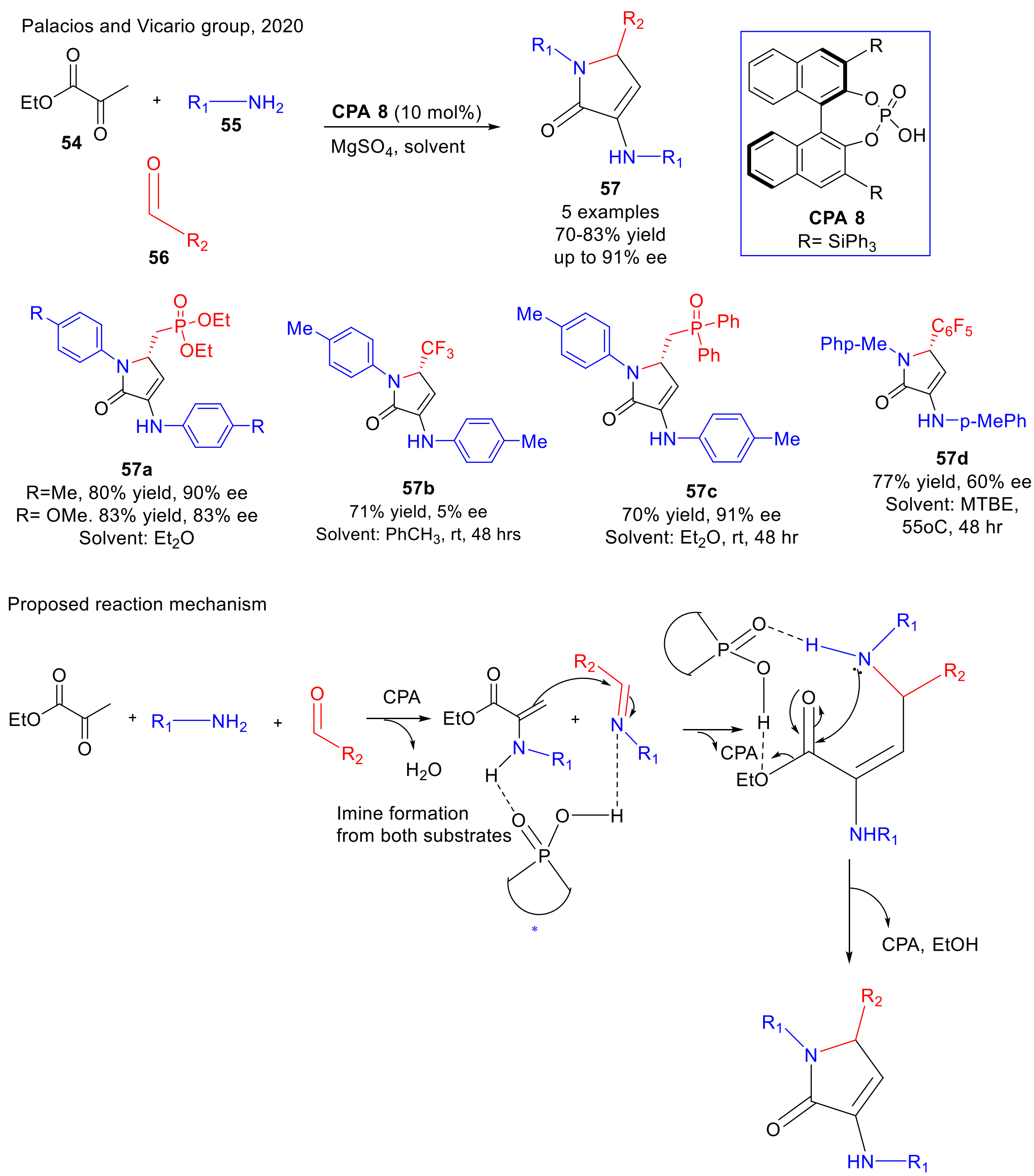
In this review, we describe recent advances in chiral phosphoric acid and metal chiral phosphoric acid cooperatively catalyzed asymmetric MCRs reported since 2015. To date, CPA-catalyzed multicomponent reactions have attracted widespread research interest due to their great importance in obtaining enantiomerically enriched compounds with high structural diversity and complexity, which play a pivotal role in the pharmaceutical and agrochemical industries as well as in synthetic and medicinal chemistry. In this review, CPAs and their cooperative metal catalysis have been identified as more efficient catalysts for the



Scheme 13 Enantioselective synthesis of syn- and anti-norstatine derivatives [67]



Scheme 14 Enantioselective synthesis of chiral β-amino-α-hydroxy ketones via three-component reaction [68]



Scheme 15 Synthesis enantioenriched γ-lactam derivatives via CPA catalysis and its reaction pathway [72]

enantioselective three- and four-component Ugi reaction, the asymmetric three-component Passerini reaction, the Povarov reaction, the stereoselective Biginelli reaction, and other asymmetric multicomponent reactions. However, the versatility of the CPA catalyst in multicomponent reactions is far from being fully explored. Therefore, more CPA-catalyzed enantioselective MCRs are needed to synthesize organic compounds with molecular complexity and diversity, and will continue to be a hot research topic in the future.

References

1. J.W. Li, J.C. Vederas, Science **325**, 161 (2009)
2. J. Zhang, P. Yu, S.Y. Li, H. Sun, S.H. Xiang, J.J. Wang, K.N. Houk, B. Tan, Science **361**, 1072 (2018)
3. T. Zarganes-Tzitzikas, A. Dömling, Org. Chem. Front. **1**, 834 (2014)
4. Q. Wang, D.X. Wang, M.X. Wang, J. Zhu. Acc. Chem. Res. **51**, 1290 (2018)
5. P.S.G. Nunes, H.D.A. Vidal, A.G. Corrêa, Org. Biomol. Chem. **18**, 7751 (2020)

6. E. Ruijter, R. Scheffelaar, R.V. Orru, Angew. Chem. Int. Ed. **50**, 6234 (2011)
7. B. Ganem, Acc. Chem. Res. **42**, 463 (2009)
8. J. Zhu, H. Bienaymé, *Multicomponent Reactions* (John Wiley & Sons, Hoboken, 2006), pp. 1–26
9. S.G. Dawande, V. Kanchupalli, B.S. Lad, J. Rai, S. Katukojvala, Org. Lett. **16**, 3700 (2014)
10. J.-P. Wan, L. Gan, Y. Liu, Org. Biomol. Chem. **15**, 9031 (2017)
11. G.K. Reen, A. Kumar, P. Sharma, Beilstein J. Org. Chem. **15**, 1612 (2019)
12. J.S. Quesnel, B.A. Arndtsen, Pure Appl. Chem. **85**, 377 (2013)
13. F. Lorenzini, J. Tjutrins, J.S. Quesnel, B.A. Arndtsen. Multicomponent reactions in organic synthesis, 207 (2014)
14. L. Zhu, X. Ren, J. Du, J.-H. Wu, J.-P. Tan, J. Che, J. Pan, T. Wang, Green Chem. **22**, 7506 (2020)
15. A. Bhunia, T. Roy, P. Pachfule, P.R. Rajamohanan, A.T. Biju, Angew. Chem. **125**, 10224 (2013)
16. A. Dömling, Chem. Rev. **106**, 17 (2006)
17. A. Dömling, I.I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
18. X. Guo, H. Huang, L. Yang, W. Hu, Org. Lett. **9**, 4721 (2007)
19. G. Xiao, C. Ma, D. Xing, W. Hu, Org. Lett. **18**, 6086 (2016)
20. J. Jiang, X. Ma, S. Liu, Y. Qian, F. Lv, L. Qiu, X. Wu, W. Hu, Chem. Commun. **49**, 4238 (2013)
21. C.M. Marson, Chem. Soc. Rev. **41**, 7712 (2012)
22. D.J. Ramón, M. Yus, Angew. Chem. Int. Ed. **44**, 1602 (2005)
23. P.-S. Wang, D.-F. Chen, L.-Z. Gong (eds.), *Asymmetric Organocatalysis Combined with Metal Catalysis* (Springer, Berlin, 2020), p. 185
24. S.-H. Xiang, B. Tan, Nat. Commun. **11**, 3786 (2020)
25. T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, Angew. Chem. Int. Ed. **43**, 1566 (2004)
26. D. Uraguchi, M. Terada, J. Am. Chem. Soc. **126**, 5356 (2004)
27. A.A. Desai, W.D. Wulff, Synthesis **2010**, 3670 (2010)
28. T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, Adv. Synth. Catal. **347**, 1523 (2005)
29. T. Akiyama, Chem. Rev. **107**, 5744 (2007)
30. G.C. Fang, Y.F. Cheng, Z.L. Yu, Z.L. Li, X.Y. Liu, Top. Curr. Chem. **377**, 23 (2019)
31. M. Melikian, J. Gramüller, J. Hioe, J. Greindl, R.M. Gschwind, Chem. Sci. **10**, 5226 (2019)
32. R.J. Phipps, G.L. Hamilton, F.D. Toste, Nat. Chem. **4**, 603 (2012)
33. A. Rahman, X. Lin, Org. Biomol. Chem. **16**, 4753 (2018)
34. C. Yang, X.-S. Xue, J.-L. Jin, X. Li, J.-P. Cheng, J. Org. Chem. **78**, 7076 (2013)
35. V. Nair, C. Rajesh, A. Vinod, S. Bindu, A. Sreekanth, J. Mathen, L. Balagopal, Acc. Chem. Res. **36**, 899 (2003)
36. L.A. Wessjohann, D.G. Rivera, O.E. Vercillo, Chem. Rev. **109**, 796 (2009)
37. J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu, B. Tan, J. Am. Chem. Soc. **137**, 14039 (2015)
38. C.C. Musonda, D. Taylor, J. Lehman, J. Gut, P.J. Rosenthal, K. Chibale, Bioorg. Med. Chem. Lett. **14**, 3901 (2004)
39. N. Isambert, R. Lavilla, Chem. Eur. J. **14**, 8444 (2008)
40. L. El Kaim, L. Grimaud, Tetrahedron **65**, 2153 (2009)
41. J. Almaliti, K.L. Malloy, E. Glukhov, C. Spadafora, M. Gutiérrez, W.H. Gerwick, J. Nat. Prod. **80**, 1827 (2017)
42. L.A. Wessjohann, B. Voigt, D.G. Rivera, Angew. Chem. Int. Ed. **44**, 4785 (2005)
43. Y. Zhang, Y.F. Ao, Z.T. Huang, D.X. Wang, M.X. Wang, J. Zhu. Angew. Chem. Int. Ed. **55**, 5282 (2016)
44. I. Ugi, A. Dömling, W. Hörl, Endeavour **18**, 115 (1994)
45. J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J.J. Wang, K.N. Houk, B. Tan. Science, **361** (2018)
46. J. Zhang, Y.-Y. Wang, H. Sun, S.-Y. Li, S.-H. Xiang, B. Tan, Sci. China Chem. **63**, 47 (2020)
47. M. Filice, J.M. Palomo, ACS Catal. **4**, 1588 (2014)
48. D. Crich, A. Banerjee, Acc. Chem. Res. **40**, 151 (2007)
49. L. Wang, J. Zhong, X. Lin, Angew. Chem. Int. Ed. **58**, 15824 (2019)
50. S.C. Zheng, Q. Wang, J. Zhu. Angew. Chem. Int. Ed. **58**, 9215 (2019)
51. T.Z. Li, S.J. Liu, W. Tan, F. Shi, Chem. Eur. J. **26**, 15779 (2020)
52. W. Dai, X.-L. Jiang, J.-Y. Tao, F. Shi, J. Org. Chem. **81**, 185 (2016)
53. X. Hu, J. Guo, C. Wang, R. Zhang, V. Borovkov, Beilstein J. Org. Chem. **16**, 1875 (2020)
54. C.M. Volla, I. Atodiresei, M. Rueping, Chem. Rev. **114**, 2390 (2014)
55. H. Wu, Y.P. He, L.Z. Gong, Org. Lett. **15**, 460 (2013)
56. L. Cala, A. Mendoza, F.J. Fañanás, F. Rodríguez, Chem. Commun. **49**, 2715 (2013)
57. L. Cala, P. Villar, Á.R. de Lera, F.J. Fañanás, R. Álvarez, F. Rodríguez, Chem. Sci. **11**, 9181 (2020)
58. X. Lv, S. Liu, S. Zhou, G. Dong, D. Xing, X. Xu, W. Hu, CCS Chem. **3**, 1903 (2020)
59. R. Suhas, S. Chandrashekar, D.C. Gowda, Eur. J. Med. Chem. **48**, 179 (2012)
60. C. David, L. Bischoff, H. Meudal, A. Mothé, N. De Mota, S. DaNascimento, C. Llorens-Cortes, M.C. Fournié-Zaluski, B.P. Roques, J. Med. Chem. **42**, 5197 (1999)
61. C.H. Ding, X.L. Hou, Chem. Rev. **111**, 1914 (2011)
62. S. Yu, R. Hua, X. Fu, G. Liu, D. Zhang, S. Jia, H. Qiu, W. Hu, Org. Lett. **21**, 5737 (2019)
63. J.-S. Lin, T.-T. Li, J.-R. Liu, G.-Y. Jiao, Q.-S. Gu, J.-T. Cheng, Y.-L. Guo, X. Hong, X.-Y. Liu. J. Am. Chem. Soc. **141**, 1074 (2018)
64. M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggon, A.T. McPhail, J. Am. Chem. Soc. **93**, 2325 (1971)
65. H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, T. Takeuchi, J. Antibiotics **29**, 97 (1976)
66. T. Mimoto, J. Imai, S. Kisanuki, H. Enomoto, N. Hattori, K. Akaji, Y. Kiso, Chem. Pharm. Bull. **40**, 2251 (1992)
67. T. Shi, C. Jing, Y. Qian, X. Xu, G.K.R. Alavala, X. Lv, W. Hu, Org. Biomol. Chem. **17**, 9792 (2019)
68. J. Che, L. Niu, S. Jia, D. Xing, W. Hu, Nat. Commun. **11**, 1511 (2020)
69. X. Mo, Q. Li, J. Ju, RSC Adv. **4**, 50566 (2014)
70. R. Schobert, A. Schlenk, Bioorg. Med. Chem. **16**, 4203 (2008)
71. R. Bruckner. Organic Mechanisms: Reactions, Stereochemistry and Synthesis, 487 (2010)
72. X. Del Corte, A. López-Francés, A. Maestro, E. Martinez de Marigorta, F. Palacios, J. Vicario, J. Org. Chem. **85**, 14369 (2020)

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