REVIEW

An overview of the applications of chiral phosphoric acid organocatalysts in enantioselective additions to C=O and C=N bonds

Xabier del Corte,[a] Edorta Martinez de Marigorta,[a] Francisco Palacios,[a] Javier Vicario,*[a] and Aitor Maestro*[a]

Chiral phosphoric acids (CPAs) have been used as efficient organocatalysts since the first examples were reported 18 years ago by Akiyama and Terada. Although they were originally developed for enantioselective additions to imines, a wide reaction scope has been demonstrated using this type of catalysts. In this review, the known applications of CPA for enantioselective additions to C=O and C=N bonds are covered.

Summary

1. Introduction

The modern chemical industry demands the intensification of chemical processes in order to save chemicals, energy and waste treatments. There, asymmetric catalysis represents the most efficient and atom-economic tool to build up stereochemical complexity. In this context, over the last decade, chiral phosphoric acids (CPAs) have become one of the most relevant structures in the field of asymmetric organocatalysis, due to their versatility and functional group tolerance, together with the mild reaction conditions that are often employed in such processes. Since Terada[1] and Akiyama[2] reported the first examples of CPA-catalysed enantioselective reactions in early 2004, their applications as Brønsted acid catalysts has attracted growing interest in chemistry, which is reflected in the consequent increase in the number of published articles on this topic along the coming years (Figure 1).

During the last decade, CPAs have inspired the synthesis of new and more acidic organocatalysts such as disulfonimides, *N*-triflylphosphoramides or imidodiphosphorimidates.[3–8] However, the interest in the applications of CPAs in chemistry is still growing and, up to date, they have proved to be highly efficient catalysts for several enantioselective transformations such as S_N1,[9] transfer hydrogenation,[10–13] dearomatization[14] or cycloadition[15] reactions among others.[16–20] Moreover, they have also gained attention in kinetic resolution and deracemization processes,[21] as chiral ligands for metal-catalysed reactions[22,23] or metal-CPA co-catalysis,[24–27] and have promising perspectives as chiral inductors in photocatalytic reactions.[28]

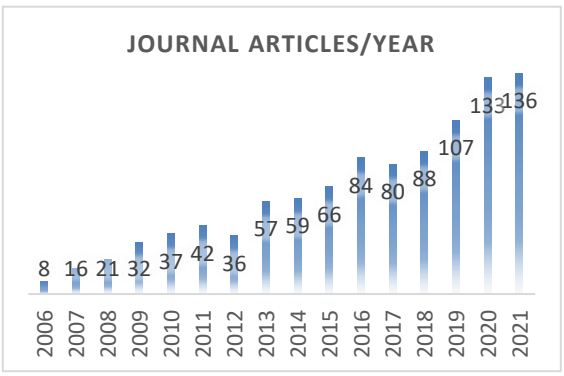


Figure 1. Scifinder search and refine "Chiral phosphoric acid > enantioselective > Journal > English".

Department of Organic Chemistry I, Faculty of Pharmacy, University of the Basque Country, UPV/EHU. Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain. Email: aitor.maestro@ehu.eus, javier.vicario@ehu.eus.

Several attempts to further improve the structure of CPAs have been made, slowly moving from the initially developed BINOL derivatives[3,29,30] to some new chiral diols like SPINOL-derived phosphoric acids.[31,32] In addition, with the purpose of understanding the nature of the activation in CPA-mediated reactions, computational models have been developed in order to try to predict the optimal catalyst structure.[33–37]

Keeping into account the considerations mentioned above, many reviews have been published in the past, covering the diverse aspects of the applications of CPAs in chemistry. The seminal work in this field comprises enantioselective addition reactions of nucleophiles to carbonyl compounds and their imine analogues. For this reason, an updated revision that highlights the most recent developments about this topic would be of great interest in order to help to find the strengths and weaknesses of CPA-mediated enantioselective additions to C=O and C=N bonds. Thus, the aim of this review is to summarise the CPA-organocatalysed stereoselective nucleophilic addition reactions to carbonyl and iminic compounds.

2. The CPA-catalysed addition strategy

Brønsted base/H-bond donor organocatalysts have demonstrated their huge potential in the field of asymmetric synthesis. Key features of those bifunctional catalysts are a basic centre and a hydrogen bond donor group, both properly located in a chiral atmosphere. Phosphoric acids are able to catalyse organic reactions by activating both the nucleophile and the electrophile substrates, making use of the basic character of the P=O moiety and, simultaneously, establishing hydrogen bond interactions (Figure 2). Due to the high relevance of the H-donor effect of CPAs on the asymmetric induction and the possibility of combining them with metal salts for several transformations,[26,27] the effect of trace phosphate salts formed during the synthesis of CPAs has been reported as a relevant factor that might affect the obtained results.[38,39] In a typical CPA-catalysed nucleophilic addition, the enantioselectivity of the process is governed by the axial chirality of the BINOL structure, while the reactivity and the level of the asymmetric induction can be modulated by the size and nature of the substituents present at the aromatic rings.[40] The conventional model of addition proposed for a CPA-catalysed reaction is based on a hydrogen-bonding interaction between the substrates and the catalyst, anchoring the structures to the catalyst, thus favouring the transition state that leads to one of the enantiomers, due to a lower steric hindrance between the substrates and the catalyst substituents (Figure 2, a).[34] Additionally, other approaches are focused on the complementary presence of noncovalent interactions (e.g. π-stacking, CH/π) between the substrates and the catalyst substituents (Figure 2, b).[41–45]

Usually, large bulky groups are required for the accomplishment of high enantiomeric excesses. However, an excessive steric hindrance may also be an obstacle, leading to a drop in the catalytic activity or the stereocontrol.[46] Rationally selecting the correct catalyst to obtain the desired selectivity is necessary but, even though there are numerous computational

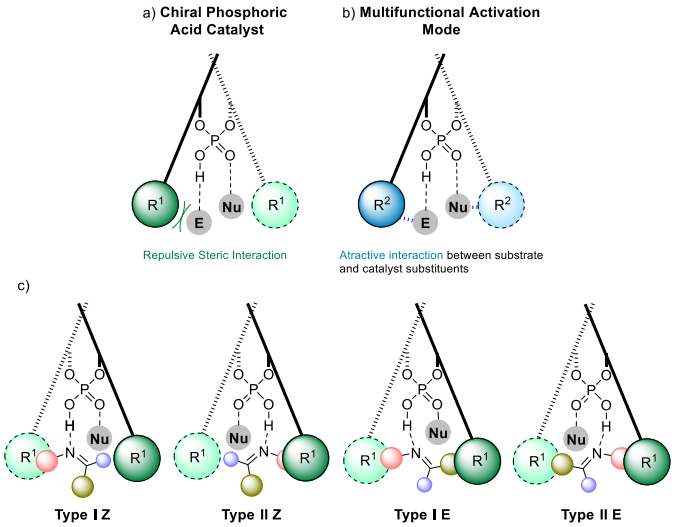


Figure 2. a and b)Different activation modes of CPA catalysts. (Adapted from Toste and coworkersl).[42] c) Possible transition states of imines for the prediction of the stereoselectivity. (Adapted from Goodman and co-workers).[46]

and experimental studies on the rational design of CPA catalysts, the selectivity trends are not still well understood and the selection of the optimal catalyst structure is always a challenging task.

In the particular case of imines, Goodman and co-workers reported four possible activation pathways. Since it is well known that imines can adopt either *E* or *Z* configuration (Figure 2, c),[46] they propose two possible transition states for each imine type depending on the orientation of the imine with respect to the catalyst:[41]

- Type I TS: The nitrogen substituent of the imine is directed towards the empty side of the oxygen to which it is H-bonded. This transition state is preferred when small or symmetrical nucleophiles are used, as well as when the protecting groups are highly sterically demandant (ie: Ts, Trt) if compared with the large substituent of the imine.
- Type II TS: The nitrogen substituent of the imine is directed toward the bulky catalyst goup. This type of transition state is more common when non-symmetrical nucleophiles (ie: enamines, enamides, indole), and when less sterically demandant protecting groups are used at the imine (ie: Boc, Bn, Ac).

Thus, the mechanistic choice between these four pathways depends on numerous factors, such as the configuration of the imine bond and the nature of the nucleophile,[40] but the role of the 3,3' substituents at the naphthyl rings is always decisive.

Concerning the configuration of the imine bond, the *Z* isomer has a higher energy if compared to the *E* isomer for aldimines, but ketimines might not follow this rule.

On the other hand, with respect to the 3,3' groups BINOL moiety, the existing catalysts can be mainly divided into two steric regions as shown in Figure 3: proximal regions, quantified by a rotation barrier, and distant regions, quantified by a remote environment angle, AREA(θ), which measures steric effects distant from the phosphoric acid group.[46] Using this clasification, Goodman and co-workers determined

theoretically the best substitution pattern for the addition of different nucleophiles to imines.[47] However, the analysed examples are limited to aldimines and a few simple ketimines, and the applicability of this predictive analysis to more complex systems is not clear.

In the following sections of this review, the recent reports regarding CPA catalysed enantioselective additions to carbonyl and iminic electrophiles are summarised. It should be noted that, even though the above-described theoretical models have been optimised for BINOL-derived phosphoric acids, this review also contains several examples related to CPAs based on other chiral diols and, thus, those approximations should only be used as a general guide.

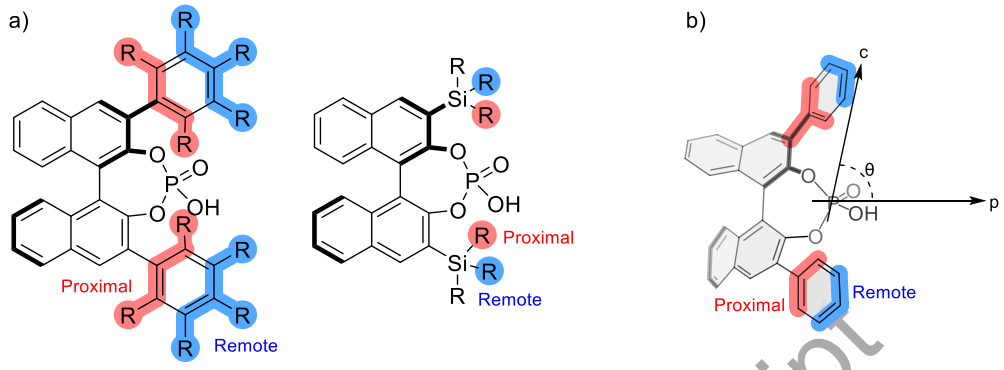
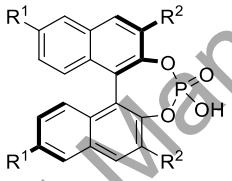


Figure 3. a) Commonly used phosphoric acid structures. b) Representation of AREA (θ) that measures steric effects distant from the phosphoric acid. (Adapted from Goodman and co-workers).[46]

Table 1: Summary of BINOL-derived chiral phosphoric acid organocatalysts. (*R* enantiomer shown).



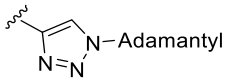
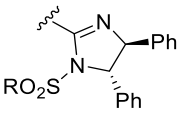
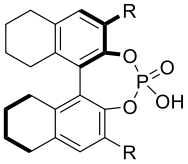
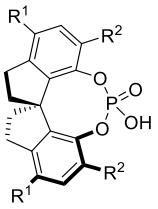
Cat.	R^1	R^2	Cat.	R^1	R^2
BPA1	H	9-Phenantryl	**BPA23**	H	3,5-$Ph_2C_6H_3$
BPA2	H	2,4,6-(^{i}Pr)$_3C_6H_2$	**BPA24**	H	^{t}Bu
BPA3	H	2,4,6-(Cy)$_3C_6H_2$	**BPA25**	H	4-PhC_6H_4
BPA4	H	2,4,6-(Me)$_3C_6H_2$	**BPA26**	H	CPh_2OH
BPA5	H	3,5-$(CF_3)_2C_6H_3$	**BPA27**	H	3,5-(2,4,6-$(CH_3)_3C_6H_2)_2C_6H_3$
BPA6	H	I	**BPA28**	H	1-Naphthyl
BPA7	H	C_6F_5	**BPA29**	$PPh_3^+PF_6^-$	2,4,6-(^{i}Pr)$_3C_6H_2$
BPA8	H	2-Naphthyl	**BPA30**	H	2,6-(^{i}Pr)$_2$-4-(9-antryl)-C_6H_2
BPA9	H	Ph	**BPA31**	H	4-Adamantanyl-2,6-(^{i}Pr)$_2C_6H_2$
BPA10	H	$SiPh_3$	**BPA32**	H	4-^{t}Bu-C_6H_4
BPA11	H	2,4,6-(Me)$_3$-3,5-$(NO_2)_2C_6$	**BPA33**	H	$P(4\text{-}CH_3C_6H_4)^+$ $B(3,5\text{-}(CF_3)_2C_6H_3)_4^-$
BPA12	H	Cy	**BPA34**	H	$C_6(CH_3)_5$
BPA13	H	3,5-(^{t}Bu)$_2$-4-$OMeC_6H_2$	**BPA35**	C_8H_{17}	
BPA14	H	3,5-(4-$FC_6H_4)_2C_6H_3$			
BPA15	H	9-Antryl			
BPA16	H	4-^{t}Bu-2,6-(Me)$_2C_6H_2$	**BPA36**	H	 R: ^{i}Pr
BPA17	H	Si(4-^{t}Bu$C_6H_4)_3$	**BPA37**	H	R: 1-Naphtyl
BPA18	H	Me	**BPA38**	H	R: Et
BPA19	H	4-$NO_2C_6H_4$	**BPA38**	H	R: Tolyl

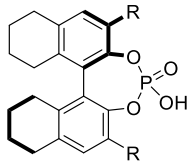
Table 2 (continuation): Summary of chiral phosphoric acid organocatalysts. (*R* enantiomer shown).



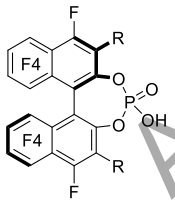
Cat.	R
H$_8$BPA1	2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
H$_8$BPA2	9-Antryl
H$_8$BPA3	3,5-(CF$_3$)$_3$C$_6$H$_3$
H$_8$BPA4	Ph
H$_8$BPA5	SiPh$_3$
H$_8$BPA6	4-ClC$_6$H$_4$
H$_8$BPA7	9-Phenantryl
H$_8$BPA8	CHPh$_2$



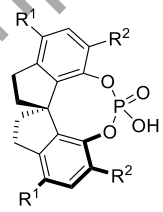
Cat.	R^1	R^2
SPA1	H	9-Phenantryl
SPA2	H	9-Antryl
SPA3	H	2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
SPA4	H	2,4,6-(^{c}Pent)$_3$C$_6$H$_2$
SPA5	H	2,4,6-(Cy)$_3$C$_6$H$_2$
SPA6	H	3,5-(CF$_3$)$_2$C$_6$H$_3$
SPA7	H	2,4,6-(Me)$_3$C$_6$H$_2$
SPA8	Me	9-Anthryl



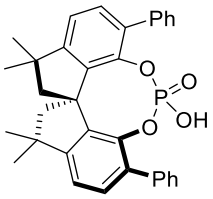
Cat.	R
H$_8$BPA9	2-Naphthyl
H$_8$BPA10	C$_6$F$_5$
H$_8$BPA11	1-Naphthyl



Cat.	R
FBPA1	Ph
FBPA2	6-MeO-2-Naphthyl



Cat.	R^1	R^2
SPA9	H	2-Me-4-^{t}BuC$_6$H$_2$
SPA10	H	3,5-(Me)$_2$-4-((3,4,5-F$_3$)C$_6$H$_2$)C$_6$H$_2$
SPA11	H	10-(2-Naphthyl)-9-antryl
SPA12	H	SiPh$_3$
SPA13	H	2,6-(Me)$_2$-4-^{t}BuC$_6$H$_2$
SPA14	H	3,5-(^{t}Bu)$_2$-4-MeOC$_6$H$_2$
SPA15	H	1-Naphthyl
SPA16	H	3,5-(3,5-(CF$_3$)$_3$C$_6$H$_3$)$_2$C$_6$H$_3$
SPA17	H	4-PhC$_6$H$_4$



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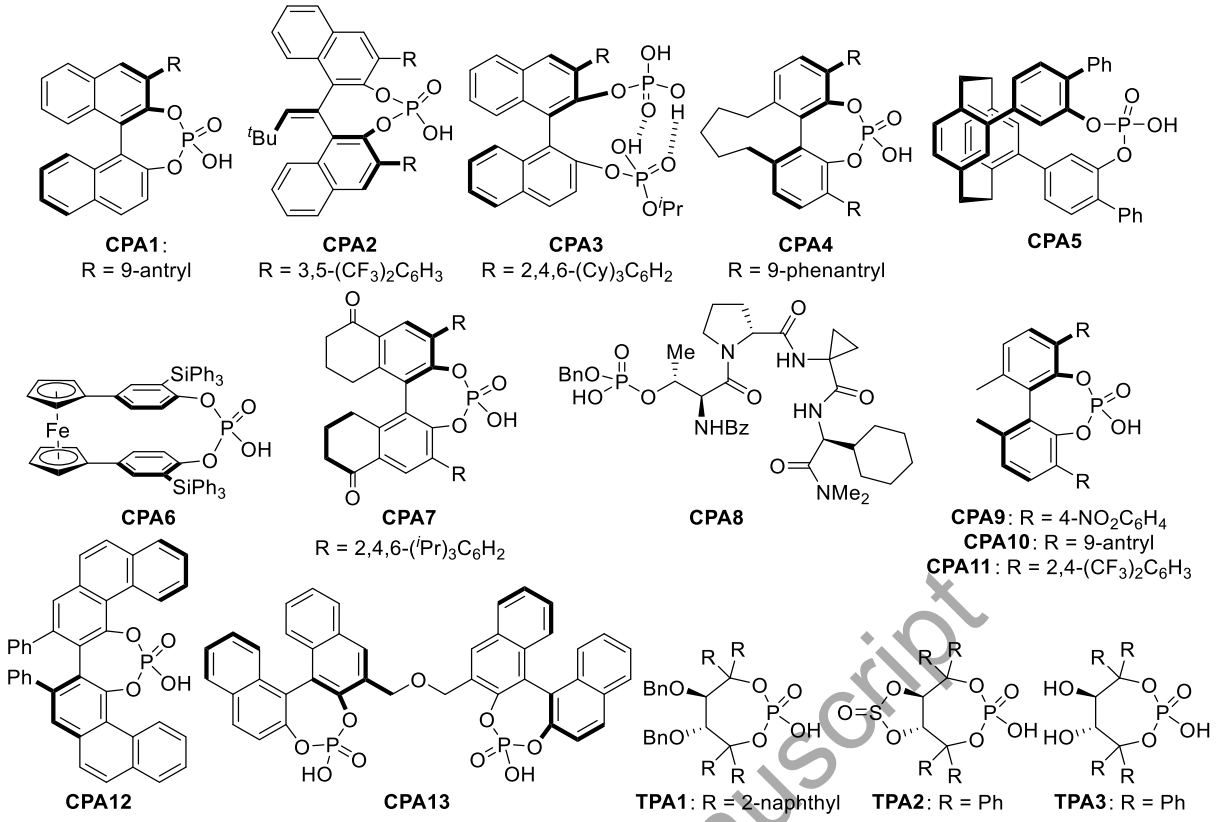
SPA18

Table 2 (continuation): Summary of chiral phosphoric acid organocatalysts. (*R* enantiomer shown).

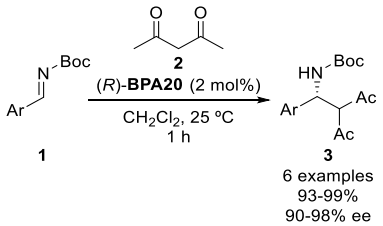


3. Enantioselective nucleophilic additions to C=N bonds

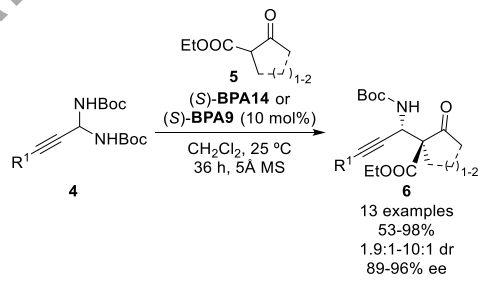
3.1. Addition of enol and enamine derivatives

3.1.1. Addition of enols and enolates

The Mannich reaction represents one of the main procedures for the addition of carbon nucleophiles to imines. Based on this strategy, many synthetic routes to access optically active α-chiral amines have been developed.[48–50] Terada's group reported in 2004 the first direct Mannich addition to imines **1** catalysed by CPAs (Scheme 1).[1] Although the scope was limited to aromatic aldimines, they obtained chiral amines **3** in excellent yield and enantiocontrol, with just slight differences between electron-donating and electron-withdrawing groups.



Scheme 1. First direct CPA-catalysed Mannich addition to imines.



Scheme 2. Stereocontrolled addition of β-keto esters **5** to *in situ* formed propargyl imines.

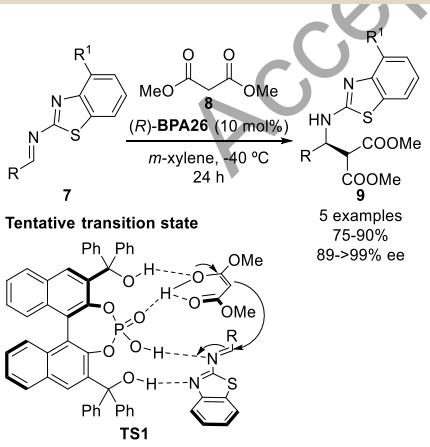
Remarkably, their reaction was performed under mild reaction conditions, using 2 mol% of (*R*)-**BPA20** catalyst. A few years later, they extended the reaction to *N*-Boc enamines as an alternative to more challenging aliphatic imines.[51] In this case, a 5 mol% of (*R*)-**BPA2** is required, and higher reaction temperatures to displace the equilibrium towards the formation of aliphatic imines, with the consequent decrease on the enantiocontrol (20-73%, 49-89% ee).

Some years later, Maruoka and co-workers reported the use of *N*-Boc-aminals **4** as practical precursors of *N*-Boc imines in organic synthesis (Scheme 2),[52,53] and they illustrated the applicability of their methodology by an enantioselective nucleophilic addition of β-keto esters **5** to *N*,*N*-aminals **4**, catalysed by (*S*)-**SPA14** or (*S*)-**BPA9**. The authors were able to construct a few optically active propargylamine derivatives **6** in high yields and excellent enantioselectivities (89-98%, 90-96% ee), but with moderate diastereocontrol (5:1 to 10:1 dr). However, the use of non-cyclic ketoesters resulted in a drop in

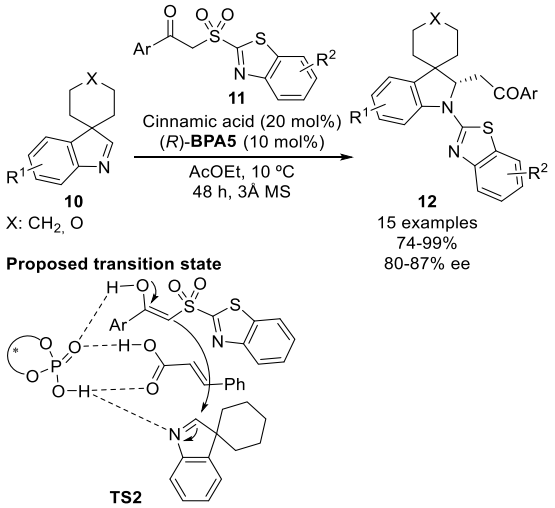
the diastereocontrol but still observing high enantioselectivities (53-99%, 2.4:1 to 1.9:1 dr, 89-91% ee). In addition, they also tested other acetyl acetone **2** and aliphatic aldehydes as nucleophiles, obtaining in all cases enantioselectivities above 80%. More recently, Sun and co-workers described a homologous decarboxilative Mannich addition of β-keto acids to C-alkynyl N,O-acetals.[54] In this case, (*R*)-**H$_8$BPA1** was selected as the optimal catalyst, affording excellent yields (67-95%) and enantiomeric excesses up to 90%.

In 2015, Xue and co-workers reported the synthesis of new BINOL-derived chiral phosphoric acids and evaluated their effectiveness in an organocatalysed Mannich addition using malonic ester **8** (Scheme 3).[55] Remarkably, they avoided the usual Suzuki coupling strategy in their synthetic pathway, making the overall synthesis more accessible. In particular, (*R*)-**BPA26** provided the optimal results, obtaining chiral β-amino esters **9** in high yields and enantioselectivities (75-90%, 89->99% ee). This is probably due to the presence of the additional hydroxy groups in the structure of the catalyst, that can act as hydrogen donors in the reaction, increasing the binding points between the imine **7** and the catalyst, thus making (*R*)-**BPA26** more acidic than other similar organocatalysts (**TS1**).

Regarding enantioselective additions to endocyclic imines, Shao and Cheng reported the Mannich addition of α-substituted aryl ketones **11** to spirocyclic indolenines **10** (Scheme 4).[56] The presence of a catalytic amount of cinnamic acid as an additive in the reaction allows an improvement in the yield and enantioselectivity of the reaction. That is probably due to the (*R*)-**BPA5**-cinnamic acid heterodimer formed in the reaction media that improves the acidic character of the phosphoric acid catalyst as shown in the transition state **TS2**. After the initial Mannich addition, a subsequent Smiles rearrangement leads to the formation of indolines **12** in yields ranging from 74 to 99% and enantioselectivities above 80%.



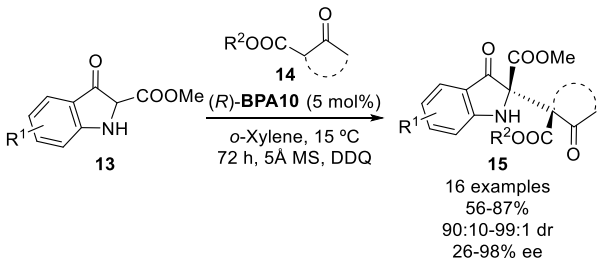
Scheme 3. Organocatalytic asymmetric Mannich addition.



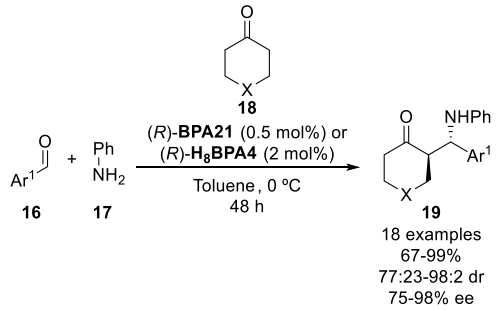
Scheme 4. (*R*)-**BPA5**-cinnamic acid heterodimer catalysed enantioselective Mannich addition.

More recently, Reddy's group reported the (*R*)-**BPA10**-catalysed enantioselective Mannich addition of β-keto esters **14** to *in situ* generated indolenines (Scheme 5).[57] They used both cyclic and non-cyclic keto esters successfully in order to obtain α-amino acid derivatives **15**, bearing at least one chiral tetrasubstituted carbon, in good yields (56-87%). Even though the enantiocontrol of the reaction was highly dependent on the substituents (26-98% ee), the diastereomeric ratio was found to be above 9:1 in all cases.

In 2007, Gong and co-workers described the nucleophilic addition of cyclic ketones **18** to *in situ* formed aromatic imines (Scheme 6).[58] In this case, they used both, (*R*)-**BPA21** or (*R*)-**H$_8$BPA4**, to yield predominantly the *anti* product **19** in high yields and moderate to excellent stereocontrol (67-99%, 77:23 to 98:2 dr, 75-98% ee). However, they did not report any example using aliphatic or strong electron-donating aromatic aldehydes. On the other hand, the authors also reported the addition of non-cyclic ketones, such as acetone or acetophenone, in similar reaction conditions, obtaining slightly lower yield and enantiocontrol (42-76%, 70-86% ee). Almost simultaneously, Rueping and co-workers also reported the (*R*)-**BPA8**-catalysed nucleophilic addition of acetophenone to *N*-Aryl protected imines, obtaining modest yields and moderate to good enantiocontrol (22-51%, 34-86% ee).[59]



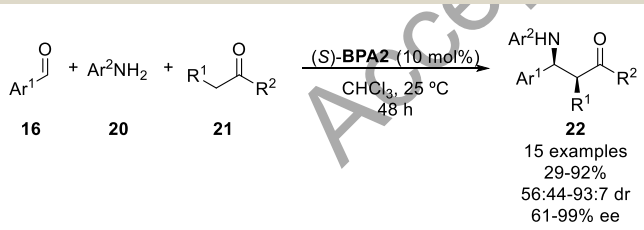
Scheme 5. Functionalization of 3-oxindoles **161** with β-keto esters **162**.



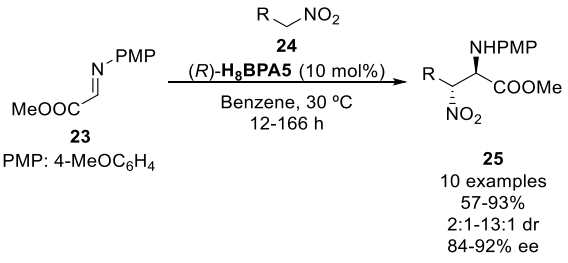
Scheme 6. Enantioselective addition of cyclic ketones **165** to aldimines.

Based on Gong´s work, Zhu and co-workers reported in 2018 a CPA-catalysed three-component reaction of acyclic ketones **21**, aldehydes **16** and anilines **20** (Scheme 7).[60] As often happens in Mannich reactions, the initial condensation of aldehydes and primary amines lead to the imine intermediate that acts as an electrophile in the reaction. The reaction using (*S*)-**BPA2** provides β-aminoketones **22** in moderate yield and diastereocontrol (29-92%, 56:44 to 93:7 dr), but with excellent enantioselectivities (61-99% ee). Moreover, in most cases, the scope of ketones is limited to non-symmetric aryl alkyl ketones or symmetric dialkyl ketones, keeping the regioselective addition of non-symmetric dialkyl ketones still unconquered.

In 2008, Rueping´s group reported the (*R*)-**H$_8$BPA5** -catalysed nitro-Mannich reaction using several nitroalkanes **24** and methyl glyoxalate-derived *N*-*p*-methoxyphenyl (PMP) imine **23** (Scheme 8).[61] This methodology allows the generation of β-nitro amines **25** containing two contiguous stereocentres in good yield and stereocontrol when alkyl or benzyl substituted nitromethane derivatives are used (R= Alk, CH_2Ar, 57-93%, 7:1 to 13:1 dr, 84-92% ee). However, the presence of aryl groups results in a drastic decrease in the diastereocontrol, although the enantioselectivity of the reaction remains high (R=*p*-Tolyl, 64%, 2:1 dr, 92% ee).



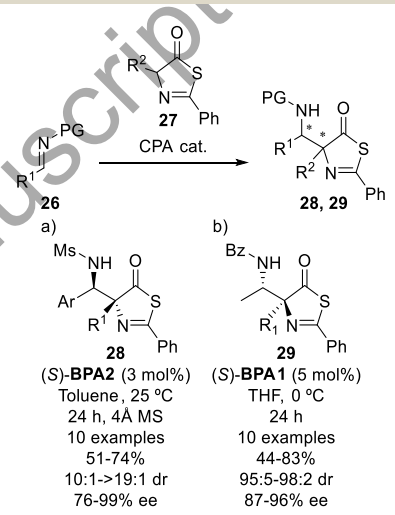
Scheme 7. Enantio- and diastereocontrolled synthesis of β-aminoketones **167**.



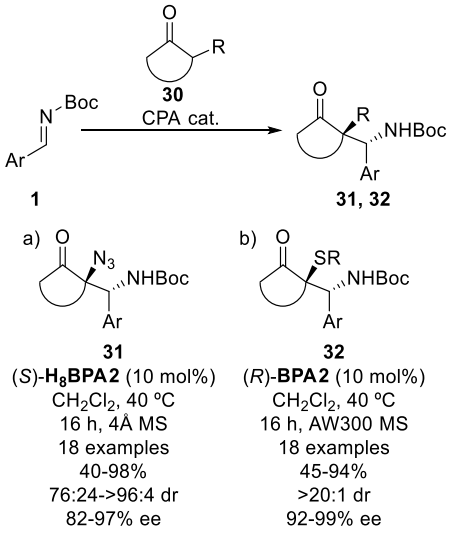
Scheme 8. Enantioselective addition of nitroalkanes **169** to aldimine **168**.

A few years later, Amarante reported the addition of azlactones **27** to aldimines **26** using CPA catalyst (*S*)-**BPA2** (Scheme 9, a).[62] This reaction provides access to several chiral amines **28** bearing vicinal chiral centres with high stereocontrol (51-74%, 10:1 to >19:1 dr, 76-99% ee). Further transformations of these products include the ring-opening reaction, affording optically pure α-amino acid derivatives bearing a tetrasubstituted chiral centre.

Following with the interest in nucleophilic addition reactions of enolizable carbonyl compounds, Terada´s group reported the (*S*)-**BPA1**-catalysed reaction of azlactones **27** with enamides (Scheme 9, b).[63] The CPA catalyst promotes the addition of the enol species derived from thiazolones **27** to the *in situ* formed *N*-benzoyl imines **26**, as a result of the acid-catalysed isomerization of enamide. Although the scope and the reported yields are moderate (44-83%), the diastereocontrol and enantiomeric excesses of substrates **29** are excellent (>95:5 dr, 87-96% ee).



Scheme 9. Stereoselective nucleophilic addition of thiazolones **27** to aldimines **26**.

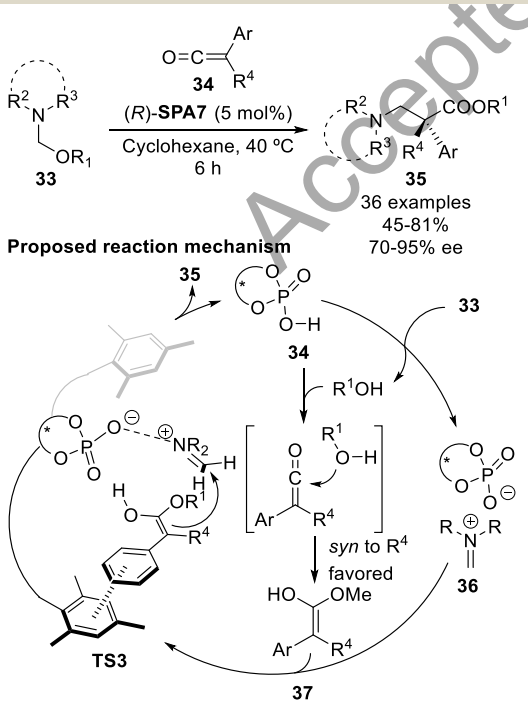


Scheme 10. Stereoselective Mannich reaction of cyclic ketones to aldimines **1**.

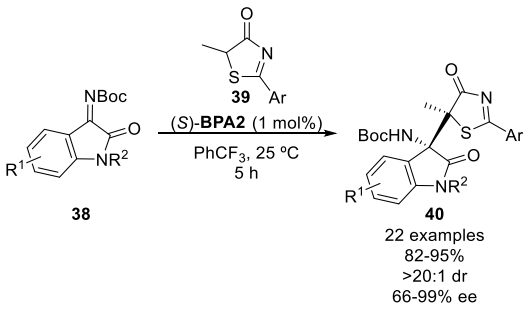
The selectivity of those reactions can be easily explained using Goodman´s model. For instance, when low sterically demandant mesyl group is combined with more steric-demanding aromatic groups at the imine, a Type II E transition state predicts the absolute configuration (Scheme 9, a). However, Terada´s example using benzoyl protected alkyl imines completely invert the steric demand of the imine, forcing a Type I E transition state.

In 2019, Yang´s group reported the Mannich reaction of cyclic α-azido ketones **30** to *N*-Boc protected aldimines **1**, using (*S*)-**H$_8$BPA2** as the catalyst (Scheme 10, a).[64] The reaction results in the synthesis of chiral amines **31** with moderate to excellent diastereocontrol (76:24 to >96:4 dr), but with excellent yields and enantioselectivities up to 97%. In addition, they also reported the nucleophilic addition of sulfur-containing cyclic ketones to imines **1** (Scheme 10, b).[65] The use of 10 mol% of chiral phosphoric acid (*R*)-**BPA2** affords the target products **32** in good yields (45-94%) and excellent stereocontrol (>20:1 dr, 92-99% ee). It is curious to note that the use of catalyst with oposite absolute configuration afforded the same enantiomer, since in both cases the type of the nucleophile and the imine are the same. Thus, unlike to the previous examples, predictive models reported by Goodman and coworkers can´t predict this difference. In this case, the most relevant difference between both catalysts is the presence of large aromatic substituents for (*S*)-**H$_8$BPA2** catalyst which may present attractive effects with the substrate, while catalyst (*R*)-**BPA2**, used in the second example, is less likely to favour that type of interaction, due to the large bulky substituents present at the aromatic ring.

Sun´s research group reported the synthesis of chiral β-amino acid derivatives starting from *N*,*O*-acetals **33** and ketenes **34** (Scheme 11).[66] In the first reaction step, the



Scheme 11. Enantioselective reaction between *N*,*O*-acetals and ketenes.



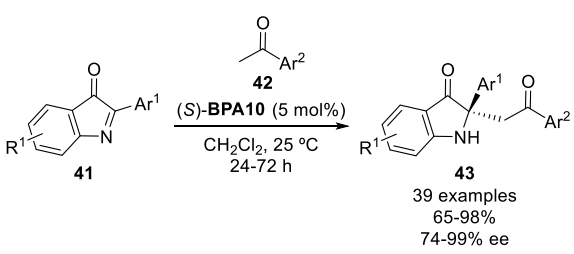
Scheme 12. Stereoselective nucleophilic addition of thiazolones **39** to isatin-derived imines **38**

phosphoric acid (*R*)-**SPA7** catalyses the elimination of the alcohol, leading to iminium ion **36**. After that, the *in situ* formed alcohol reacts with the ketene species in order to form the enol ester intermediate **37,** which reacts with the previously formed iminium ion (**TS3**), affording the final β-amino esters **35**. The reaction represents a highly versatile methodology that allows high modulation in the substituents of the final product, which are obtained in yields ranging from 45 to 81% and enantioselectivities up to 95% ee.

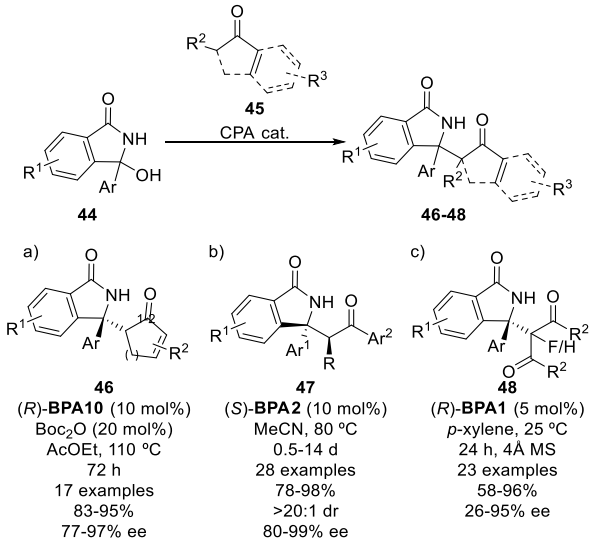
In 2008, Li´s group reported the (*S*)-**BPA2**-catalysed Mannich reaction of 5*H*-thiazol-4-ones **39** to isatin-derived *N*-Boc imines **38** (Scheme 12).[67] The reaction results in a highly efficient organocatalytic reaction in which two vicinal tetrasubstituted chiral centres are formed in excellent yields (82-95%). Moreover, even though the catalyst loading was decreased to 1 mol%, the reaction products **40** were obtained with diastereomeric ratios above 20:1 and enantioselectivities up to 99%.

On the other hand, a direct CPA-catalysed Mannich reaction of indolones **41** was described by Ma and co-workers for the synthesis of 3-indolynones **43**, using aryl methyl ketones **42** as nucleophiles (Scheme 13).[68] In this case, the loading of BINOL derivative (*S*)-**BPA10** was decreased to 5 mol%, resulting still in high yields and enantioselectivities (65-98%, 74-99% ee). A wide scope of imines **41** was used, including several imines bearing an indole moiety as a heteroaromatic ring.

In a similar way, in 2019, Reddy´s group published a parent reaction using 3-hydroxyisoindolin-1-ones **44** as the imine precursors and cyclic enones **45** as nucleophiles (Scheme 14, a).[69] Functionalised isoindolin-1-ones **46** are obtained in this case in excellent yields and enantioselectivities (83-95%, 77-97% ee) by combining the use of a catalytic amount of Boc anhydride with chiral phosphoric acid catalyst (*R*)-**BPA10**,

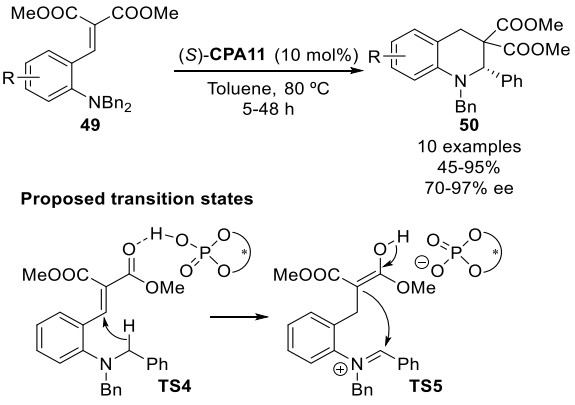


Scheme 13. Enantioselective nucleophilic addition of ketones to endocyclic imines **41**.



Scheme 14. Stereoselective nucleophilic addition reaction to *in situ* generated imines.

although the role of the anhydride in the reaction is not completely clear. Following this work, in late 2021, Grediˇcak´s group reported the analogous addition of aryl alkyl ketones in presence of (*S*)-**BPA2** catalyst (Scheme 14, b).[70] The reaction tolerates the presence of several acetophenone derivatives **45** as well as benzyl phenyl ketone, furnishing tetrasubstituted isoindolin-1-ones **47** in excellent yield and stereocontrol (78-98%, >20:1 dr, 80-99% ee). However, only modest yield and enantiocontrol were obtained when α-branched ketones **45** were tested in combination with *ortho*-substituted aryl imines (Ar = *o*-tolyl, R^1 = Ph; 39%, >20:1 dr, 20% ee). Besides, long-chain alkyl ketones (R^1 = Alk) resulted in overall yields above 93%, but poor stereocontrol (diastereomeric ratios not determined, 12-74% ee). In 2022, Singh and coworkers have published the analogous addition of 1,3 diones to *in situ* formed imines (Scheme 14, c).[71] Using 5 mol% of (*R*)-**BPA1**, they obtained moderate to excellent yields and enantiocontrol (58-96%, 26-95% ee). In contrast to the previous reports in which high temperatures and long reaction times were required, this reaction represents the first example of enantioselective addition to **44** under mild reaction conditions.



Scheme 15. Enantioselective synthesis of tetrahydroquinolines **50** through a CPA-catalysed intramolecular Mannich reaction.

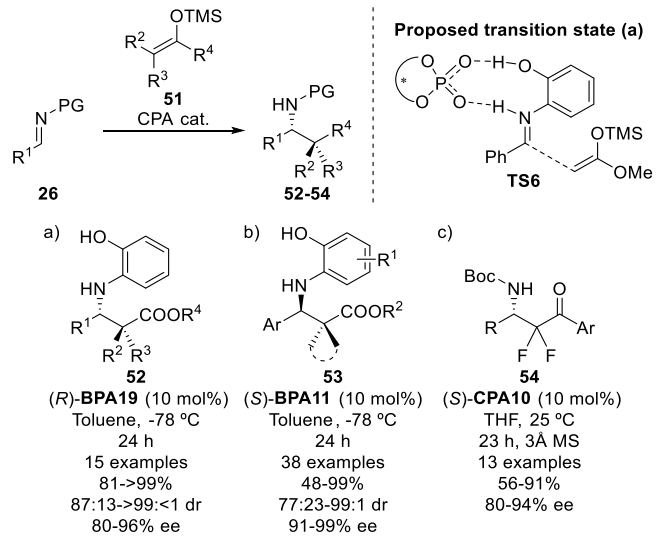
In 2011, Akiyama described an organocatalytic approach to chiral tetrahydroquinoline derivatives **50** through an intramolecular redox/Mannich reaction (Scheme 15).[72] The initial step of this transformation consists of the (*S*)-**CPA11**-catalysed benzylic hydrogen transfer (**TS4**) leading to malonate intermediate for the intramolecular Mannich addition (**TS5**). Although high temperatures are required for this transformation, the reaction provides access to highly enantioenriched tetrahydroquinolines (45-95%, 70-97% ee).

In this section, several reactions have been summarized, including aldimines and ketimines as well as many different types of enolates. Although the choice of the catalyst is always a challenging task, it is clear that aromatic 3,3´-substituents are preferred rather than extremely bulky sylilated groups. However, there are a few reactions in which small nucleophiles are used and bulky catalysts are required, such as the addition of nitroalkanes or acetophenone derivatives.

3.1.2. Addition of enol ethers

A typical reaction often catalysed by CPA-species is the Mukaiyama-Mannich reaction, using silyl enol ethers as nucleophiles. In this context, Akiyama and co-workers reported in 2004 the first example of a CPA-catalysed nucleophilic addition of silyl enol ethers **51** to 2-hydroxyphenyl protected imines **26** as a new strategy for the synthesis of chiral β-amino esters **52**, using (*R*)-**BPA19** as the catalyst (Scheme 16, a).[2] The initial study showed that, at low temperatures, the reaction provides quantitative yields and enantioselectivities above 80% ee. In addition, the authors also extended the reaction to unsymmetrical nucleophiles, obtaining excellent yields and stereocontrol (81 to > 99%, 87:13 to >99:<1 dr, 80-96% ee). In order to shed some light on the mechanism of the reaction, Akiyama and Yamanaka reported an extensive study including the evaluation of several protecting groups and DFT calculations and they theorised a double hydrogen bonding activation between the hydroxyl, the iminium ion, and the chiral phosphate (**TS6**).[73] A few years later years, they also developed a new (*S*)-**CPA9** catalyst, based on chiral bis-phenol for this transformation, providing diastereomeric ratios up to 94:6 and up to 93% enantiomeric excesses.[74]

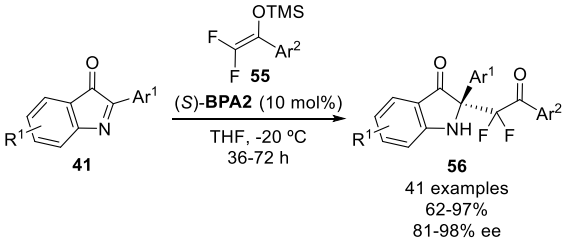
More recently, Yamamoto´s group described a CPA-catalysed Mukaiyama-Michael reaction of tri- and tetrasubstituted silyl enol ethers **51** to 2-hydroxyphenyl protected aryl imines **26**, using (*S*)-**BPA11** as organocatalyst (Scheme 16, b).[75] Similarly to the transition state proposed in Akiyama´s report (**TS6**), the presence of a hydroxyl group at the imine group has a strong effect on the enantioselectivity, acting as a bidentate coordination point for the chiral catalyst and activating the imine moiety for the enantioselective addition of the silyl enol ether. The dual hydrogen bonding between the phosphoric acid catalyst and the imine group provides amino esters **53** in good yields (48-99%) and enantioselectivities above 91% ee. Moreover, when non-symmetric silyl enol ethers are used, diastereoselectivities up to 99:1 are observed. In the same year, Widhalm´s group reported the same transformation using (*R*)-**TPA1** as the catalysts.[76] In this case, the reaction was carried out at slightly higher temperatures, obtaining excellent yields



Scheme 16. Stereocontrolled Mukaiyama-Mannich reaction with aldimines using a CPA as organocatalyst.

and enantioselectivities up to 96% ee. Unfortunately, the scope of the reaction is limited to α-dimethyl silyl enol ethers, and only the formation of a single chiral carbon is reported. In 2011, Akiyama´s group developed a CPA-catalysed enantioselective addition of fluorinated silyl enol ethers **51** to aldimines **26** (Scheme 16, c).[77] The reaction represents an efficient method for synthesis of β-Amino-α,α-difluoro ketones **54** in moderate to high yields and excellent enantiocontrol (56-91%, 80-94% ee) using (*S*)-**CPA10** catalyst. In addition, the authors also report the synthesis of the corresponding esters through Baeyer-Villiger oxidation, providing a versatile methodology to access several highly enantioenriched carbonyl compounds.

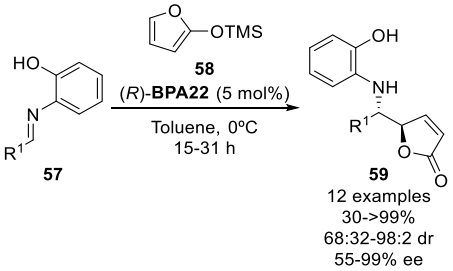
More recently, Ma´s group described the enantioselective addition of fluorinated silyl enol ethers **55**, derived from α-difluoro ketones, to cyclic ketimines **41** (Scheme 17).[78] The presence of 10 mol% of (*S*)-**BPA2** catalyst afforded functionalised indolinones **56** in excellent yields and enantioselectivities (62-97%, 81-98% ee). Following a similar approach, in late 2020, Ma[79,80] and Lin[81] simultaneously reported the addition of difluorinated silyl enol ethers **55** to imines derived from *iso*-indolone in this case generated *in situ* from 3-hydroxy *iso*-indolinones. Ma's group achieved in most cases high yields (55-97%) and enantioselectivities above 90% by using 5 mol% of (*S*)-**SPA16** catalyst and hexafluoro-*iso*-propanol as an additive. Even though the authors also report a single example for the nucleophilic addition reaction to an aliphatic imine in a similar yield, a drastic decrease in the enantiocontrol is observed in this case (85%, 48% ee). Similarly, Lin and co-workers used 10 mol% of (*S*)-**SPA2** as the catalyst, obtaining the same substrates in yields and enantioselectivities above 70% in all cases.



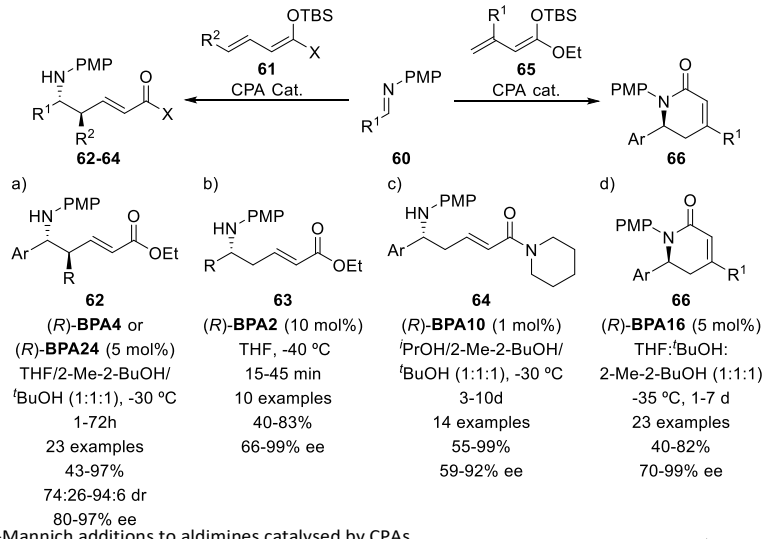
Scheme 17. Stereoselective addition of silyl enol ethers **55** to imines **41**.

Using *o*-hydroxyphenyl imines **57**, and based on the previously published mechanistic studies,[73] in 2008, Akiyama and co-workers extended their methodology to the vinylogous nucleophilic addition reaction of furane-derived cyclic silyl enol ethers **58**, using in this case (*R*)-**BPA22** as the catalyst (Scheme 18).[82] The reaction tolerates several aliphatic and aromatic imines **57** bearing electron-withdrawing groups to affords chiral amines **59** in moderate to excellent yields and stereocontrol (77 to >99%, 68:32 to 98:2 dr, 55-99% ee). Surprisingly, although a strong electron-withdrawing effect is expected from 4-pyridyl substituted imine **57** (R^1 = 4-Py), in this case, a drastic drop in the reaction yield was observed (30%, 94:6 dr, 98% ee).

In 2008, Schneider and co-workers published the enantioselective vinylogous Mukaiyama-Mannich reaction of dienolates **61** with *N*-aryl imines **60** using CPA catalysts (*R*)-**BPA4** or (*R*)-**BPA24** (Scheme 19, a).[83] The optimization conditions showed that an uncommon mixture of THF, 2-Me-2-BuOH and ^{t}BuOH resulted in an increase of the enantiomeric excesses, providing highly enantioenriched chiral amines **62** (R = H, 66-94%, 80-92% ee). Remarkably, they demonstrated the utility of their methodology, applying it to the total synthesis of (*S*)-Anabasine (92% ee).[84] In addition, they also evaluated ^{t}Bu substituted imines in the reaction using the catalyst (*R*)-**BPA2**, obtaining similar results (83%, 82% ee). The use of γ-methyl dienolates **61** (R = Me), resulted in the formation of substrates *anti*-**62** in excellent yield and stereocontrol (43-97%, 74:26 to 94:6 dr, 90-97% ee).[85] In 2011, Schneider and Belder adapted this methodology to a single microfluidic nanospray chip, obtaining similar results that were found for bath chemistry.[86]



Scheme 18. CPA-catalyzed vinylogous Mukaiyama-Mannich addition of cyclic silyl enol ethers **58** to aldimines **57**.



Scheme 19. Vinylogous Mukaiyama-Mannich additions to aldimines catalysed by CPAs.

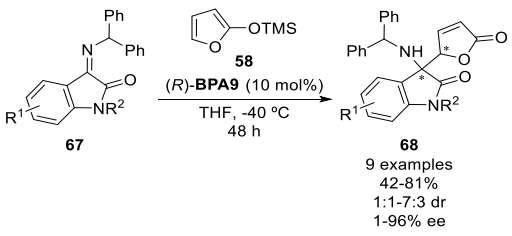
In the same year, Schneider and co-workers also reported the use of aliphatic aldimines in this transformation using dienolates **61** and (*R*)-**BPA2** as the catalyst (Scheme 19, b). The reaction was found to be extremely fast, with yields up to 83% and enantioselectivities up to 99% ee within 15-45 minutes. However, the extension of the synthetic protocol to γ-methyl dienolates, leads to higher reaction times for the same transformation to obtain moderate yields although an excellent stereocontrol is observed (40-96%, 91:9 to 96:4 dr, 72-90% ee).[87] This reaction was next further optimised to access optically pure piperidine alkaloids.[88]

On the other hand, the same authors also described the (*R*)-**BPA10**-mediated nucleophilic addition of silyl *N*,*O* acetals to aryl imines **60** (Scheme 19, c).[89] In this case, the authors made an extensive study on the *N*-substituents for the nucleophiles, showing that cyclic amide derivatives provided higher stereocontrol. On the other hand, they were able to decrease the catalyst loading to 1 mol% without losing enantiocontrol, although the reaction times were increased. Using this methodology, they reported the synthesis of several chiral amines **64** in yields and enantiomeric excesses ranging from moderate to excellent (55-99%, 59-92% ee).

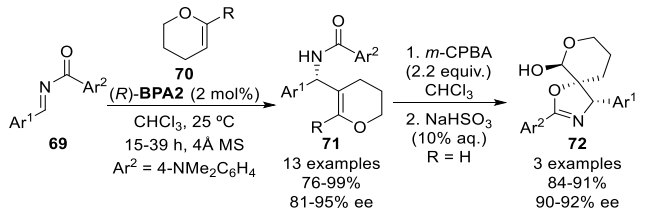
More recently, Schneider and co-workers reported a CPA-catalysed enantioselective multicomponent tandem Mukaiyama-Mannich/cyclization reaction, using (*R*)-**BPA16** catalyst (Scheme 19, d).[90]The initial condensation of aromatic aldehydes with *p*-anisidine leads to the *in situ* formation of the required imine intermediate **60**, followed by the vinylogous addition of silyl enol ethers **65** to afford chiral amines. The subsequent intramolecular cyclization leads to the formation of 6-membered cyclic chiral lactams **66** in moderate to good yields (40-82%) and enantioselectivities higher than 70%.

Silvani and co-workers developed a vinylogous Mukaiyama-Mannich reaction of 2-trimethylsiloxyfuran (**58**) to isatin-derived ketimines **67** catalysed by 10 mol% of BINOL derivative (*R*)-**BPA9** (Scheme 20).[91] Due to the low diastereoselectivity of the reaction (1:1 to 7:3 dr), they were able to determine the enantiomeric excesses of both diastereoisomers of **68**, observing enantioselectivities up to 96%.

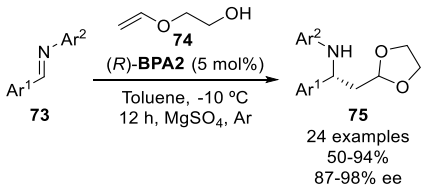
Concerning the addition of non-silylated enol ethers, in 2010, Antilla reported a CPA-catalysed reaction as the key step for the synthesis of chiral oxazolines **72** (Scheme 21).[92] The initial (*R*)-**BPA2** mediated asymmetric Mannich reaction of cyclic enol ethers **70** to aldimines **69** provides chiral amines **71** with excellent results (76-99%, 81-95% ee). Moreover, while exploring the epoxidation of the alkene with *m*-CPBA, the authors obtained oxazolines **72** in high yields (84-91%) without any loss of the optical purity, which presumably takes place through an initial epoxidation and the subsequent intramolecular addition that results from the epoxide opening.



Scheme 20. Vinylogous Mukaiyama-Mannich reaction of 2-trimethylsiloxyfuran **58** and ketimines **67**.



Scheme 21. Enantioselective synthesis of oxazolines **72**.



Scheme 22. Enantioselective addition of enol ethers to *N*-aryl imines **73**.

On the other hand, Wu et al. reported in 2019 the addition of enol ethers **74** to *N*-Aryl imines **73** catalysed by 5 mol% of (*R*)-**BPA2** (Scheme 22).[93] The initial nucleophilic addition results in the formation of an oxonium ion that is trapped through an intramolecular addition of the terminal alcohol, affording chiral secondary amines bearing a dioxolane moiety, which can be used for further transformations. The reaction yields substrates **75** in good yields (50-94%) and enantioselectivities above 87% ee.

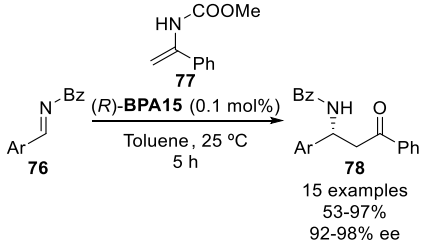
Unlike the other reactions shown in this review, where a bifunctional activation of the electrophile and the nucleophile by the CPA-catalyst is proposed, a single imine activation is theorized for Mukaiyama-Mannich reactions. In consequence, some examples involve a double interaction between the imine and the catalyst in order to obtain high stereocontrol.

3.1.3. Addition of enamides/enecarbamates and enamines

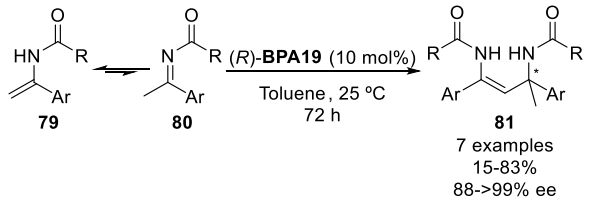
In 2006, Terada reported the (*R*)-**BPA15**-catalysed nucleophilic addition of enecarbamates **77** to aromatic aldimines **76**, leading to β-amino ketones **78** (Scheme 23).[94] Mild reaction conditions are required in the reaction to afford highly enantioenriched amines **78** in high yields (53-97%, 92-98% ee). In this case, they also evaluated the lowering of the catalyst loadings to 0.05 mol%, obtaining slightly higher reaction times but a similar enantiocontrol.

Following a similar approach, in 2008, Tsogoeva described the self-addition of enamides **79** to afford chiral diamides **81**, using the catalyst (*R*)-**BPA19** (Scheme 24).[95] The presence of a chiral phosphoric acid in this transformation makes slightly more favourable the tautomerization of enamide species **79** to their iminic form, **80**, allowing the stereocontrolled addition of a second molecule of the enamide nucleophile. Although a limited scope is presented and moderate yields are obtained in some cases (15-83%), enantioselectivities up to 99% are reported.

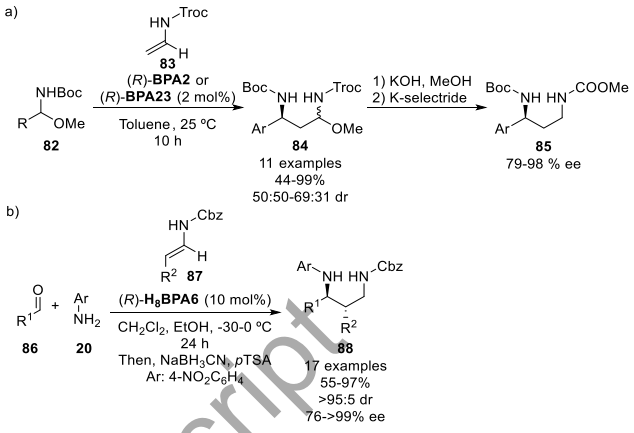
In 2009, Terada´s group reported the use of hemiaminal ethers **82** as surrogates of imines for the (*R*)-**BPA2** or (*R*)-**BPA23**-mediated enantioselective nucleophilic addition of enecarbamates **83** (Scheme 25, a).[96]



Scheme 23. CPA-catalysed synthesis of β-amino ketones **78**.

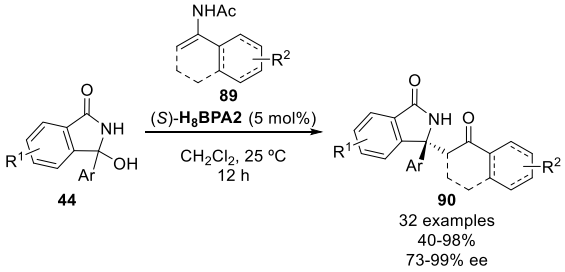


Scheme 24. Enantioselective self-coupling of enamides **79**.

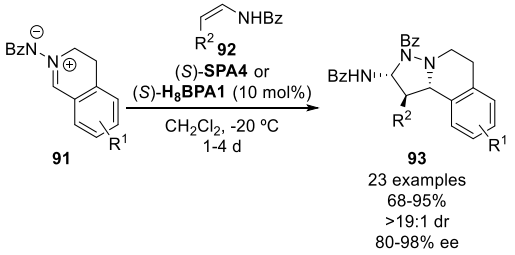


Scheme 25. CPA-catalysed synthesis of enantioenriched 1,3-diamines.

This strategy allows the trapping of the imines resulting from the nucleophilic addition of the enecarbamates **83** as hemiaminals **84** in good yields but moderate to low diastereocontrol (44-99%, 50:50 to 69:31 dr). Substrates **84** were transformed into 1,3-dicarbamates **85** in order to determine their absolute configuration (79-98% ee). The authors also reported the 'one-pot' addition of indole to substrates **84**, affording the corresponding 1,3-diaminal in high yield and enantiocontrol but with moderate *syn* selectivity (70%, 76:24 dr, >99% ee). Moreover, they also evaluated the presence of a methyl substituent at the enecarbamate **83**, showing high yield and stereocontrol when *E* isomer was used (*anti* product, 99%, 98:2 dr, 94% ee). On the other hand, the use of *Z*-enecarbamate resulted in a lower yield but high stereocontrol (*syn* product, 67%, 95:5 dr, 88% ee). In addition, this stereoselective transformation was extensively explored by Masson and Zhu,[97] using in this case *in situ* formed imines as electrophiles starting from aldehydes **86** and anilines **20** (Scheme 25, b) and (*R*)-**H8BPA6** as the catalyst. Following this approach, 1,3-diaminals **88** are obtained in excellent yields and stereocontrol (55-97%, >95:5 dr, 76 to >99% ee).



Scheme 26. Enantioselective addition of ketones to *in situ* generated imines.



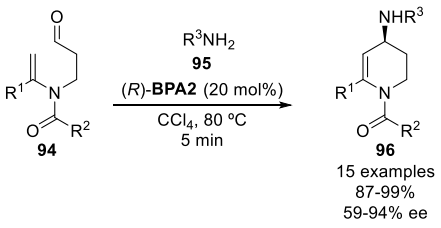
Scheme 27. Enantioselective nucleophilic addition of enamides **92** to dihydroisoquinolinium ions **91**.

Ma and co-workers reported the (*S*)-**H$_8$BPA2**-catalysed nucleophilic addition of enamides **89** to *in situ* formed imines from 3-hydroxy isoindolinones **44**, affording the corresponding functionalised isoindolinones **90** in moderate to excellent yields and high enantiocontrol (40-98%, 73-99% ee) (Scheme 26).[98] In addition, the authors also reported the addition of cyclohexyl methyl ketone, obtaining similar results (41%, 84% ee). In contrast, when a cyclic ketone is used, no diastereocontrol is observed, and only enantiocontrol for one of the two possible diastereoisomers (85%, 1:1 dr, 96/0% ee). Using an identical methodology, they also reported the addition of enamides to cyclic α-imino esters in order to synthesise non-canonical chiral α-amino acid derivatives in yields and enantiomeric excesses up to 99%.[99]

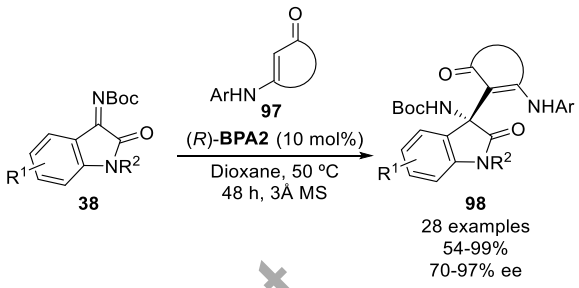
In 2016, Zhu´s group reported the use of (*S*)-**SPA4** and (*S*)-**H$_8$BPA1** organocatalysts for the synthesis of pyrazolidines **91**. The proposed reaction mechanism comprises an initial nucleophilic addition of enamides **92** to azomethine imines **91**, derived from dihydroisoquinolines, followed by an intramolecular cyclization leading to the formation of the pyrazolidine moiety (Scheme 27).[100] The reaction afforded tricyclic molecules **93** bearing three chiral stereocentres as a single diastereomer in high yields (68-95%, >19:1 dr) and enantioselectivities up to 98% ee.

A few years later, Wang´s group reported the (*R*)-**BPA2**-catalysed intramolecular cyclization of tertiary enamides, leading to the formation of tetrahydropyridines **96** (Scheme 28).[101] After the initial condensation of the aldehyde **94** with the selected amines **95**, the reaction is heated at reflux, affording the desired products in excellent yields (87-99%) after only 5 minutes. Surprisingly, despite the high temperatures used in this transformation, the authors report enantioselectivities up to 94%.

Shi´s group reported in 2016 the addition of cyclic enamines **97** to *N*-Boc protected imines **38**, derived from isatins, catalysed by 10 mol% of (*R*)-**BPA2** (Scheme 29).[102] Remarkably, the reaction tolerates the presence of several substituents at the aromatic ring of the isatin moiety as well as alkyl, aryl, allyl or even no substituent in the nitrogen atom (R^2). Using this methodology, several 3-substituted 3-amino-2-oxindoles **98** are obtained, bearing a tetrasubstituted carbon stereocentre, in yields ranging from 54% to 99% and with high enantiocontrol (70-97% ee).



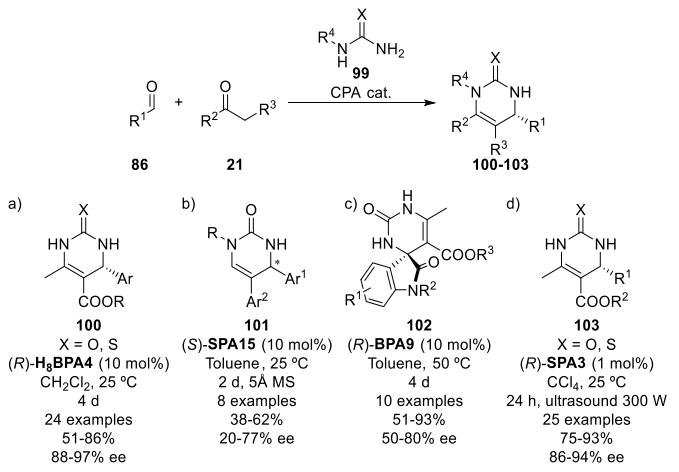
Scheme 28. Intramolecular enantioselective addition of tertiary enamides to aldimines.



Scheme 29. Enantioselective addition of cyclic enamines to isatin-derived imines.

During the last years, the reports of enantioselective multicomponent reactions have grown in order to benefit from the high efficiency and the structural complexity of the reaction products.[103–105] In particular, multicomponent reactions involving the addition of enamines or their derivatives to imines have attracted attention because of the high versatility of the resulting heterocyclic reaction products. Regarding the CPA-catalysed multicomponent reactions, one of the most explored reactions is the enantioselective Biginelli reaction. In 2006, Gong published the first example of a BPA-catalysed of this multicomponent reaction (Scheme 30, a).[106] In the presence of 10 mol% of (*R*)-**H$_8$BPA4**, highly substituted pyrimidine derivatives **100** are obtained in good yields and excellent enantiomeric excesses (51-86%, 88-97% ee) from benzaldehydes **86**, acetoacetates **21** and urea derivatives **99**. Moreover, they also reported the use of styryl and cyclohexyl substituted aldehydes with lower yields (40-44%) but high enantiocontrol (88-92% ee). Further development of this reaction allowed to selectively obtain both enantiomers of pyrimidines **100** by simply switching to (*R*)-**BPA10** organocatalyst, even though the *R* isomer of the catalyst was used in both cases.[107,108] This makes evident that highly bulky catalyst such as a $SiPh_3$ susbtituted one modifies the orientation of the reagents in the transition state, thus making possible to obtain opposite stereochemistry by modulating the active centre of the CPA-catalyst. However, most of the reported theoretical models do not exhaustively consider the type of the 3,3´substituents and leave examples as the one reported by Gong´s group out of the predicted area.

A few years later, Lin and co-workers were able to decrease the catalyst loading in a similar reaction to 5 mol%, using (*S*)-**SPA15** as the catalyst.[109] Nevertheless, excellent yields and enantiomeric excesses were reported (80-96%, 90-99% ee). In addition, the authors also reported the use of enolizable aldehydes instead of acetoacetate derivatives **21**, under similar reaction conditions (Scheme 30, b).[110] However, in this



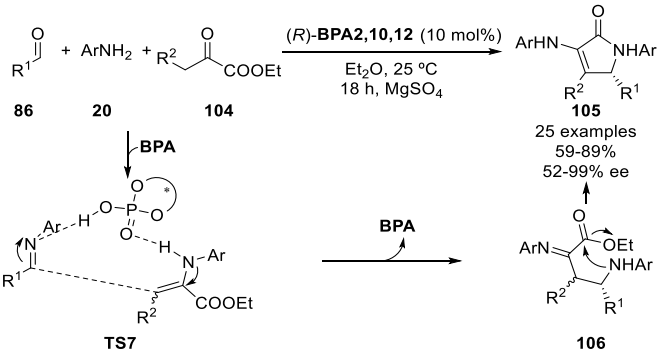
Scheme 30. CPA-mediated enantioselective Biginelli reactions.

case, the Biginelli products **101** were obtained in modest yields and enantioselectivities (38-62%, 20-77% ee). Based on this report, Hu and co-workers reported Biginelli processes with aromatic aldehydes in presence of TADDOL-derived phosphoric acids (*R*)-**TPA2** and (*R*)-**TPA3**, obtaining enantioselectivities up to 99% ee.[111,112]

Using urea **99**, ethyl acetoacetate **21** and isatin derivatives, Silvani and co-workers reported the (*R*)-**BPA9**-catalysed asymmetric synthesis of chiral spirocycles **102** in good yields (51-93%) and enantioselectivities ranging from 50 to 80% (Scheme 30, c).[113] Following this approach, in 2017, Zou´s group reported the enantioselective version of the classical Biginelli reaction with aliphatic aldehydes, using in this case (*R*)-**BPA13** as a chiral catalyst.[114] Besides, they applied their methodology to the synthesis of the guanidine core of Crambescin A and Batzelladine A.[115] Even though their yields are sometimes moderate (50-75%), good enantioselectivities are obtained (73-85% ee).

Likewise, very recently, Guo *et al.* reported the (*R*)-**SPA3**-catalysed enantioselective Biginelli reaction with aliphatic aldehydes **86** (R^1= Alk) (Scheme 30, d).[116] Although it has not any effect on the reaction yield or the enantiocontrol, the reaction times can be shorted from 5 to 1 day by applying 300W ultrasounds to the reaction media. In order to obtain high enantiocontrol, a SPINOL-derived organocatalyst is required to provide chiral pyrimidine derivatives **103** in excellent yield (75-93%) and enantiomeric excesses above 86%. Remarkably, even the use of α-branched *iso*-propyl (50%, 81% ee) and cyclohexyl (91%, 93% ee) aldehydes were successfully used in the reaction.

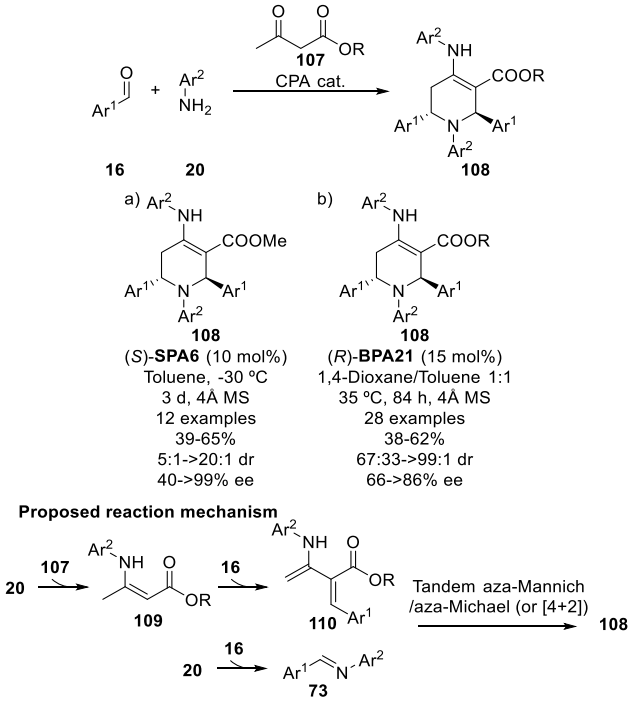
Concerning miscellaneous multicomponent processes involving Mannich reactions, in 2006, our research group reported a Brønsted acid-catalysed synthesis of 3-amino 3-pyrrolin-2-ones through a multicomponent reaction, making use of amines, **20**, aldehydes **86** and pyruvate derivatives **104** to afford racemic γ-lactams **105**.[117] A couple of years later, Cheng´s group explored the use of CPAs in this transformation, using benzaldehyde (**86**, R^1 = Ph), *p*-anisidine (**20**, Ar = *p*-$MeOC_6H_4$), and ethyl pyruvate (**104**, R^2 = H) to obtain the corresponding



Scheme 31. Highly enantioselective multicomponent synthesis of dihydropyrrol-2-ones.

γ-lactam in high yield but moderate enantiocontrol (77%, 44% ee).[118]On our pursuit of a highly enantioselective multicomponent protocol for this transformation, in 2018, our research group presented a thorough optimization of the diverse aspects involved in this multicomponent process.[190] Under the optimal conditions, it was established that different CPA-catalyst have to be used, depending on the character of the aldehyde and amine substrates. Although a single general catalytic system could not be developed, the use of three different BINOL-derived CPA catalysts, (*R*)-**BPA2**, (*R*)-**BPA10** and (*R*)-**BPA12**, provided excellent results (Scheme 31). The pathway of the reaction consists of an initial aza-Mannich reaction between the *in situ* generated enamine and imine species (**TS7**), most probably through a Type II *E* mechanism, followed by an intramolecular cyclization of the adduct **106**, that leads to γ-lactam derivatives **105**. The methodology was found to be a very efficient method for the synthesis of densely functionalised dihydropyrrol-2-ones in high yields (59-89%) and enantioselectivities up to 99% ee. In addition, the reaction can be extended to the preparation of phosphorus and/or fluorine-containing heterocycles[119,120] using phosphine oxide, phosphonate or fluorinated substituents containing aldehydes **86** and/or pyruvate derivatives **104**. However, a significant drop into the enantioselectivity is often observed when substituted pyruvates are used. In addition, using this methodology, both pure enantiomers of substrates **105** were obtained using either (*R*) and (*S*)-**BPA10** as the catalysts, in order to evaluate their biological activity separately.[121] The reaction can be also extended to the use of acetylenedicarboxylate esters instead of pyruvates as efficient precursors of enamine intermediates. However, due to the harsh reaction conditions required in this case, a drastic drop into the enantioselectivity is observed and no significant enantiomeric excesses are obtained for this reaction using substituted BINOL-derived CPAs.[122]

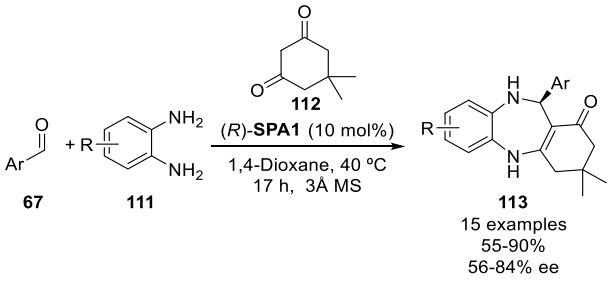
In 2013, Lin described a multicomponent reaction involving two aromatic aldehydes **16**, anilines **20** and acetoacetic esters **107**, providing densely functionalised tetrahydropyridines **108** (Scheme 32, a).[123] The authors make use of 10 mol% of (*S*)-**SPA6** catalyst in the reaction, obtaining moderate yields and a moderate to excellent stereocontrol (39-65%, 5:1 to >20:1 dr, 40-99% ee). In the same year, Shi and Tu reported the same transformation under similar reaction conditions (Scheme 32, b),[124] using in this case 15 mol% of BINOL-derived



Scheme 32. Enantioselective synthesis of tetrahydropyridines through a multicomponent reaction.

phosphoric acid (*R*)-**BPA21**, presenting a broader scope of substrates **108** with similar results in terms of yield and stereoselectivity (38-62%, 67:33 to >99:1 dr, 66-86% ee). Although the reaction mechanism is not fully understood, the initial step may consist of an aldol condensation between the amine, aldehyde and acetoacetic ester, leading to the formation of diene **110**. Then, the reaction of diene species with the imine **73** is proposed to proceed through a tandem aza-Mannich/aza-Michael reaction to yield tetrahydropyridines **108**. However, a [4+2] cycloaddition process for this final step cannot be discarded. The fact that both research groups obtained the same absolute configuration in their final products even though they employed opposite enantiomers of the selected catalyst remains unexplained. Moreover, according to the catalyst classification shown in section 2 of this review, the optimal 3,3´substituents are aromatic groups with remote substitution in both cases. Therefore, the the main difference between both reactions is the selected solvent that could favour one or the other possible transition states for the synthesis of heterocyclic compounds **108**.

One year later, Shi and co-workers described an enantioselective synthesis of 1,4-benzodiazepines **113** through the (*R*)-**SPA1**-catalysed multicomponent reaction of aromatic aldehydes **16**, 2-aminoanilines **111** and cyclic 1,3 diketones **112** (Scheme 33).[125] The reaction, presumably, proceeds through an initial condensation of the diamine with one equivalent of the aldehyde **16** and the cyclic ketone **112**, followed by an intramolecular Mannich reaction. Benzodiazepines **113** are obtained in moderate to good yields and enantioselectivities (55-90%, 56-84% ee). Shortly after this report, the authors also described the homologous reaction using isatin derivatives,



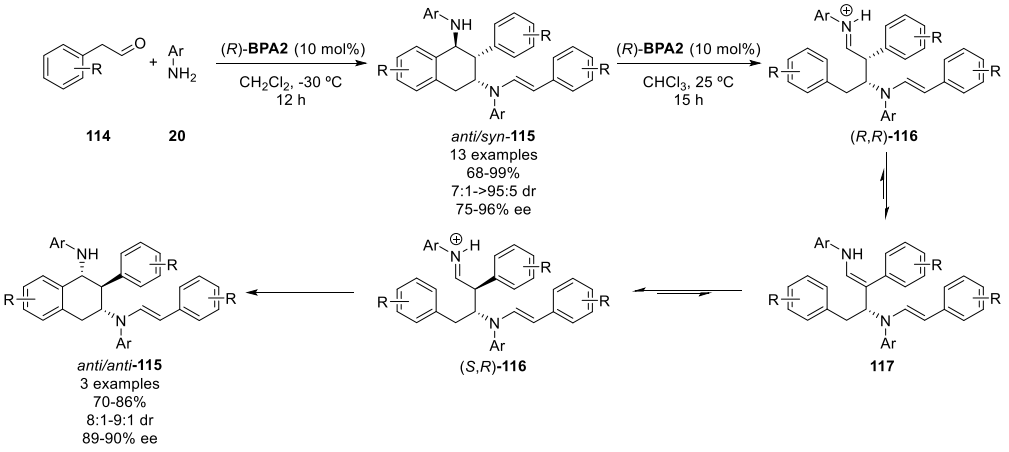
Scheme 33. Enantioselective synthesis of benzodiazepines.

generating, in this case, tetrasubstituted stereogenic carbons with high enantiocontrol (40-99%, 74-99% ee).[126,127]

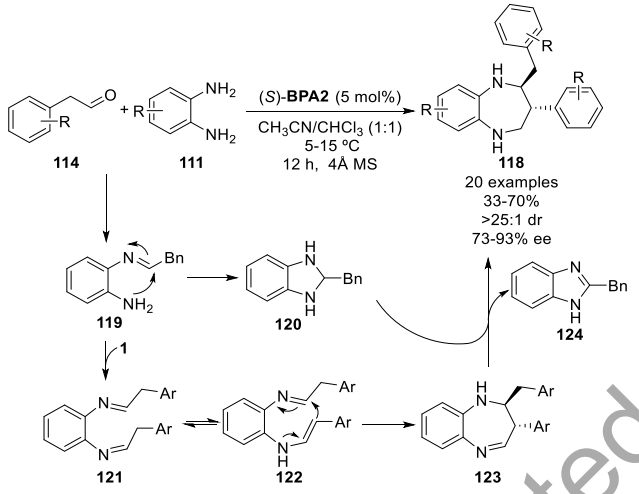
In the same year, Masson reported a pseudo-multicomponent reaction between three equivalents of arylacetaldehydes **114** and two equivalents of anilines **20** using (*R*)-**BPA2** as the catalyst (Scheme 34).[128] The proposed mechanism may start with an initial condensation of aldehydes and anilines to form an imine species. Then, a self-addition process occurs, followed by intramolecular cyclization. The reaction proceeds with moderate to excellent yields and stereocontrol to afford *anti*/*syn*-**115** (68-99%, 7:1 to >95:5 dr, 75-96% ee). Due to the presence of small amounts of *anti*/*anti*-**115** in the reaction crude, the authors further explored this isomerization process. In the presence of mild acidic conditions and a chiral environment, *anti*/*syn*-**115** rapidly evolve into *anti*/*anti*-**115** isomer with no racemization during the process. The authors propose an acid-catalysed ring-opening that provides (*R*,*R*)-**116** imine which, after tautomerization, leads to enamine species **117** to finaly provide imine (*S*,*R*)-**116**, that suffers a ring closure resulting in the isomerization of both chiral centres.

Based on Shi's and Masson's reports, in 2014, Li, Tang and co-workers reported in 2021 a new synthesis of benzodiazepines **118** using aryl acetaldehydes **114** and 2-aminoanilines **111** as precursors (Scheme 35) in the presence of chiral catalyst (*S*)-**BPA2**.[129] The selective mono-condensation of the aldehyde with diamines **111** leads to imine intermediate **119**. Then, two competing reactions may take place. On the one hand, benzoimidazole derivatives **120** are obtained through an intramolecular cyclization. On the other hand, a second condensation of the free amine **111** with a second equivalent of aldehyde **114** leads to di-imine intermediate **121**. The isomerization of one of the imine moieties into species **122** facilitates an intramolecular aza-Mannich reaction, leading to imines **123**, that are reduced *in situ* through a transfer hydrogenation process to yield benzodiazepines **118** and benzoimidazoles **124**. Although benzodiazepines are obtained in moderate to good yields, the stereocontrol of the process is high (33-70%, >25:1 dr, 73-93% ee).

In 2011, Gong and co-workers reported the (*R*)-**BPA25**-catalysed Friedländer synthesis of quinolines **127** (Scheme 36).[130] They used nonchiral 4-substituted cyclohexanones **126** as substrates, which resulted in a highly efficient desymmetrization of the cyclohexanone ring.



Scheme 34. CPA-catalysed multicomponent reaction.



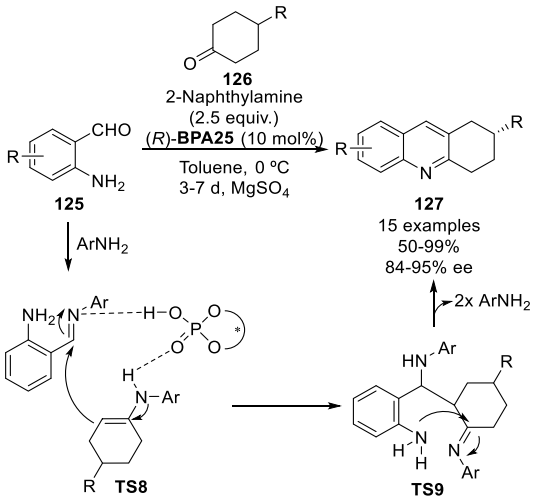
Scheme 35. CPA-catalysed multicomponent synthesis of benzodiazepine derivatives **262**.

The authors propose a Friedländrer-type reaction mechanism in which an initial addition of *in situ* formed enamine reacts with an aromatic imine (**TS8**). The high relevance of a 2-Naphthylamine additive on the enantiocontrol, if compared with other aromatic amines, may indicate some non-covalent interactions between the naphthyl group and the chiral catalyst. Then, an intramolecular amine exchange (**TS9**), followed by a subsequent amine elimination, lead to the resulting acridine derivatives in yields up to 99% and enantioselectivities above 84%.

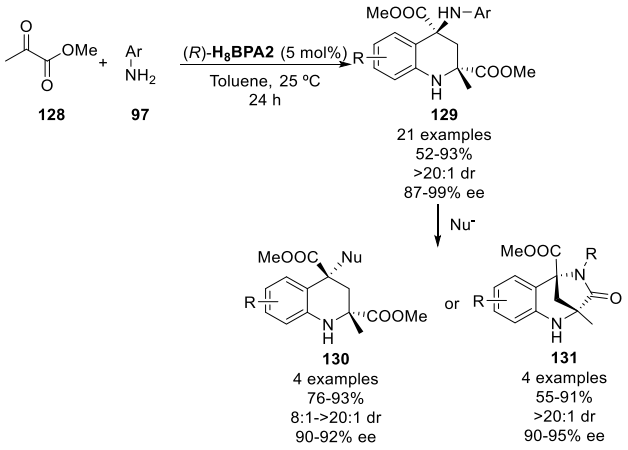
Likewise, in 2013, Huang published a multicomponent synthesis of tetrahydroquinolines **129** bearing two tetrasubstituted chiral centres (Scheme 37).[131] The reaction consists of an initial condensation of aromatic amines **20** with methyl pyruvate (**128**), followed by a (*R*)-**H$_8$BPA2**-catalysed self-addition of the *in situ* formed enamine to the corresponding ketimine. The authors obtained several tetrahydroquinolines in excellent yields and stereocontrol when using a single amine (65-93%, >20:1 dr, 87-99% ee). Moreover, some combinations of different aromatic amines **20** were also reported with high selectivity but moderate yields (52-72%, >20:1 dr, 90-99% ee).

Further transformations of tetrahydroquinolines **129** into **130** were performed through S_N2 additions of several nucleophiles in good yields and diastereoselectivity, and without any relevant change on the enantiomeric ratios (76-93%, 8:1 to >20:1 dr, 90-92% ee). On the other hand, when aliphatic or benzylic amines were used as nucleophiles, an intramolecular lactamization reaction occurs after the substitution, leading to polycyclic tetrahydroquinolines **131** with excellent results (55-91%, >20:1 dr, 90-95% ee).

Concerning the addition of enamine derivatives to imines, several types of transformations have been reported and, thus, it is difficult to extract clear conclusions about the optimal catalyst type. As shown in previous lines, although some examples match Goodman´s predicctions, those models are often applied to simple nucleophiles and electrophiles such as the addition of enamines/enamides/enecarbamates to aldimines. However, in this section several multicomponent and/or intramolecular reactions that skip the predictive models have been described.



Scheme 36. Enantioselective synthesis of chiral quinolines through a CPA-catalysed Friedländer condensation.



Scheme 37. Enantioselective synthesis of tetrahydroquinolines through a CPA-catalysed intramolecular Mannich reaction.

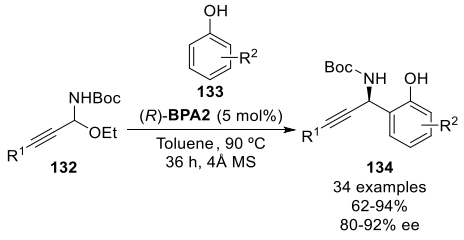
3.2. Friedel-Crafts reactions

The addition of aromatic and heteroaromatic nucleophiles to imines has been widely explored using CPA-catalysis. Although the main nucleophiles in this type of transformation are indole derivatives, other nucleophiles such as pyrrole, furan or phenol derivatives have also been used in homologous transformations. Reactions that imply the use of aldimine or ketimine substrates will be described separately in this chapter.

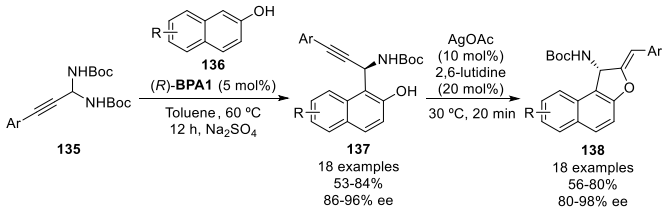
3.2.1. Friedel-Crafts reactions with aldimines

In 2016, Shao and co-workers reported the addition of phenols **133** to propargyl imines formed *in situ* from *N*,*O* acetals **132** (Scheme 38).[132] The reaction is performed in the presence of 5 mol% of (*R*)-**BPA2** catalyst and provides access to a wide number of chiral propargyl amines **134** in high yields (62-94%) and enantiomeric excesses up to 92%. In addition, some simple modifications of the methodology also allows the efficient addition of 1- or 2-naphthols, a few indole derivatives, pyrrole and 2-methoxyfuran with similar results.

Following a similar approach, in 2021, Fu and co-workers reported the addition of 2-naphthols **136** to *N*,*N*-propargyl aminals **135** (Scheme 39) in the presence of catalyst (*R*)-**BPA1**.[133] Despite the high temperatures required for this transformation, the reaction affords highly enantioenriched propargylamines **137** (53-84%, 86-96% ee). Moreover, the subsequent 'one-pot' cyclization reaction leads to the formation of benzofuran derivatives **138** in similar yields and enantiocontrol (56-80%, 80-98% ee).



Scheme 38. Enantioselective arylation of propargyl aldimines.



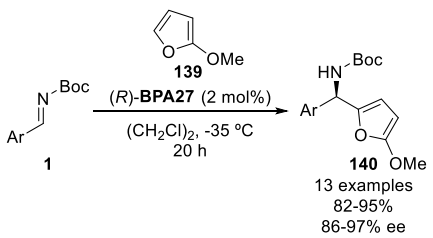
Scheme 39. CPA-catalysed arylation of propargyl aminals **279**.

There are several examples of CPA-catalysed Friedel-Craft reactions using activated methoxyfurans. In particular, Terada reported in 2004 the first enantioselective arylation of *N*-Boc protected aldimines **1** catalysed by a CPA, using 2-dimethoxyfuran (**139**) as the nucleophile and in the presence of 2 mol% of (*R*)-**BPA27** (Scheme 40).[134] The resulting chiral amines **140** were obtained in excellent yield and enantiocontrol (82-95%, 86-97% ee).

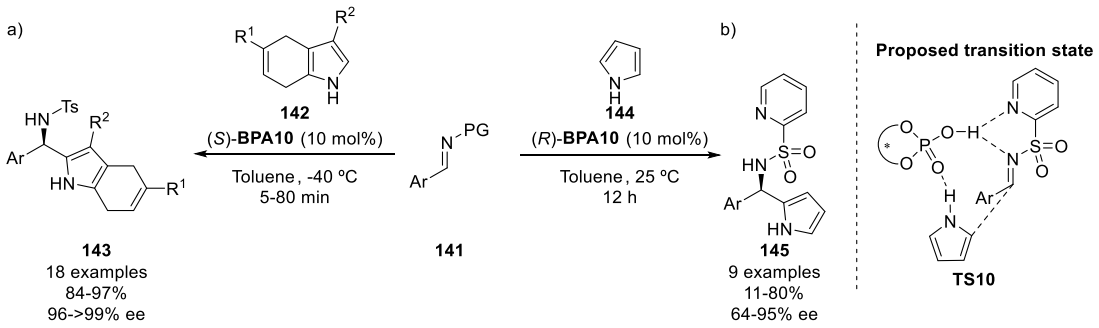
Pyrrole derivatives are also often used as nucleophile substrates in Friedel-Crafts reactions. In this regard, You and co-workers developed in late 2008 the enantioselective nucleophilic addition of 4,7-dihydroindole derivatives **142** to *N*-sulfonyl imines **141** in the presence of (*S*)-**BPA10** (Scheme 41, a).[135] This strategy provides access to 2-substituted indole derivatives **143**, which are commonly unavailable when indoles are used as nucleophiles, after the addition reaction and the subsequent oxidation of the aromatic ring. The resulting chiral amines are obtained in excellent yields (84-97%) and enantiomeric excesses above 96% ee.

The addition of simple pyrrole (**144**) to *N*-sulfonyl aldimines **141** was reported in 2009 by Nakamura *et al.* using (*R*)-**BPA10** as the catalyst (Scheme 41, b).[136] Using a similar strategy as Akiyama previously used for the Mannich reaction,[2,73] Nakamura proposed the use of 2-pyridyl sulfonyl protecting group, in order to add an additional binding point for the phosphoric acid catalyst (**TS10**). Thus, the reaction adducts **145** are obtained in yields ranging from 11 to 80% and moderate to high enantioselectivities (64-95% ee). A single example of the enantioselective addition of indole in 92% yield and 92% enantiomeric excess is also presented, using similar reaction conditions. However, the authors did not evaluate the effect of substituted pyrroles or indoles in this reaction.

The indole ring is a nitrogen-containing heterocycle that is widely used in organic chemistry. Due to the presence of the indole moiety in several molecules such as tryptophan and other bioactive molecules and natural products, the



Scheme 40. CPA-catalysed arylation of aldimines.

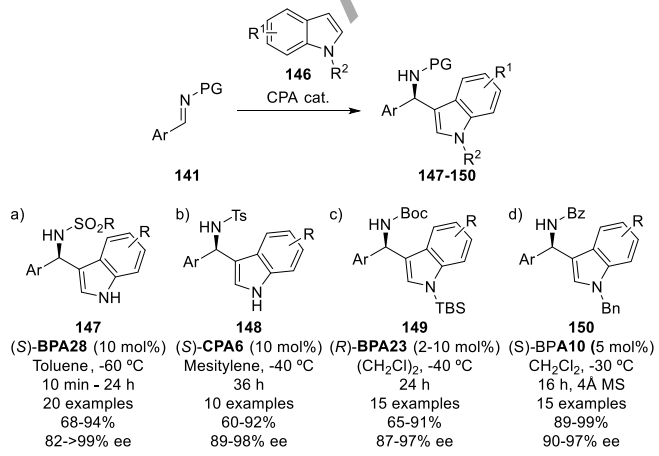


Scheme 51. CPA-catalysed addition of pyrroles to N-sulfonyl imines.

functionalization of the indole scaffold is of great interest in organic and medicinal chemistry.[137–139]

Indole derivatives have been widely used as nucleophiles in organic chemistry for the functionalization of electrophiles such as aldehydes and imines not only in a racemic way but also through enantioselective pathways.[140–142] In this regard, You reported in 2007 the first CPA-catalysed enantioselective addition of indole derivatives **146** to *N*-sulfonyl aryl imines **141** in presence of (*S*)-**BPA28** (Scheme 52, a).[143] The resulting chiral amines **147** were obtained in good yields and enantioselectivities above 82%. Unfortunately, the use of cyclohexyl imine resulted in a drastic drop in both, the reactivity and enantioselectivity (56%, 58% ee). This limitation was successfully overcome by Terada in 2007, using *N*-Boc enecarbamates as precursors of aliphatic imines.[144] In this case, they reported yields up to 91% and enantioselectivities above 90% ee.

In the following years, several authors have reported enantioselective additions of indoles to *N*-sulfonyl imines using mainly new BINOL and SPINOL-derived phosphoric acids[145–147] and several mechanistic studies have also been reported.[41,148] In fact, the facile synthesis of *N*-tosyl aryl imines has made this transformation one of the most straightforward methods to evaluate the effectiveness of new CPA catalysts. For instance, in 2014, Pericás developed a continuous flow protocol for this transformation, using a polymer-supported version of (*R*)-**BPA5**.[149]



Scheme 52. CPA-catalysed addition of indoles to aromatic aldimines.

Using this flow system, enantioselectivities up to 98% ee were reported. On the other hand, Marinetti and co-workers developed the synthesis of ferrocene-derived (*S*)-**CPA6**-catalyst and they evaluated its effectiveness in the Friedel-Crafts reaction of indole derivatives **146** to *N*-tosyl aldimines **141** (Scheme 52, b).[150] Their catalyst afforded the corresponding chiral secondary amines **148** in high yields (60-92%) and enantioselectivities above 89% ee. Remarkably, while the use of 2-methylindole usually results in a loss of the enantiocontrol in this case it afforded the target product in 90% ee.

In the same context, Terada reported in 2007 the enantioselective addition of *N*-substituted indoles to imines catalysed by (*R*)-**BPA23** (Scheme 52, c).[151] In this example *N*-TBS indole derivatives are used as nucleophiles in the reaction with *N*-Boc protected imines. The resulting chiral amines **149** were obtained in moderate to high yields (65-91%) and enantioselectivities above 87% ee.

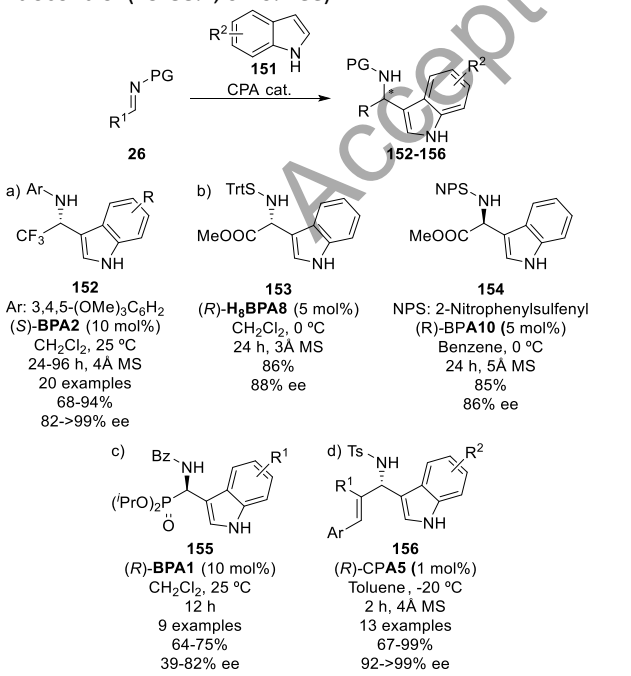
In the same year, Antilla and co-workers described a highly enantioselective addition of *N*-benzyl indoles **146** to aromatic aldimines **141** (Scheme 52, d).[152] In this methodology, the presence of a catalytic amount of (*S*)-**BPA10** catalyst provides chiral amines **150** bearing an indole moiety in excellent yield and enantiocontrol (89-99%, 90-97% ee). However, even though the use of 2-methyl substituted indole was well tolerated, in terms of reactivity, a drastic decrease in the enantiocontrol was observed (91%, 64% ee). Moreover, they also reported several addition reactions of *N*-alkyl pyrroles under similar reaction conditions, affording the chiral amines in yields up to 97% and enantioselectivities ranging from 42% to 99% ee.[153]

More recently, Tan´s group reported the enantioselective synthesis of new EBINOL-derived catalysts (a*R*)-**CPA2**,[154] and it was evaluated in the nucleophilic addition of simple indole to benzaldehyde derived *N*-tosyl imines. Surprisingly, in this case, the use of 1 mol% of (*aR*)-**CPA2** resulted in an increase in the enantiocontrol (70% ee) if compared with similar BINOL (55% ee) or SPINOL (68% ee) derived chiral phosphoric acids. It should be noted that the synthesis of optically active EBINOL moieties was performed through an organocatalysed reaction, using 5 mol% of (*S*)-**SPA8** as a catalyst.

In 2008, Ma's group reported a multicomponent reaction involving trifluoacetaldehyde hydrate, aromatic amines and indoles **151**, using (*S*)-**BPA2** as organocatalyst (Scheme 53, a).[155]

Since trifluoroacetaldehyde is normally in the form of hydrate or acetal, the authors propose an *in situ* formation of the corresponding imines **26** with aniline. The subsequent phosphoric acid-catalysed enantioselective Friedel-Crafts addition provides chiral amines **152** bearing a trifluoromethyl group in α-position with high yields (68-94%) and enantioselectivities up to 99% ee.

In 2008, Hiemstra and co-workers reported the synthesis of indolyl glycines **153** and **154** in an asymmetric fashion through CPA-catalysed Friedel-Crafts additions of indole (**151**) to glyoxalate-derived imines **26** (Scheme 53, b).[156] They optimised the reaction using sulfur-containing protecting groups that allow to selectively obtain the *R* or *S* enantiomer of the resulting indolyl glycine derivative, using either (*R*)-**H$_8$BPA8** or (*R*)-**BPA10** as the catalysts. The fact that, in both cases, the same configuration is obtained even though BINOL-derived catalysts presented an *R* absolute configuration can be easily explained using Goodman´s model.[41] Trityl group is a large and highly sterically demanding scaffold, which pushes the reaction through a Type I *E* mechanism, similar to what is observed when tosyl protecting group is used in Goodman´s model. In contrast, Nps protecting group is a planar and more flexible moiety that can be oriented out of the active centre of the catalyst, thus favouring the Type II *E* mechanism, as shown for *N*-Boc protected imines. Another method to obtain indolyl glycine derivatives was reported in 2009 by You and co-workers.[157] In this case they tested *N*-PMP protected imines in presence of 10 mol% of (*S*)-**BPA1**, affording several glycine derivatives in yields above 85% but moderate enantiocontrol (51-87% ee). In 2014, Mattson published an unconventional strategy leading to indolyl glycine derivatives through a multicomponent reaction of nitro-diazo esters, anilines and indole derivatives. However, this methodology was found to be limited in terms of yields and enantiocontrol (49-88%, 6-40% ee).[158]



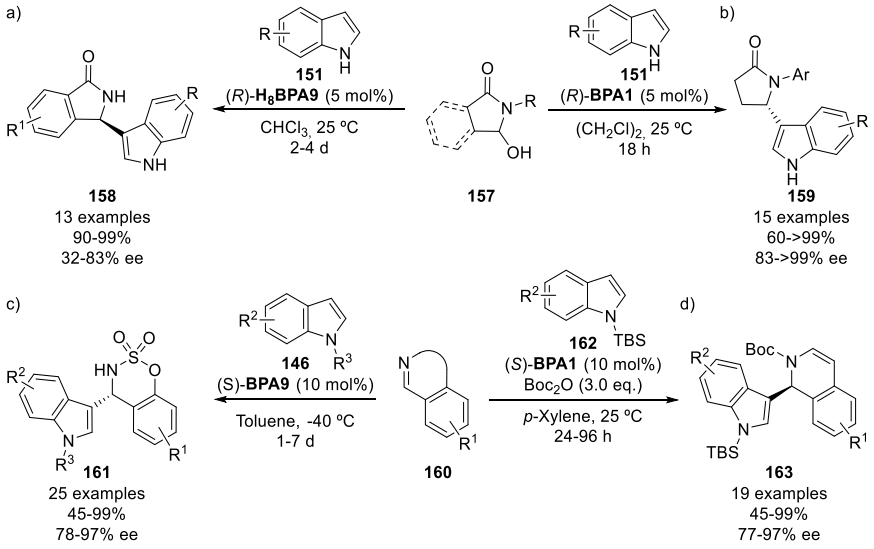
Scheme 53. CPA-catalysed addition of indoles to aldimines.

Inspired in You's and Hiemstra's reports, in 2019, our research group reported the addition of indole derivatives **151** to highly reactive α-aldiminophosphonates **26** (Scheme 53, c).[159] Using (*R*)-**BPA1** as the catalysts, we were able to develop a new synthetic protocol to provide access to optically active indolyl phosphoglycines **155** in good yields and moderate to good enantioselectivities (64-75%, 39-82% ee). A drastic drop in the enantioselectivity was found (39% ee) when 2-methylindole was tested in the reaction, even though a 70% yield was obtained. In addition, the functionalization at C-2 in the heterocycle is obtained when a 3-substituted indole is used, although in this case a high decrease on the enantiocontrol is observed (72%, 19% ee). This reaction is strongly dependent on the benzoyl group, since the use of bulky amines as protecting group resulted in a double addition of indole moiety to the imine,[160] in a similar way to the previously mentioned double addition to aldehydes. Following a similar approach, Inokuma *et al.* reported the same Friedel-Crafts addition to *N*-Nps (2-nitrophenylsulfenyl) protected aldiminophosphonates,[161] which proved to be more stable than *N*-benzoyl aldimines **26**. The authors report yields from 58 to 95% and enantioselectivities ranging from 40 to 87% ee. In addition, some pyrroles were tested in the reaction, showing similar results for simple pyrrole (83%, 75% ee) but yields below 25% when substituted pyrroles were tested.

More recently, Lin´s group reported a highly regio- and enantioselective 1,2 nucleophilic addition of indole derivatives to *N*-tosyl styryl aldimines **26** (Scheme 53, d).[162] The authors developed a new chiral phosphoric acid family, which was found to be even more effective than BPA and SPA derivatives in their reaction. Using (*R*)-**CPA5** as the chiral catalysts they were able to drop the catalyst loading to 1 mol% without losing any enantioselectivity, affording the desired chiral sulfonamides **156** in excellent yields and enantioselectivities up to 99% ee after two hours. In addition, the effectiveness of their catalysts in Friedel-Crafts reaction of indoles was evaluated using several aryl and alkyl *N*-tosyl imines **26**. In this case, yields up to 99% and enantioselectivities ranging from 77 to 99% ee are obtained in the presence of only 2 mol% of the catalyst.

Concerning the CPA-catalysed enantioselective Friedel-Crafts reactions using endocyclic aldimines, in 2011, Wang described the alkylation reaction of 3-hydroxyisoindolin-1-ones **157** with indoles **151**, using (*R*)-**H$_8$BPA9** as the catalysts (Scheme 54, a).[163] As shown in other examples, the initial elimination of water leads to *in situ* generated imines as electrophiles for the subsequent CPA-catalysed enantioselective nucleophilic addition of the indole scaffold. After the optimization of the reaction using the precursors of endocyclic aldimines and (*R*)-**H$_8$BPA9** as the catalyst, the nucleophilic addition products **158** were obtained in yields above 90% but modest enantiocontrol (32-83% ee).

In 2013, Masson reported the functionalization of the γ-lactam ring through a (*R*)-**BPA1**-catalysed enantioselective addition of indoles **151** to *in situ* generated cyclic iminium ions from γ-hydroxy γ-lactams **157** (Scheme 54, b).[164]



Scheme 54. Stereoselective Friedel-Crafts reaction of indole derivatives to endocyclic imines.

The reaction tolerates different EDG and EWG at the indole ring, affording chiral γ-lactams **159** in yields and enantioselectivities up to 99% ee. Even the use of 2-methylindole, which usually results in a drop in the enantiocontrol, provides efficiently the nucleophilic addition product (90%, 90% ee). However, the use of bulkier nucleophiles such as 2-phenylindole has an adverse effect on the enantioselectivity (90%, 10% ee). On the other hand, if a 3-substituted indole is used, the reaction affords slightly enantioenriched *N*-substituted chiral indol (84%, 20% ee), while *N*-benzylindole affords the 3-substituted indole in low yield and enantiocontrol (38%, 19% ee).

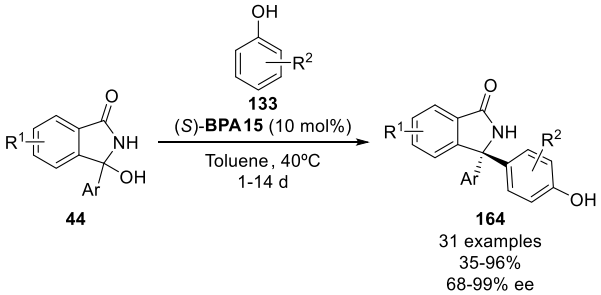
Kim´s group reported in 2019 the addition of *N*-alkyl indoles **146** to 6-membered cyclic sulfonyl aldimines **160** (Scheme 54, c).[165] The activation of the imine by the phosphoric acid catalyst, along with π-stacking interactions between indole and the phenyl groups on the (*S*)-**BPA9** catalyst, provides chiral amines **161** in yields ranging from 45% to 99% and enantioselectivities up to 97% ee. In the next years, the same group also reported the addition of *N*-substituted pyrroles and 2-methoxyfuran to the sane imines, obtaining yields above 62% and enantioselectivities ranging from 14% to 97% ee using the (*S*)-**BPA6** and (*S*)-**BPA4** organocatalysts respectively.[166,167]

In 2016, Zhang et al. described the organocatalysed dearomatization of isoquinolines **160** through a nucleophilic addition *N*-silyl protected indoles **162** in presence of di-*tert*-butyl pyrocarbonate (Boc_2O) and 10 mol% of catalyst (*S*)-**BPA1** (Scheme 54, d),[168] affording *N*-Boc protected dihydroisoquinolines **163** in yields ranging from 45 to 99% and enantioselectivities up to 97% ee.

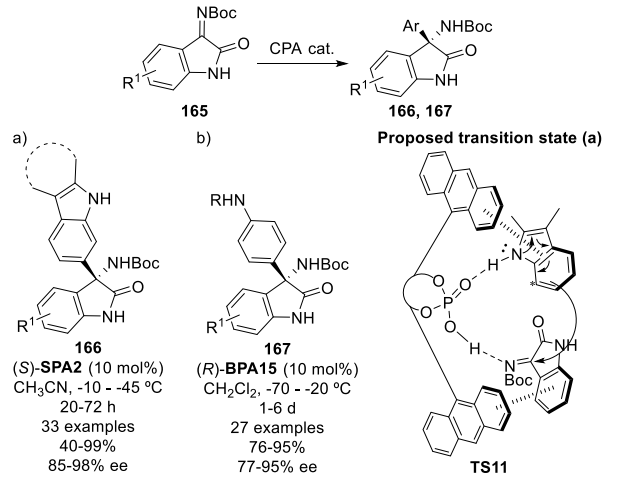
In contrast to the previous sections (including the Friedel-Crafts reaction with carbonyl compounds) in which the use of large polyaromatic substituents in the CPA catalysts such as antryl, phenantryl or naphthyl groups was scarce, these are some of the most common 3,3´substituents for Friedel-Craft processes with aldimines. These types of polyaromatic substituents are less common when small nucleophiles (such as pyrrole, methoxyfuran or phenol derivatives) or non-aromatic substituents are present in imines, suggesting the participation of attractive interactions between aromatic groups of the imine and the nucleophile. Although several authors have already suggested this type of interaction based on experimental results, more general theoretical analyses are still missing in the literature. Nevertheless, it should be noted that predictive methods reported for Friedel-Crafts reactions are quite effective when talking about non-cyclic aldimines.

3.2.2. Friedel-Crafts reactions with ketimines

Due to the poor electrophilic character of the ketimine groups and the additional steric hindrance expected on the substrates Friedel-Crafts reactions using ketimines is a challenging task if compared with the parent aldimine substrates. In addition, in enantioselective methodologies, the enantiotopic faces of ketimines are not as easily discriminated as those of aldimines. This lack of discrimination is even greater when acyclic ketimines are used, due to the higher degree of freedom of the substituents if compared with cyclic ketimine substrates. In this regard, in late 2021, You and Gredičak reported the addition of phenol derivatives **133** to endocyclic ketimines derived from **44**, catalysed by (*S*)-**BPA15** (Scheme 55).[169]



Scheme 55. Asymmetric arylation of *in situ* formed ketimines.

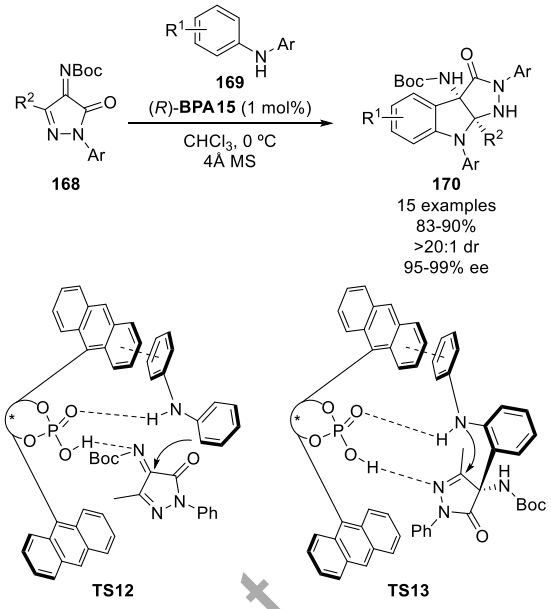


Scheme 56. Enantioselective arylation of isatin imines with indoles and anilines.

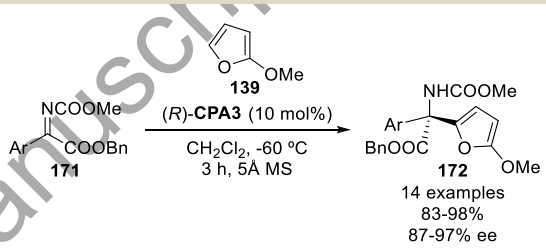
The reaction tolerates several phenols and aryl imines bearing EDG and EWG, affording isoindolin-1-one derivatives **164** in moderate to high yield and high enantiocontrol in most cases (35-96% 68-99% ee). However, the presence of substituents next to reactive carbons (*ortho* for the aryl imine and *metha* for the phenols) resulted in drastic drops of the enantiocontrol while maintaining similar yields (23-89%, 4-32% ee).

A novel CPA-catalysed C-6 functionalization of 2,3-disubstituted indole derivatives was described by Zhang´s group in 2019 (Scheme 56, a).[170] This type of remote nucleophilic additions of indole derivatives was previously described using Pd catalysts, but Zhang´s work represents the first organocatalytic approach for the C-6-addition of indoles to electrophiles. According to their proposal, the selected (*S*)-**SPA2** catalyst activates both, the indole and the isatin-derived imine **165** as shown in transition state **TS11**. Besides, the fact that polyaromatic substituents were found to be the most effective ones, a π-π stacking effect is also predicted. Using this methodology, the authors report scope with more than 30 substrates **166** in high yields (40-99%) and enantioselectivities above 85% ee. Following this approach, the enantioselective *para* C−H aminoalkylation of aniline derivatives with isatin-derived imines **165** is also reported (Scheme 56, b).[171] The reaction proceeds in similar reaction conditions, using in this case (*R*)-**BPA15** as the catalyst, providing access to several optically active molecules **167** (77-95% ee), in yields above 76%.

In 2021, Zhang and co-workers reported formal [3+2] cycloaddition reaction through a tandem arylation/cyclization using *N*-Boc protected imines **168** and diarylamines **169** in presence of only 1 mol% of (R)-**BPA15** (Scheme 57).[172] The initial step consists of the enantioselective ortho functionalization of arylamines (**TS12**), followed by the intramolecular addition of the nitrogen atom to the endocyclic imine (**TS13**). The reaction is applicable to not only symmetric diarylamines but also to non-symmetric ones, affording indoline derivatives **170** as a single diastereoisomer in excellent yield and enantiocontrol (83-90%, >20:1 dr, 95-99% ee).



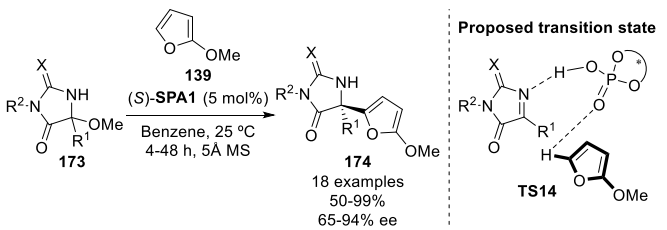
Scheme 57. Enantioselective formal [3+2] cycloaddition reaction through a tandem arylation/amination with diaryl amines.



Scheme 58. Stereocontrolled nucleophilic addition of 2-methoxyfuran to activated ketimines.

Moreover, they also applied the methodology to strone-derived diarylamine, obtaining the corresponding product **170** in almost quantitative yield but lower diastereomeric ratio (95%, 3.5:1 dr).

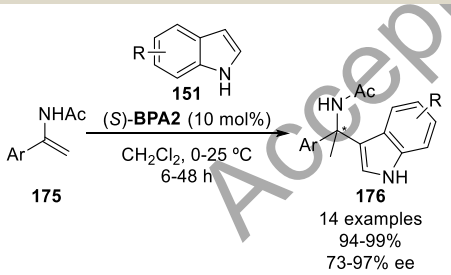
Hatano et al. reported in 2018 the use of BINOL-derived bisphosphoric acid catalysts in the nucleophilic addition reaction of 2-methoxyfuran (**139**) to acyclic iminoesters **171** (Scheme 58),[173] leading to the formation of tetrasubstituted chiral amino acid derivatives **172** in excellent yields and enantiocontrol (83-98%, 87-97% ee). Due to the expected hydrogen bonds between both phosphoric acids present in (*R*)-**CPA3**, this catalyst presents a stronger acid character, making providing a faster reaction than if the common chiral BPA-catalysts are used.



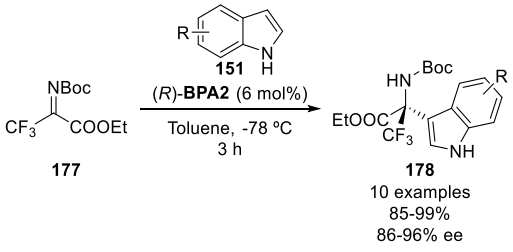
Scheme 59. Enantioselective nucleophilic addition of 2-methoxyfuran to endocyclic ketimines.

In the same context, the addition of 2-methoxyfuran (**139**) to cyclic ketimines **173** was described in 2016 (Scheme 59).[174] The use of 5 mol% of SPINOL-derived chiral phosphoric acid (*S*)-**SPA1** provides cyclic (thio)ureas **174** in good to excellent yields and enantioselectivities (50-99%, 65-94% ee). Regarding the reaction mechanism, it is proposed that the Brønsted acid may act as a bifunctional catalyst, improving the electrophilicity of the imine and the nucleophilicity of the furan species through a double hydrogen bonding (**TS14**).In 2007, Zhou reported the Friedel-Craft addition of indoles **151** to enamides **175** in presence of 10% of (*S*)-**BPA2** as a catalyst (Scheme 60).[175] Tetrasubstituted chiral indole derivatives **176** were obtained in excellent yield and enantiocontrol (94-99%, 73-97% ee). A few years later, in 2010, Toy described the synthesis of 6,6'-phosphonium salt-substituted (*R*)-**BPA29** as a recyclable catalyst for enantioselective transformations.[176] The authors evaluated the effectiveness of the organocatalyst in the enantioselective addition of indoles **151** to acyclic *N*-acyl enamines **175**, leading to tetrasubstituted chiral amines **176** inhigh yields and good enantiocontrol (81-98%, 70-90% ee). Although they were able to recover above 93% of their organocatalyst, the following trials resulted in a decrease of the enantiocontrol from 90% ee (1st run) to 74% ee (4th run).

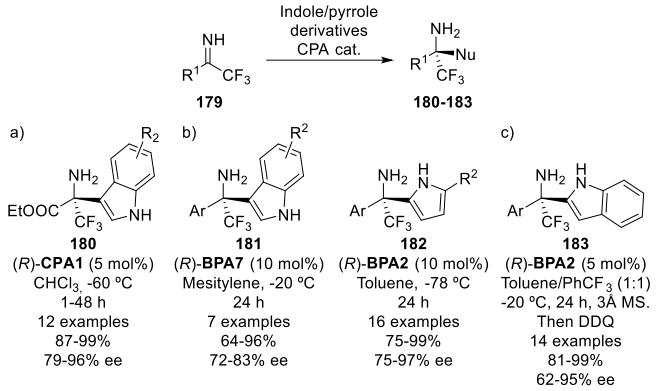
One year later, Bolm reported the (*R*)-**BPA2**-catalysed Friedel-Crafts reaction of indoles **151** to highly activated trifluoromethyl ketimines **177** (Scheme 61).[177] This transformation furnishes α-amino esters **178** bearing a tetrasubstituted chiral stereocentre in yields up to 99% and enantioselectivities above 86% ee. However, the use of *N*-methyl indole resulted in a drastic drop of both, the reactivity and the enantioselectivity (22%, 8% ee), making evident the high relevance of the hydrogen-bonding donor N-H group of the indole ring in the reaction.



Scheme 60. CPA-catalysed addition of indoles to enamines **175**.

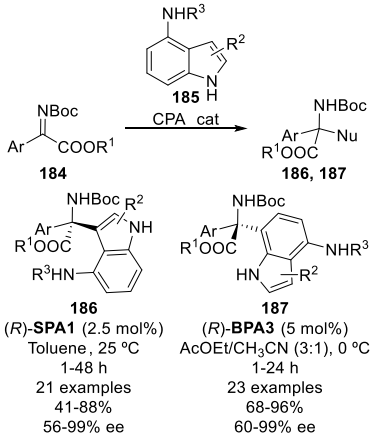


Scheme 61. Enantioselective Friedel-Crafts reaction of indoles **151** to activated ketimines **177**.

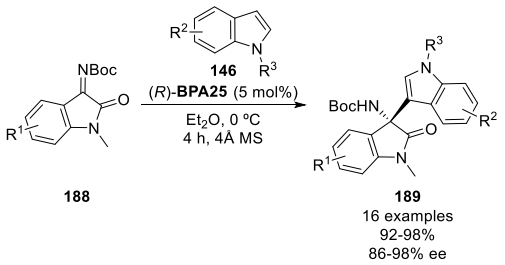


Scheme 62. Synthesis of tertiary chiral amines through Friedel-Crafts reactions with *N*-unprotected ketimines.

In 2016, Ohshima´s group described the Friedel-Crafts addition of indoles to unprotected ketiminoesters **179** catalysed by 5 mol% of monosubstituted BINOL derivative (*R*)-**CPA1** (Scheme 62, a).[178] The catalysts demonstrated to be efficient, leading to highly enantioenriched (87-99%, 79-96% ee) *N*-unprotected α-amino acid derivatives **180** containing a quaternary chiral carbon in their structure. In addition, the authors also tested a few pyrrole derivatives in the same reaction, observing enantioselectivities up to 62%. Following this approach, in 2019, Akiyama´s group reported the Friedel-Crafts reaction of several indole and pyrrole derivatives to *N*-unprotected trifluoromethyl aryl ketimines **179** (Scheme 62, b).[179] Using BINOL-derived phosphoric acids (*R*)-**BPA7** and (*R*)-**BPA2** as the catalysts, they were able to obtain tetrasubstituted amines **181** and **182** in high yields (64-99%) and enantioselectivities above 72% ee. In order to further improve the scope of the reaction,[180] the same authors also reported the (*R*)-**BPA2**-catalysed nucleophilic addition of 4,7-dihydroindole to the same imines, followed by one-pot oxidation, leading to the formation 2-substituted chiral indoles **183** in excellent yields (81-99%) and enantioselectivities up to 95% ee (Scheme 62, c).



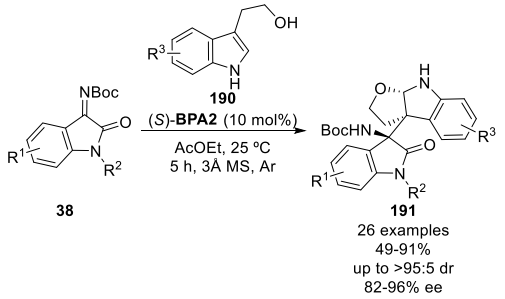
Scheme 63. Solvent dependent C3 and C7 addition of 4-aminoindoles **185** to ketimines **184**.



Scheme 64. First CPA-catalysed addition of indoles to isatin-derived imines.

It is interesting to note that the use of large proximal substituted catalysts is required in order to obtain high enantiocontrol when *N*-unsubstituted imines are used. This seems to be similar to what happens with ketones, where the same type of catalyst has proved to be the optimal and makes evident the high relevance of the protecting group in the transition state (Type II E). Moreover, Zhao´s group reported a strongly solvent dependent regioselective Friedel-Crafts reaction of 4-aminoindoles **185** to *N*-Boc protected ketimines **184** (Scheme 63).[181] The C-3 functionalization is observed with catalyst (*R*)-**SPA1** if toluene is used as a solvent, obtaining products **186** in moderate yields (41-88%) and enantioselectivities ranging from 56% to 99% ee. In contrast, the use of a AcOEt/CH_3CN mixture and (*R*)-**BPA3** as the catalyst, results in C-7 substituted chiral indoles **187** in high yields (68-96%) and enantioselectivities up to 99% ee.

In 2012, Wang's group reported an organocatalytic Friedel-Crafts process with isatin-derived imines **188** and *N*-substituted indole derivatives **146**, using (*R*)-**BPA25** as the catalyst (Scheme 64).[182] The reaction proceeds fast, providing chiral amines **189** in high yield and enantiocontrol (92-98%, 86-98% ee). It should be noted that the use of *N*-alkyl or *N*-benzyl indoles is highly relevant since the addition of simple indole in the same reaction conditions resulted in a drastic drop in the enantiocontrol (97%, 64% ee). Moreover, the authors also reported the analogue Friedel-Crafts process using simple pyrrole derivatives. In this case, yields above 95% and enantioselectivities ranging from 88 to 99% ee were obtained after only 3 minutes. Curiously, unlike the case of indoles, this transformation requires the use of *N*-unprotected pyrroles, since *N*-methylpyrrole only afforded the target product in 49% yield and 70% enantiomeric excess.



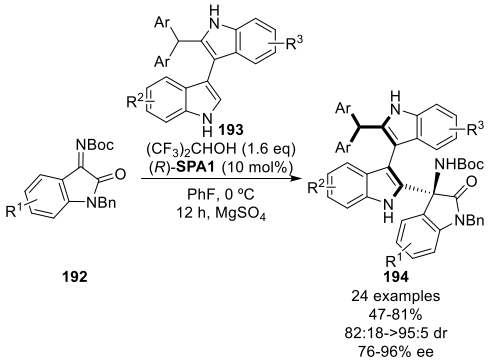
Scheme 65. Stereocontrolled tandem Friedel-Crafts/dearomatization reaction of isatin imines **38** and indoles **190**.

Regarding the Friedel-Crafts reaction of exocyclic ketimines, Shi et al. reported the dearomative addition of tryptophan-derived alcohols **190** to isatin-derived imines **38** catalysed by BINOL-derived phosphoric acid (*S*)-**BPA2** (Scheme 65).[183] After the initial Friedel-Crafts addition to the imine an intramolecular addition of the alcohol to the carbon 2 of the indole happens, leading to the dearomatization of the indole moiety. Remarkably, this intramolecular dearomative reaction delivers chiral indolines **191** with two tetrasubstituted chiral centres in moderate to good yields (49-91%) and high stereocontrol (up to >95:5 dr, 82-96% ee).

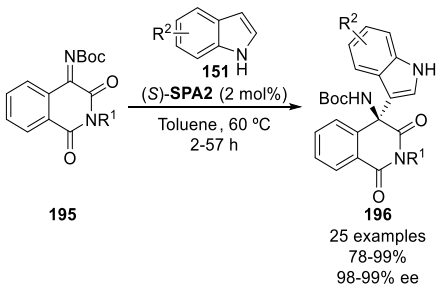
One of the most recent examples of CPA-catalysed enantioselective addition of indoles to cyclic imines was reported in 2020 by Shi and co-workers, who described the synthesis of chiral bis-indoles **194**, derived from isatin imines **192**, bearing a double central and axial chirality (Scheme 66).[184] The use $(CF_3)_2CHOH$ and $MgSO_4$ as additives was found to be crucial in order to obtain reasonable yields (47-81%). Moreover, the use of (*R*)-**SPA1** as the catalyst ensures high diastereo- and enantiocontrol (82:18 to >95:5 dr, 76-96% ee) in the reaction.

Yuan and co-workers reported in 2019 the synthesis of isoquinoline-1,3(2*H*,4*H*)-diones **196** through the nucleophilic addition of indole **151** derivatives to 6-membered imines **195** (Scheme 67).[185] The reaction demonstrated to be highly efficient with a catalyst loading of only 2 mol% of (*S*)-**SPA2** for the preparation of a wide scope of products **196** in excellent yields (78-99%) and enantioselectivities above 98% ee. Besides, a few examples of the addition of pyrrole to the same exocyclic imines are included in this report, observing high yields (65-99%) and enantioselectivities ranging from 86 to 93%.

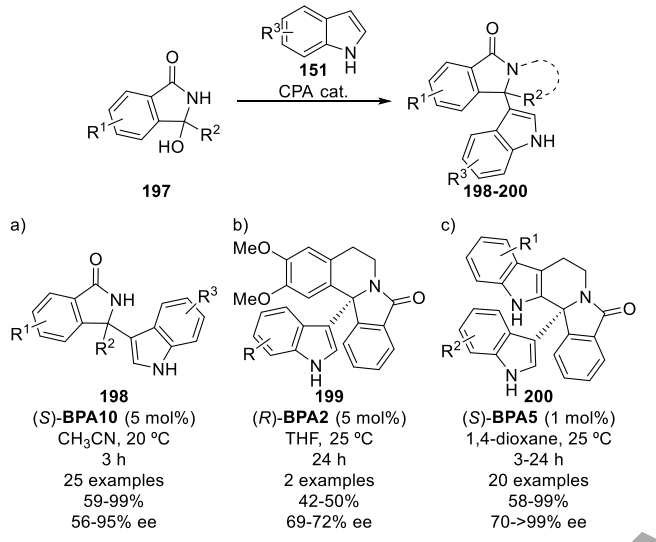
In 2011, Zhou reported the generation of ketimines from 3-substituted 3-hydroxyisoindolin-1-ones **197** in the presence of 5 mol% of (*S*)-**BPA10** (Scheme 68, a),[186] providing good yields of the adducts **198** and moderate to high enantiomeric excesses (59-99%, 56-95% ee). Remarkably, the reaction tolerates not only aromatic substituents on the ketimine substrates but also several alkyl or allyl groups, making it an advantageous method for the generation of tetrasubstituted chiral carbons.



Scheme 66. Stereocontrolled synthesis of axially-chiral indole derivatives **194** from isatines **192**.



Scheme 67. Friedel-Crafts reaction of indoles to 6-membered cyclic imines **195**.



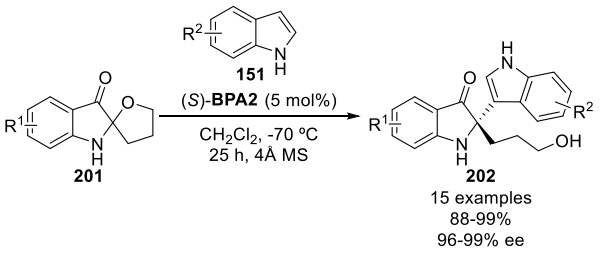
Scheme 68. Stereoselective Friedel-Crafts reaction of indole derivatives to *in situ* generated iminium ions.

Similarly, Lette reported the enantioselective synthesis of isoindoloisoquinolines **199** from 3-hydroxyisoindolin-1-one derivatives **197** (Scheme 68, b).[187,188] The initial elimination of the hydroxyl group of **197** leads to the formation of the corresponding iminium ion for the subsequent (*S*)-**BPA2**-mediated asymmetric addition of indole derivatives **151**. However, the presence of strong electron-withdrawing groups at the indole ring results in a very low reactivity. In consequence, a limited scope of substrates **199** is presented, in moderate yields and enantiomeric excesses (42-50%, 69-72% ee). In addition, the use of *N*-methylindole had an adverse effect on both, the reactivity and the enantiocontrol (21%, 37% ee). Following this strategy, Shi's group reported the synthesis of isoindolo-β-carboline derivatives **200**, using 1 mol% of (*S*)-**BPA5** (Scheme 68, c).[189] However, in this case, high yields and enantiomeric excesses (58-99%, 70 to >99% ee) are obtained.

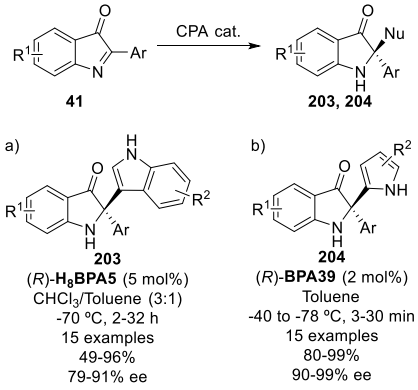
In 2011, You described the (*S*)-**BPA2**-catalysed reaction of indole derivatives with racemic N,O-spiroacetals **201** (Scheme 69).[190] The acidic reaction media favours the opening of the acetal moiety to form the corresponding imine. The subsequent Friedel-Crafts reaction of indoles **151** results in the generation of products **202** with a tetrasubstituted chiral centre in excellent yields and enantioselectivities up to 99% ee. Following with the interest in CPA-catalysed Friedel-Crafts reactions of endocyclic ketimines, in 2011, Rueping reported the enantioselective addition of indoles **151** to indolones **41** in the presence of 5 mol% of (*S*)-**H$_8$BPA5** catalyst (Scheme 95, a).[191] The reaction proceeded in similar reaction conditions as the procedure described by You, affording the reaction indolinones **203** in yields up to 96% and enantiomeric excesses ranging from 79 to 91%. In 2016, Nakamura and coworkers have reported the analogous reaction with pyrroles, using 2% of imidazoline containing phosphoric acid (*R*)-**BPA39** as a catalyst (Scheme 70, b).[192] The reaction proceeds in a few minutes at low temperatures, affording the products **204** in excellent yields and enantiocontrol (80-99%, 96-99% ee). It should be noted that, although the use of substituted pyrroles often results in a drastid decrease of the enantiocontrol, the authors reported a few 3-substituted pyrroles with a minimal effect on the reactivity or the stereocontrol (98-99%, 90-91% ee).

Moreover, in 2020, Fu´s group reported the synthesis of axially-chiral indoles using endocyclic imines **41** and 3-aryl indoles **205** and (*R*)-**BPA1** as the catalyst (Scheme 71).[193] Unlike Shi´s work,[184] they did not require any additive in the reaction to afford **206** products as a single diastereoisomer, of all the possible reaction products, in yields ranging from 69 to 99% and enantiomeric excesses above 85%.

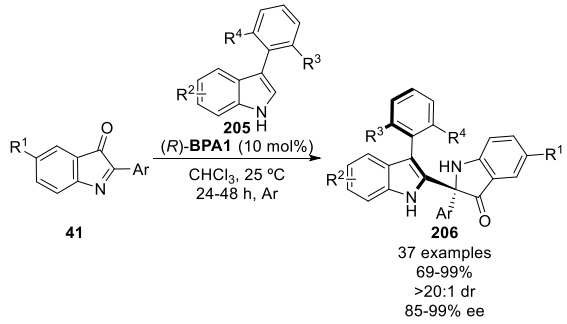
In addition, Ling et al. reported in 2017 the enantioselective addition of indoles **151** to 5-membered cyclic sulfonyl ketimines **207**, leading to the formation of tetrasubstituted α-amino acid derivatives **208** using 5 mol% of chiral catalyst (*R*)-**BPA8** (Scheme 72, a).[194] Simultaneously, Zhou´s group published the homologous nucleophilic addition reaction to cyclic α-ketiminophosphonates. In this case, BINOL-derived (*S*)-**H$_8$BPA3** is used as the catalyst to obtain enantioenriched α-aminoposphonic acid derivatives **209** (Scheme 72, b).[195] It should be noted that, although both authors used the opposite



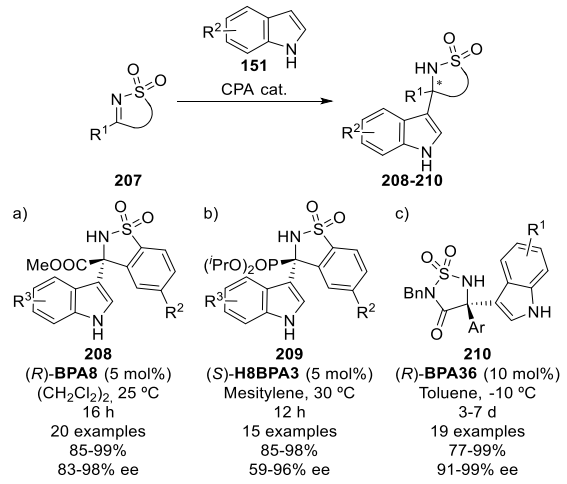
Scheme 69. Enantioselective reaction of indoles and *N,O*-spiroacetals **201**.



Scheme 70. Enantioselective Friedel-Crafts additions to endocyclic imines **41**.



Scheme 71. Stereocontrolled synthesis of axially-chiral indole derivatives from endocyclic imines **41**.



Scheme 72. Enantioselective Friedel-Crafts reaction of indoles with cyclic ketimines.

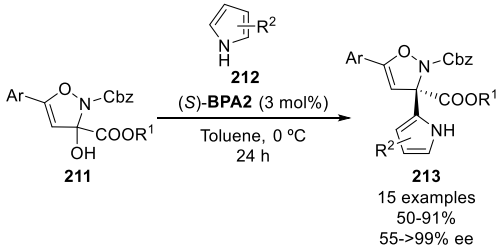
absolute configuration of the optimal catalyst, the same absolute configuration was determined in their reaction products. Although Goodman´s model has not been extensively applied to cyclic imines, it is clear that, for the case of imino esters (Scheme 72, a), the most sterical demanding substituent of the imine is the aromatic group, leading to a cyclic Z imine. In contrast to planar esters, phosphonates are bulkier tridimensional groups that switch the steric demand on the imine (Scheme 72, b). This probably has a drastic effect on the transition state, which could explain the observed selectivity. Besides, both authors reported the addition of simple pyrrole to the same cyclic imines in similar reaction conditions, affording the corresponding products in yields above 85% and enantioselectivities ranging from 83% to 93% ee for α-amino ester derivatives and from 59% to 96% for α-aminophosphonate substrates.

In the same context, Nakamura´s group reported a new methodology to obtain tetrasubstituted chiral α-amino acid derivatives through the enantioselective addition of indoles **151** to cyclic sulfonyl imines **207** (Scheme 72, c).[196] In this case, imidazoline substituted BINOL derivatives were found to be the optimal catalysts, obtaining the best results with 10 mol% of (*R*)-**BPA36**. The selected catalyst delivers cyclic sulfonyl amines **210** in excellent yields and enantioselectivities up to 99%. ee

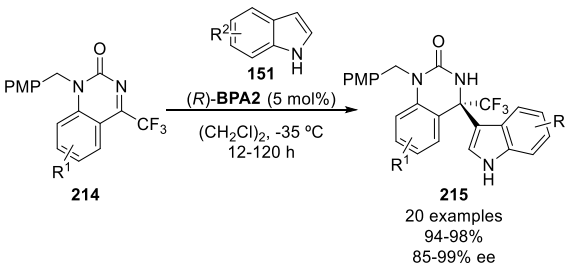
Very recently, Gurubrahamam and Chen published a route for the functionalization of pyrroles (Scheme 73).[197] In this case 3 mol% of (*S*)-**BPA2** organocatalyst is used in order to promote the formation of oxazolium ions from **211**, as electrophiles for the addition of pyrrole derivatives **212**. Functionalised pyrroles **213** were obtained in moderate to good yields (50-91%) and enantiomeric excesses up to 99% ee. Moreover, they also reported a few examples of the addition of indoles, obtaining, in this case, similar yields (62-99%) and enantiomeric excesses up to 75%.

In 2013, Ma's group reported the enantioselective synthesis of trifluoromethyldihydroquinazolines **215** through a CPA-catalysed addition of indoles to six-membered cyclic imines **214**, activated by a trifluoromethyl group (Scheme 74).[198,199] The reaction affords the functionalised indoles bearing a tetrasubstituted chiral centre with high yield and enantiocontrol (94-98%, 85-99% ee) by using 5 mol% of (*R*)-**BPA2** as the catalyst. Moreover, the authors also reported the addition of simple pyrrole (92%, 80% ee), or 3-(dimehtylamino)phenol (94%, 63% ee) in high yields but lower enantiomeric excesses. In addition, the authors present some mechanistic studies, justifying the loss of the enantiocontrol when *N*-substituted indoles are used (84%, 3% ee). On the other hand, the *N*-substitution at the electrophile is also crucial, since debenzylated imines seem to quench the proper activation of the indole by the CPA, with the consequent loss on the enantiomeric excess (98%, 55% ee).

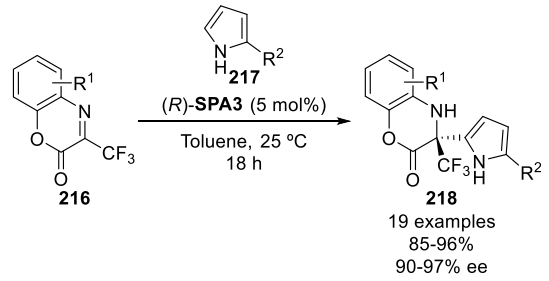
In 2016, Lin´s group reported the CPA-mediated nucleophilic addition of pyrroles **217** to activated cyclic trifluoromethyl ketiminoesters **216** (Scheme 75).[200] Using this methodology, tetrasubstituted chiral amino acid derivatives **218** were obtained in excellent yields and enantioselectivities (85-96%, 90-97% ee) in the presence of 5 mol% of (*R*)-**SPA3** as chiral catalysts. Following this strategy, in 2017, Zhao´s group reported the homologous nucleophilic addition to cyclic aryl ketimines using indole derivatives as nucleophiles.[201] Although



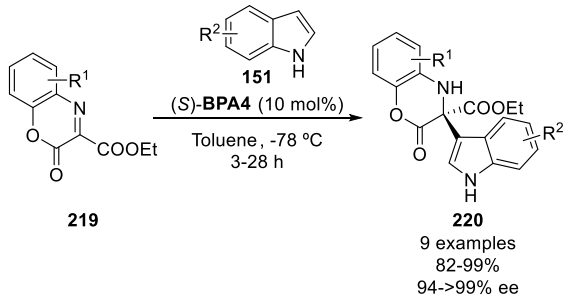
Scheme 73. Enantioselective nucleophilicaddition of pyrroles **212** to oxazolium ions.



Scheme 74. CPA-catalyzde Enantioselective synthesis of trifluoromethyl dihydroquinazolines **215**.



Scheme 75. Enantioselective nucleophilic addition of pyrroles **217** to imines **216**.

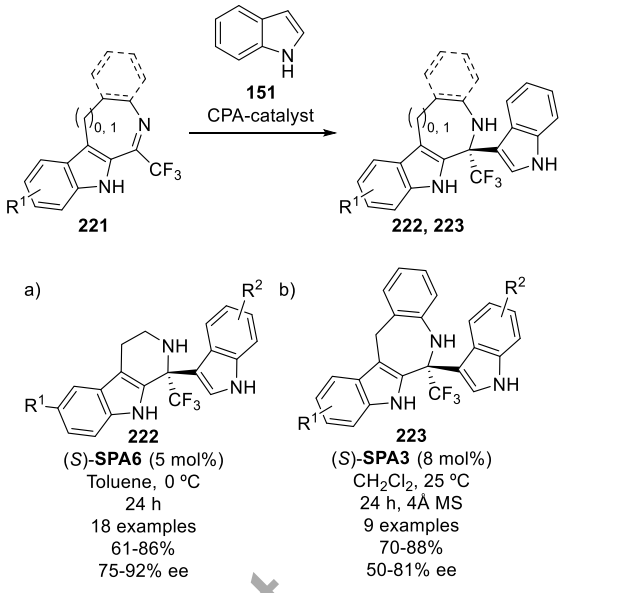


Scheme 76. Enantioselective addition of indole derivatives **151** to cyclic iminoesters **219**.

they use 10 mol% of (*R*)-**BPA10** catalyst, their methodology resulted in lower yields and enantioselectivities (75-85%, 46-93% ee). In addition, Zhao also tested a few pyrrole derivatives. However, (*R*)-**BPA10** was probed to be a less effective catalyst than (*R*)-**SPA3**, since enantioselectivities up to 70% were obtained.

One year later, Maruoka's group published the asymmetric synthesis of cyclic α-amino esters **220** mediated by (*S*)-**BPA4** organocatalyst (Scheme 76).[202] The nucleophilic addition of indoles **151** to highly activated cyclic ketimino diesters **219** afforded α-amino acid derivatives **220** in excellent yields (82-99%) and enantiomeric excesses above 94%. Moreover, the extension of this methodology to the addition of pyrrole delivered the expected α-amino acids in quantitative yield but lower stereocontrol (99%, 75% ee).

More recently, Lin's group reported the addition of indoles **151** to indol-derived 6-membered cyclic *N*-Alkyl trifluoromethyl ketimines **221** (n= 0), catalysed by 5 mol% of SPINOL-derived (*R*)-**SPA6** (Scheme 77, a).[203] The reaction was found to be highly effective, affording chiral amines **222** bearing a tetrasubstituted chiral centre in good yields (61-86%) and enantioselectivities up to 75%, even when it was scaled up to a gram scale. A few later, the same authors extended the reaction to the 7-membered cyclic imines **221** (n = 1), in this case in the presence of SPINOL-derived phosphoric acid (*S*)-**SPA3** to afford cyclic amines **223** (Scheme 77, b)[204] in similar yields and enantioselectivities (70-93%, 50-93% ee). Remarkably, this synthetic protocol is also applicable to the addition of pyrroles with the same degree of efficiency.

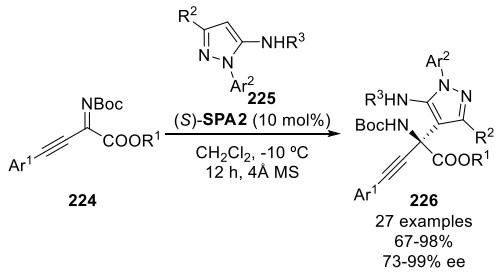


Scheme 77. Enantioselective addition of indole derivatives **151** to cyclic trifluoromethyl imines **221**.

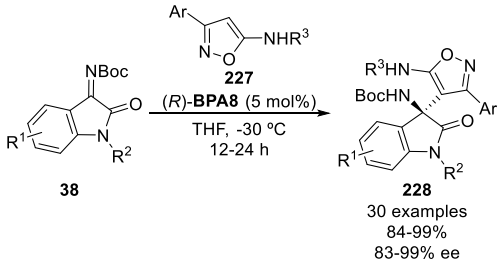
In late 2021, Lin and co-workers described the enantioselective functionalization of pyrazoles **225** to *C*-alkynyl substituted ketiminoesters **224** in the presence of (*S*)-**SPA2** organocatalyst (Scheme 78).[205] This transformation provides access to a broad scope of non-natural amino acid derivatives **226** in high yield (67-98%) and enantiomeric excesses up to 99%.

The same year, Zhang reported a CPA-catalysed addition of 5-aminoxazoles **227** to isatin-derived imines **38** using (*R*)-**BPA8** as the catalyst (Scheme 79).[206] The reaction implies the generation of tetrasubstituted chiral centres in excellent yield and enantiocontrol (84-99%, 83-99% ee) and is applicable to several substituted isatin-derived imines as well as a wide range of oxazoles. However, the presence of an alkyl group in the C-3 of the oxazole ring, results in a drastic drop of the enantiomeric excesses (53-69% ee), although chiral amines **228** were obtained in quantitative yields.

As previously shown for Friedel-Crafts reactions with aldimines, polyaromatic substituents at the CPA catalysts are widely used in this type of reaction when using ketimines, indicating that π-stacking effects may be involved in the transition state. However, some relevant differences should be appreciated. In contrast to aldimines, where tosyl, benzoyl and other large and sterically demanding protecting groups were the most common choice, fewer demandant groups such as Boc provide the optimal results in this section. Another strategy to minimize the steric demand of the imine is the use of endocyclic imines such as benzoxazin-2-ones or indol-3-ones. This suggests that less steric demand at the imine is required in order to obtain high stereocontrol. Unlike in the case of aldimines, predictive methods related to ketimines are limited, but the stereochemistry-determining step seems to be highly dependent on the imine substituent; potentially forcing Type II transition states when large *N*-substituents are used in endocyclic imines.



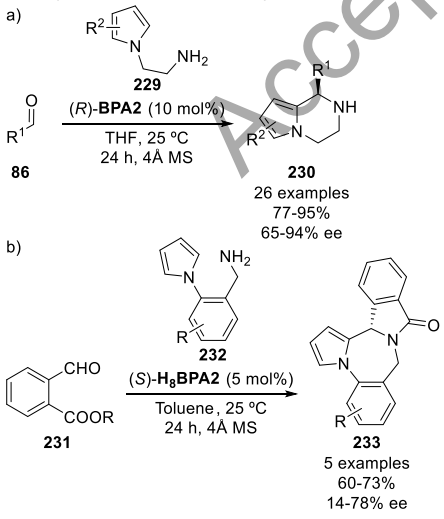
Scheme 78. Enantioselective addition of pyrazoles **225** to alkynyl imines **224**.



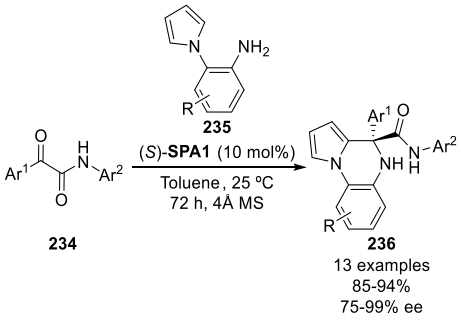
Scheme 79. Enantioselective nucleophilic addition of 5-aminoxazoles **227** to isatin-derived imines **38**.

3.3. Pictet-Spengler reaction

As a particular example of Friedel-Crafts reactions, some asymmetric Pictet-Spengler reactions have been developed using CPAs as catalysts. Regarding the Pictet-Spengler-type reactions with pyrrole derivatives, Antilla and co-workers reported in 2011 the asymmetric addition of pyrrole derivatives **229** to *in situ* generated *N*-alkyl aldimines, catalysed by (*R*)-**BPA2** (Scheme 80, a).[207] The reaction consists of an initial condensation of the amine moiety in **229** with aromatic or aliphatic aldehydes **86**, followed by an intramolecular addition of the pyrrole derivatives to the *in situ* formed imines. Chiral piperazine derivatives **230** were isolated in excellent yields and enantiocontrol (77-95%, 65-94% ee).



Scheme 80. Asymmetric intramolecular addition of pyrroles to aldimines.

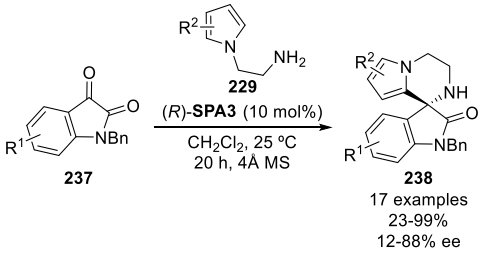


Scheme 81. Asymmetric intramolecular addition of pyrroles to ketimines.

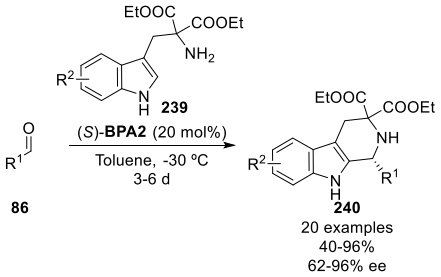
However, the use of 3 substituted pyrroles led to lower regioselectivity (up to 1.2:1 rr). More recently, Zhang and Jiang applied a similar strategy for the asymmetric synthesis of benzodiazepines **233**, using (*S*)-**H$_8$BPA2** as the catalyst (Scheme 80, b).[208] In this case, after the initial intramolecular addition of the pyrrole ring to the imine moiety, a tandem lactamization takes place, affording benzodiazepines **233** in moderate yield and stereocontrol (60-73%, 14-78% ee).

In 2015, Lin described the homologous reaction using activated ketones **234** and anilines **235** as starting materials and (*S*)-**SPA1** as the catalyst (Scheme 81).[209] The reaction proceeds in similar reaction conditions, delivering highly enantioenriched cyclic amino acid derivatives **236** in excellent yields and enantioselectivities (85-94%, 75-99% ee).

A similar intramolecular Friedel-Crafts reaction was reported by Chen et al (Scheme 82).[210] The initial condensation of the pyrrole-containing amines **229** with isatins **237** leads to the *in situ* formation of isatin-derived imines. Then, (*R*)-**SPA3** catalyses the intramolecular addition leading to the corresponding spirocyclic compounds **238** in moderate to good yields and enantioselectivities (23-99%, 12-88% ee).

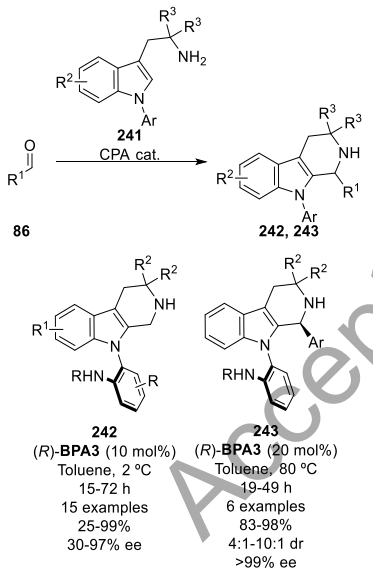


Scheme 82. Intramolecular arylation of isatin-derived imines with pyrroles **229**.

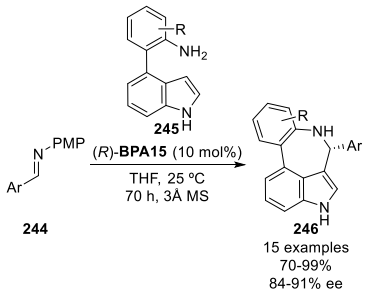


Scheme 83. First asymmetric Pictet-Spengler reaction of indoles **239** catalysed by a CPA.

Concerning reactions involving indole derivatives, in 2006, List reported for the first time the use of CPA-catalysts in an enantioselective Pictet-Spengler reaction (Scheme 83).[211] The reaction consists of an initial *in situ* condensation between tryptamine derivatives **239** and aldehydes **86**, followed by an (*S*)-**BPA2**-catalysed intramolecular functionalization of the indole moiety at C-2. The reaction was applied to several aliphatic aldehydes and a few aromatic aldehydes bearing strong electron-withdrawing groups to obtain indole-fused tetrahydropyridines **240** in yields up to 96% and high enantiocontrol (72-96% ee). However, the use of non-activated aldehydes **86** such as benzaldehyde resulted in a drop of the enantiomeric excess to 62%, even if 82% yield was obtained. Some of the main limitations of List´s report, such as the high catalyst loading required in the reaction (20 mol%), were successfully overcome by Lin and Wang in 2011,[212] using (*S*)-**SPA15** as the catalyst in a 2 mol% loading. In this case, they extended the reaction scope not only to aliphatic aldehydes but also to several aromatic and heteroaromatic aldehydes bearing both, EDG and EWG groups. Moreover, they were also able to perform the reaction at temperatures close to rt, making the reaction set up simpler while maintaining high yields and enantiocontrol (76-99%, 90-98% ee).



Scheme 84. CPA-catalysed atroposelective Pictet-Spengler reaction.



Scheme 85. Synthesis of 7-membered chiral heterocycles **246** through a CPA-catalysed Pictet-Spengler reaction.

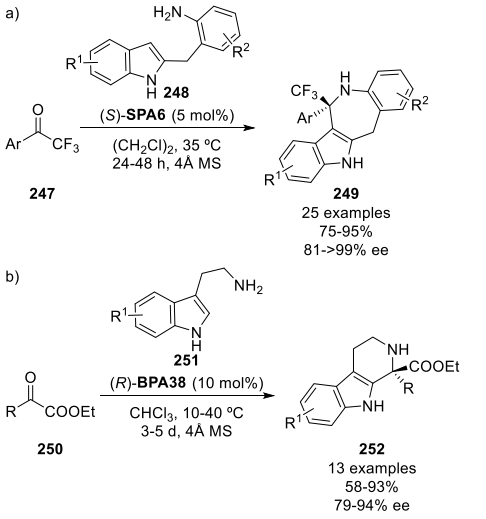
Following this strategy, in 2021, Kwon and co-workers reported a similar process using *N*-aryl protected tryptamine derivatives **241** and (*R*)-**BPA3** as the catalyst (Scheme 84).[213] In this case, a highly atroposelective reaction is described using paraformaldehyde and sterically hindered *N*-aryl groups. The intramolecular nucleophilic addition to formaldehyde-derived imine, again, limits the free-rotation of the *N*-aryl group, generating axially-chiral heterocycles **242** in yields up to 99% and enantiomeric excesses up to 97%. Moreover, they also evaluated the use of aromatic aldehydes in order to generate both, axial and central chirality. In this case, higher temperatures and catalyst loading are required, but optically pure products **242** are obtained in high yield, although the diastereomeric ratios are moderate (83-98%, 4:1 to 10:1 dr, >99% ee).

In 2011, Tian described another reaction on this topic.[214] In this case 4-(2-aminophenyl)-indole derivatives **245** and 4-methyoxyphenyl protected aromatic imines **244** were used as starting materials and (*R*)-**BPA15**, as the catalyst (Scheme 85). The reaction affords 7-membered ring-containing heterocycles **246** through an intramolecular functionalization of the indole with the *in situ* formed imine. Curiously, the initial transamination process was found to be very relevant in the reaction, since the use of aromatic aldehydes instead of *N*-PMP imines afforded lower enantiomeric excesses. For this reason, the authors assume that *p*-anisidine has some relevant role in the transition state that, somehow, can affect the stereochemistry of the final product. This methodology was found to be highly efficient, providing access to several fused indoles **246** in yields up to 99% and high enantiocontrol (84-91% ee).

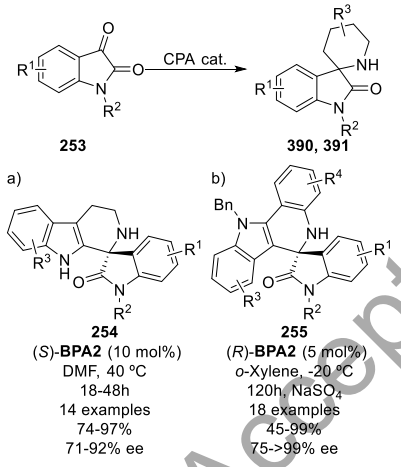
Regarding enantioselective Pictet-Spengler processes with activated ketimines, in 2014, Lin reported an asymmetric synthesis of 7-membered polycyclic molecules **249** through an intramolecular Friedel-Crafts reaction catalysed by (*S*)-**SPA6** (Scheme 86, a).[215] After the initial condensation of indole-containing aniline **248** with trifluoromethyl aryl ketones **247**, the asymmetric nucleophilic addition of indole to the highly reactive ketimine affords chiral polycyclic substrates **249** in excellent yield and enantiocontrol (75-95%, 81 to >99% ee). In a similar way, Nakamura *et al.* have recently published the enantioselective synthesis of **252** using triptamines **251** and aliphatic keto esters **250** as precursors (Scheme 86, b).[216] Using 10 mol% of (*R*)-**BPA38** as a chiral catalyst, they obtained piridoindole derivatives **252** in moderate to high yield (58-93%) and enantiomeric excesses up to above 79%. Moreover, when using isatin as the starting material, excellent yield and enantiocontrol was reported (90%, 99% ee).

Following this approach, in 2011, Bencivenni and co-workers reported the homologous process using isatin derivatives **253** (Scheme 87, a).[217] In this case, the use of 10 mol% catalyst loading of (*S*)-**BPA2** in the reaction, provided spirocyclic compounds **254** in high yield and enantiomeric excess (74-97%, 71-92% ee). In the same year, Franz described a similar reaction using 10 mol% of (*S*)-**BPA2**,[218] leading to the target spirocyclic substrates in quantitative yields and enantiomeric excesses up to 94%. More recently, Zhou has

described the synthesis of similar polycyclic indole derivatives **255** through a Pictet-Spengler process using in this case 2-(2-aminophenyl)-indoles and 5 mol% of catalyst (*R*)-**BPA2** (Scheme 87, b),[219] obtaining substrates **255** in yields and enantioselectivities up to 99%.



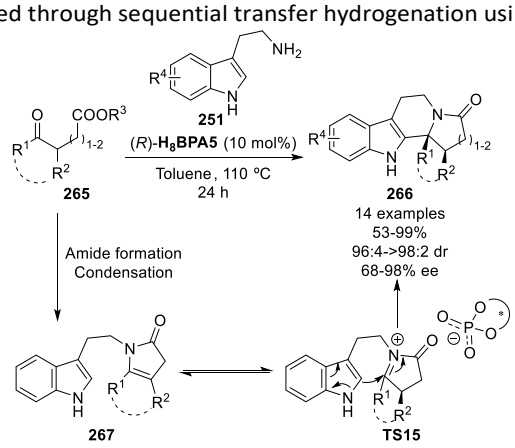
Scheme 86. Intramolecular asymmetric synthesis of heterocyclic amines.



Scheme 87. Enantioselective Pictet-Spengler reactions with isatin derivatives.

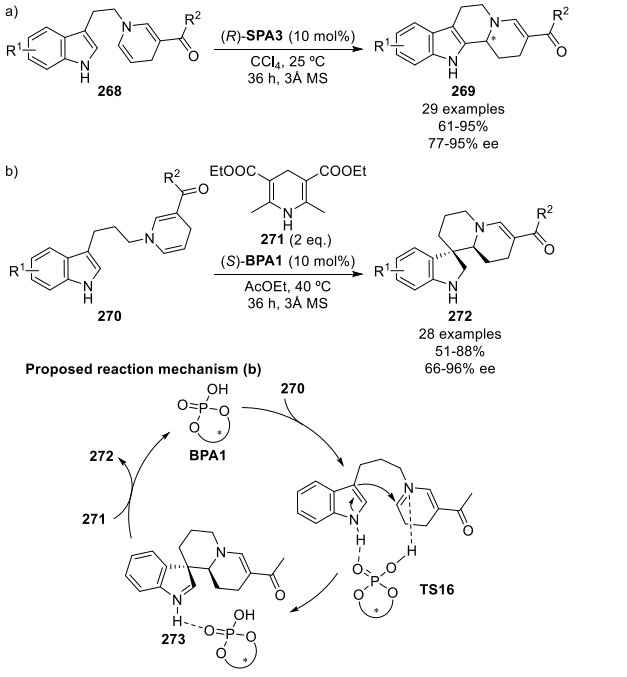
Dixon reported in 2010 an enantioselective cascade reaction involving an intramolecular Friedel-Crafts reaction (Scheme 88).[220] The initial amide formation/condensation step leads to the non-chiral enamine intermediate **267**. Then, the (*R*)-**H$_8$BPA5**-catalysed formation of the iminium ion intermediate promotes the intramolecular functionalization of the indole moiety as shown in transition state **TS15**, leading to polycyclic indole derivatives **266** in moderate to high yields and high stereocontrol (53-99%, >95:5 dr, 68-98% ee).

In 2017, You reported the (*R*)-**SPA3**-catalysed asymmetric Pictet-Spengler reaction of indolyl dihydropyridines **268** (Scheme 89, a).[221] The reaction leads to the formation of the polycyclic compounds **269** in high yields and enantiocontrol (61-95%, 77-95% ee). A few later, the same authors reported a similar reaction where the dearomatization of the indole ring is achieved through sequential transfer hydrogenation using



Scheme 88. Tandem enantioselective reaction involving a Friedel-Crafts process.

Hantzsch ester **271** as a hydrogen source (Scheme 89, b).[222] In this case, good yields and excellent enantiocontrol are also obtained (51-88%, 66-96% ee). Regarding the reaction mechanism, as in the previous example, the reaction may start with the isomerization of dihydropyridine **270**, followed by an intramolecular Friedel-Crafts addition of the indole species to the imine (**TS16**). After the formation of spirocyclic 3*H*-indole intermediate **273**, a hydrogen transfer occurs, affording spirocyclic compounds **272**. In both examples, the reaction tolerates the presence of EWG and EDG substituents at the indole ring but requires the presence of a EWG group at the enamine moiety, such as ketones or esters. Based on these reports, Xia´s group described an example of isomerization/dearomatization reaction using 2-substituted indoles as starting materials and 10 mol% of (*R*)-**SPA1** organocatalyst.[223] This strategy makes possible the enolization



Scheme 89. CPA-catalysed Pictet-Spengler reactions.

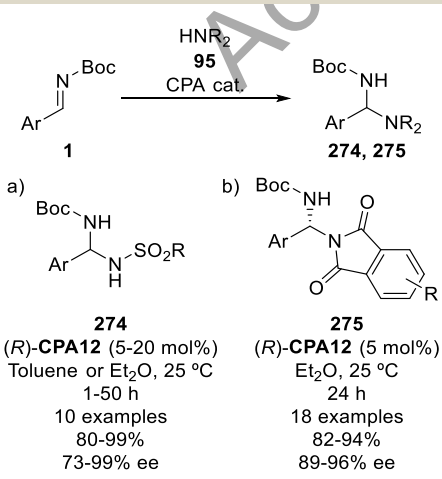
of the indolenine intermediate, interrupting the Pictet-Spengler pathway through the formation of more stable enamines.

As a particular case of intramolecular Friedel-Craft, similar tendencees can be observed for Pictet-Spengler reactions. In particular, these types of transformations have proved to be more effective when using large proximal 3,3´-substituted aromatic rigns, including fushed aromatic ringhs as well as bulky substituents containing phenyl rigns. The steric effect close to the phosphoric acid unit is, therefore, highly relevant in the transition state, but the abundance of polyaromatic groups also suggests the existence of relevant attractive interactions.

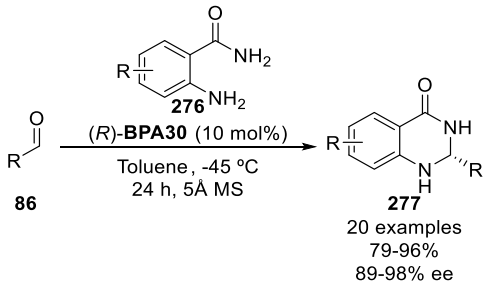
3.4. C-Heteroatom bond formation

During the last years, a few CPA-catalysed enantioselective additions of Nitrogen, Oxygen, Sulfur or Phosphorus nucleophiles to imines have also been reported. As a particular example of enantioselective C-heteroatom bond formation involving imines and CPA species, in 2005, Antilla reported the (*R*)-**CPA12**-catalysed synthesis of chiral *N*,*N*-acetals **274** through the nucleophilic addition of several sulfonamides **95** to *N*-Boc protected imines **1** (Scheme 90, a).[224] Surprisingly, VAPOL-derived (*R*)-**CPA12** was found as the optimal catalyst, even though it usually induces low enantiocontrol for C-C bond formation reactions, providing *N*,*N*-acetals **274** in yields and enantioselectivities up to 99%. Shortly after this report, the same authors also reported the nucleophilic addition of phthalimides to the imines **1** under similar reaction conditions (Scheme 90, b), obtaining *N*,*N*-acetals **275** in excellent yields and enantioselectivities (82-94%, 89-96% ee).[225]

Following Antilla's approach, List published in 2008 the formation of cyclic aminals **276** from aliphatic aldehydes **86**, catalysed by (*R*)-**BPA30** (Scheme 91).[226] In this example, the scope of the aldehyde substrate is limited to α-unbranched aliphatic aldehydes (80-94%, 93-98% ee), since α-branched or aromatic aldehydes show a drastic drop in the enantiocontrol (67-72%, 26-50% ee). Moreover, the authors also describe the use of isatin imines as electrophiles, obtaining high yield and enantiocontrol under similar reaction conditions (85%, 84% ee).



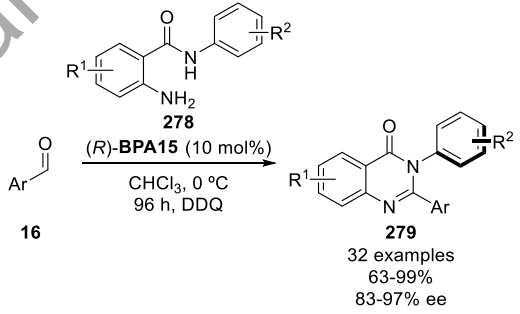
Scheme 90. Enantioselective addition of nitrogen based nucleophiles to aldimines **1**.



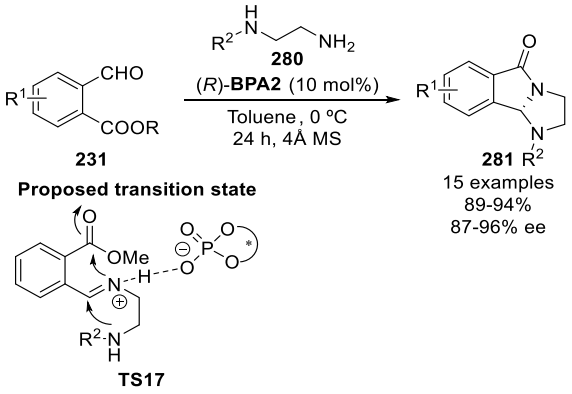
Scheme 91. Asymmetric synthesis of cyclic aminals.

Variations on the substitution in the aminobenzamides **277** afforded excellent results in all cases (79-96%, 92-98% ee). Further optimization of this reaction was performed by Rueping[227] and Tian [228] by using anthryl substituted (*R*)-**BPA15** catalyst, and by Lin[229] with an anthryl group bearing SPINOL analogue (*S*)-**SPA2**. This improvement extended the scope to aromatic aldehydes to deliver *N*,*N*-acetals **277** in high yields and enantioselectivities up to 99%.

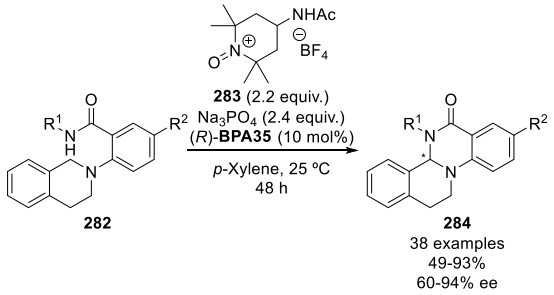
In 2017, Tan´s group published the synthesis of a wide number of axially-chiral arylquinazolinones **279** through a CPA-catalysed sequential reaction involving C-N bond formation (Scheme 92).[230] After the initial condensation of anilines **278** with aromatic aldehydes **16**, the nucleophilic addition of the amide to the imine moiety takes place, leading to the formation of a *N*,*N*-acetals intermediate, which is oxidised with DDQ.



Scheme 92. Atroposelective synthesis of quinazolin-4(3*H*)-ones **279**.



Scheme 93. Asymmetric synthesis of cyclic aminals.



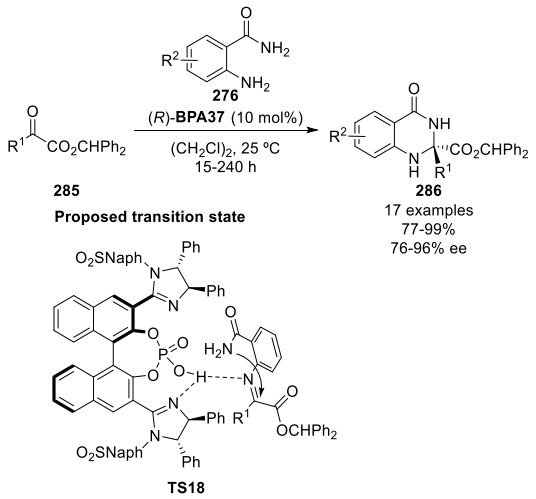
Scheme 94. Intramolecular synthesis of chiral aminals **284**.

Quinazolinones **279** are obtained in high yields (63-99%) and enantioselectivities up to 97% using (*R*)-**BPA15** catalyst. In addition, alkyl-substituted quinazolinones are also obtained with similar results by simple modifications of their synthetic protocol.

Another strategy for the CPA-catalysed asymmetric synthesis of chiral *N*,*N*-acetals was reported in 2014 by Qiu and co-workers (Scheme 93).[231] In this example, the synthesis of polycyclic molecules is reported through a tandem intramolecular *N*-functionalization/lactamization reaction (**TS17**) using in situ formed imines from aldehydes **231** and diamines **280** in the presence of a catalytic amount of (*R*)-**BPA2**. By means of this synthetic protocol, several tricyclic *N*,*N*-acetals **281** were obtained in excellent yields and enantiocontrol (89-94%, 87-96% ee). However, the substitution in the *ortho* position of the aldehyde had an adverse effect on the enantiocontrol, with a drop on the ee of 30%, even if 92% yield was obtained.

In recent years, this transformation has been applied to more challenging reaction substrates. For instance, Toste reported an enantioselective intramolecular C-N bond construction through the nucleophilic addition of oxopiperidinium salts **283** to *in situ* generated isoquinolinium ions derived from tetrahydro-*iso*-quinolines **282** (Scheme 94).[42] In this case, triazole substituted (*R*)-**BPA35** was found to be the optimal catalyst, providing polycyclic *N*,*N*-acetals **284** in moderate to high yields and enantioselectivities (38-93%, 60-94% ee). The authors do not report the absolute configuration of the reaction products. The scope includes several secondary benzamides bearing aromatic, benzylic or aliphatic substituents with no significate effect in terms of reactivity or selectivity. However, the consequences of the substitution at the isoquinoline moiety was not evaluated.

In 2020, Nakamura reported the synthesis of *N*,*N*-acetals **286** using (*R*)-**BPA37** catalyst, from α-ketoesters **285** and 2-aminobenzamides **276** as reactants, thus, generating a tetrasubstituted chiral centre (Scheme 95).[232] The use of electron-donating and electron-withdrawing groups in 2-aminobenzamides furnished substrates **286** in excellent yield and enantioselectivities (77-99, 82-96% ee). In addition, the use of several aromatic substituted α-ketoesters **285** provided the target products in very good yields and high enantiocontrol (77-95%, 85-95% ee). However, the use of methyl-substituted α-ketoesters **285** (R^1 = Me) resulted in a slight decrease in the enantioselectivity (95%, 76% ee).

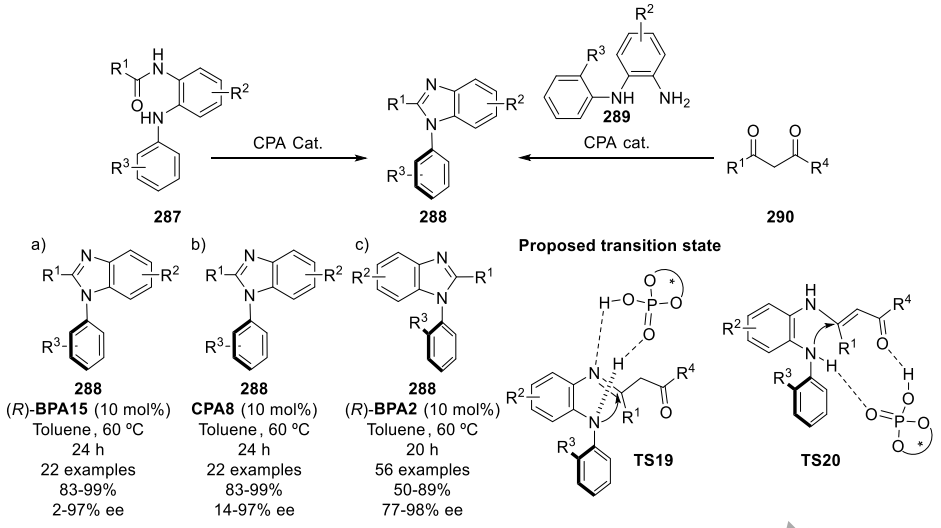


Scheme 95. Enantioselective synthesis of dihydroquinazolin-4(1*H*)-ones.

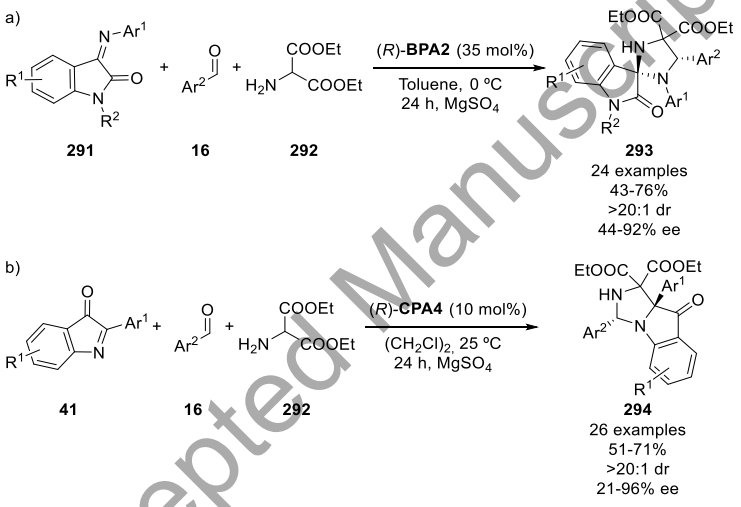
The authors also extended the scope of the reaction using *N*-benzyl isatines, as well as benzylcarboxaldehyde, and benzaldehyde as electrophiles, obtaining moderate yields and excellent enantiomeric excesses (58-94%, 91-93% ee). In the tentative transition state for this enantioselective reaction (**TS18**), (*R*)-**BPA37** enhances the electrophilicity of ketimine, obtained from the reaction of pyruvate **285** with amide **276**, by hydrogen bonding. Then, the amide group attacks the *Re*-face of the ketimine moiety, avoiding the steric hindrance with the phenyl group on the imidazoline, thus affording the enantioenriched *N*,*N*-Acetals **286**.

In 2019 Sigman, Toste and Miller described a new methodology to access axially-chiral benzimidazoles **288** starting from formamides **287** using (*R*)-**BPA15** or peptide-derived **CPA8** as catalysts (Scheme 96, a-b).[233] The use of the phosphoric acid catalyst (*R*)-**BPA15**, provided benzoimidazoles **288** in a wide range of enantiomeric excess (2-97% ee). The authors noticed that worse results are obtained when a nitrogen atom is present at the diamine substituted aromatic ring and formamides **287** (R^2 = H) are used as substrates (Scheme 121, a), proving that the presence of bulky groups at this position favours the enantiocontrol. On the other hand, the results obtained with peptidic catalyst **CPA8** are pretty similar (14-97% ee), also observing that R^2 substituent is essential to obtain high enantioselectivities.

One year later, Fu and co-workers reported the asymmetric synthesis of benzoimindazoles **288** using *N*1-(aryl)benzene-1,2-diamines **289**, 1,3-dicarbonylic compounds **290** and catalyst (*R*)-**BPA2**, obtaining in all cases good yields and high enantioselectivities (50-88%, 77-96% ee) (Scheme 96, c).[234] The authors also extended the reaction, to the use of a couple of cyclic β-dicarbonyl compounds, methyl or ethyl 2-oxocyclopentanecarboxylates as electrophiles, obtaining substrates **288** in good yields and higher enantiomeric excesses (65-89%, 93-98% ee). The author's proposal for the reaction pathway consists of an initial condensation of diamines **289** and 1,3-dicarbonylic derivatives **290**. Then, two possible transition states are hypothesised, both leading to benzoimidazoles **288**. One of the plausible reaction pathways consists of the



Scheme 96. Atroposelective synthesis of benzimidazoles **288**.



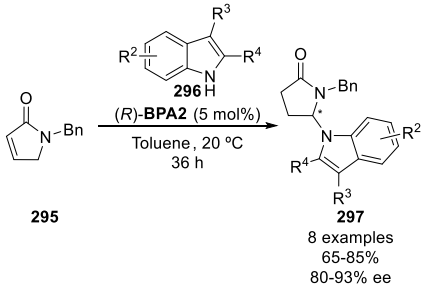
Scheme 97. Enantioselective 3+2 dipolar reactions with imines.

nucleophilic attack of the diarylamine **289** to the *in situ* formed iminic species through transition state **TS19**. The other proposed possibility may consist of the isomerization of the *in situ* formed imine, generating an α,β-unsaturated ketone for a subsequent aza-Michael addition (**TS20**).

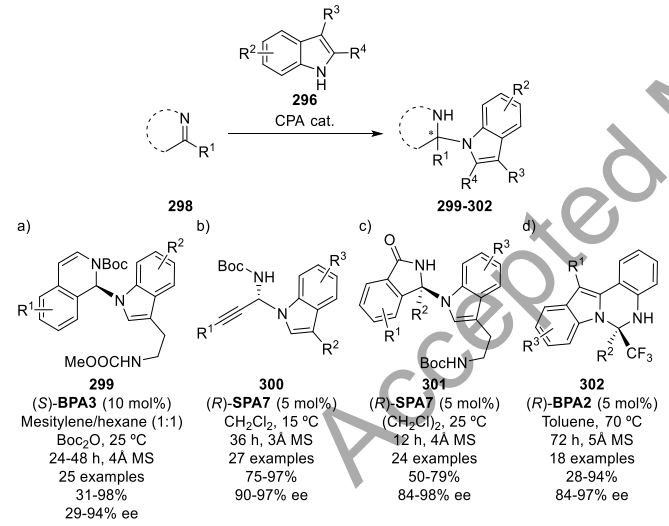
In 2016, Shi´s group reported the synthesis of chiral imidazolidines **293** by using *in situ* formed imines derived from aldehydes **16** and diethyl 2-aminomalonates **292**, in the presence of an isatin-derived imine **291** and 35 mol% of CPA-catalyst (*R*)-**BPA2** (Scheme 97, a).[235] The reaction is assumed to start with the addition of the 1,3-dicarbonyl moiety of **292** to the isatin imines, followed by the addition of the newly formed amine to aryl imine. In this way, the synthetic protocol affords the spirocyclic derivatives **293** as a single diastereoisomer in moderate yields (43-76%, >20:1 dr) and enantioselectivities up to 92%. Following a similar approach, Fu and co-workers reported a similar sequential reaction using 3-oxo-indolenines **41**, aldehydes **16** and diethyl 2-aminomalonate **292** as starting materials (Scheme 97, b).[236] In this case, they used a newly developed chiral CPA catalyst (*R*)-**CPA4** in the reaction, providing a single diastereoisomer of polycyclic imidazolidines **294** in moderate yields (51-71%) and enantioselectivities up to 96%.

On the other hand, some examples of *N*-functionalization of indole scaffolds have been developed by several authors. The CPA-catalysed *N*-substitution of indoles was reported by Huang in 2011 (Scheme 98).[237] The use (*R*)-**BPA2** as the catalyst promoted the isomerization of the conjugated γ-lactam **295** into the corresponding iminium ion, acting as an electrophile in the reaction. Curiously, even the use of 3-unsubstituted indoles **296** afforded the *N*-substitution products **297** in good yields (65-85%) and with enantiomeric excesses up to 93%. In 2018, You´s group reported the (*S*)-**BPA3**-catalysed addition of an indolic nitrogen to isoquinolinium ions (Scheme 99, a),[238] leading to the formation of optically active dihydroisoquinolines **299** in moderate to good yields and enantiocontrol (31-98%, 29-94% ee). In order to avoid the C-3 functionalization, tryptamine derivatives are used as nucleophiles. In addition, an example

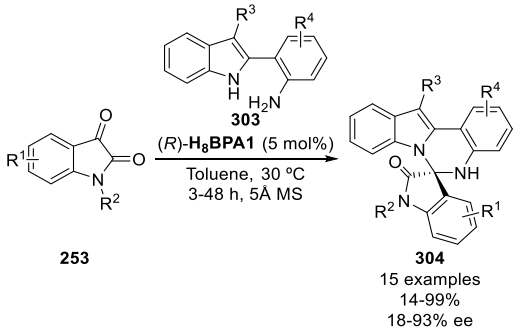
using simple 3-methyilndole as a nucleophile is also described, obtaining the target product **299** in high yield and enantiocontrol (98%, 85% ee). More recently, Wang´s group described the asymmetric synthesis of *N*-propargyl aminals **300** starting from *in situ* prepared propargylimines (Scheme 99, b).[239] The reaction in the presence of 5 mol% of catalyst (*R*)-**SPA7** affords *N*-functionalised-indoles **300** in excellent yields and enantioselectivities up to 97% ee. Following this approach, Zhong and co-workers reported the *N*-alkylation of *in situ* generated cyclic *N*-acyl ketimines **301** (Scheme 99, c).[240] The use of (*R*)-**SPA7** as a chiral catalyst afforded chiral indoles **301** bearing a tetrasubstituted carbon in good yields (50-79%) and enantioselectivities above 84% ee. In the same year,



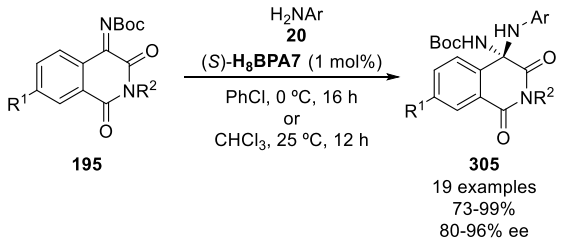
Scheme 98. Enantioselective *N*-functionalziation of indoles **296** with γ-lactams.



Scheme 99. Enantioselective *N*-functionalisation of indoles with imines.



Scheme 100. Enantioselective *N*-alkylation of indoles with isatines **253**.



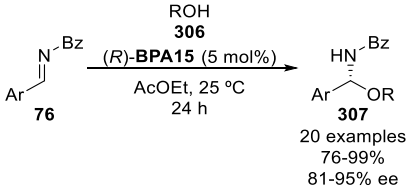
Scheme 101. Enantioselective synthesis of N,*N*-aminals **305**.

Zhou´s group described a sequential condensation/intramolecular *N*-alkylation of indoles (Scheme 99, d).[241] In this case, they used 2-(2-aminophenyl) substituted indoles that condensate with trifluoromethyl ketones. Then, the intramolecular addition of indolic nitrogen promoted by catalyst (*R*)-**BPA2** affords polycyclic molecules **302** bearing a quaternary chiral stereocentre in variable yields (28-94%) and enantioselectivities from 84 to 97% ee. Remarkably, they also reported the use of 3-*H* indoles in the reaction, obtaining similar results (74%, 88% ee).

In 2021, Zhou described an intramolecular *N*-alkylation of indoles with isatin-derived imines catalysed by (*R*)-**H$_8$BPA1** obtaining spirocycles **304** (Scheme 100).[242] In most of the cases, the *N*-substitution is favoured against the intramolecular Friedel-Craft addition, even when 3-unsubstituted indoles **303** are used. However, the regioselectivity is found to be highly dependent on the substituents in both, isatin **253** and aniline derivatives **303** (1:3.3 to 13.8:1 dr). In consequence, no clear tendencies were observed on the yield or the enantiomeric excesses (14-99%, 18-93% ee).

In the same year, Li and co-workers reported the addition of arylamines **20** to ketimines **195** catalysed by (*S*)-**H$_8$BPA7** (Scheme 101).[243] The reaction affords *N*,*N*-acetals **305** in yields up to 99% and enantiomeric excesses ranging from 80 to 96% in most cases. As a limitation, *ortho*-hindered arylamines such as 1-naphthylamine have adverse effects on the stereocontrol (73%, 12% ee), and the use of alkylamines as nucleophiles produces the racemic product in excellent yield (95%, 0% ee). On the other hand, strongly deactivated arylamines such as 3-aminopyridine are unreactive in these reaction conditions.

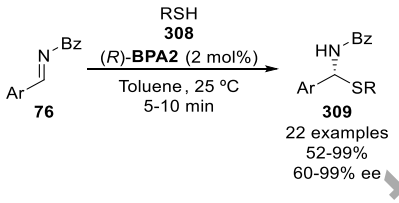
Regarding the CPA-catalysed nucleophiic addition to imine species involving C-O bond formation, in 2008, Antilla reported the synthesis of *N*,*O*-acetals **307** through the addition of alcohols **306** to aromatic aldmines **76**, catalysed by (*R*)-**BPA15** (Scheme 102).[244] The reaction is applicable to simple aliphatic or benzylic alcohols **306**, obtaining excellent yields (76-99%) and enantioselectivities up to 95% ee. The reaction also furnishes



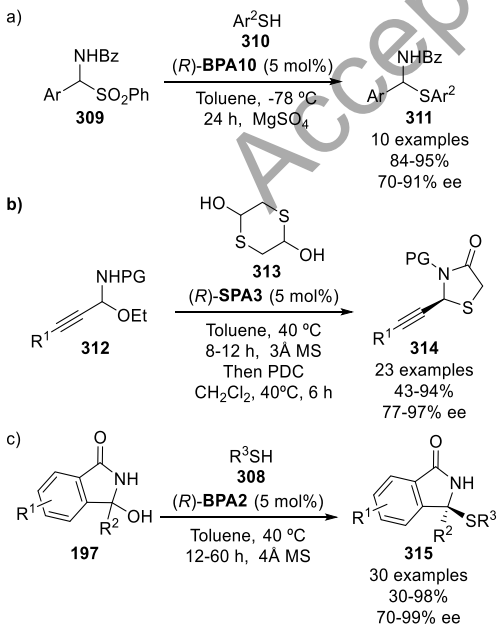
Scheme 102. Enantioselective synthesis of *N*,*O*-acetals.

the expected *N*,*O*-acetals if aliphatic aldimines are used, although lower yields and enantiocontrol are obtained in this case (62%, 65% ee). This decrease in the enantiocontrol seems to indicate that the steric demand at the imine substrate is inverted when aliphatic aldehydes are used, making the benzoyl protecting group more sterically demanding than the alkyl group from the aldehyde and, thus, favouring different orientations of the imine with respect to the catalyst. Using a similar approach, in 2010, the same authors extended the reaction to the addition of organic hydroperoxides to *N*-benzoyl aromatic imines with excellent yields and enantioselectivity (75-92%, 89-98% ee).[245]

Besides, in regard to CPA-catalysed reactions that imply C-S bond formation, Antilla reported in 2011 a highly enantioselective synthesis of *N*,*S*-acetals through the addition of thiols **308** to aromatic aldimines **76** in the presence of 2 mol% of (*R*)-**BPA2** as the catalyst (Scheme 103).[246] The reaction proved to be extremely fast, providing *N*,*S*-acetals **309** in 5 to 10 minutes. Moreover, a high tolerance was observed in the scope of thiol species, obtaining, in most cases, yields above 75% and 95 to 99% enantiomeric excesses. However, the use of 3,5-trifluoromethyl thiol (**308**, R = CF_3) results in a drop in the enantiocontrol to a 60% ee even if the reaction yield is still high (91%). Remarkably, the authors also reported the direct addition of sulfide at -78ºC, obtaining a lower yield but excellent stereocontrol (52%, 99% ee).



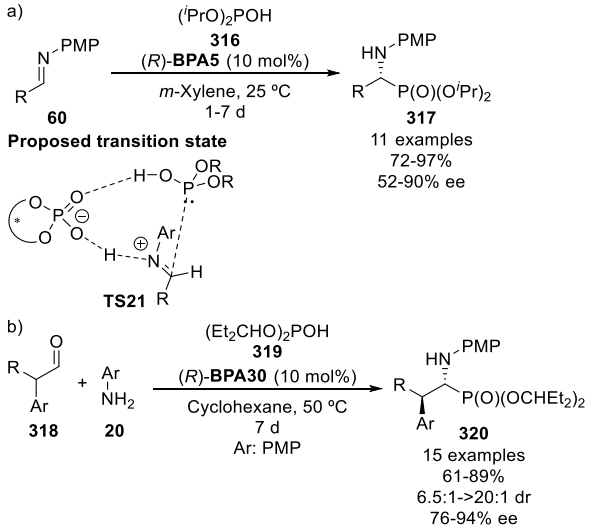
Scheme 104. Enantioselective synthesis of *N*,*S*-acetals.



Scheme 105. Enantioselective formation of C-S bond with *in situ* formed imines.

A few years later, Guo and co-workers reported a few examples of the (*R*)-**BPA10**-catalysed nucleophilic addition of thiophenols **310** to *in situ* generated non-cyclic aldimines derived from sulfonylamines **309**, affording the target *N*,*S*-acetals **311** in good yields and enantiocontrol (84-95%, 70-91% ee) (Scheme 105, a).[247] More recently, Shao´s group published a synthetic protocol to provide access to optically active thiazolidones **314** starting from *N*,*O*-propargyl acetals **312** and diols **313**, using (*R*)-**SPA3** as the catalyst, obtaining moderate to high yields (43-94%) and enantioselectivities up to 97% ee (Scheme 105, b).[248] Moreover, in 2017 Singh´s group reported the synthesis of *N*,*S*-ketals **315** through the nucleophilic addition of thiols **308** to endocyclic ketimines, generated *in situ* from 3-hydroxyisoindolinones **197** (Scheme 105, c).[249] The reaction, using (*R*)-**BPA2** catalyst, tolerates several alkyl, aryl and benzyl thiols, as well as α-thioesters, obtaining cyclic *N*,*S*-ketals **315** in yields up to 98% and enantioselectivities up to 99% ee.

With respect to CPA-catalysed reactions involving C-P bond formation, in 2005, Akiyama developed an enantioselective (*R*)-**BPA5**-catalysed hydrophosphonylation of aldimines **60**, leading to the formation of enantioenriched di-*iso*-propyl α-aminophosphonates **317** (Scheme 106, a).[250] The reaction was found to be highly dependent on the size of the phosphite **316**, since the use of less bulky diethyl phosphite resulted in a drop of both, the yield and enantioselectivity (^{i}Pr: 92%. 88% ee; Et: 70%, 73% ee). The scope of the substituent at the imine substrates was extended to several aryl and styryl groups, affording the corresponding α-aminophosphonates in high yields and stereocontrol (72-97%, 52-90% ee). A few years later, this reaction was extended to the synthesis of fluorine-containing α-aminophosphonates by Song and co-workers,[251] obtaining chiral aminophosphonates with enantiomeric excesses ranging from 23 to 90% in presence of (*R*)-**BPA5**-catalyst. In addition, Lin improved the enantiomeric excesses of this transformation up to 98% by using (*R*)-**SPA17** as a catalyst.[252]



Scheme 106. Enantioselective hydrophosphonylation reactions.

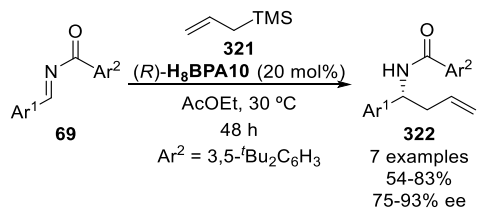
Moreover, Akiyama, Yamanaka and Shi, in 2009, described DFT studies in order to further understand the origins of the enantioselectivity for this transformation,[253–255] showing a bifunctional activation of the dialkyl phosphite and the imine by the CPA-catalyst (**TS21**). Based on those reports, List reported in 2009 the (*R*)-**BPA30**-catalysed multicomponent Kabacnick-Fields reaction of α-branched aldehydes **318**, *p*-anisidine, and 3-pentyl substituted dialkylphosphite **319** (Scheme 106, b).[256] This reaction provides several enantioenriched aminophosphonates **320** in good yields and stereocontrol when branched alkyl groups, such as cyclopentyl or isopropyl, are present in the aldehyde (61-89%, 6.5:1 to >20:1 dr, 76-94% ee). However, non-branched alkyl groups, such as ethyl or methyl, afford the target α-aminophosphonates with low stereocontrol (63-84%, 1.5:1 to 3:1 dr, 2-84% ee).

It is interesting to note that, although most of the C-het bond formation with imines involves the use of large proximal substituents in the catalyst, the addition of phosphorus nucleophiles is mostly driven by remote substitution of 3,3´ aryl groups. Although this does not affect the preferred TS for aldimines with symmetrical nucleophiles, (Type I E) it may indicate that bulky phosphites are more sterically demanding if compared with alcohols, thiols or amines, resulting in a higher repulsive effect when large substituents are close to the phosphoric acid moiety.

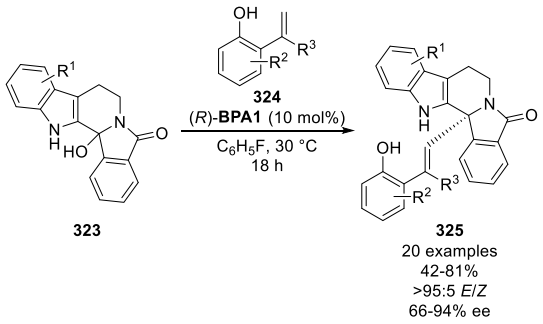
3.5. Miscellaneous reactions

In 2011, Momiyama and Terada reported the (*R*)-**H_8BPA10**-organocatalysed Hosomi-Sakurai reaction of aromatic imines **69** and allylsilanes **321** (Scheme 107).[257] Although a high catalyst loading is required, the obtained yields of the addition substrates **322** were found to be moderate in most cases (54-83%). However, the resulting amides were obtained with high enantiocontrol (75-93% ee). Moreover, the use of methyl-substituted allyltrimethylsilanes afforded the corresponding product holding two vicinal chiral centres with very high stereocontrol (80%, 93:7 dr, 95% ee).

In addition, in 2014, Shi and co-workers reported a metal-free formal alkenylation reaction of *in situ* formed iminium ions derived from indoles **323** (Scheme 108).[258] The authors used 2-hydroxystyrenes **324** as alkenyl source for the vinylogous addition in the presence of (*S*)-**BPA1** as the catalyst. Remarkably, the reaction worked with high selectivity, affording predominantly the *E* alkene of adduct **325** (>95:5 *E*/*Z*). Although moderate to good isolated yields were observed (42-81%), the enantiomeric excesses were found to be up to 94%.



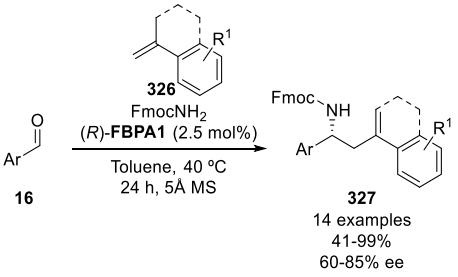
Scheme 107. Organocatalysed Sakurai reaction with imines **69**.



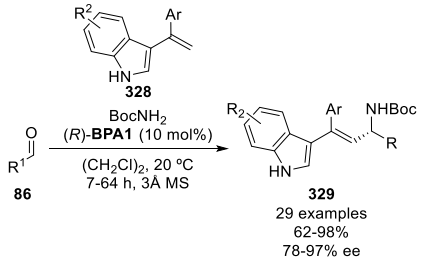
Scheme 108. CPA-catalysed enantioselective addition to *in situ* formed iminium ions.

One year later, Terada and co-workers reported ene-reactions of aromatic imines, generated *in situ* from aldehydes **16**, with styrene derivatives **326** (Scheme 109).[259,260] They compared perfluorinated BINOL-derived phosphoric acid catalysts and non-fluorinated BPA catalysts in the reaction, proving that the perfluorinated species provided a higher enantiocontrol in the reaction. Thus, using only 2.5 mol% of (*R*)-**FBPA1** catalyst, Fmoc-carbamates **327** were obtained in yields up to 99% and enantioselectivities ranging from 60 to 85% ee. These fluorinated catalysts allow avoiding the use of additional lewis acids, as it has been reported for similar transformations in which the sole use of a chiral phosphoric acid gives unsatisfactory results.[261,262]

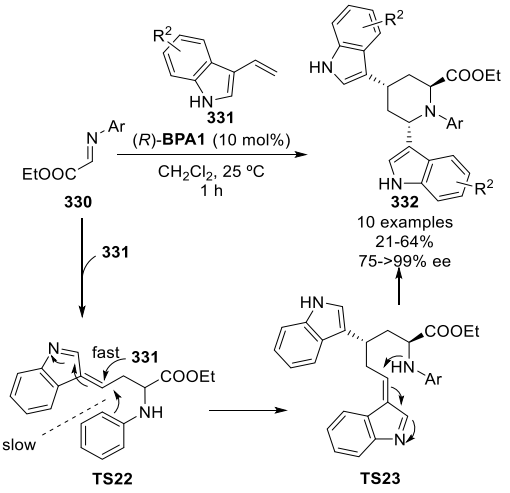
The addition of 3-vinyl indoles **328** to *in situ* generated *N*-Boc aldimines catalysed by BINOL-derived phosphoric acid (*R*)-**BPA1** was reported by Guo and co-workers (Scheme 110).[263] The reaction tolerates the presence of both, aromatic and aliphatic aldehydes **86**, as well as several EDG and EWG substituents in the indole and aromatic moieties of the vinyl indoles, providing a wide scope of chiral *N*-Boc amines **329** in high yields and enantiocontrol (62-98%, 78-97%).



Scheme 109. Enantioselective ene-reaction with *N*-Fmoc protected aldimines.



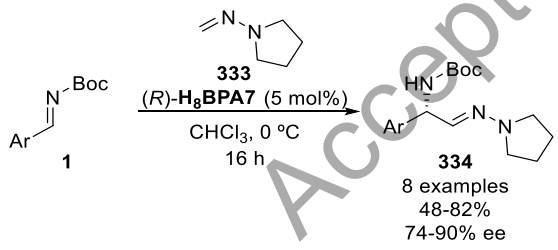
Scheme 110. Vinylogous addition of vinyl indole derivatives **328** to aldimines.



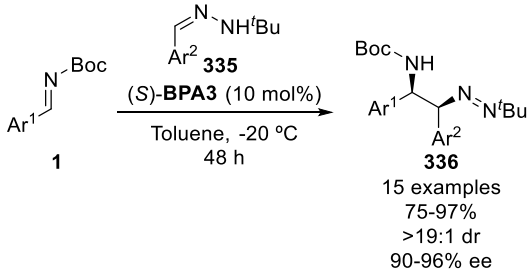
Scheme 111. Multicomponent reaction of vinylindoles and imines for the synthesis of chiral piperidines.

Using a similar approach, Bräse reported in 2014 the (*R*)-**BPA1**-catalysed asymmetric synthesis of chiral piperidines **332** (Scheme 111).[264,265] The initial vinylogous addition of vinyl indoles **331** to the imine **330** leads to an azafulvene intermediate, here, the addition of a second molecule of the vinylindole species competes with the slower Povarov pathway (**TS22**). Finally, the new azafulvene is trapped by the amine (**TS23**), leading to a single diastereoisomer of highly enantioenriched piperidines **332** in moderate yields but very good enantioselectivity (21-64%, 75-99% ee).

In 2007 Rueping reported the (*R*)-**H$_8$BPA7**-catalysed nucleophilic addition of methylene hydrazines **333** to *N*-Boc protected imines **1** (Scheme 112),[266] obtaining chiral β-amino hydrazines **334** in moderate to good yields and enantiocontrol (48-82%, 74-90% ee).



Scheme 112. Enantioselective addition of methylene hydrazines **333** to imines **1**.



Scheme 113. Highly enantio and diastereoselective synthesis of vicinal diamines **336**.

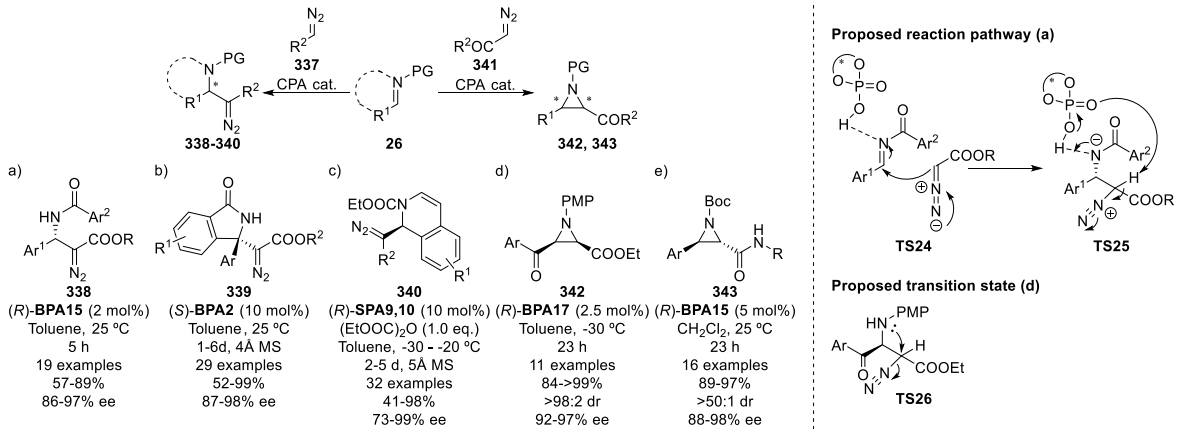
Following a similar approach, in 2017, Zhu´s group dscribed the synthesis of enantioenriched vicinal diamines using (*S*)-**BPA3** as organocatalyst (Scheme 113).[267] In this case, the addition of hydrazones **335** to arylimines **1** afforded optically active 1,2-diamines **336** as a single diastereoisomer in high yields (75-97%, >19:1 dr) and enantioselectivities above 90%.

In addition, Terada's group reported the CPA-catalysed addition of α-diazo esters to imines (Scheme 114, a).[268] The activation of the imine **171** by (*R*)-**BPA15**, through the formation of a hydrogen bond, allows the stereoselective addition of diazo ester species **337** through transition state **TS24**. The acidic media prevents the side aza-Darzens reaction, restoring the diazo group as shown in **TS25**. The authors reported several additions to imines **26**, providing α-chiral amines **338** in moderate to good yields and high stereocontrol (57-89%, 86-97% ee). A few years later, Peng's group published the analogue reaction using α-diazo phosphonates. In this case, the reaction is performed at lower temperatures using (*R*)-**BPA2** as a catalyst.[269] Remarkably, using only 0.1 mol% loading of (*R*)-**BPA2**, excellent yields are obtained (84-97%) with enantioselectivities above 92% ee. The use of 2-substituted aromatic imines results in a relevant drop of the reactivity, although the stereoselectivity is not affected (52-55%, 97-98% ee).

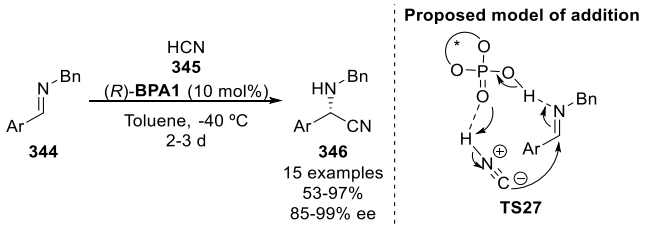
Using a similar strategy, and (*S*)-**BPA2** as organocatalyst, Unhale *et al.* reported in 2018 the addition of α-diazo esters **337** to *in situ* generated endocyclic imines **26** derived from 3-hydroxyisoindolinones (Scheme 114, b).[270] Following that methodology, a wide scope of isoindolinones **339** bearing a tetrasubstituted chiral centre was reported, obtaining yields up to 99% and enantiomeric excesses above 87%.

An additional example of the enantioselective addition of diazomethane derivatives **337** was recently published by Peng´s group for the dearomatization of isoquinolines (Scheme 114, c).[271] The initial reaction of isoquinolines with an anhydride leads to the protection of the nitrogen atom in isoquinoline ring, through the formation of the *N*,*O*-acetal. Then, either (*S*)-**SPA9** or (*S*)-**SPA10** catalysts promote the elimination of the alcohol and thus, the formation of an isoquinolinium ion, which reacts with diazomethane **337** leading to the formation of optically active dihydroisoquinolines **340** in moderate to good yields and high enantiocontrol (41-98%, 73-99% ee).

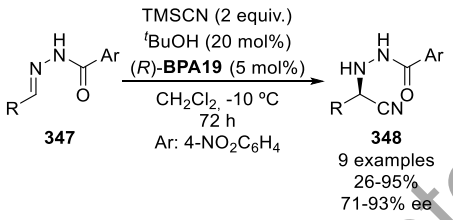
In 2009, Akiyama and Zhong simultaneously reported the enantioselective CPA-catalysed aza-Darzens reaction (Scheme 114, d-e).[272,273] Akiyama used *in situ* formed imines **26** from anisidine and aldehyde hydrates as electrophiles in the presence of diazoesters **341** (R^2= OEt) and catalyst (*R*)-**BPA17**. Unlike the above-mentioned additions of diazoesters to imines (Scheme 114, a-c), the reaction conditions favoured the subsequent intramolecular cyclization reaction, leading to chiral *syn* aziridines **342** through transition state **TS26** in excellent yields and enantiomeric excesses (84-99%, >98:2 dr, 92-97% ee). On the other hand, Zhong described a similar reaction using *N*-Boc protected aromatic imines **26** (PG = Boc), diazoamides **341** (R^2= NHR) and (*R*)-**BPA15** catalyst, obtaining excellent yield and stereocontrol (89-97%, >50:1 dr, 88-98% ee).



Scheme 114. Enantioselective reaction of diazoesters to imines **26**.



Scheme 115. First CPA-catalysed asymmetric Strecker reaction.



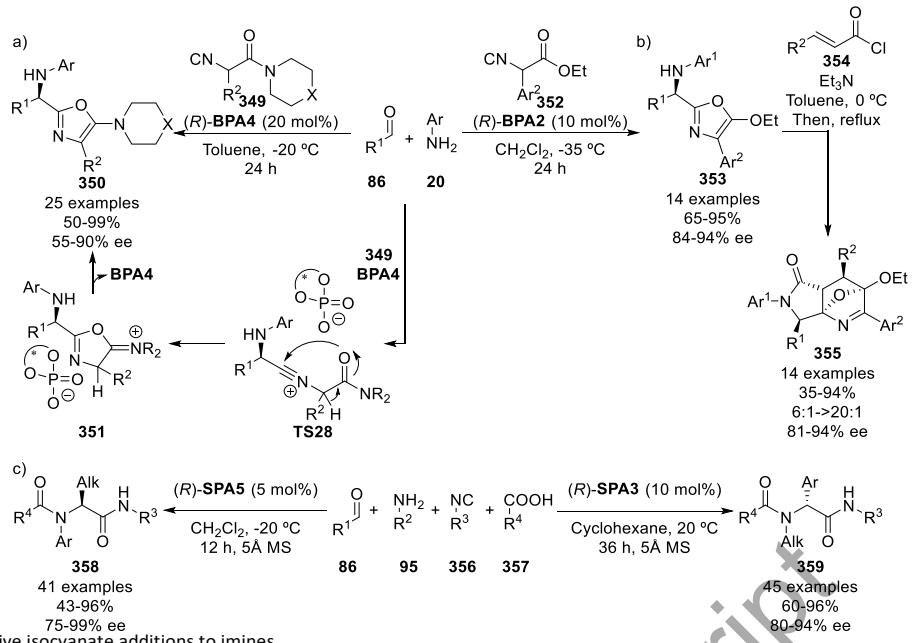
Scheme 116. Asymmetric Strecker reaction using TMSCN as cyanide source.

The Strecker reaction has been widely used in organic synthesis to access α-amino acid derivatives.[274] Regarding the applications of CPA catalysts in this transformation, Rueping reported in 2006 the first enantioselective hydrocyanation of aldimines **344** catalysed by (*R*)-**BPA1** (Scheme 115).[275] The reaction provides the corresponding α-aminonitriles **346** in variable yields (53-97%), but with enantiomeric excesses above 85% in all cases. In addition, they were also able to extend this transformation to the use aryl methyl ketimines with similar yields but lower enantiocontrol (69-95%, 56-80% ee).[276] In order to further understand the reaction mechanism, Goodman described a DFT analysis of the reaction, theorizing a bifunctional activation of hydrogen cyanide and the imine by the catalyst as the most plausible reaction mechanism (**TS27**).[277]

In 2009, Tsogoeva´s group reported a similar Strecker process, using in this case less electrophilic hydrazones **347** (Scheme 116).[278] In this example, the use of hazardous hydrogen cyanide is avoided by using TMSCN as the cyanide source. Remarkably, the addition of a catalytic amount of *tert*-butanol contributes to the maximization of the yield, allowing to increase it up to 95% while keeping enantiomeric excesses above 71% ee. Following a similar approach, Ma described the racemic version of a CPA-catalysed multicomponent Strecker reaction involving ketones, aniline derivatives and TMSCN.[279] Although yields above 80% are reported, the enantioselective version of this reaction in presence of chiral (*R*)-**BPA1** catalyst only affords enantiomeric excesses up to 40% ee. Although is nos strictly an organocatalyzed transformation, in 2009, Feng and coworkers published a closely related Strecker reaction with ketimines. In this case, they used a CPA-derived sodium phosphate catalyst, obtaining chiral α-amino nitriles in yields ranging 88-95% and enantioselectivities above 79%.[280]

On the other hand, the Ugi reaction is an efficient multicomponent process leading to peptidemimetic derivatives from readily available starting materials.[104,281] This transformation has a great interest in organic and medicinal chemistry, as well as for the pharmaceutical industry. Regarding the CPA-catalysed enantioselective Ugi-type reactions, Zhu´s group published in 2009 an asymmetric reaction involving isocyanides **349**, aldehydes **86** and anilines **20** (Scheme 117, a).[282] The three-component reaction provides access to chiral oxazoles **351** in moderate to high yield and moderate enantiocontrol (50-99%, 55-90% ee) in the presence of 20 mol% of (*R*)-**BPA4**. According to the authors, after the initial asymmetric addition of the isocyanide **349** to the *in situ* generated *N*-aryl imine, a subsequent intramolecular cyclization leads to intermediate **351** (**TS28**), which rapidly evolves to adducts **350**, regenerating the phosphoric acid catalyst in the process. Using the same strategy, they also used isocyanides **352**, containing an ester moiety, for the synthesis of oxazoles **353** in presence of (*R*)-**BPA2** catalyst (Scheme 117, b),[283] obtaining, in this case, better enantioselectivity (65-95%, 84-94% ee). Moreover, the *in situ* protection of chiral amines with cinnamyl chlorides **354**, followed by high reaction temperatures, afforded polycyclic molecules **355** in yields up to 94% and high stereocontrol (6:1 to >20:1 dr, 81-94% ee).

In 2018, Tan´s group reported a highly enantioselective four-component Ugi reaction between aldehydes **86**, amines **95**, isocyanides **356** and carboxylic acids **357** (Scheme 117, c),[284] which was unconquered up to the date.[281] The use of SPINOL-



Scheme 117. Enantioselective isocyanate additions to imines.

derived phosphoric acid catalysts (*R*)-**SPA5** and (*R*)-**SPA3** resulted in a higher enantiocontrol if compared to BINOL derivatives, allowing enantioselectivities up to 99%. The authors reported two different protocols to afford the Ugi adducts depending on the substituent of the aldehyde **86**. When aliphatic aldehydes were used, (*R*)-**SPA5** catalyst was selected to obtain the corresponding Ugi adducts **358** in moderate to high yields and excellent enantiocontrol (43-96%, 75-99% ee).

In contrast, (*R*)-**SPA3** organocatalyst was found as the optimal one for aromatic aldehydes, affording pseudo peptides **359** in high yields and stereocontrol (60-96%, 80-94%). Curiously, although the same absolute configuration of the CPA-catalyst was used, the opposite absolute configuration was obtained in the Ugi products. This can be rationalized due to the inversion of the steric demand on the imine. When aromatic aldehydes are used the authors also used aliphatic amines, ensuring that the substituent of the aldehyde has a larger effect on the transition state of the reaction (Type I E). However, when using aliphatic aldehydes in combination with aromatic amines, the most steric demanding moiety is the protecting group of the imine, pushing an alternative transition state (Type II E). Based on these reports, other examples of enantioselective Ugi reactions catalysed by CPAs have also been reported.[285,286]

4. Enantioselective nucleophilic additions to C=O bonds

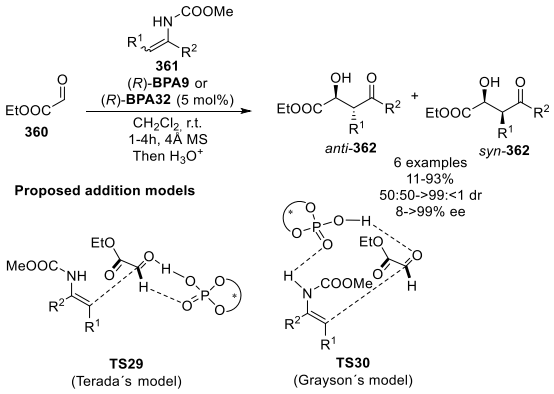
4.1. Nucleophilic addition of enols and enamines

Terada's group described in 2008 the first example of the activation of aldehydes using CPA catalysts (Scheme 118).[287] This aldol-type reaction between enamines **361** (R^1 =H; R^2 = Ph, Me) and glyoxalate **360** in presence of (*R*)-**BPA9** gave β-hydroxy ketones **362** in excellent yields and enantioselectivities (78-93%, 95% ee), after the subsequent hydrolysis. Furthermore, the authors performed the reaction with β-substituted enecarbamates **361**, using the catalyst (*R*)-**BPA32** and obtaining *syn* (major) and *anti* (minor) mixtures of products **362**. When the reaction is carried out with *(E)*-**361** enamines, higher yields, diastereoisomeric ratios and enantiomeric excesses are observed (73-89%, 96:4 to >99:1 dr, 53-74% ee *syn* and 99->99% ee *anti*) in comparison to when *(Z)*-**2** enamines are used (11-74%, 50:50 to 92:8 dr, 69-74% ee *syn* and 8-28% ee *anti*).

The key feature for the obtaining of enantiopure products, as the authors described based on DFT computational analysis, is the formation of a double hydrogen bond between glyoxalate **360** and the catalyst (**TS29**) forcing a coplanar orientation of **360** and the phosphoric acid subunit. At this point, the *re* face is shielded by one of the phenyl rings in comparison to the *si* face, which is fully accessible, hence, enecarbamates **361** attack from this less hindered side (Scheme 118). In 2021 Grayson shed more light on this reaction mechanism.[288] These new investigations suggest that the CPA acts as a bifunctional catalyst, activating both, the nucleophile and the electrophile towards the enantioselective addition (**TS30**).

Yuan and co-workers described in 2014 a single example of the (*R*)-**BPA25** catalysed enantioselective addition of enamine **364** to ethyl trifluoropyruvate (**363**) affording 3-hydroxy-3-(trifluoromethyl)-pyrrol-2-one **365** in excellent yield but moderate enantioselectivity (Scheme 119).[289] The proposed mechanism consists of an initial attack of the enamine to activated ketone **363**, leading to intermediate **366**. Next, catalyst (*R*)-**BPA25** is released yielding species **367** that subsequently suffers an intramolecular cyclization, to provide γ-lactam **365**.

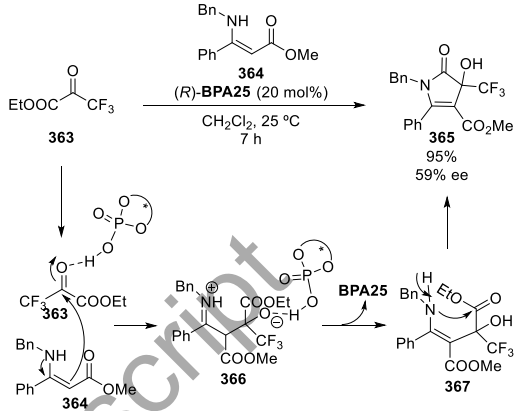
In 2019, Cheng and co-workers described the atroposelective reaction of 2-aminoaryl ketones **367** with acetoacetate derivatives **290** catalysed by phosphoric acid (*R*)-**SPA1** in presence of glycine *tert*-butyl ester additive, obtaining



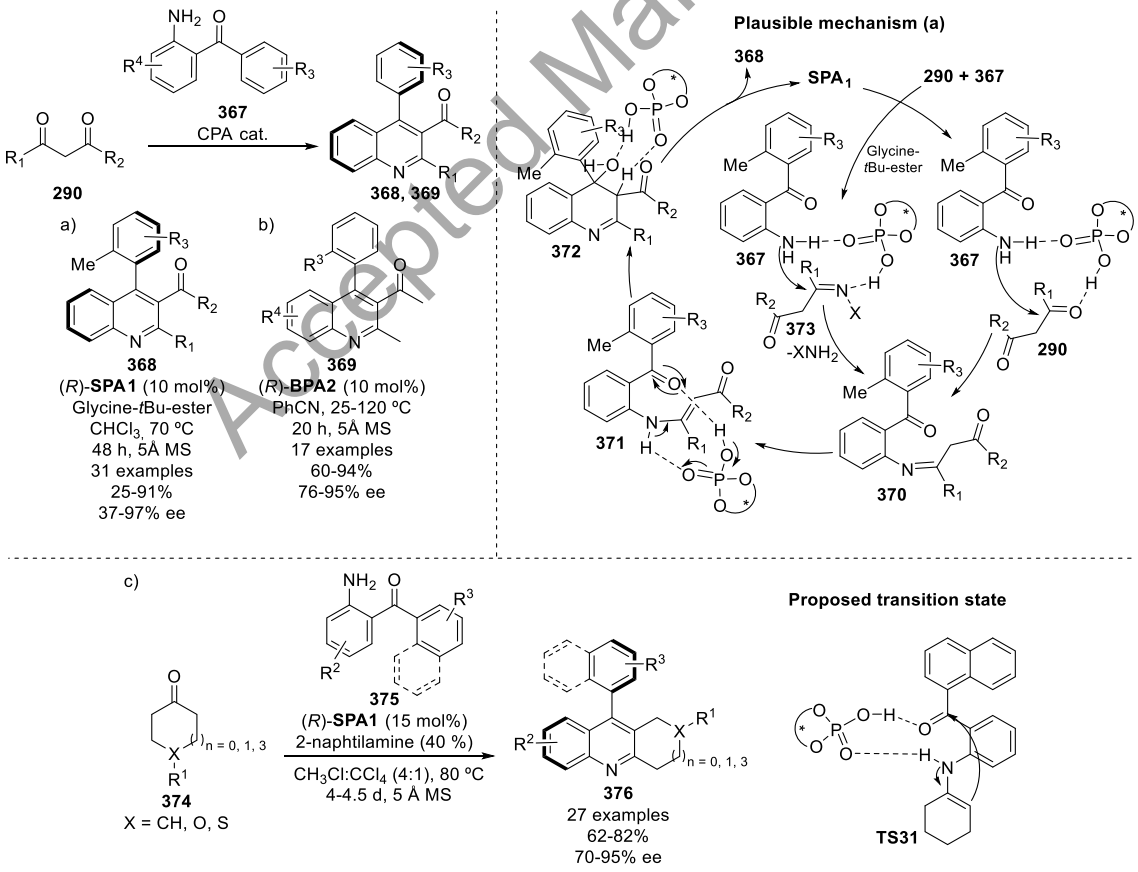
Scheme 118. The first example of CPA activation of aldehydes.

axially-chiral quinolines **368** in a wide range of yields and enantioselectivities (25-91%, 37-97% ee) (Scheme 120).[290] The use of amines **367**, holding different substitutions in *ortho*-, *meta*-, and *para*- positions, or fused rings, had little effect on the reaction efficiency. However, variation of the R^1 group on acetoacetate derivatives **290** had a very strong influence on the reaction, resulting in a dramatic drop in the stereocontrol when sterically demanding β-keto esters are used as electrophiles.

The authors propose the following catalytic process: the first step consists of the condensation of the primary amine group in 2-aminoaryl ketones **367** with acetoacetates **290** under the promotion of (*R*)-**SPA1**, obtaining imine intermediate **370**, which tautomerise to enamine species **371**. Then, a ring closure through an intramolecular aldol reaction leads to intermediate **372**. The CPA catalyst plays a crucial role in asymmetric induction, creating a chiral environment through hydrogen bonding interactions. Finally, compound **372** loses water, providing chiral quinolines **368** (Scheme 120, a). The authors observed that a catalytic loading of a glycine *tert*-butyl ester (an achiral amine) can accelerate the reaction, forming imine **15**, which is beneficial for the initial condensation.



Scheme 119. Synthesis of 3-hydroxy-3-(trifluoromethyl)-pyrrol-2-one **365**.



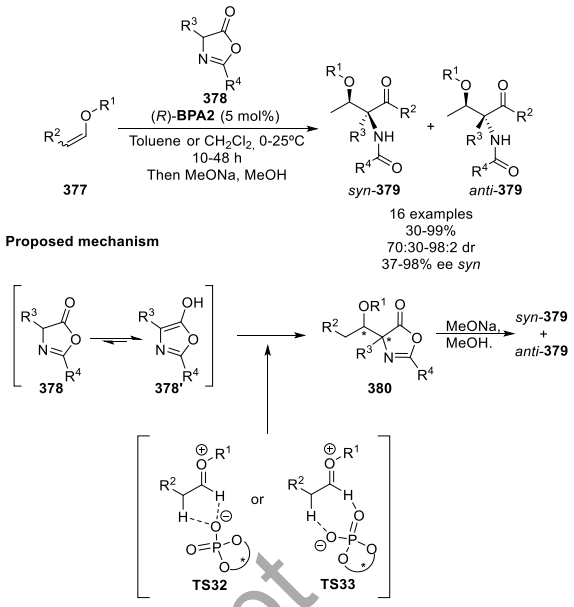
Scheme 120. Synthesis of axially-chiral quinolines through the Friedländer reaction.

Another example of CPA catalysed atroposelective Friedländer reaction was described by Jiang's group in 2019, using in this case acetylacetone (**290**, R^1, R^2 = H) and amines **367** as starting materials and (*R*)-**BPA2** catalyst to obtain quinolones **369** (Scheme 120, b).[291] The reaction was carried out using diverse 2'-substituted 2-aminobenzophenones **367**, obtaining the desired products **369** in good yields and enantiomeric excesses (60-94%, 76-95% ee) and noticing that the lowest ee values were obtained in 5-substituted quinolones.

In addition, in 2020, Chen´s group described the (*R*)-**SPA1** catalysed atroposelective synthesis of 9-aryltetrahydroacridines **376** through the Friedländer reaction (Scheme 120, c).[292] The reaction is initiated by the condensation of amines **375** with ketones **374** mediated by catalyst (*R*)-**SPA1**, obtaining an enamine intermediate. Then, the key cyclization step takes place through an intramolecular aldol reaction to obtain axially chiral 9-aryltetrahydroacridines **376**. In the cyclization step, the double hydrogen bonding formed between (*R*)-**SPA1** and enamine is essential for the reaction to take place in a highly diastereo- and enantioselective fashion (**TS31**). The reaction works with a variety of cyclic ketones (R^1 = H; X = C, O or S) and several anilines **375**, with substituted aromatics or fused aromatics in at the aromatic ring, obtaining excellent yields and enantioselectivities (62-82%, 70-95% ee). Moreover, the authors also extended these conditions to substituted ketones **374** ($R^1 \neq$ H; X = CH), being able to promote the enantioselective desymmetrisation with the simultaneous control of the stereogenic carbon centre at the newly-formed products, obtaining 9-aryltetrahydroacridines **376** with good diastereoselectivities and excellent enantioselectivities (68-75%, 75:25 to 90:10 dr, 87-92% ee).

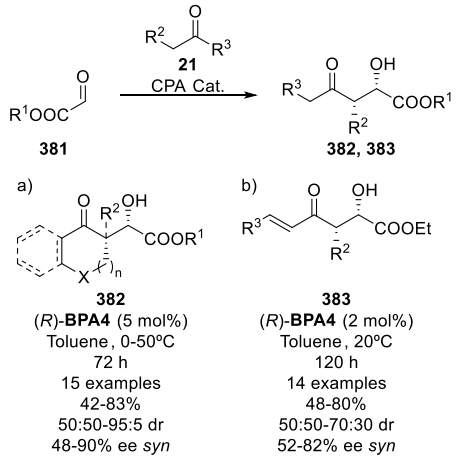
In 2009 Terada and co-workers described the (*R*)-**BPA2**-catalysed aldol-type reaction between vinyl ethers **377** and azlactones **378** to obtain β-hydroxy-α-amino acid derivatives **379** with a quaternary stereogenic centre (Scheme 121).[293] In this case oxocarbenium ion interacts with the catalyst through two possible bonding models (**TS32** and **TS33**), enabling the enantioselective aldol-type addition of azlactones *via* oxazole tautomer **378'**, thus obtaining cyclic intermediates **380**, which are transformed in substrates **379** after treatment with sodium methoxide in methanol.

The reaction proceeds efficiently using diverse aromatic substituted azlactones **378** (R^3 = Ph; R^4 = Ph, α- or β-naphthyl, 4-BrC_6H_4, 4-MeC_6H_4) in toluene at room temperature, obtaining the *syn* substrate as the major diastereoisomer in excellent yields and moderate to good diastereo and enantioselectivities (60-99%, 68:32 to 81:19 dr, 39-82% ee *syn* and 35-70% ee *anti*). If the reaction is performed in dichloromethane at 0ºC with azlactone **378** (R^3 = Ph; R^4 = 3,5$(MeO)_2C_6H_3$) an increase in the diastereoselectivity and the enantioselectivity is then obtained (99%, 98:2 dr, 98% ee *syn*). For this reason, several vinyl ethers **377** (R^1 = ^{t}Bu, ^{n}Bu, Bn; R^2 = H, Me, ^{n}Pr) were tested under the previous conditions (0ºC or 25ºC) obtaining *syn*-**379** products with good yields, and excellent diastereo- and enantioselectivities in most cases (45-99%, 70:30 to 98:2 dr, 37-97% ee *syn*).

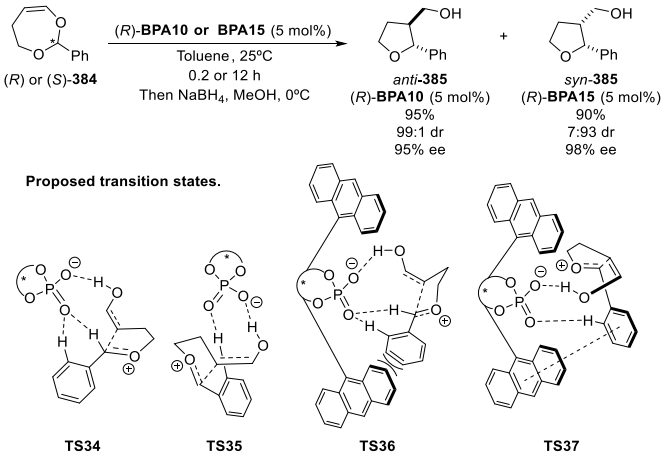


Scheme 121. Aldol-type reaction of vinyl ethers **377** and azlactones **378**.

One year later, another example of CPA catalysed enantioselective aldol reaction was described by Blanchet's group (Scheme 122, a).[294] The (*R*)-**BPA4** catalysed reaction (5 mol%) consists of the enantioselective nucleophilic addition of ketones **21** to glyoxylates **381** (R^1 = Me, Et, Bn). Despite the reaction can be carried out with very different cyclic (heterocyclic, different ring size, fused cycle) or acyclic ketones, the ketone:aldehyde ratio used is 10:1, which suggest a non-efficient reaction, obtaining substrates **382** moderate yields, but good diastereoselectivities and enantiomeric excesses (42-83%, up to 95:5 dr, 48-90% ee *syn*). In addition, a few later, the same group extended the protocol to the aldol reaction of α,β-unsaturated ketones **25** with ethyl glyoxalate **360** (Scheme 122, b).[295] In this case, the catalyst-loading was reduced down to 2% and the ketone:aldehyde ratio was 1:2. When ketones **21** ($R^2 \neq$ H, R^3 = Ar) are used, moderate diastereoselectivities and



Scheme 122. The aldol-type reaction of ketones **21** and glyoxalates **381**.



Scheme 123. Petasis–Ferrier type rearrangement.

moderate to good enantioselectivities are observed (48-80%, 50:50 to 70:30 *syn:anti* ratio, 58-82% ee *syn*). Similar results are observed using α,β-unsaturated ketones **21** (R^2 = H, R^3 = Ar) as substrates (66-72%, 52-70% ee). The authors also describe a couple of examples using conjugated dienones as nucleophiles, obtaining yields ranging from 61 to 71% and enantiomeric excesses from 64 to 68%.

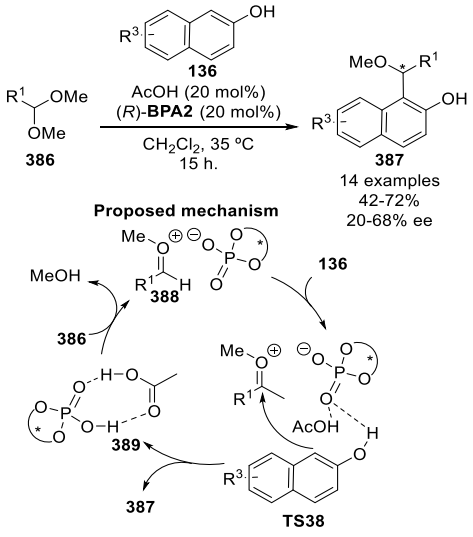
Terada's group studied in 2014 the Petasis–Ferrier-type rearrangement of cyclic vinyl acetal **384** catalysed by chiral phosphoric acids (Scheme 123).[296] On the one hand, the use of (*R*)-**384** and (*R*)-**BPA10** in toluene for 12 hours, gave the *anti*-**385** substrates as the mayor diastereoisomer in excellent yield, diastereo- and enantioselectivity (95%, 99:1 dr, 95% ee *anti*). DFT studies revealed that the formation of the *anti* isomer is more favourable, due to the stabilization of **TS34** with three hydrogen bonds (one O–H/O and two C–H/O) in contrast to energetically disfavoured **TS35**, which is stabilised by only one O–H/O and one C–H/O bond. On the other hand, the use of (*S*)-**384** and (*R*)-**BPA15** in toluene for 0.2 hours, gave the *syn*-**385** product as the mayor diastereoisomer, also in excellent yield, diastereoselectivity and enantiomeric excess (90%, 7:93 dr, 98 % ee *syn*). In this case, although **TS36** presents three hydrogen bonds (one O–H/O and two C–H/O), in comparison to the two hydrogen bonds formed in **TS37** (one O–H/O and one C–H/O), the phenyl ring of the anthryl group in (*R*)-**BPA15** develops some steric congestion in **TS36**, destabilizing the transition state. However, better stabilization can be expected in **TS37** due to π-π stacking interactions enabled by the parallel orientation of the phenyl group of **384** and the 9-anthryl group of (*R*)-**BPA15**.

Although there are not many examples related to enantioselective additions of enol and enamine derivatives to carbonyl compounds, there are some patterns that could be relevant to be considered. The addition of enamines/enecarbamates with small substutents at the nitrogen (ester or benzyl groups) are more likely to provide high enantiomeric excesses when using remotely substituted CPAs. In contrast, proximal substitution of the catalyst is preferred when using enolates rather than enamines. However, polyaromatic substituents provide better results in Friedländer reactions. This can be due to attractive interactions between the substrate and the catalyst in the stereochemistry-determining step. In view of the published results, the catalyst selection is most likely to be dependant on the type of the nucleophile rather than the carbonyl group.

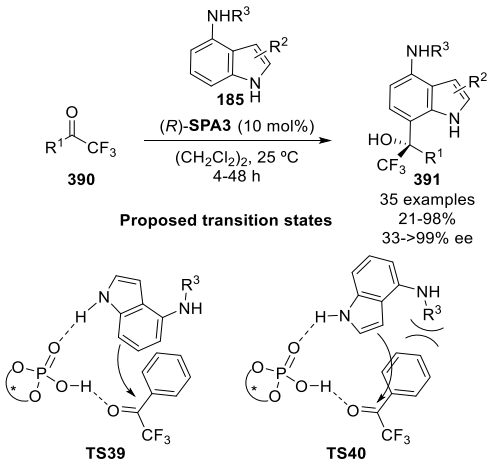
4.2. Friedel-Crafts reactions

Brønsted acid-catalysed enantioselective Friedel-Crafts reaction is a very practical method for the preparation of enantioenriched substituted aromatic compounds.[142,297] The Friedel-Crafts reaction with carbonyl compounds is particularly challenging since the resulting alcohol substrates are susceptible to a further alkylation reaction step with a second electron-rich arene.[298,299] For those reasons, relatively weak acid catalysts and very reactive carbonyl compounds are required in order to achieve good yields and/or enantiomeric excesses.

Da described in 2016 the use of dimethyl acetals **386** as aldehyde surrogates in the Friedel-Crafts reaction of β-naphthols **136** catalysed by (*R*)-**BPA2** to obtain chiral methyl ethers **387** (Scheme 124).[300] The catalytic cycle may start with the acid-mediated formation of the very reactive oxocarbonium species **388** by the loss of methanol in acetal **386**, promoted by the phosphoric acid-derived heterodimer **389**. Then, the basic phosphoryl oxygen atom of the catalyst establishes an H-bond, with acetic acid, which results in an increase of the acidity of the phosphoric acid group, and a second H-bond with the β-naphthol group, which increases the nucleophilicity of the aromatic ring, as shown in **TS38**. The nucleophilic attack of the activated naphthol ring to oxocarbonium species leads to the formation of chiral ethers **387**, while the active catalytic species is released in order to proceed with the next cycle. 2-Naphthol and 6-bromo-2-naphthol are effective nucleophiles in this reaction with diverse aromatic substituted acetals **386** (R^1 = Ar), obtaining chiral naphthols **387** in moderate yields and enantiocontrol (44-68%, 33-68% ee). However, the use of 1-naphthol as a nucleophile leads to a drastic drop into the observed ee value (72%, 20% ee).



Scheme 124. Friedel–Crafts reaction of β-naphthols and dimethyl acetals.



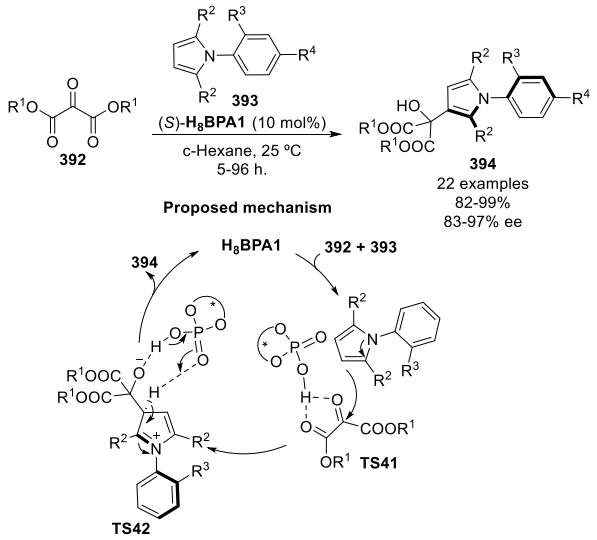
Scheme 125. Enantioselective functionalization of 4-aminoindoles **185**.

A similar reaction using 4-amino substituted indoles **185** has been more recently described by Chan and Zhao, using spirocyclic (*R*)-**SPA3** (Scheme 125).[301] In contrast to the examples described below, the Friedel-Crafts reaction with trifluoromethyl ketones **35** takes place selectively at the C7 of the indole ring (**TS39**) instead of the C3 (**TS40**), due to the steric hindrance caused by the amino substituent at C4 of indoles **185**. Good to excellent yields (42-98% and 78->99% ee) are obtained in this reaction when trifluoroacetophenones **390** (R^1 = Ar) are used. However, the use of non-aromatic ketones (R^1 = Me, CO_2Et, CH_2-R) under the same conditions lead to a notable drop in the enantioselectivity (33-80% ee).

In 2019, Tan and co-workers described the (*S*)-**H_8BPA1** catalysed reaction of pyrroles **393** and diethyl ketomalonates **392** for the preparation of axially-chiral aryl pyrroles **394**. In all cases, with different kinds of substituents, the reaction proceeds smoothly, obtaining products **40** with excellent yields and enantioselectivities (42-99%, 83-97% ee) (Scheme 126).[302,303] The authors also describe the application of this technique to the kinetic resolution of racemic aryl pyrroles **393**, by using a 2:1 ratio of **393**:**392**. Using this simple strategy, they obtained highly enantioenriched (*R*)-aryl pyrroles **394** (46-54%, 71-89% ee) and (*S*)-aryl pyrroles **394** (42-47%, 87-94% ee).

The authors propose for this transformation a monofunctional activation mode, where the hydrogen bonding between ketomalonate **392** and (*S*)-**H_8BPA1** is the essential interaction for the induction of chirality (**TS41**). Then, the second carbonyl of ketomalonate fixes the whole system in a rigid configuration, as shown in **TS42**. Besides, such a pathway agrees with the mechanism theorised by other authors.[304,305]

Concerning the enantioselective addition of indole derivatives to carbonyl compounds, the first example of such reaction was reported by Ma and co-workers in 2009 (Scheme 127, a).[306] In particular, they discovered that the trifluoromethyl group has a double role for the enantioselective Friedel-Crafts addition to ketones. First, it increases the electrophilicity of the ketone, making the addition easier. On the other hand, perfluoroalkyl groups also prevent the elimination of the alcohol, avoiding the formation of the bisindolyl methane

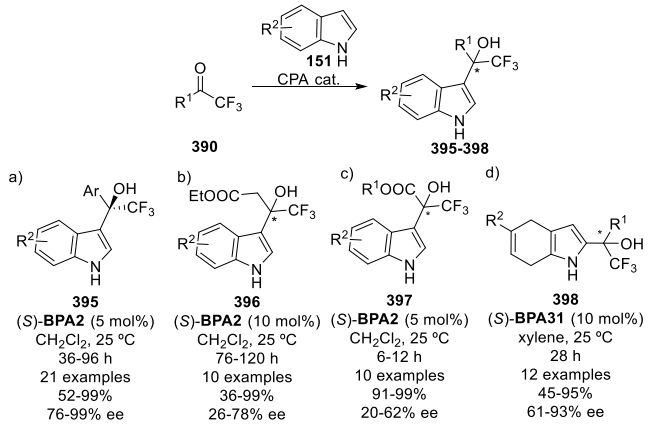


Scheme 126. Friedel-Crafts reaction for the preparation of axially-chiral aryl pyrroles **394**.

derivatives that are commonly obtained in similar reactions with aldehydes or ketones. Initially, they reported the (*S*)-**BPA2** catalysed addition of indoles **151** to trifluoroacetophenones **390** (R^1 = Ar), to obtain products **395** in yields up to 99% and high enantiocontrol (76-99% ee). Next, they extended this methodology to trifluoroacetoacetates (R^1 = CH_2COOEt) and trifluoropyruvates (R^1 = COOEt) to afford products **396** and **397**, respectively (Scheme 127, b-c).[307] Even though the yields were almost quantitative in most cases, the enantiomeric excesses were found to be modest in this case (20-78% ee). The authors also extended this methodology to some 4,7-dihydroindoles using (*S*)-**BPA31** catalyst, leading to 2-substituted indole derivatives **398** in moderate yields and good enantiocontrol (45-95%, 61-93% ee) (Scheme 127, d).[308]

In order to overcome the drawbacks of Ma´s methodology, Akiyama´s group further optimised the addition to trifluoropyruvates **390** (R^1 = CO_2Me) by using lower reaction temperatures (-78°C), (*R*)-**H_8BPA11** catalyst and toluene as solvent.[309] This improvement allowed to obtain functionalised indols **397** in yields above 95% and enantiomeric excesses ranging from 80 to 98%. Other authors have made several attempts to further improve Ma´s work in this field. For instance, in 2015, Shi reported a new phosphoric acid organocatalyst ((*R*)-**CPA7**) and its effectiveness was evaluated by the addition of indole **151** to trifluoroacetophenone **390** (R^1 = Ar), showing higher reactivity than the homologous (*R*)-**BPA2** or (*R*)-**H_8BPA1** catalyst, but with similar results in terms of enantiocontrol.[310]

In the same context, in 2017 Kwiatkowski and co-workers described the enantioselective Friedel-Crafts reaction of indoles **41** and activated trifluoroacetophenones **35** (R^1 = Ar), using only0.1 mol% of (*R*)-**BPA2** organocatalyst (Scheme 127, a). The reaction requires 9 kbar pressure, in order to obtain functionalised indole derivatives **395** in good yields and enantiomeric excesses (63-93%, 84-94% ee).[311] One year later, the Kass group described some examples of the same reaction by using 5 mol% of a new (*R*)-**BPA33** organocatalyst.[312]

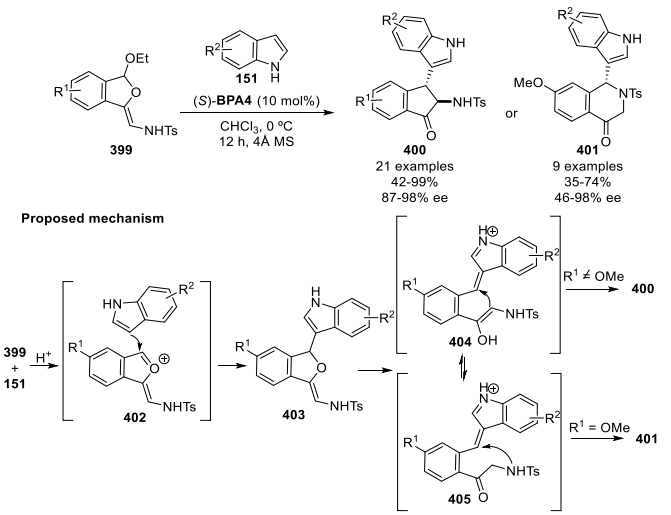


Scheme 127. CPA catalysed Friedel-Crafts reactions of indole derivatives with fluorinated ketones **390**.

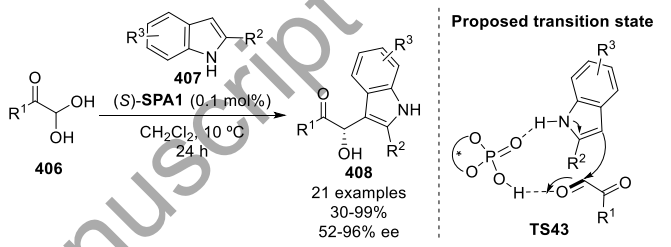
In general, indoles **395** are obtained in excellent yields and enantiomeric excesses when different indoles **151** and trifluoroacetophenones **390** are used as substrates (36-94, 79-91% ee), but a notable drop in the enantioselectivity is observed if perfluorophenyl-derived trifluoroacetophenone **390** (R^1 = C_6F_5) is used as the electrophile (28%, 64% ee). Remarkably, in this reaction, the catalyst loading can be reduced to 1.5 mol%, noticing a slight increase in the enantiocontrol (91-96% ee), although the reaction conditions require lower temperatures and longer reaction times.

The use of dihydroisobenzofurane acetals **399** as aldehyde surrogates is a very elegant example of a Friedel-Crats reaction that prevents the formation of acid-sensitive alcohol substrates and allows the efficient synthesis of five-membered indanones **400** or six-membered tetrahydroisoquinolones **401** in good to excellent yields and excellent enantiomeric excesses (42-99%, 87-98% ee) (Scheme 128).[313] Under the acidic conditions, provided by the presence of CPA catalyst (*S*)-**BPA4**, the elimination of the ethoxy group leads to the formation of oxocarbenium species **402,** which is subsequently attacked by indole nucleophile **151** to provide indole-substituted dihydroisobenzofurane intermediate **403**. Then, a C-O bond cleavage at the furane ring leads to a keto/enol equilibrium between species **404** and **405**. Ketone species **405** are favoured if a strong electron-donating methoxy substituent is present at the *para* position, leading to the formation of a 6-membered ring substrate **401** through an intramolecular aza-Michael addition of the amino moiety. On the contrary, without the presence of the methoxy group, the intramolecular Michael addition of enol intermediate **404** delivers five-membered amino indanones **400** in good to excellent yields (42-99%) and excellent enantiomeric excesses (87-98% ee). However, lower yield and enantiocontrol are obtained in the case of six-membered tetrahydroisoquinolones derivatives **401** (35-74%, 46-98% ee).

Similarly, in 2020, Li, Zao and Tang described the use of glyoxal derivatives **406** as electrophiles in an enantioselective Friedel-Crafts reaction of indoles **407** with, using only a 0.1 mol% chiral phosphoric acid (*S*)-**SPA1**, obtaining chiral α-hydroxyketones **408** (Scheme 129).[314] A bulky substituent is required at the indole 5-membered subunit in order to avoid



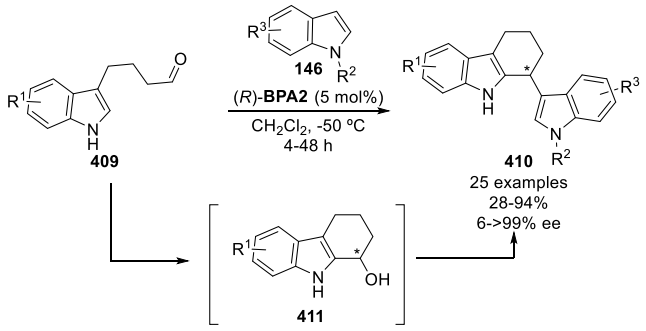
Scheme 128. Enantioselective Friedel-Crafts addition of indoles to dihydroisobenzofuran acetals **399**.



Scheme 129. Synthesis of chiral α-hydroxyl ketones **408** through Friedel-Crafts reaction of indoles and glyoxals.

the formation of bis-indole substrates. While aromatic glyoxal derivatives **406** (R = Ar), give the Friedel-Crafts adducts **408** in high yields and excellent enantioselectivities (68-99%, 80-96% ee), a drastic drop in the yield and ee (30%, 52% ee) is observed if the use of aliphatic substituted glyoxal (R^1 = penthyl) is used. Remarkably, the use of *N*-methyl substituted indole substrates in this reaction, leads to a complete loss of the enantioselectivity. This result may suggest a crucial role of the NH group in asymmetric induction. Accordingly, the tentative transition state (**TS43**) proposed for this reaction consists of a typical double hydrogen bonding interaction between the CPA catalyst (*S*)-**SPA1** and the indole substrate **407** and glyoxal derivative **406**.

Following with the use of indole rings in CPA catalysed Friedel-Crafts reactions, Nielsen's group described an example of the phosphoric acid-catalysed enantioselective domino type intramolecular cyclization/Friedel-Crafts reaction, of indole-3-butanal **409** and indole derivatives **146**, in presence of (*R*)-**BPA2** to obtain tetrahydrocarbazoles **410** with 28 to 94% yield and enantiomeric excesses up to >99% (Scheme 130).[315] As proposed by the authors, first the cyclization of aldehydes **409** occurs, obtaining intermediate **411**, and then, the external nucleophilic attack happens, in a domino Friedel–Crafts type process. These authors also describe some examples where thiols, pyrazole and indazole rings are used as nucleophiles, obtaining good yields but lower enantioselectivities (74-95%, 10-49% ee). A few years later, Xiaomei Zhang extended the scope of the reaction, this time performed in dichloroethane at



Scheme 130. Enantioselective domino type intramolecular cyclization/Friedel-Crafts reaction.

-30°C (instead of using dichloromethane at -50°C), using also chiral phosphoric acid (*R*)-**BPA2** catalyst, obtaining products **410** in good yields and enantioselectivities (33-99%, 40-81% ee).[316]

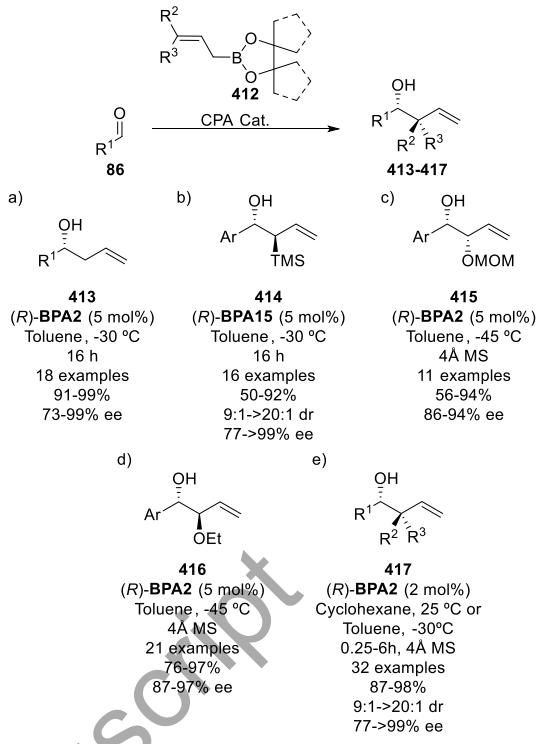
The scope limitations for Friedel-Crafts reactions with carbonyl compounds are clear since they are most likely to give subsequent eliminations of the formed alcohol, losing the stereochemical induction obtained during the process. However, some aldehydes and ketones that minimize the elimination step have been explored by several authors. In this regard, it should be noted that the optimal catalyst substituents in most of the reported examples include proximal substituted aromatic groups such as TRIP-CPAs. Thus, the enantioselective process is most likely directed by steric interactions rather than attractive effects between the catalyst and the substrate.

4.3. Allylboration and related reactions

The addition of allylic boranes and boronates to carbonyl compounds is a well-known procedure, where generally homoallylic alcohols are obtained with high stereocontrol.[317] Although in many cases metal catalysts are used for this transformation (Sn, Cu, Ni, In) in combination with chiral ligands, chiral CPAs have also been reported as efficient catalysts for the enantioselective allylation of aldehydes using boronates as reagents.[318]

Antilla´s group described the first example of such type of reaction in 2010. In particular, the synthetic methodology consists of the enantioselective synthesis of homoallylic alcohols **413** by reacting aldehydes **86** with allylboronic acid pinacol esters **412** (R^2, R^3 = H) using (*R*)-**BPA2** catalyst in toluene at -30ºC (Scheme 131, a).[319] This reaction is not only very effective in promoting the asymmetric allylboration of a wide range of electron-rich and electron-poor aromatic aldehydes **86** but also works with aliphatic ones. In all cases, excellent yields and enantioselectivities are obtained (91-99%, 73-99% ee). In addition, the authors also perform the reaction in the same conditions with (*Z*)-crotylboronate **412** (R^2 = H; R^3 = Me), obtaining the corresponding *syn*-**413** product with excellent yield and stereocontrol (95%, 98:2 dr, 94% ee). In contrast, when the reaction is carried out at 0ºC with (*E*)-crotylboronate **412** (R^2 = Me; R^3 = H), the *anti*-**413** product is obtained with excellent stereoselectivity (96%, 98:2 dr, 99% ee).

In 2012, Hu and co-workers described the same reaction, but in this case, using toluene as solvent at -70ºC and using (*R*)-



Scheme 131. Several reactions for the enantioselective synthesis of homoallylic alcohols **413**-**417**.

SPA3 catalyst (Scheme 14, a), perceiving a slight increase in the enantioselectivities (86-99%, 91-99% ee). In addition, the use of (*Z*)-crotylboronate **412** (R^2 = H; R^3 = Me) and (*E*)-crotylboronate **412** (R^2 = Me, R^3 = H) gave the corresponding *syn*-**413** and *anti*-**413** products also with an increase in the stereocontrol for both cases (98-99%, 99:1 dr, 99% ee).[320]

A few years later, the same protocol was also used by Barrio and Akiyama using (*R*)-**BPA15** as the catalyst, allylboronic acid pinacol esters **412** (R^2 = TMS or $SiMe_2Ph$; R^3 = H) and aromatic aldehydes **86** (Scheme 131, b).[321] Products **414** are obtained as single *anti* diastereoisomers, in moderate to excellent yields and enantiomeric excesses (50-92%, 52-96% ee). The use of electron-withdrawing groups (2-BrC_6H_4, 2-$NO_2C_6H_4$) in the *ortho* position and electron-donating group (3-MeC_6H_4) in *metha* position in aromatic aldehydes **86**, gave the poorest results in terms of stereocontrol (65-84%, 52-58% ee)

A similar protocol was used by Chen´s group in 2018. In his case, the authors performed the reaction with (*Z*)-(γ-methoxymethoxyallyl)-boronates **412** (R^2= H; R^3 = OMOM) in toluene at -45ºC, using (*R*)-**BPA2** catalyst (Scheme 131, c). When aromatic aldehydes are used as electrophiles, homoallylic alcohols **415** are obtained as single *syn* diastereoisomers, in good yields and high enantioselectivities (56-94%, 86-94% ee).[322] The authors also describe a single example using an aliphatic aldehyde **86** (R^1 = $(CH_2)_2Ph$) obtaining also very good results (60%, 90% ee). Remarkably, if the reaction is performed using (*E*)-γ-ethoxyallylboronates **412** (R^2 = OEt; R^3= H) and aromatic aldehydes **86**, *anti*-alkoxyallylation products **416** are obtained as single diastereoisomers with comparable yields and enantiocontrol (76-97%, 87-97% ee) (Scheme 131, d).

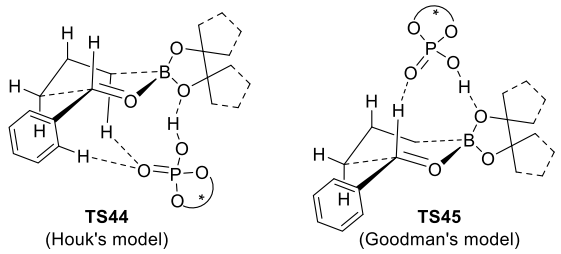


Figure 4. Plausible transition states for allylation of aldehydes.

Remarkably, the reaction also works with aliphatic aldehyde **86** (R^1 = $(CH_2)_2$-Ph) (89%, 87% ee) and with chiral aldehydes, observing high stereocontrol in the reaction (89%, 8:1 dr).

More recently, Antilla´s group described the (*R*)-**BPA2**-catalysed allylboration reaction of aldehydes **86** for the synthesis of homoallylic alcohols **417** (Scheme 131, e).[323] In this case, they used bis-(cyclopentyl) diol-derived allylic boronates **412** (R^2 = Me; R^3 = Alk), to obtain homoallylic alcohols **417**, in excellent yields and enantiomeric excesses (87-98%, 77->99% ee). In this example, the use of backbone-modified boronate **412** (cyclopentyl instead of dimethyl) in the reaction, allows the dropping of the catalyst loading while retaining high stereocontrol. Unsubstituted bis-(cyclopentyl) diol-derived allylic boronates **412** (R^2, R^3 = H) react smoothly with aromatic, heteroaromatic and α, β-unsaturated aldehydes in cyclohexane at room temperature. However, aliphatic aldehydes require toluene as solvent, at lower temperatures and longer reaction times, in order to achieve high stereocontrol. The same reaction conditions are applied to alkyl-substituted bis-(cyclopentyl) diol-derived allylic boronates **412** (R^2 = Alk; R^3 = H, Alk), leading to the formation of *anti*-homoallylic alcohol as the major diastereoisomer.

In order to shed some light into the reaction mechanism, Goodman and Houk carried out DFT studies of the transition states in the previously described allylboronation reaction of aldehydes (Figure 4).[324–326] In these models, the CPA catalyst is able to activate the boronate species by forming a hydrogen bond either with the pseudoequatorial oxygen (**TS44**, Houk's model)[326] or with the pseudoaxial oxygen (**TS45**, Goodman's model)[324] of the boronate. In both cases, a closed six-membered chair-like transition state is formed and the phosphoryl oxygen interacts with the relatively positive hydrogens of the substrate through electrostatic attractions, providing further stabilization of the transition states, and a two-point orientation of the catalyst. The two competing pathways gave very similar energy profiles, suggesting that both may be involved in the allylboration reactions. The theoretical calculations suggest that the high degree of enantioselectivity arises from the repulsive interactions between bulky tri-*iso*-propylphenyl substituents at BINOL-derived CPA catalyst and the alkyl groups at the boronate. Consequently, the enantioselectivity is strongly affected by the steric hindrance at the catalyst or boronate structures.

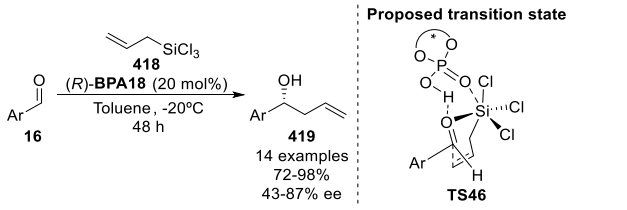
A slightly different pathway for the synthesis of homoallylic alcohols **419** was described by Jian's group in 2011 (Scheme 132).[327] For this purpose, the authors used allyltrichlorosilane **418** in presence of (*R*)-**BPA18** catalyst, which proved to be very efficient with aromatic aldehydes **16**, obtaining substrates **419** in good yields and enantioselectivities (72-98%, 59-87% ee). However, the enantiomeric excess decreases when aliphatic aldehyde **86** (R = $(CH_2)_2$Ph) is used (88%, 43% ee).

For this reaction, the authors propose a bicyclic transition structure (**TS46**), featuring a hexavalent silicon species and the presence of hydrogen bond between (*R*)-**BPA18** and aldehyde **16** and between phosphoryl oxygen and the silicon atom. Despite that a six-membered chair-like transition state is formed in the same manner as in **TS44** and **TS45**, in this case, the CPA catalyst interacts directly with the oxygen atom of aldehyde substrate **16** and the silicon atom, in contrast with the H bonds formed in **TS44** and **TS45**, with the oxygen of the boronate and different hydrogens of the aldehyde.

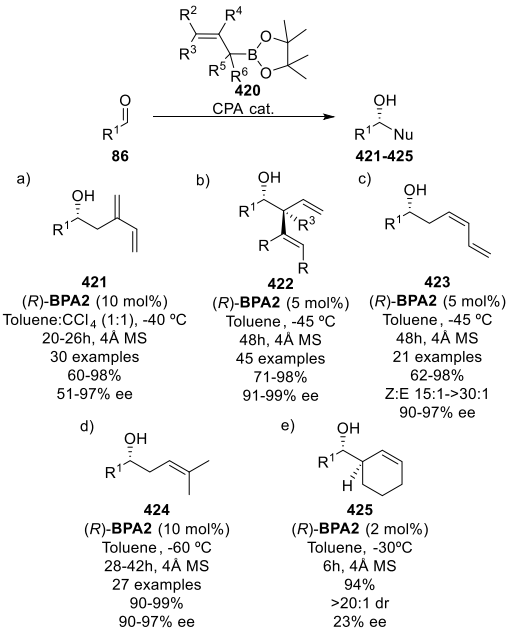
Allylation reactions leading to homoallylic alcohols with non-substituted terminal double bonds have been also described. However, this type of reaction has also been applied to the synthesis of homoallylic alcohols with substituted terminal double bonds and dienes. For example, in 2019 Huang used pinacolyl isoprenylboronate **420** (R^2, R^3, R^4, = H; R^5, R^6 = CH_2=) as allylating agent, in a mixture of toluene: CCl_4 in presence of (*R*)-**BPA2** to afford isoprene substituted alcohols **421** in good yields and enantioselectivities (90-98%, 66-97% ee) (Scheme 133, a).[328] The scope of this reaction can be applied to a wide array of aromatic, aliphatic and conjugated aldehydes **86**.

One year later, Chen´s group described the nucleophilic addition of 1,3-pentadienylboronates **420** (R^2 = CR=CHR; R^3 = Me or H; R^4, R^5, R^6 = H) to aldehydes **86**, using the same CPA-catalyst, obtaining 1,4-pentadien-3-yl carbinols **422** in excellent yields and enantiomeric excesses (71-98%, 91-99% ee) (Scheme 133, b).[329] The reaction tolerates the use of many different aromatic, aliphatic and conjugated aldehydes **86** in combination with substituted 1,3-pentadienylboronates **420** holding or not different methyl substituents (in R^2 and R^3), obtaining compounds **422** as single *anti* diastereoisomers. Following an identical procedure, the *Z*-selective allylation of aldehydes **86** with α-vinyl allylboronates **420** (R^2, R^3, R^4, R^6 = H; R^5 = CH=CH_2), affords homoallylic alcohols **423** in good yields (62-98%), high *Z*-selectivities (15:1 to >30:1 *Z: E*) and excellent enantioselectivities (90-97% ee) (Scheme 133, c).[330]

In the same context, in 2020, Huang and co-workers reported the chiral phosphoric acid (*R*)-**BPA2** catalysed reaction of aldehydes **86** with α,α-dimethyl allyl boronic esters **420** (R^2, R^3, R^4 = H; R^5, R^6 = Me) for the preparation of homoprenyl alcohols **424** in excellent yields and enantioselectivities (90-99%, 90-97% ee) (Scheme 133, d).[331]



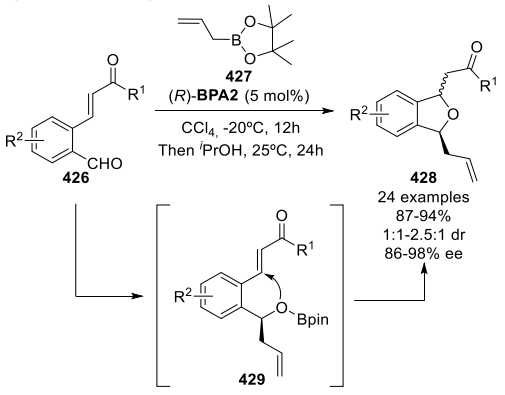
Scheme 132. Use of allyltrichlorosilane for the synthesis of homoallylic alcohols.



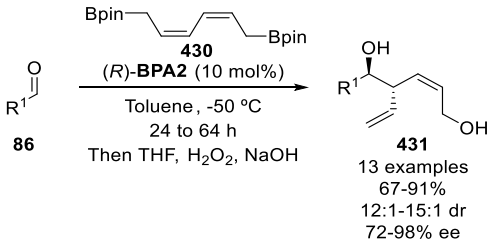
Scheme 133. Enantioselective additions of boron reagents to aldehydes.

The reaction can be efficiently applied to a wide variety of benzaldehydes **86** holding electron-donating and electron-withdrawing groups at different positions, as well as to heteroaromatic and aliphatic aldehydes **86**, proving the versatility of the methodology. In addition, the authors describe the application of this protocol for the preparation of natural products (-)-rosiridol and (-)-bifurcadiol. Similarly, Antilla´s group described a single example of the use of cyclohexene-derived boronate **420** to afford homoallylic alcohol **425** in excellent yield and diastereoselectivity, although low enantioselectivity is observed in this case (94%, 23% ee) (Scheme 133, e).[323]

In connection to the examples described above, in 2017, Huang and co-workers described the (*R*)-**BPA2**-catalysed cascade reaction of *o*-formyl chalcones **426** with allyl boronate **427**, leading to enantioenriched 1,3-dihydroisobenzofurans **428**. The reaction is assumed to start with an asymmetric allylboration process, that leads to intermediate **429**, followed by a subsequent intramolecular asymmetric oxo-Michael reaction (Scheme 134).[332]



Scheme 134. Cascade reaction of *o*-formyl chalcones 81 with allylboronates **427**.



Scheme 135. CPA-catalysed reaction of diboronates **430** and aldehydes.

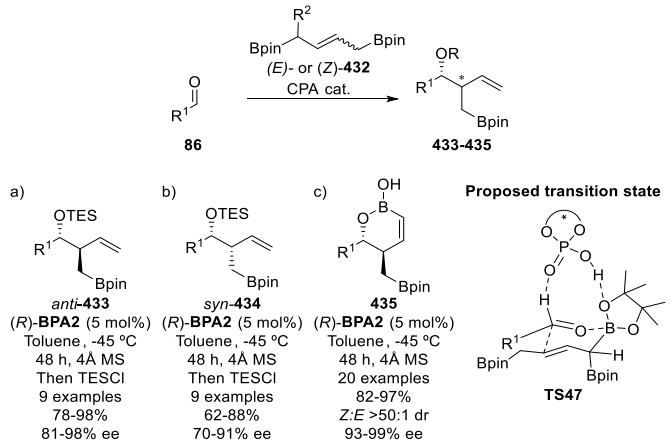
The use of *o*-formyl chalcones **426** with electron-donating groups or halogen substituents at the different positions of the internal and external aryl groups (R^1 and R^2) are well tolerated in this cascade reaction, affording chiral 1,3-dihydroisobenzofurans **428** in high yields and enantioselectivities (87–94%, 85–98% ee), although with low diastereoisomeric ratios (1.0:1–2.5:1 dr). In addition, the asymmetric cascade reaction can be extended to the use of allenylboronic pinacol ester, obtaining similar results in terms of yield, enantio- and diastereoselectivity (92%, 1.8:1 dr, 93% ee *cis*).

As a particular case of an allylboration reaction, in 2018 Trauner and co-workers described the (*R*)-**BPA2** catalysed reaction of aldehydes **86** using diboronates **430** (Scheme 135).[333] The reaction can be applied to a variety of aromatic, aliphatic and α,β-unsaturated aldehydes **86** that, after oxidative workup, yields 1,5-diols **431** in good yield, diastereo- and enantioselectivity (67-91%, 12:1 to 15:1 dr, 72-98% ee).

In the same context, Chen and co-workers reported the (*R*)-**BPA2** catalysed reaction between (*E*)-γ-borylmethyl allylboronates (*E*)-**432** (R^2 = H) and aldehydes **86**, followed by the *in situ* trapping of the resulting secondary alcohol as a triethylsilyl (TES) ether, obtaining exclusively the *anti*-**433** isomer in excellent yields and enantioselectivities (78-98%, 81-98% ee) (Scheme 136, a).[334] In contrast, the parent reaction using (*Z*)-γ-borylmethyl allylboronates (*Z*)-**432** (R^2 = H) yields *syn*-**434** adducts in good yields but slightly lower enantiomeric excesses (78-98%, 70-91% ee) (Scheme 136, b). An elegant application of this reaction is also described for the synthesis of neolignan Morinol D.

In a similar way, the (*R*)-**BPA2**-catalysed reaction between aldehydes **86** and tris-boronate substrates **432** (R^2 = Bpin) affords cyclic 6'-boryl-*anti*-1,2- oxaborinan-3-enes **435** with excellent *anti*-selectivity (>50:1 dr) (Scheme 136, c).[335] The reaction is applicable to a broad spectrum of carbonyl substrates, including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes, obtaining in all cases cyclic boronic acids **435** in excellent yields and enantiomeric excesses (82-97%, 93-99% ee). In the transition state **TS47** proposed by the authors, there is no apparent steric interaction between the Bpin group, occupying the pseudoaxial position, and the other additional Bpin groups.

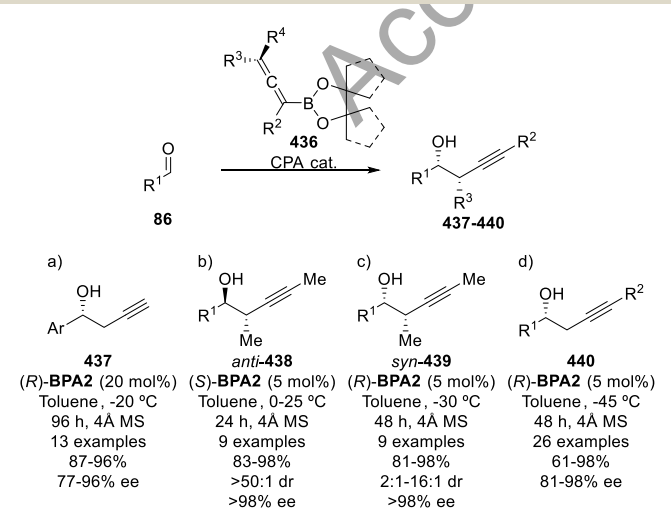
In their most recent reports, Chen and co-workers describe allylboration reactions using enantioenriched CH_2Bpin substituted *E*-crotylboronate.[336] Curiously, in this case, the absolute configuration of the CPA-catalyst allows controlling



Scheme 136. BPA2-catalysed allylboration reaction of diboronates **432** and aldehydes.

the *E*/*Z* selectivity of the reaction, providing access to a wide variety of new chiral alcohols with high stereocontrol. Moreover, the authors illustrated the applicability of their method to the synthesis of ACRL toxin IIIB. Thus, the allylation of the aldehydes proceeds with a high degree of stereocontrol.

Allenyl boronates are also interesting substrates in enantioselective nucleophilic addition reactions to carbonylic compounds. In 2012, Antilla and Houk described the first example of a CPA catalysed asymmetric propargylation of aldehydes (Scheme 137, a).[337] For this reaction the authors used boronate **436** (R^2, R^3, R^4 = H) and aromatic aldehydes holding electron-donating and electron-withdrawing groups in the presence of 20 mol% of (*R*)-**BPA2**. In all cases, excellent yields and enantioselectivities are observed (87-96%, 91-96% ee). However, the author also used some aliphatic aldehydes, observing a slight decrease in the stereocontrol (89-92%, 77-82% ee). In 2012 Reddy performed the same reaction, in this case using cyclohexane as solvent at 10ºC and using a lower loading of (*R*)-**BPA2** (5 mol%), obtaining also substrates **437** with better enantiomeric excesses (92-98%, 84->99% ee).[338]



Scheme 137. Enantioselective synthesis of homopropargyl alcohols **437-440**.

In 2020, Antilla´s group also reported the same reaction using bis(cyclopentyl)diol-derived allenyl boronates **436** (R^2 = H, R^3, $R^4 \neq$ H) and aromatic, heteroaromatic, and α,β-unsaturated aldehydes **86** in cyclohexane at 25ºC with 5 mol% of (*R*)-**BPA2.**[323]In all cases homopropargylic alcohols **437** are obtained in excellent yields and enantioselectivities (91-96%, 91-99% ee), making clear that the use of cyclopentyl substituted allenyl boronates **436** enables the reaction in milder conditions with lower catalyst loading and obtaining even better results.

Following Antilla´s work,[337] in 2012 Roush, and co-workers noticed that these reactions suffer from a lack of diastereochemical control. As they report, citing Ito's work,[339] *anti*-isomers are generally obtained in allenylboronation reactions with aliphatic aldehydes, while *syn*-isomers predominate in reactions with aromatic aldehydes. To solve this situation they propose the use of a secondary external source of chirality to control the reaction, and they used enantioenriched allenyl boronates **436** (R^2, R^3 = Me; R^4 = H) for this purpose (Scheme 137, b).[340,341] The use of different aromatic, aliphatic and conjugated aldehydes **86** in toluene at 0ºC or room temperature in the presence of (*S*)-**BPA2** provided *anti*-**438** products with excellent yields and stereocontrol (83-98%, >50:1 dr, >98% ee). However, if the reaction is performed in the presence of (*R*)-**BPA2** in toluene at -30ºC, *syn*-**439** products are obtained in excellent yields and enantioselectivities, but moderate diastereoisomeric ratios (81-98%, 2:1 to 16:1 dr, >98% ee) (Scheme 137, c).

Based on the model presented by Antilla and Houk,[337] the authors suggested a boat-like transition state for both cases, where the catalyst interacts with the pseudoaxial oxygen of the boronate. However, the DFT studies made by Goodman indicate the existence of an additional interaction between the phosphoryl oxygen of the catalyst and the formyl proton (Figure 5).[325] When (*R*)-**BPA2** is used, the terminal methyl group of allenylboronate **436** and the R^1 group of aldehyde **86** are eclipsed, as shown in **TS49**. If R^1 groups are less demanding from a sterical point of view (i.e., flat aromatic rings), the enantioselectivity of the chiral catalyst is capable of overriding this interaction, thus obtaining the *syn* isomers. However, if the aldehyde R^1 group is bulkier (e.g., a cyclohexyl group), the eclipsing interaction is sufficiently large so that the (*R*)-**BPA2** is unable to overcome this interaction. By comparison, in **TS48** *anti* products are obtained because the terminal methyl group of allene **436** and the aldehyde **86** R^1 group are aligned in such a way that serious steric repulsion is not apparent in the transition state.[337]

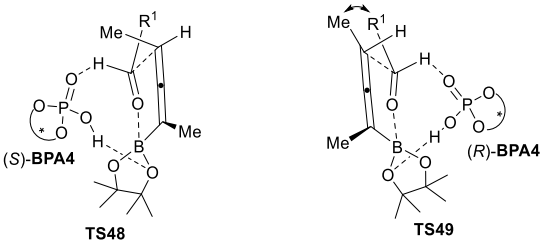
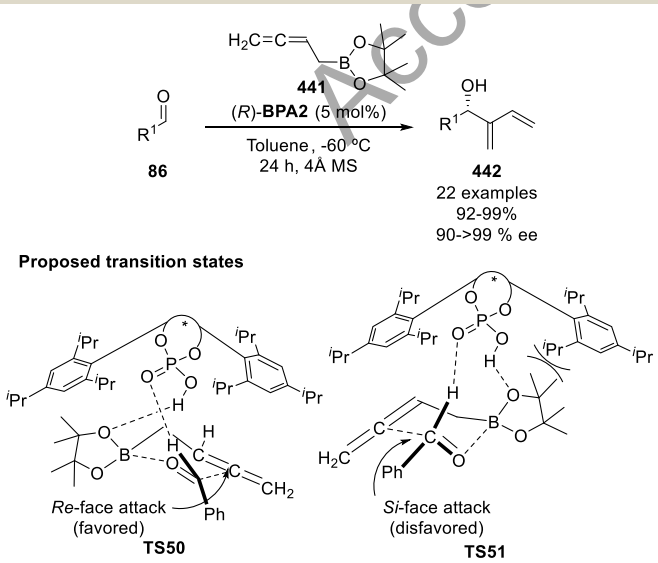


Figure 5. Plausible transition states for propargylation reaction of aldehydes.

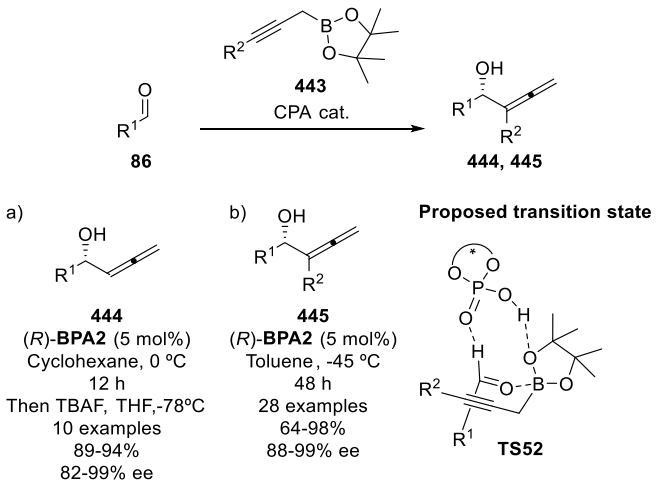
One year later, the same authors realised that the reaction of allenyl boronates **436** (R^2, R^3 = Me; R^4 = H) and aldehydes **86** in the presence of (*S*)-**BPA4** proceeds at a faster rate than the reaction with (*R*)-**BPA4**. Thus, a single enantiomer of the catalyst might be able to select the more reactive enantiomer of the racemic allenylboronate **436** (R^2, R^3 = Me; R4 = H) and then to direct its addition to the aldehyde **86**.[342,343] The authors perform the reaction using aliphatic, conjugated and aromatic aldehydes **86** with 2.8 equivalents of racemic allenylboronate **436** (R^2, R^3 = Me; R^4 = H) in toluene at -50ºC with (*R*)-**BPA2**, obtaining *anti*-**439** products in good yields, diastereoselectivities and enantioselectivities (83-95%, 9:1 to 20:1 dr, 73-95% ee).

Chen and co-workers described in 2018 the synthesis of enantioenriched homopropargylic alcohols **440**, using in this case 1-alkyl substituted allenyl boronates **436** (R^2 = Me, Et, Pent.; R^3, R^4 = H) (Scheme 137, d).[344] The reaction can be applied to a variety of aromatic aldehydes with electron-donating, electron-withdrawing and halogen substituents, obtaining products **440** with good yields and excellent enantioselectivities (70-95%, 81-98% ee). Density functional theory (DFT) calculations conclude that (*R*)-**BPA2** catalyst can coordinate the aldehyde-boronate complex through hydrogen bonding in a bidentate manner, as proposed by Goodman.[325]

One last example of an allenylboronation reaction was described by Huang and Pei in 2015. In this case, the reaction is carried out using 2,3-dienylboronic ester **441** and aldehydes **86**, also catalysed by (*R*)-**BPA2** (Scheme 138).[345] The reaction works efficiently with different aromatic or conjugated aldehydes **86** in toluene at -60ºC, obtaining (*R*)-(1,3-butadien-2-yl)methanol derivatives **442** in high yields and enantioselectivities (95-99%, 96->99% ee). In addition, the authors describe a couple or examples of the same reaction using aliphatic aldehydes **86**, obtaining also substrates **442** with high stereocontrol (92-96%, 90-92% ee), although the reactions have to be carried out in cyclohexane:CCl_4 (1:1) or in CCl_4.



Scheme 138. Asymmetric dienylboration reaction between pinacol ester **441** and aldehydes.



Scheme 139. Asymmetric synthesis of α-allenic alcohols **444** and **445**.

In accordance with what has been described so far, DFT calculations suggest a chair like transitions state, where the CPA catalyst captures two reactive components by means of two hydrogen bonds (**TS50** and **TS51**). The energy barrier for the formation of the *R* stereoisomer is smaller than for the *S* isomer, due to the steric repulsions between the large substituent of (*R*)-**BPA2** and the pinacol methyl groups of **441** in **TS51**. Thus, the *Re* face attack in **TS50** is favoured.

In contrast to the use of allenyl boronates **86** or **441**, propargyl boronates **443** (R^2 = TMS) in the presence of CPA catalyst (*R*)-**BPA2**, followed by treatment with TBAF, yields enantioenriched allenic alcohols **444** (Scheme 139, a).[346] The reaction can be performed with different aromatic and aliphatic aldehydes **86**, obtaining in all cases excellent yields and enantiomeric excesses (90-94%, 90-99% ee). However, the use of a conjugated aldehyde resulted in a decrease in the stereocontrol (92%, 82% ee).

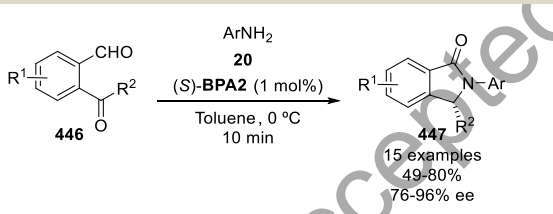
Another example of allenylation reaction was described by Chen and co-workers in 2018. In this example, substituted propargyl boronates **443** (R^2 = Me, Et, Pent.) are used in the presence of (*R*)-**BPA2**, yielding enantioenriched allenic alcohols **445** (Scheme 139, b).[347] The reaction scope is applied to aromatic aldehydes **86** bearing electron-donating or electron-withdrawing groups as well as, to the use of alkenyl aldehydes, obtaining in all cases the corresponding allenyl alcohols **445** in good yields and excellent enantiomeric excesses (64-98%, 88-99% ee). The computational data support a reaction mechanism through transition state **TS52**, where the phosphoric acid catalyst coordinates to the oxygen atom of pinacol moiety and the hydrogen atom of the aldehyde electrophile, forming a nine-membered cyclic chelate.

Based on the transition states proposed by several authors in this type of transformation, the stereocontrol seems to arise from repulsive interactions between the BPin derivatives and the catalyst. Thus, it is not surprising that most of the reported examples have been published using large proximal region substituted chiral phosphoric acids.

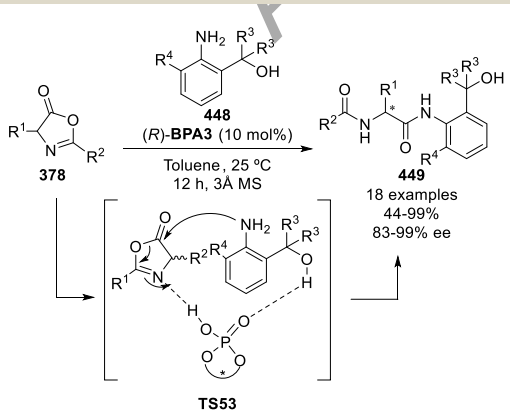
4.4. Carbon-Heteroatom bond formation reactions

Some examples of CPA catalysed enantioselective reactions, where a C-Heteteroatom bond is formed have been described during the last few years. For instance, Seidel and co-workers described in 2017 the synthesis of enantioenriched isoindolinones **447** using aromatic amines **20** with several 2-acyl-benzaldehydes **446** and (*S*)-**BPA2** as the catalyst, obtaining in all cases good yields and enantiomeric excesses (49-80%, 76-96% ee) (Scheme 140).[348] The authors also extended this reaction to the use of *o*-^{t}Bu anilines **20** (Ar = 2-^{t}BuC$_6$H$_4$) and describe three examples of atropoisomeric isoindolinones **447** (63-75%, 6:1-7.5:1 dr, 90-93% ee).

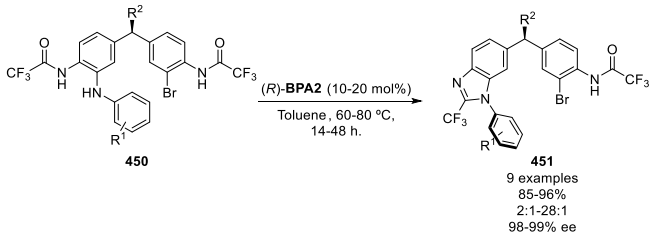
Shi's group described in 2016 a (*R*)-**BPA3** catalysed reaction where enantioenriched bisamides **449** are obtained through the addition of nucleophile anilines **448** to azlactones **378** (Scheme 141).[349] The reaction works through transition state **TS53**, where the CPA catalyst establishes hydrogen bonds with the nitrogen of azlactones **378** and the hydroxyl group of **448**. In addition, the bulky groups (R^3) present in the anilines **448** provide additional steric hindrance, thus increasing the enantiocontrol of the reaction. Diverse aromatic substituted azlactones can be used in the reaction, obtaining in all cases bisamides **449** in good yields and enantiomeric excesses (44-99%, 83-99% ee), noticing that the lowest yields are observed when *para*-substituents are used. Regarding the scope of the nucleophile reagent, the use of aniline **448** (R^4 = Me) results in a decrease in the reactivity, obtaining product **449** with 44% yield but with a high enantiomeric excess (90%). Likewise, the use of simple aniline **448** (R^4 = H) gives better results, obtaining, in this case,



Scheme 140. Synthesis of enantioenriched isoindolinones **447**.



Scheme 141. Synthesis of enantioenriched bisamides **449**.



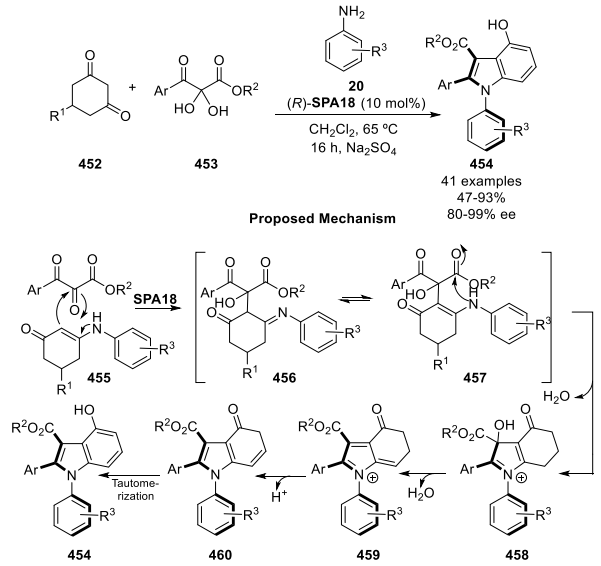
Scheme 142. Synthesis of axially-chiral *N*-aryl benzimidazoles **451**.

good yields and enantioselectivities (70-99%, 88-99% ee). The authors also tried to use anilines **448** with two different R^3 substituents, intending to perform the reaction in an enantioselective manner but, although products **449** can be obtained with moderate yield and high enantiomeric excesses for each diastereoisomer (66%, 94 and 96% ee) no diastereoselectivity is obtained.

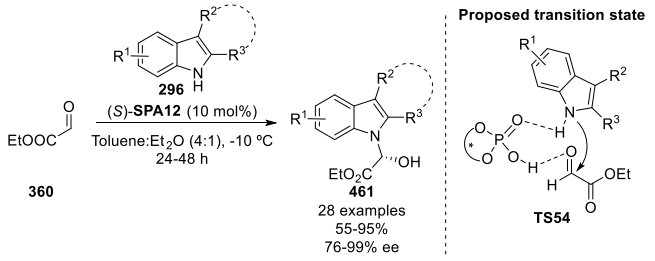
In literature, there are several examples of CPA catalysed reactions involving C-N bond formation to obtain axially-chiral final products. In 2018 Miller's group described the synthesis of axially-chiral *N*-aryl benzimidazoles **451** using the catalyst (*R*)-**BPA2** (Scheme 142).[350] The reaction consists of a diastereoselective intramolecular cyclodehydration of enantiopure products **450**, that are obtained in good yields and excellent diastereo- and enantioselectivities (86-96%, 12:1-28:1 dr, 99% ee) with *ortho*-methyl and fused rings. However, a decrease in the diastereoselectivity is observed when products **450** (R^1 = *o*-Br, *o*-Ph and *o*-Me-*o*-OMe) are used, although the enantioselectivity remains unaltered (85-94%, 2:1-9:1 dr, 98-99% ee).

In 2019 Lin and co-workers reported the atroposelective three-component cascade reaction of 1,3-cyclohexanediones **452**, 2,3-diketoesters **453** and *ortho*-substituted aryl amines **20** to provide *N*-arylindoles **454** (Scheme 143).[351] The reaction proceeds successfully using chiral spirocyclic phosphoric acid catalysts (*R*)-**SPA18** and chiral indoles **454** are obtained in good yields and enantiomeric excesses (47-93%, 80-99% ee) when different 2,3-diketoesters **453** with diverse electronic properties and substituted positions, as well as when different substituted anilines **20** are used as starting materials. The suggested mechanism for the generation of substrates **454** starts with a CPA-catalysed aldol condensation of intermediate **455** and the dehydrated 2,3-diketoesters **453** to form intermediate tautomers **456** and **457**. Intermediate **457** suffers a dehydrative cyclization, generating product **458**, and the subsequent dehydration by a γ-elimination results in intermediate **459**, which undergoes a dearomatization leading to intermediate **460** which generates substrates **454**. As stated by the authors, in this cascade reaction, (*R*)-**SPA18** might catalyse the aldol reaction to generate a new stereocentre, which is then transferred to an axial chirality during the dehydration/aromatization step.

In 2019 Zhang and Zhu described the (*S*)-**SPA12** catalysed enantioselective *N*-functionalization of indoles **296** with glyoxalate **360** to form chiral *N*,*O*-aminals **461** (Scheme 144).[352]



Scheme 143. Synthesis of *N*-arylindoles **454**.

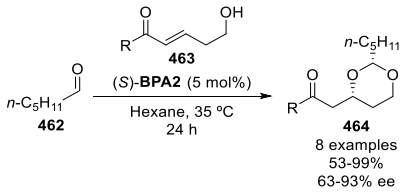


Scheme 144. Enantioselective *N*-functionalization of indoles **296** with glyoxalate **360**.

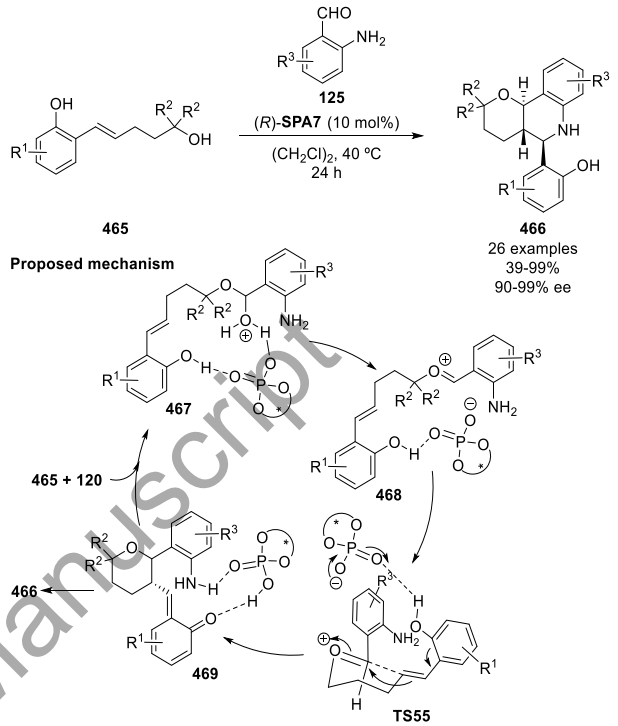
A broad range of indoles are well tolerated, bearing different substituted positions, which includes fused rings in the structure of the indole, providing corresponding *N,O*-aminal products **461** in excellent yields and enantioselectivities (61-95%, 87-99% ee). Exceptionally, when C7- position is substituted, lower yield and enantiomeric excess are observed (55%, 76% ee). The authors propose species **TS54** as the plausible transition state, where indole **296** and ethyl glyoxalate are activated by (*S*)-**SPA12**. Finally, the indole unit attacks the ethyl glyoxalate from the *Re*-face, affording (*R*)-aminoalcohols **461**.

Regarding C-O bond formation reactions, In 2015, Matsubara and co-workers reported a (*S*)-**SPA2**-catalysed tandem reaction involving an enantioselective addition of alkoxides (Scheme 145).[353] With the aim of synthesizing chiral 1,3-dioxanes **464** as precursors of 1,3-diols, they evaluated the addition of alcohols **463** to several aldehydes, selecting hexanal **462** as the optimal electrophile for this reaction. An intramolecular Oxa-Michael addition leads to chiral dioxanes **464** in moderate to excellent yields and good enantiocontrol (53-99%, 63-93% ee).

Zhou and co-workers described in 2019 another example of C-O bond formation reaction. This reaction consists of a (*R*)-**SPA7**-catalysed cascade Prins cyclization for the preparation of chiral tetrahydroquinolines **466**, using hydroxyvinylphenoles **465** and substituted *o*-amino-benzaldehydes **125** (Scheme



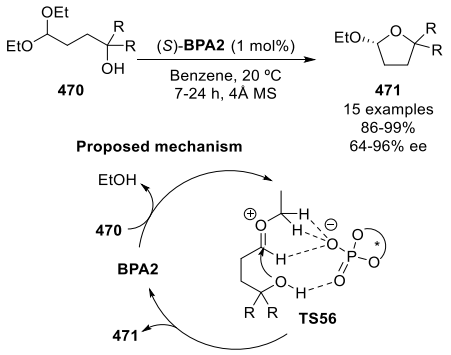
Scheme 145. Tandem protocol for the asymmetric synthesis of 1,3-dioxanes **464**.



Scheme 146. Prins cyclization for the preparation of chiral tetrahydroquinolines **466**.

146).[354] Moderate to good yields and excellent enantiomeric excesses are observed (39-99%, 90-99% ee), but a decrease in the reactivity is noticed when halogen-substituted hydroxyvinylphenoles **465** are used.The plausible mechanism starts with the generation of intermediate **467** *via* an acid-catalysed addition of hydroxyvinylphenole **465** to aldehyde **125**, leading to oxocarbenium ion **468**. Then, the asymmetric Prins cyclization occurs (**TS55**) through the dearomatization of phenol, generating a six-membered chair transition state providing intermediate **469**, which undergoes an intramolecular aza-Michael reaction, affording substrates **466**.

In 2010, List reported a (*S*)-**BPA2-**catalysed asymmetric transacetalization reaction (Scheme 147).[355,356] In this case, the CPA catalyst promotes the formation of an oxonium ion species by the elimination of the corresponding alcohol **470**. Then, the chiral phosphate acts as a bifunctional catalyst, increasing the electrophilicity of the oxonium ion while activating the nucleophilicity of the alcohol group (**TS56**). In consequence, an asymmetric intramolecular cyclization takes place, affording chiral tetrahydrofuran-derived acetals **471** in high yields (86-99%) and enantiomeric excesses up to 96%.



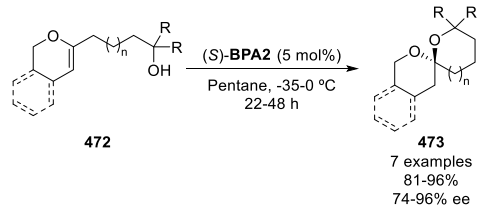
Scheme 147. (*S*)-**BPA2**-catalysed asymmetric transacetilation.

This methodology was extended by Sun´s group to new chiral new tetrahydrofuran derivatives **471** using (*S*)-**SPA3** as a catalyst.[357] In this case, symmetric diols are used as starting material, allowing the generation of two chiral centres in the resulting tetrahydrofuran moieties. Although yields and enantiomeric excesses above 90% were obtained in most cases, the diastereoselectivity of the reaction was highly dependent on the starting material, with diastereoisomer ratios ranging from 5:1 to 19:1. Slight modifications of this methodology provided access to a few chiral tetrahydropyran derivatives in excellent yield and enantiocontrol (90-95%, 93-94% ee), but low diastereomeric ratios (3:1 to 4:1 dr).

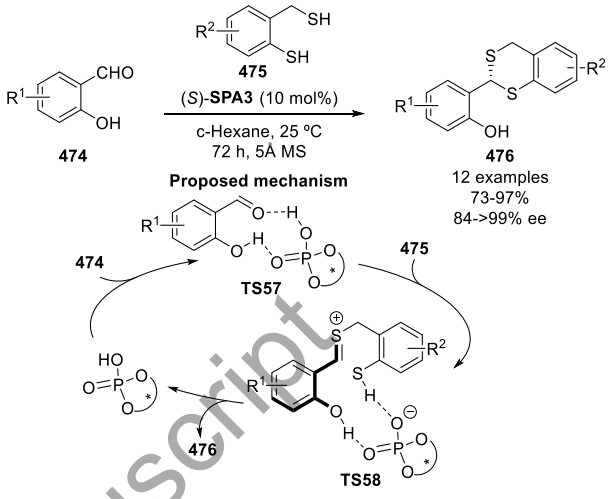
A couple of years later, Nagorny´s group reported a similar reaction using dihydropyrans **472** as starting material (Scheme 148).[358] In this case, the *in situ* formation of the corresponding oxonium ion was achieved through a (*S*)-**BPA2**-catalysed isomerization of substrate **472**. Then, as in the previous examples, an intramolecular nucleophilic addition of the alcohol to the oxonium ion leads to the formation of spirocyclic acetals **473** in high yield and enantiocontrol (81-96%, 74-96% ee). Even though it does not represent an enantioselective route, the authors also applied this methodology to chiral dihydropyran derivatives, with diastereomeric ratios up to 95:5.

In 2016 Zhou and co-workers described the chiral BINOL-derived phosphoric acid (*S*)-**SPA3**-catalysed reaction of salicylaldehydes **474** and dithiols **475** to afford dithioacetals **476** (Scheme 149).[359] The reaction proceeds successfully with different salicylaldehydes and dithiols, in all cases obtaining excellent yields and enantioselectivities (73-97%, 84->99% ee). However, the authors noticed that the use of electron-withdrawing groups in compound **474** gave a slight decrease in the enantiocontrol (84-88% ee). In addition, if 3,5-di-*tert*-butyl salicylaldehyde **474** (R^1 = ^{t}Bu) is used, seven days are required for full conversion, giving product **476** in 73% yield and 96% ee.The use of aliphatic 1,3-dithiol was also explored, with worse results than when the aromatic ring is present (71%, 55% ee), which indicated that the rigid phenyl ring structure of dithiols **475** might be important for achieving the high enantiomeric excess values.

The plausible reaction mechanism may consist of an initial, activation through hydrogen bonding among (*S*)-**SPA3** and hydroxyl and carbonyl groups of salicylaldehydes **474** that facilitates the addition of the primary thiol of the dithiol unit



Scheme 148. Enantioselective synthesis of spiroacetals **473**.



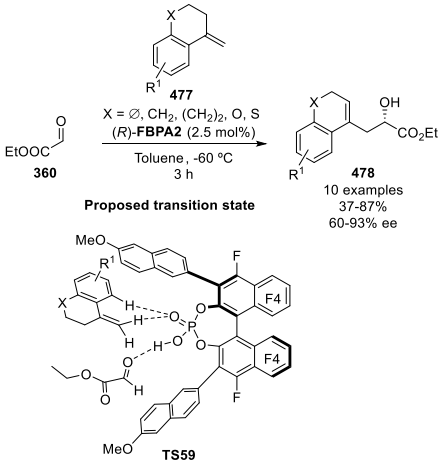
Scheme 149. Synthesis of dithioacetals **476**.

(**TS57**). Then, after the elimination of water, thiocarbenium ion is formed, which now establishes two hydrogen bonds among (*S*)-**SPA3** and hydroxyl and thiophenol groups (**TS58**). At this point, the nucleophilic attack of the thiol group occurs from the *Re* face of the thiocarbenium ion, affording the *R*-configured dithioacetals **476** while the chiral catalyst is released (Scheme 32).

As it has also been observed in the previous sections regarding enantioselective additions to C=O bonds, catalysts containing large proximal substituents have proved to be the optimal in Carbon-Heteroatom bond forming reactions. This may indicate that high steric constriction is required close to the phosphoric acid unit in order to compensate the lack of steric demand of the carbonyl group.

4.5. Miscellaneous reactions

An example concerning the addition of simple carbon nucleophiles to aldehydes was described by Terada's group in 2019. The acidity of the phosphoric acid group is, in this case, enhanced by the use of a perfluoroaryl-derived BINOL unit. Thus, the (*R*)-**FBPA2**-catalysed reaction of 1,1-disubstituted olefins **477** with ethyl glyoxylate **360** leads to homoallylic alcohols **478** in moderate to good yields and enantiomeric excesses (Scheme 150).[360] The fact that a significate drop into the yields and enantioselectivity is obtained (37%, 60% ee) when C8 substituted olefin **477** (X = CH_2, R^1 = 8-Br) is used, may suggest a crucial role for the C–H bond at the C8.

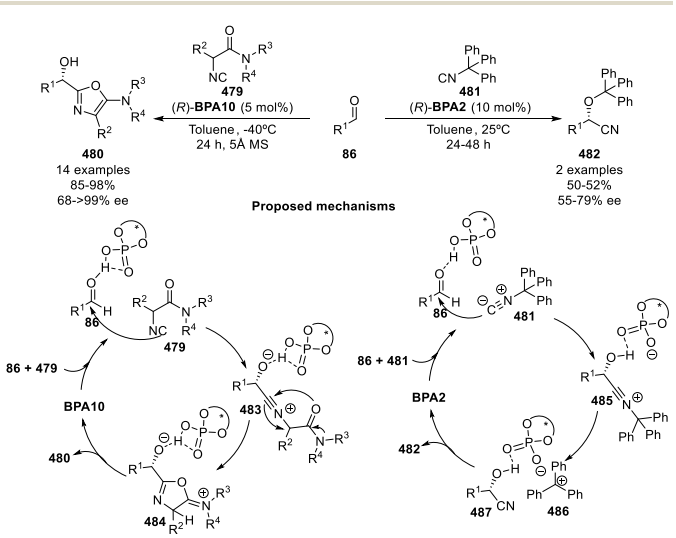


Scheme 150. Reaction of 1,1-disubstituted olefins **477** with ethyl glyoxylate.

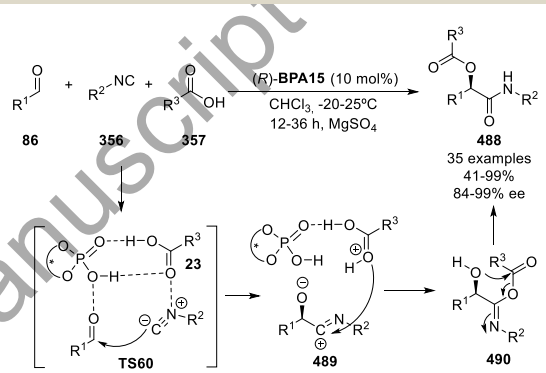
This is in agreement with DFT studies, that suggest a transition state **TS59** where the acidic proton of (*R*)-**FBPA2** (P-OH) establishes a typical hydrogen bond with the carbonyl oxygen of enophile **360** (C=O) whereas the vinylic hydrogen of ene-component **477** interacts through the C-H/O non-classical hydrogen bond at the phosphoryl oxygen (P=O). As shown in the structure of **TS59**, a second C-H/O hydrogen bond is formed between the hydrogen atom at the C8 position and the phosphoryl oxygen (P=O) of catalyst (*R*)-**FBPA2** (Scheme 150).

In 2010, Zhong and co-workers developed the enantioselective α-addition of isocyanides **479** to aldehydes **86** (Scheme 151).[361] The (*R*)-**BPA10** catalysed reaction works with different aliphatic aldehydes and diverse α-isocyanoacetamides, to obtain α-isocyanoacetamides **480** in excellent yields and enantioselectivities in all cases (85-98%, 68->99% ee). In this reaction, the CPA catalyst activates the aldehyde **86** through hydrogen bonding and this is attacked by the isocyano group, forming intermediate **483**. At this stage, oxazole intermediate **484** is formed through an intramolecular cyclization to finally release substrates **480**.

In 2016 Ruijter and Orru also described some examples of the α-addition of isocyanides to aldehydes **86** (Scheme 151).[362] In this case, the reaction was carried out using (*R*)-**BPA2** catalyst and triphenyl acetonitrile **481** as the nucleophile to obtain cyanohydrin derivatives **482**. Despite the authors describe a vast scope of racemic substrates, they only repot two enantioselective examples with moderate yields and enantiomeric excesses (50-52%, 55-79% ee). As the authors observed and, in concordance with Zhong et al.,[361] the aldehyde substrate is activated by the CPA catalyst through hydrogen-bonding to favour the nucleophilic addition by trityl isocyanide **481**, leading to the formation of nitrilium ion intermediate **485**. This intermediate is fragmented at the labile *N*-trityl bond into the free cyanohydrin **487** and reactive trityl cation **486**, which combine to afford cyanohydrins **482** and regenerate the catalyst.



Scheme 151. Enantioselective α-addition of isocyanides to aldehydes **86**.



Scheme 152. CPA-catalysed enantioselective Passerini reaction.

Tan and Liu also used isocyanide species in a CPA catalysed reaction, specifically in the Passerini reaction (Scheme 152).[363] The authors perform the multicomponent reaction using a wide range of aromatic or aliphatic aldehydes **86** and carboxylic acids **357** with bulky isocyanides **356** in presence of (*R*)-**BPA15,** obtaining in all cases amidoesters **488** in moderate to excellent yields and enantioselectivities (41-99%, 84-99% ee). The authors suggest a catalytic process where catalyst (*R*)-**BPA15** forms a heterodimer with carboxylic acid **357** and at the same time activates aldehyde and isocyanide substrates **86** and **356** *via* hydrogen-bonding and ion pair interaction (**TS60**), obtaining intermediate **489** after the addition of the isocyanide to the aldehyde group**.** Then, the nitrilium intermediate **488** is trapped by the carboxylate unit to afford species **490** that yield the final products **488** after the migration of the acyl group.

5. Final remarks

Although they were initially developled for Mannich additions almost two decades ago, the applications of chiral phosphoric acids in enantioselective processes have experienced a great increase during the last few years, demonstrating their applicability for several types of stereocontrolled transformations. In particular,

enantioselective Mannich-type and Friedel-Crafts additions to imines have been exhaustively studied, while the homologous additions to carbonyl compounds, usually afford non-chiral compounds through a subsequent aldol condensation-type elimination. Nevertheless, the applicability of CPAs in enantioselective additions to carbonyl and iminic species is not fully studied yet, and a wide number of transformations have been reported in recent years. For instance, based on the most recent reports, further evolution on CPA-mediated metal-free asymmetric photocatalytic reactions is expected in the following years. Another handicap to be addressed in the future is related to CPA-catalysed enantioselective multicomponent reactions, which represent just a few examples of this review probably due to the modest enantiocontrol obtained in most cases if compared to the analogous two-component reactions.

On the other hand, due to the high relevance of this type of organocatalyst, several authors have contributed to the mechanistic and theoretical studies of these transformations, whiling to help experimental researchers in-depth understanding of the reaction processes, which will facilitate the design of new enantioselective transformations in the future. However, although Goodman´s predictions are accurate for simple systems, like aldimines, the applicability of these methods to more complex ketimines is still limited and further analyses are required. Besides, their methods are not fully applicable to analogous aldehydes and ketones.

While several types of CPA-3,3´ substituents compete depending on many factors, such as the substituent and protecting group of the imine, the E/Z configuration or the nature of the nucleophile, when analysing the existing reports with carbonyls, most of those factors disappear and proximal-bulky aromatic groups are preferred no matter the nature of the nucleophile. Further understanding of the factors inducing the selectivity in Friedel-Crafts reactions with carbonyl groups might shed some light on the reaction, explaining why the π-stacking effects that are commonly shown for imines are not relevant enough when aldehydes or ketones are used.

In summary, from the first developed BPA catalysts to more recently reported SPA catalysts, chiral phosphoric acids have shown excellent catalytic properties for enantioselective additions to C=O and C=N bonds. The reported reactions are mostly related to C-C bond formation, but several regarding C-Het bond formations have also been summarised in this review. Thus, continuous growth and further development is expected for these versatile catalysts in the following years.

Author Contributions

The manuscript was written through the contributions of all authors: Conceptualization (AM, JV) Investigation (XdC, AM), Supervision (AM, JV, FP), Writing – original draft (XdC, AM), Writing-review&editing (EMM, FP, JV)
All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support by Ministerio de Economía, Industria y Competividad (MINECO, RTI2018-101818-B-I00) and Gobierno Vasco (GV, IT 992-16) is gratefully acknowledged. X. del Corte thank the Basque Country Government for a predoctoral grant.

Notes and references

1 D. Uraguchi and M. Terada, Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357.
2 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.
3 T. Akiyama, Stronger Brønsted Acids, *Chem. Rev.*, 2007, **107**, 5744–5758.
4 M. C. Benda and S. France, Chiral disulfonimides: a versatile template for asymmetric catalysis, *Org. Biomol. Chem.*, 2020, **18**, 7485–7513.
5 L. Schreyer, R. Properzi and B. List, IDPi Catalysis, *Angew. Chem. Int. Ed.*, 2019, **58**, 12761–12777.
6 K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping and I. Leito, On the acidity and reactivity of highly effective chiral Brønsted acid catalysts: Establishment of an acidity scale, *Angew. Chem. Int. Ed.*, 2013, **52**, 11569–11572.
7 C. Yang, X.-S. Xue, X. Li and J.-P. Cheng, Computational study on the acidic constants of chiral Brønsted acids in dimethyl sulfoxide, *J. Org. Chem.*, 2014, **79**, 4340–4351.
8 G. Caballero-García and J. M. Goodman, N-Triflylphosphoramides: highly acidic catalysts for asymmetric transformations, *Org. Biomol. Chem.*, 2021, **19**, 9565–9618.
9 A. Gualandi, G. Rodeghiero and P. G. Cozzi, Catalytic Stereoselective SN1-Type Reactions Promoted by Chiral Phosphoric Acids as Brønsted Acid Catalysts, *Asian J. Org. Chem.*, 2018, **7**, 1957–1981.
10 C. Zheng and S. L. You, Transfer hydrogenation with Hantzsch esters and related organic hydride donors, *Chem. Soc. Rev.*, 2012, **41**, 2498–2518.
11 F. Foubelo and M. Yus, Catalytic Asymmetric Transfer Hydrogenation of Imines: Recent Advances, *Chem. Rec.*, 2015, **15**, 907–924.
12 Á. M. Pálvölgyi, F. Scharinger, M. Schnürch and K. Bica-Schröder, Chiral Phosphoric Acids as Versatile Tools for Organocatalytic Asymmetric Transfer Hydrogenations, *Eur. J. Org. Chem.*, 2021, **2021**, 5367–5381.
13 J. G. De Vries and N. Mršić, Organocatalytic asymmetric transfer hydrogenation of imines, *Catal. Sci. Technol.*, 2011, **1**, 727–735.
14 Z.-L. Xia, Q.-F. Xu-Xu, C. Zheng and S.-L. You, Chiral phosphoric acid-catalyzed asymmetric dearomatization reactions, *Chem. Soc. Rev.*, 2020, **49**, 286–300.

15 T. Varlet and G. Masson, Enamides and dienamides in phosphoric acid-catalysed enantioselective cycloadditions for the synthesis of chiral amines, *Chem. Commun.*, 2021, **57**, 4089–4105.

16 Y.-D. Shao and D.-J. Cheng, Chiral Phosphoric Acid: A Powerful Organocatalyst for the Asymmetric Synthesis of Heterocycles with Chiral Atropisomerism, *ChemCatChem*, 2021, **13**, 1271–1289.

17 M. R. Monaco, G. Pupo and B. List, Phosphoric Acid Based Heterodimers in Asymmetric Catalysis, *Synlett*, 2016, **27**, 1027–1040.

18 X. Li and Q. Song, Recent advances in asymmetric reactions catalyzed by chiral phosphoric acids, *Chinese Chem. Lett.*, 2018, **29**, 1181–1192.

19 B.-C. Da, S.-H. Xiang, S. Li and B. Tan, Chiral Phosphoric Acid Catalyzed Asymmetric Synthesis of Axially Chiral Compounds, *Chinese J. Chem.*, 2021, **39**, 1787–1796.

20 J. Merad, C. Lalli, G. Bernadat, J. Maury and G. Masson, Enantioselective Brønsted Acid Catalysis as a Tool for the Synthesis of Natural Products and Pharmaceuticals, *Chem. Eur. J.*, 2018, **24**, 3925–3943.

21 W. Liu and X. Yang, Recent Advances in (Dynamic) Kinetic Resolution and Desymmetrization Catalyzed by Chiral Phosphoric Acids, *Asian J. Org. Chem.*, 2021, **10**, 692–710.

22 G.-C. Fang, Y.-F. Cheng, Z.-L. Yu, Z.-L. Li and X.-Y. Liu, Recent Advances in First-Row Transition Metal/Chiral Phosphoric Acid Combined Catalysis, *Top. Curr. Chem.*, 2019, **377**, 23.

23 P.-S. Wang, D.-F. Chen and L.-Z. Gong, Recent Progress in Asymmetric Relay Catalysis of Metal Complex with Chiral Phosphoric Acid, *Top. Curr. Chem.*, 2020, **378**, 9.

24 Y.-Y. Ren, S.-F. Zhu and Q.-L. Zhou, Chiral proton-transfer shuttle catalysts for carbene insertion reactions, *Org. Biomol. Chem.*, 2018, **16**, 3087–3094.

25 F. Lv, S. Liu and W. Hu, Recent advances in the use of chiral brønsted acids as cooperative catalysts in cascade and multicomponent reactions, *Asian J. Org. Chem.*, 2013, **2**, 824–836.

26 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.

27 D. Parmar, E. Sugiono, S. Raja and M. Rueping, Erratum: 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 (Chemical Reviews (2014) 114:18 , *Chem. Rev.*, 2017, **117**, 10608–10620.

28 S. Li, S.-H. Xiang and B. Tan, Chiral Phosphoric Acid Creates Promising Opportunities for Enantioselective Photoredox Catalysis, *Chinese J. Chem.*, 2020, **38**, 213–214.

29 A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, Chiral BINOL-derived phosphoric acids: Privileged Brønsted acid organocatalysts for C-C bond formation reactions, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276.

30 M. Terada, Chiral phosphoric acids as versatile catalysts for enantioselective transformations, *Synth.*, 2010, 1929–1982.

31 A. Rahman and X. Lin, Development and application of chiral spirocyclic phosphoric acids in asymmetric catalysis, *Org. Biomol. Chem.*, 2018, **16**, 4753–4777.

32 X. Lin, L. Wang, Z. Han and Z. Chen, Chiral Spirocyclic Phosphoric Acids and Their Growing Applications, *Chinese J. Chem.*, 2021, **39**, 802–824.

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 S. E. Wheeler, T. J. Seguin, Y. Guan and A. C. Doney, Noncovalent Interactions in Organocatalysis and the Prospect of Computational Catalyst Design, *Acc. Chem. Res.*, 2016, **49**, 1061–1069.

35 K. Rothermel, M. Melikian, J. Hioe, J. Greindl, J. Gramüller, M. Žabka, N. Sorgenfrei, T. Hausler, F. Morana and R. M. Gschwind, Internal acidity scale and reactivity evaluation of chiral phosphoric acids with different 3,3′-substituents in Brønsted acid catalysis, *Chem. Sci.*, 2019, **10**, 10025–10034.

36 J. P. Reid and M. S. Sigman, Holistic prediction of enantioselectivity in asymmetric catalysis, *Nature*, 2019, **571**, 343–348.

37 A. F. Zahrt, J. J. Henle, B. T. Rose, Y. Wang, W. T. Darrow and S. E. Denmark, Prediction of higher-selectivity catalysts by computer-driven workflow and machine learning, *Science*, 2019, **363**, eaau5631.

38 M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard and B. List, Synthesis of TRIP and analysis of phosphate salt impurities, *Synlett*, 2010, 2189–2192.

39 M. Hatano, K. Moriyama, T. Maki and K. Ishihara, Which is the actual catalyst: Chiral phosphoric acid or chiral calcium phosphate?, *Angew. Chem. Int. Ed.*, 2010, **49**, 3823–3826.

40 J. P. Reid, L. Simón and J. M. Goodman, A Practical Guide for Predicting the Stereochemistry of Bifunctional Phosphoric Acid Catalyzed Reactions of Imines, *Acc. Chem. Res.*, 2016, **49**, 1029–1041.

41 L. Simón and J. M. Goodman, A model for the enantioselectivity of imine reactions catalyzed by BINOL-phosphoric acid catalysts, *J. Org. Chem.*, 2011, **76**, 1775–1788.

42 A. J. Neel, J. P. Hehn, P. F. Tripet and F. D. Toste, Asymmetric cross-dehydrogenative coupling enabled by the design and application of chiral triazole-containing phosphoric acids, *J. Am. Chem. Soc.*, 2013, **135**, 14044–14047.

43 R. B. Sunoj, Transition State Models for Understanding the Origin of Chiral Induction in Asymmetric Catalysis, *Acc. Chem. Res.*, 2016, **49**, 1019–1028.

44 G. Jindal and R. B. Sunoj, Axially chiral imidodiphosphoric acid catalyst for asymmetric sulfoxidation reaction: Insights on asymmetric induction, *Angew. Chem. Int. Ed.*, 2014, **53**, 4432–4436.

45 L. Kötzner, M. J. Webber, A. Martínez, C. Defusco and B. List, Asymmetric catalysis on the nanoscale: The organocatalytic approach to helicenes, *Angew. Chem. Int.*

Ed., 2014, **53**, 5202–5205.
46 J. P. Reid and J. M. Goodman, Selecting Chiral BINOL-Derived Phosphoric Acid Catalysts: General Model To Identify Steric Features Essential for Enantioselectivity, *Chem. Eur. J.*, 2017, **23**, 14248–14260.
47 J. P. Reid, K. Ermanis and J. M. Goodman, BINOPtimal: A web tool for optimal chiral phosphoric acid catalyst selection, *Chem. Commun.*, 2019, **55**, 1778–1781.
48 X.-Q. Hou and D.-M. Du, Recent Advances in Squaramide-Catalyzed Asymmetric Mannich Reactions, *Adv. Synth. Catal.*, 2020, **362**, 4487–4512.
49 J. Rostoll-Berenguer, G. Blay, J. R. Pedro and C. Vila, Asymmetric Oxidative Mannich Reactions, *Adv. Synth. Catal.*, 2020, **363**, 602–628.
50 S. Saranya, N. A. Harry, K. K. Krishnan and G. Anilkumar, Recent Developments and Perspectives in the Asymmetric Mannich Reaction, *Asian J. Org. Chem.*, 2018, **7**, 613–633.
51 M. Terada, H. Tanaka and K. Sorimachi, Asymmetric direct Mannich reaction catalyzed by chiral Brønsted acid via activation of enecarbamate as an aliphatic imine alternative, *Synlett*, 2008, 1661–1664.
52 T. Kano, T. Yurino and K. Maruoka, Organocatalytic asymmetric synthesis of propargylamines with two adjacent stereocenters: Mannich-type reactions of in situ generated C-alkynyl imines with β-keto esters, *Angew. Chem. Int. Ed.*, 2013, **52**, 11509–11512.
53 T. Yurino, Y. Aota, D. Asakawa, T. Kano and K. Maruoka, N-Boc-aminals as easily accessible precursors for less accessible N-Boc-imines: Facile synthesis of optically active propargylamine derivatives using Mannich-type reactions, *Tetrahedron*, 2016, **72**, 3687–3700.
54 C.-C. Zhang, L.-J. Chen, B.-C. Shen, H.-D. Xie, W. Li and Z.-W. Sun, Enantioselective decarboxylative Mannich reaction of β-keto acids withC-alkynylN-BocN,O-acetals: access to chiral β-keto propargylamines, *Org. Biomol. Chem.*, 2021, **19**, 8607–8612.
55 Y. Yao, H. Shu, B. Tang, S. Chen, Z. Lu and W. Xue, Synthesis, characterization and application of some axially chiral binaphthyl phosphoric acids in asymmetric mannich reaction, *Chinese J. Chem.*, 2015, **33**, 601–609.
56 Y.-D. Shao and D.-J. Cheng, Catalytic Asymmetric 1,2-Difunctionalization of Indolenines with α-(Benzothiazol-2-ylsulfonyl) Carbonyl Compounds, *Adv. Synth. Catal.*, 2017, **359**, 2549–2556.
57 B. Ramesh, G. R. Kumar, S. Yarlagadda, B. Sridhar and B. V. S. Reddy, BINOL-phosphoric acid catalyzed asymmetric Mannich addition of β-ketoesters to indolenines generated in situ by DDQ, *Tetrahedron*, 2019, **75**, 130620.
58 Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu and L.-Z. Gong, Chiral Brønsted acid-catalyzed direct asymmetric Mannich reaction, *J. Am. Chem. Soc.*, 2007, **129**, 3790–3791.
59 M. Rueping, E. Sugiono and F. R. Schoepke, Development of the first Brønsted acid assisted enantioselective Brønsted acid catalyzed direct Mannich reaction, *Synlett*, 2007, 1441–1445.
60 S. Tong, Q. Wang, M.-X. Wang and J. Zhu, Chiral phosphoric acid-catalyzed enantioselective three-component Mannich reaction of acyclic ketones, aldehydes and anilines, *Tetrahedron*, 2018, **74**, 5143–5149.
61 M. Rueping and A. P. Antonchick, Brønsted-acid-catalyzed activation of nitroalkanes: A direct enantioselective aza-henry reaction, *Org. Lett.*, 2008, **10**, 1731–1734.
62 E. P. Ávila, R. M. S. Justo, V. P. Gonçalves, A. A. Pereira, R. Diniz and G. W. Amarante, Chiral Brønsted Acid-Catalyzed Stereoselective Mannich-Type Reaction of Azlactones with Aldimines, *J. Org. Chem.*, 2015, **80**, 590–594.
63 J. Kikuchi, N. Momiyama and M. Terada, Chiral Phosphoric Acid Catalyzed Diastereo- and Enantioselective Mannich-Type Reaction between Enamides and Thiazolones, *Org. Lett.*, 2016, **18**, 2521–2523.
64 X. Ye, Y. Pan and X. Yang, Direct enantioselective Mannich reactions of α-azido cyclic ketones: Asymmetric construction of chiral azides possessing an α-quaternary stereocenter, *Chem. Commun.*, 2019, **56**, 98–101.
65 X. Ye, Y. Pan, Y. Chen and X. Yang, Enantioselective Construction of Sulfur-Containing Tetrasubstituted Stereocenters via Asymmetric Functionalizations of α-Sulfanyl Cyclic Ketones, *Adv. Synth. Catal.*, 2020, **362**, 3374–3379.
66 K. Wang, J. Yu, Y. Shao, S. Tang and J. Sun, Forming All-Carbon Quaternary Stereocenters by Organocatalytic Aminomethylation: Concise Access to β 2,2 -Amino Acids, *Angew. Chem. Int. Ed.*, 2020, **59**, 23516–23520.
67 Q. Huang, Y. Cheng, H. Yuan, X. Chang, P. Li and W. Li, Organocatalytic enantioselective Mannich-type addition of 5H-thiazol-4-ones to isatin-derived imines: access to 3-substituted 3-amino-2-oxindoles featured by vicinal sulfur-containing tetrasubstituted stereocenters, *Org. Chem. Front.*, 2018, **5**, 3226–3230.
68 J.-S. Li, Y.-J. Liu, S. Li and J.-A. Ma, Chiral phosphoric acid-catalyzed direct asymmetric mannich reaction of cyclic: C -acylimines with simple ketones: Facile access to C2-quaternary indolin-3-ones, *Chem. Commun.*, 2018, **54**, 9151–9154.
69 K. N. Reddy, M. V. K. Rao, B. Sridhar and B. V. Subba Reddy, BINOL Phosphoric Acid-Catalyzed Asymmetric Mannich Reaction of Cyclic N-Acyl Ketimines with Cyclic Enones, *Chem. Asian J.*, 2019, **14**, 2958–2965.
70 M. Matišić and M. Gredičak, Enantioselective construction of a tetrasubstituted stereocenter in isoindolinones via an organocatalyzed reaction between ketones and 3-hydroxyisoindolinones, *Chem. Commun.*, 2021, **57**, 13546–13549.
71 M. M. Sadhu, S. K. Ray, R. A. Unhale and V. K. Singh, Brønsted acid-catalyzed enantioselective addition of 1,3-diones to in situ generated N-acyl ketimines, *Org. Biomol. Chem.*, 2022, **20**, 410–414.
72 K. Mori, K. Ehara, K. Kurihara and T. Akiyama, Selective Activation of Enantiotopic C (sp 3) ÀHydrogen by Means of, *J. Am. Chem. Soc.*, 2011, 6166–6169.
73 M. Yamanaka, J. Itoh, K. Fuchibe and T. Akiyama, Chiral Brønsted Acid Catalyzed Enantioselective Mannich-Type Reaction, *J. Am. Chem. Soc.*, 2007, **129**, 6756–6764.
74 T. Akiyama, T. Katoh, K. Mori and K. Kanno,

Enantioselective Mannich-type reaction catalyzed by a chiral phosphoric acid bearing an (S)-biphenol backbone, *Synlett*, 2009, 1664–1666.

75 F. Zhou and H. Yamamoto, A Powerful Chiral Phosphoric Acid Catalyst for Enantioselective Mukaiyama–Mannich Reactions, *Angew. Chem. Int. Ed.*, 2016, **55**, 8970–8974.

76 T. Budragchaa, M. Abraham, W. Schöfberger, A. Roller and M. Widhalm, New tartrate based cyclic phosphoric acids as organocatalysts in Mannich reactions, *Asymmetric Catal.*, 2016, **3**, 1–14.

77 W. Kashikura, K. Mori and T. Akiyama, Chiral phosphoric acid catalyzed enantioselective synthesis of β-amino-α,α-difluoro carbonyl compounds, *Org. Lett.*, 2011, **13**, 1860–1863.

78 J.-S. Li, Y.-J. Liu, G.-W. Zhang and J.-A. Ma, Catalytic Asymmetric Mukaiyama-Mannich Reaction of Cyclic C-Acylimines with Difluoroenoxysilanes: Access to Difluoroalkylated Indolin-3-ones, *Org. Lett.*, 2017, **19**, 6364–6367.

79 M.-Y. Rong, J.-S. Li, Y. Zhou, F.-G. Zhang and J.-A. Ma, Catalytic enantioselective synthesis of difluoromethylated tetrasubstituted stereocenters in isoindolones enabled by a multiple-fluorine system, *Org. Lett.*, 2020, **22**, 9010–9015.

80 M.-Y. Rong, J.-S. Li, Y. Zhou, F.-G. Zhang and J.-A. Ma, Correction to 'Catalytic enantioselective synthesis of difluoromethylated tetrasubstituted stereocenters in isoindolones enabled by a multiple-fluorine system', *Org. Lett.*, 2021, **23**, 623.

81 L. Wang, J. Zhong and X. Lin, Enantioselective synthesis of difluoroalkylated isoindolinones via chiral spirocyclic phosphoric acid catalyzed mannich-type reaction, *Synlett*, 2021, **32**, 417–422.

82 T. Akiyama, Y. Honma, J. Itoh and K. Fuchibe, Vinylogous Mannich-type reaction catalyzed by an iodine-substituted chiral phosphoric acid, *Adv. Synth. Catal.*, 2008, **350**, 399–402.

83 M. Sickert and C. Schneider, The enantioselective, brønsted acid catalyzed, vinylogous Mannich reaction, *Angew. Chem. Int. Ed.*, 2008, **47**, 3631–3634.

84 D. S. Giera, M. Sickert and C. Schneider, A straightforward synthesis of (S)-Anabasine via the catalytic, enantioselective vinylogous mukaiyama-Mannich reaction, *Synth.*, 2009, 3797–3802.

85 M. Sickert, F. Abels, M. Lang, J. Sieler, C. Birkemeyer and C. Schneider, The Brønsted acid catalyzed, enantioselective vinylogous Mannich reaction, *Chem. Eur. J.*, 2010, **16**, 2806–2818.

86 S. Fritzsche, S. Ohla, P. Glaser, D. S. Giera, M. Sickert, C. Schneider and D. Belder, Asymmetric organocatalysis and analysis on a single microfluidic nanospray chip, *Angew. Chem. Int. Ed.*, 2011, **50**, 9467–9470.

87 F. Abels and C. Schneider, A modified and highly useful protocol for the Brønsted acid catalyzed, enantioselective, vinylogous Mannich reaction with aliphatic aldimines, *Synth.*, 2011, 4050–4058.

88 F. Abels, C. Lindemann and C. Schneider, A general strategy for the catalytic, highly enantio- and diastereoselective synthesis of indolizidine-based alkaloids, *Chem. Eur. J.*, 2014, **20**, 1964–1979.

89 D. S. Giera, M. Sickert and C. Schneider, Brønsted Acid-Catalyzed, Enantioselective, Vinylogous Mannich Reaction of Vinylketene Silyl N,O-Acetals, *Org. Lett.*, 2008, **10**, 4259–4262.

90 C. Weilbeer, M. Sickert, S. Naumov and C. Schneider, The Brønsted Acid-Catalyzed, Enantioselective Aza-Diels–Alder Reaction for the Direct Synthesis of Chiral Piperidones, *Chem. Eur. J.*, 2017, **23**, 513–518.

91 G. Rainoldi, A. Sacchetti, A. Silvani and G. Lesma, Organocatalytic vinylogous Mannich reaction of trimethylsiloxyfuran with isatin-derived benzhydryl-ketimines, *Org. Biomol. Chem.*, 2016, **14**, 7768–7776.

92 G. Li, M. J. Kaplan, L. Wojtas and J. C. Antilla, Chiral phosphoric acid catalyzed addition of dihydropyrans to N -acyl imines: Stereocontrolled access to enantioenriched spirocyclic oxazoletetrahydropyrans with three contiguous stereocenters, *Org. Lett.*, 2010, **12**, 1960–1963.

93 X. Wu, X. Yuan, H. Yang and H. Fu, Chiral Phosphoric Acid Catalyzed Asymmetric Addition of 2-(Vinyloxy)ethanol to Imines and Applications of the Products, *Org. Lett.*, 2019, **21**, 5335–5340.

94 M. Terada, K. Machioka and K. Sorimachi, High substrate/catalyst organocatalysis by a chiral Brønsted acid for an enantioselective aza-ene-type reaction, *Angew. Chem. Int. Ed.*, 2006, **45**, 2254–2257.

95 C. Baudequin, A. Zamfir and S. B. Tsogoeva, Highly enantioselective organocatalytic formation of a quaternary carbon center via chiral Brønsted acid catalyzed self-coupling of enamides, *Chem. Commun.*, 2008, 4637–4639.

96 M. Terada, K. Machioka and K. Sorimachi, Activation of hemiaminal ethers by chiral brønsted acids for facile access to enantioselective two-carbon homologation using eneearbamates, *Angew. Chem. Int. Ed.*, 2009, **48**, 2553–2556.

97 G. Dagousset, F. Drouet, G. Masson and J. Zhu, Chiral Brønsted Acid-Catalyzed Enantioselective Multicomponent Mannich Reaction: Synthesis of anti-1,3-Diamines Using Enecarbamates as Nucleophiles, *Org. Lett.*, 2009, **11**, 5546–5549.

98 F.-F. Feng, J.-S. Li, S. Li and J.-A. Ma, Enantioselective Addition of Enamides to Cyclic Ketimines: Access to Chiral 3,3-Disubstituted Isoindolin-1-Ones, *Adv. Synth. Catal.*, 2019, **361**, 4222–4226.

99 Y. Zhang, J.-K. Li, F.-G. Zhang and J.-A. Ma, Catalytic Asymmetric Access to Noncanonical Chiral α-Amino Acids from Cyclic Iminoglyoxylates and Enamides, *J. Org. Chem.*, 2020, **85**, 5580–5589.

100 Y. Wang, Q. Wang and J. Zhu, Chiral Phosphoric Acid-Catalyzed Enantioselective Formal [3+2] Cycloaddition of Azomethine Imines with Enecarbamates, *Chem. Eur. J.*, 2016, **22**, 8084–8088.

101 S. Tong and M.-X. Wang, Catalytic Enantioselective Synthesis of 4-Amino-1,2,3,4-tetrahydropyridine Derivatives from Intramolecular Nucleophilic Addition

Reaction of Tertiary Enamides, *Synlett*, 2019, **30**, 483–487.
102 L.-J. Zhou, Y.-C. Zhang, F. Jiang, G. He, J. Yan, H. Lu, S. Zhang and F. Shi, Enantioselective Construction of Cyclic Enaminone-Based 3-Substituted 3-Amino-2-oxindole Scaffolds via Catalytic Asymmetric Additions of Isatin-Derived Imines, *Adv. Synth. Catal.*, 2016, **358**, 3069–3083.
103 D. J. Ramón and M. Yus, Asymmetric multicomponent reactions (AMCRs): The new frontier, *Angew. Chem. Int. Ed.*, 2005, **44**, 1602–1634.
104 C. de Graaff, E. Ruijter and R. V. A. Orru, Recent developments in asymmetric multicomponent reactions, *Chem. Soc. Rev.*, 2012, **41**, 3969–4009.
105 T. Ahmadi, G. Mohammadi Ziarani, P. Gholamzadeh and H. Mollabagher, Recent advances in asymmetric multicomponent reactions (AMCRs), *Tetrahedron: Asymm.*, 2017, **28**, 708–724.
106 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.
107 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.
108 N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan and L.-Z. Gong, Correction to 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.*, 2010, **132**, 10953.
109 F. Xu, D. Huang, X. Lin and Y. Wang, Highly enantioselective Biginelli reaction catalyzed by SPINOL-phosphoric acids, *Org. Biomol. Chem.*, 2012, **10**, 4467–4470.
110 H. Qu, X. Li, F. Mo and X. Lin, Efficient synthesis of dihydropyrimidinones via a three-component Biginelli-type reaction of urea, alkylaldehyde and arylaldehyde, *Beilstein J. Org. Chem.*, 2013, **9**, 2846–2851.
111 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: Asymm.*, 2017, **28**, 69–74.
112 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.
113 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.
114 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, **28**, 2041–2045.
115 Y. Guo, Z. Gao, C. Fan, J. Chen, J. Li, Y. Huang, G. Huang, H. Yu and C. Zou, Enantioselective Biginelli Reaction of Aliphatic Aldehydes Catalyzed by a Chiral Phosphoric Acid: A Key Step in the Synthesis of the Bicyclic Guanidine Core of Crambescin A and Batzelladine A, *Synth.*, 2018, **50**, 2394–2406.
116 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.
117 F. Palacios, J. Vicario and D. Aparicio, An efficient synthesis of achiral and chiral cyclic dehydro-α-amino acid derivatives through nucleophilic addition of amines to β,γ-unsaturated α-keto esters, *Eur. J. Org. Chem.*, 2006, **2006**, 2843–2850.
118 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, **2008**, 4350–4356.
119 X. Del Corte, A. Maestro, J. Vicario, E. Martinez De Marigorta and F. Palacios, Brönsted-Acid-Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes, and Pyruvate Derivatives. Enantioselective Synthesis of Highly Functionalized γ-Lactam Derivatives, *Org. Lett.*, 2018, **20**, 317–320.
120 X. del Corte, A. López-Francés, A. Maestro, E. Martinez de Marigorta, F. Palacios and J. Vicario, Brönsted Acid Catalyzed Multicomponent Synthesis of Phosphorus and Fluorine-Derived γ-Lactam Derivatives, *J. Org. Chem.*, 2020, **85**, 14369–14383.
121 X. del Corte, A. López-Francés, A. Maestro, I. Villate-Beitia, M. Sainz-Ramos, E. Martínez de Marigorta, J. L. Pedraz, F. Palacios and J. Vicario, A multicomponent protocol for the synthesis of highly functionalized γ-lactam derivatives and their applications as antiproliferative agents, *Pharmaceuticals*, 2021, **14**, 782.
122 X. del Corte, E. Martinez de Marigorta, F. Palacios and J. Vicario, A Brønsted acid-catalyzed multicomponent reaction for the synthesis of highly functionalized γ-lactam derivatives, *Molecules*, 2019, **24**, 2951.
123 X. Li, Y. Zhao, H. Qu, Z. Mao and X. Lin, Organocatalytic asymmetric multicomponent reactions of aromatic aldehydes and anilines with β-ketoesters: Facile and atom-economical access to chiral tetrahydropyridines, *Chem. Commun.*, 2013, **49**, 1401–1403.
124 F. Shi, W. Tan, R.-Y. Zhu, G.-J. Xing and S.-J. Tu, Catalytic asymmetric five-component tandem reaction: Diastereo- and enantioselective synthesis of densely functionalized tetrahydropyridines with biological importance, *Adv. Synth. Catal.*, 2013, **355**, 1605–1622.
125 Y. Wang, M.-S. Tu, F. Shi and S.-J. Tu, Enantioselective construction of the biologically significant dibenzo[1,4]diazepine scaffold via organocatalytic asymmetric three-component reactions, *Adv. Synth. Catal.*, 2014, **356**, 2009–2019.
126 Y. Wang, F. Shi, X.-X. Yao, M. Sun, L. Dong and S.-J. Tu, Catalytic asymmetric construction of 3,3′-spirooxindoles fused with seven-membered rings by enantioselective tandem reactions, *Chem. Eur. J.*, 2014, **20**, 15047–15052.

127 M. Sun, Y. Wang, L. Yin, Y.-Y. Cao and F. Shi, Enantioselective Construction of the Biologically Important Cyclopenta[1,4]diazepine Framework Enabled by Asymmetric Catalysis by Chiral Spiro-Phosphoric Acid, *Eur. J. Org. Chem.*, 2015, **2015**, 7926–7934.

128 G. Dagousset, W. Erb, J. Zhu and G. Masson, Phosphoric acid catalyzed diastereo- and enantioselective synthesis of substituted 1,3-diaminotetralins, *Org. Lett.*, 2014, **16**, 2554–2557.

129 G.-F. Yang, G.-X. Li, J. Huang, D.-Q. Fu, X.-K. Nie, X. Cui, J. Z. Zhao and Z. Tang, Regioselective, Diastereoselective, and Enantioselective One-Pot Tandem Reaction Based on an in Situ Formed Reductant: Preparation of 2,3-Disubstituted 1,5-Benzodiazepine, *J. Org. Chem.*, 2021, **86**, 5110–5119.

130 L. Ren, T. Lei and L.-Z. Gong, Brønsted acid-catalyzed enantioselective Friedländer condensations: Achiral amine promoter plays crucial role in the stereocontrol, *Chem. Commun.*, 2011, **47**, 11683–11685.

131 C. Luo and Y. Huang, A highly diastereo- and enantioselective synthesis of tetrahydroquinolines: Quaternary stereogenic center inversion and functionalization, *J. Am. Chem. Soc.*, 2013, **135**, 8193–8196.

132 Y. Wang, L. Jiang, L. Li, J. Dai, D. Xiong and Z. Shao, An Arylation Strategy to Propargylamines: Catalytic Asymmetric Friedel–Crafts-type Arylation Reactions of C-Alkynyl Imines, *Angew. Chem. Int. Ed.*, 2016, **55**, 15142–15146.

133 N. Man, Y. Li, J. Jie, H. Li, H. Yang, Y. Zhao and H. Fu, Synthesis of Chiral Propargylamines, Chiral 1,2-Dihydronaphtho[2,1-b]furans and Naphtho[2,1-b]furans with C-Alkynyl N,N′-di-(tert-butoxycarbonyl)-aminals and β-Naphthols, *Chem. Eur. J.*, 2021, **27**, 12884–12889.

134 D. Uraguchi, K. Sorimachi and M. Terada, Organocatalytic asymmetric aza-Friedel-Crafts alkylation of furan, *J. Am. Chem. Soc.*, 2004, **126**, 11804–11805.

135 Q. Kang, X.-J. Zheng and S.-L. You, Highly enantioselective friedel-crafts reaction of 4,7-dihydroindoles with imines by chiral phosphoric acids: Facile access to 2-indolyl methanamine derivatives, *Chem. Eur. J.*, 2008, **14**, 3539–3542.

136 S. Nakamura, Y. Sakurai, H. Nakashima, N. Shibata and T. Toru, Organocatalytic enantioselective aza-Friedel-crafts alkylation of pyrroles with N-(heteroarenesulfonyl)imines, *Synlett*, 2009, 1639–1642.

137 V. Sharma, P. Kumar and D. Pathak, Biological Importance of the Indole Nucleus in Recent Years: A Comprehensive Review, *J. Heterocycl. Chem.*, 2010, **47**, 491–502.

138 N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, Biomedical importance of indoles, *Molecules*, 2013, **18**, 6620–6662.

139 S. Kumar and Ritika, A brief review of the biological potential of indole derivatives, *Futur. J. Pharm. Sci.*, , DOI:10.1186/s43094-020-00141-y.

140 G. Bartoli, G. Bencivenni and R. Dalpozzo, Organocatalytic strategies for the asymmetric functionalization of indoles, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465.

141 R. Dalpozzo, Strategies for the asymmetric functionalization of indoles: An update, *Chem. Soc. Rev.*, 2015, **44**, 742–778.

142 S.-L. You, Q. Cai and M. Zeng, Chiral Brønsted acid catalyzed Friedel–Crafts alkylation reactions, *Chem. Soc. Rev.*, 2009, **38**, 2190–2201.

143 Q. Kang, Z.-A. Zhao and S.-L. You, Highly enantioselective Friedel-Crafts reaction of indoles with imines by a chiral phosphoric acid, *J. Am. Chem. Soc.*, 2007, **129**, 1484–1485.

144 M. Terada and K. Sorimachi, Enantioselective Friedel-Crafts reaction of electron-rich alkenes catalyzed by chiral Brønsted acid, *J. Am. Chem. Soc.*, 2007, **129**, 292–293.

145 F. Xu, D. Huang, C. Han, W. Shen, X. Lin and Y. Wang, SPINOL-derived phosphoric acids: Synthesis and application in enantioselective Friedel-Crafts reaction of indoles with imines, *J. Org. Chem.*, 2010, **75**, 8677–8680.

146 C. Xing, Y. Liao, J. Ng and Q. Hu, Optically Active 1,10-Spirobiindane-7,70-diol (SPINOL)-Based Phosphoric Acids as Highly Enantioselective Catalysts for Asymmetric Organocatalysis, *J. Org. Chem.*, 2011, **76**, 4125–4131.

147 L. Bernardi, G. Bolzoni, M. Fochi, M. Mancinelli and A. Mazzanti, An Atropisomerically Enforced Phosphoric Acid for Organocatalytic Asymmetric Reactions, *Eur. J. Org. Chem.*, 2016, **2016**, 3208–3216.

148 L. Simón and J. M. Goodman, DFT study on the factors determining the enantioselectivity of friedel-crafts reactions of indole with N-acyl and N-tosylimines catalyzed by BINOL-phosphoric acid derivatives, *J. Org. Chem.*, 2010, **75**, 589–597.

149 L. Osorio-Planes, C. Rodríguez-Escrich and M. A. Pericàs, Enantioselective continuous-flow production of 3-indolylmethanamines mediated by an immobilized phosphoric acid catalyst, *Chem. Eur. J.*, 2014, **20**, 2367–2372.

150 J. Stemper, K. Isaac, N. Ghosh, H. Lauwick, G. Le Duc, P. Retailleau, A. Voituriez, J.-F. Betzer and A. Marinetti, Silyl-Substituted Planar Chiral Phosphoric Acids with Ferrocene-bridged Paracyclophane Frameworks: Synthesis, Characterization, and Uses in Enantioselective aza-Friedel-Crafts Reactions, *Adv. Synth. Catal.*, 2017, **359**, 519–526.

151 M. Terada, S. Yokoyama, K. Sorimachi and D. Uraguchi, Chiral phosphoric acid-catalyzed enantioselective aza-Friedel-Crafts reaction of indoles, *Adv. Synth. Catal.*, 2007, **349**, 1863–1867.

152 G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman and J. C. Antilla, The highly enantioselective addition of indoles to N-acyl imines with use of a chiral phosphoric acid catalyst, *Org. Lett.*, 2007, **9**, 2609–2611.

153 G. Li, G. B. Rowland, E. B. Rowland and J. C. Antilla, Organocatalytic enantioselective friedel - Crafts reaction of pyrrole derivatives with imines, *Org. Lett.*, 2007, **9**, 4065–4068.

154 Y.-B. Wang, P. Yu, Z.-P. Zhou, J. Zhang, J. (Joelle) Wang, S.-H. Luo, Q.-S. Gu, K. N. Houk and B. Tan, Rational design, enantioselective synthesis and catalytic applications of axially chiral EBINOLs, *Nat. Catal.*, 2019, **2**, 504–513.

155 G.-W. Zhang, L. Wang, J. Nie and J.-A. Ma, Chiral Brønsted acid-mediated enantioselective organocatalytic three-

component reaction for the construction of trifluoromethyl-containing molecules, *Adv. Synth. Catal.*, 2008, **350**, 1457–1463.

156 M. J. Wanner, P. Hauwert, H. E. Schoemaker, R. De Gelder, J. H. Van Maarseveen and H. Hiemstra, Synthesis of enantiopure (S)-indolylglycine by organocatalyzed Friedel-Crafts alkylation of indole, *Eur. J. Org. Chem.*, 2008, **2008**, 180–185.

157 Q. Kang, Z.-A. Zhao and S.-L. You, Enantioselective synthesis of (3-indolyl)glycine derivatives via asymmetric Friedel-Crafts reaction between indoles and glyoxylate imines, *Tetrahedron*, 2009, **65**, 1603–1607.

158 S. S. So and A. E. Mattson, Stereoselective N-H insertion-arylation reactions of nitrodiazoesters, *Asian J. Org. Chem.*, 2014, **3**, 425–428.

159 A. Maestro, E. Martinez de Marigorta, F. Palacios and J. Vicario, Enantioselective α-Aminophosphonate Functionalization of Indole Ring through an Organocatalyzed Friedel-Crafts Reaction, *J. Org. Chem.*, 2019, **84**, 1094–1102.

160 A. Maestro, E. Martín-Encinas, C. Alonso, E. Martinez de Marigorta, G. Rubiales, J. Vicario and F. Palacios, Synthesis of novel antiproliferative hybrid bis-(3-indolyl)methane phosphonate derivatives, *Eur. J. Med. Chem.*, 2018, **158**, 874–883.

161 T. Inokuma, T. Sakakibara, T. Someno, K. Masui, A. Shigenaga, A. Otaka and K. ichi Yamada, Asymmetric Synthesis of α-Amino Phosphonic Acids using Stable Imino Phosphonate as a Universal Precursor, *Chem. Eur. J.*, 2019, **25**, 13829–13832.

162 E. Xie, S. Huang and X. Lin, Design of Planar Chiral Phosphoric Acids with a [2.2]Paracyclophanyl Backbone as Organocatalysts for the Highly Enantioselective Aza-Friedel-Crafts Reaction, *Org. Lett.*, 2019, **21**, 3682–3686.

163 X. Yu, A. Lu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, Chiral phosphoric acid catalyzed asymmetric Friedel-Crafts alkylation of indole with 3-hydroxyisoindolin-1-one: Enantioselective synthesis of 3-indolyl-substituted isoindolin-1-ones, *Eur. J. Org. Chem.*, 2011, **2011**, 892–897.

164 T. Courant, S. Kumarn, L. He, P. Retailleau and G. Masson, Chiral phosphoric acid-catalyzed enantioselective aza-Friedel-Crafts alkylation of indoles with γ-hydroxy-γ-lactams, *Adv. Synth. Catal.*, 2013, **355**, 836–840.

165 S. G. Lee and S.-G. Kim, An asymmetric Brønsted acid-catalyzed Friedel-Crafts reaction of indoles with cyclic: N -sulfimines, *RSC Adv.*, 2017, **7**, 34283–34286.

166 S. Choi and S.-G. Kim, Enantioselective Aza-Friedel–Crafts Reaction of Pyrroles with Cyclic N-Sulfimines Catalyzed by Chiral BINOL-Phosphoric Acid, *Bull. Korean Chem. Soc.*, 2018, **39**, 1340–1343.

167 J. Lee and S.-G. Kim, Asymmetric Phosphoric Acid-catalyzed Aza-Friedel–Crafts Reaction of Furan with Cyclic N-Sulfimines, *Bull. Korean Chem. Soc.*, 2019, **40**, 606–609.

168 M. Zhang, W. Sun, G. Zhu, G. Bao, B. Zhang, L. Hong, M. Li and R. Wang, Enantioselective Dearomative Arylation of Isoquinolines, *ACS Catal.*, 2016, **6**, 5290–5294.

169 A. Beriša, D. Glavač, C. Zheng, S.-L. You and M. Gredičak, Enantioselective construction of a congested quaternary stereogenic center in isoindolinones bearing three aryl groups via an organocatalytic formal Betti reaction , *Org. Chem. Front.*, 2022, **9**, 428–435.

170 J. Zhou, G.-D. Zhu, L. Wang, F.-X. Tan, W. Jiang, Z. G. Ma, J.-C. Kang, S.-H. Hou and S.-Y. Zhang, Remote C6-Enantioselective C-H Functionalization of 2,3-Disubstituted Indoles through the Dual H-Bonds and α-πInteraction Strategy Enabled by CPAs, *Org. Lett.*, 2019, **21**, 8662–8666.

171 C. Liu, F.-X. Tan, J. Zhou, H.-Y. Bai, T.-M. Ding, G.-D. Zhu and S.-Y. Zhang, Highly Chemo-, Site-, and Enantioseletive para C-H Aminoalkylation of N-Monosubstituted Aniline Derivatives Affording 3-Amino-2-oxindoles, *Org. Lett.*, 2020, **22**, 2173–2177.

172 G. J. Wang, L. Wang, G. D. Zhu, J. Zhou, H. Y. Bai and S. Y. Zhang, Organocatalytic Direct Asymmetric Indolization from Anilines by Enantioselective [3 + 2] Annulation, *Org. Lett.*, 2021, **23**, 8434–8438.

173 M. Hatano, H. Okamoto, T. Kawakami, K. Toh, H. Nakatsuji, A. Sakakura and K. Ishihara, Enantioselective aza-Friedel-Crafts reaction of furan with α-ketimino esters induced by a conjugated double hydrogen bond network of chiral bis(phosphoric acid) catalysts, *Chem. Sci.*, 2018, **9**, 6361–6367.

174 A. Kondoh, Y. Ota, T. Komuro, F. Egawa, K. Kanomata and M. Terada, Chiral Brønsted acid-catalyzed enantioselective Friedel-Crafts reaction of 2-methoxyfuran with aliphatic ketimines generated in situ, *Chem. Sci.*, 2016, **7**, 1057–1062.

175 Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, Chiral Brønsted acid catalyzed enantioselective Friedel-Crafts reaction of indoles and α-aryl enamides: Construction of quaternary carbon atoms, *Angew. Chem. Int. Ed.*, 2007, **46**, 5565–5567.

176 J. Hermeke and P. H. Toy, Phosphonium ion tagged chiral phosphoric acids and their application in Friedel-Crafts reactions of indoles, *Tetrahedron*, 2011, **67**, 4103–4109.

177 R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping and C. Bolm, Enantioselective Organocatalytic Synthesis of Quaternary α-Amino Acids Bearing a CF3 Moiety, *Org. Lett.*, 2011, **13**, 1044–1047.

178 R. Yonesaki, Y. Kondo, W. Akkad, M. Sawa, K. Morisaki, H. Morimoto and T. Ohshima, 3-Mono-Substituted BINOL Phosphoric Acids as Effective Organocatalysts in Direct Enantioselective Friedel–Crafts-Type Alkylation of N-Unprotected α-Ketiminoester, *Chem. Eur. J.*, 2018, **24**, 15211–15214.

179 M. Miyagawa, M. Yoshida, Y. Kiyota and T. Akiyama, Enantioselective Friedel–Crafts Alkylation Reaction of Heteroarenes with N-Unprotected Trifluoromethyl Ketimines by Means of Chiral Phosphoric Acid, *Chem. Eur. J.*, 2019, **25**, 5677–5681.

180 T. Uchikura, R. Suzuki, Y. Suda and T. Akiyama, Enantioselective Synthesis of 2-Substituted Indoles Bearing Trifluoromethyl Moiety by the Friedel-Crafts Alkylation Reaction of 4,7-Dihydroindole with N–H Trifluoromethyl Ketimines, *ChemCatChem*, 2020, **12**, 4784–4787.

181 Y. Zhao, L. Cai, T. Huang, S. Meng, A. S. C. Chan and J. Zhao, Solvent-Mediated C3/C7 Regioselective Switch in Chiral Phosphoric Acid-Catalyzed Enantioselective Friedel-Crafts Alkylation of Indoles with α-Ketiminoesters, *Adv. Synth. Catal.*, 2020, **362**, 1309–1316.

182 J. Feng, W. Yan, D. Wang, P. Li, Q. Sun and R. Wang, The highly enantioselective addition of indoles and pyrroles to isatins-derived N-Boc ketimines catalyzed by chiral phosphoric acids, *Chem. Commun.*, 2012, **48**, 8003–8005.

183 F. Jiang, D. Zhao, X. Yang, F.-R. Yuan, G.-J. Mei and F. Shi, Catalyst-controlled chemoselective and enantioselective reactions of tryptophols with isatin-derived imines, *ACS Catal.*, 2017, **7**, 6984–6989.

184 F.-T. Sheng, Z.-M. Li, Y.-Z. Zhang, L.-X. Sun, Y.-C. Zhang, W. Tan and F. Shi, Atroposelective Synthesis of 3,3'-Bisindoles Bearing Axial and Central Chirality: Using Isatin-Derived Imines as Electrophiles, *Chinese J. Chem.*, 2020, **38**, 583–589.

185 Y. You, W.-Y. Lu, K.-X. Xie, J.-Q. Zhao, Z.-H. Wang and W.-C. Yuan, Enantioselective synthesis of isoquinoline-1,3(2: H,4 H)-dione derivatives via a chiral phosphoric acid catalyzed aza-Friedel-Crafts reaction, *Chem. Commun.*, 2019, **55**, 8478–8481.

186 X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, Organocatalyzed Enantioselective Synthesis of Quaternary Carbon-Containing Isoindolin-1-ones, *Eur. J. Org. Chem.*, 2011, **2011**, 3060–3066.

187 E. Aranzamendi, N. Sotomayor and E. Lete, Brønsted acid catalyzed enantioselective α-amidoalkylation in the synthesis of isoindoloisoquinolines, *J. Org. Chem.*, 2012, **77**, 2986–2991.

188 A. Gómez-Sanjuan, N. Sotomayor and E. Lete, Enantioselective intramolecular α-amidoalkylation reaction in the synthesis of pyrrolo[2,1-a]isoquinolines, *Tetrahedron Lett.*, 2012, **53**, 2157–2159.

189 F. Fang, G. Hua, F. Shi and P. Li, Organocatalytic enantioselective Friedel-Crafts reaction: An efficient access to chiral isoindolo-β-carboline derivatives, *Org. Biomol. Chem.*, 2015, **13**, 4395–4398.

190 Q. Yin and S.-L. You, Chiral phosphoric acid-catalysed Friedel-Crafts alkylation reaction of indoles with racemic spiro indolin-3-ones, *Chem. Sci.*, 2011, **2**, 1344–1348.

191 M. Rueping, S. Raja and A. Núñez, Asymmetric Brønsted acid-catalyzed Friedel-Crafts reactions of indoles with cyclic imines - Efficient generation of nitrogen-substituted quaternary carbon centers, *Adv. Synth. Catal.*, 2011, **353**, 563–568.

192 S. Nakamura, N. Matsuda and M. Ohara, Organocatalytic Enantioselective Aza-Friedel–Crafts Reaction of Cyclic Ketimines with Pyrroles using Imidazolinephosphoric Acid Catalysts, *Chem. Eur. J.*, 2016, **22**, 9478–9482.

193 X. Yuan, X. Wu, F. Peng, H. Yang, C. Zhu and H. Fu, Organocatalytic asymmetric synthesis of arylindolyl indolin-3-ones with both axial and central chirality, *Chem. Commun.*, 2020, **56**, 12648–12651.

194 L. Wang, A. Rahman and X. Lin, Enantioselective synthesis of cyclic quaternary α-amino acid derivatives by chiral phosphoric acid catalysis, *Org. Biomol. Chem.*, 2017, **15**, 6033–6041.

195 Z. Yan, X. Gao and Y.-G. Zhou, Enantioselective synthesis of quaternary α-aminophosphonates by organocatalytic Friedel-Crafts reactions of indoles with cyclic α-ketiminophosphonates, *Chinese J. Catal.*, 2017, **38**, 784–791.

196 S. Nakamura, T. Furukawa, T. Hatanaka and Y. Funahashi, Enantioselective aza-Friedel-Crafts reaction of cyclic ketimines with indoles using chiral imidazoline-phosphoric acid catalysts, *Chem. Commun.*, 2018, **54**, 3811–3814.

197 Y.-S. Cheng, S.-H. Chan, G. A. Rao, R. Gurubrahamam and K. Chen, Enantioselective Aza-Friedel-Crafts Reaction of Heteroarenes with in situ Generated Isoxazolium Ions via Chiral Phosphoric Acid Catalysis, *Adv. Synth. Catal.*, 2021, **363**, 3502–3506.

198 K.-F. Zhang, J. Nie, R. Guo, Y. Zheng and J.-A. Ma, Chiral phosphoric acid-catalyzed asymmetric aza-friedel-crafts reaction of indoles with cyclic N-acylketimines: Enantioselective synthesis of trifluoromethyldihydroquinazolines, *Adv. Synth. Catal.*, 2013, **355**, 3497–3502.

199 K.-F. Zhang, J. Nie, R. Guo, Y. Zheng and J.-A. Ma, Chiral phosphoric acid-catalyzed asymmetric aza-friedel-crafts reaction of indoles with cyclic N-acylketimines: Enantioselective synthesis of trifluoromethyldihydroquinazolines, *Adv. Synth. Catal.*, 2014, **356**, 2133.

200 H. Lou, Y. Wang, E. Jin and X. Lin, Organocatalytic Asymmetric Synthesis of Dihydrobenzoxazinones Bearing Trifluoromethylated Quaternary Stereocenters, *J. Org. Chem.*, 2016, **81**, 2019–2026.

201 Y. Zhao, L. Wang and J. Zhao, Chiral phosphoric acid catalyzed aza-Friedel-Crafts alkylation of indoles with cyclic aryl α-ketimino esters, *Tetrahedron Lett.*, 2017, **58**, 213–217.

202 T. Kano, R. Takechi, R. Kobayashi and K. Maruoka, Chiral Brønsted acid-catalyzed enantioselective addition of indoles to ketimines, *Org. Biomol. Chem.*, 2014, **12**, 724–727.

203 E. Xie, A. Rahman and X. Lin, Asymmetric synthesis of CF3- and indole-containing tetrahydro-β-carbolines: Via chiral spirocyclic phosphoric acid-catalyzed aza-Friedel-Crafts reaction, *Org. Chem. Front.*, 2017, **4**, 1407–1410.

204 A. Rahman, E. Xie and X. Lin, Organocatalytic asymmetric synthesis of benzazepinoindole derivatives with trifluoromethylated quaternary stereocenters by chiral phosphoric acid catalysts, *Org. Biomol. Chem.*, 2018, **16**, 1367–1374.

205 A. G. Woldegiorgis, Z. Han and X. Lin, Chiral Phosphoric Acid-Catalyzed Enantioselective Synthesis of Pyrazole-Based Unnatural α-Amino Acid Derivatives, *Adv. Synth. Catal.*, 2022, **364**, 274–280.

206 H. Liu, Y. Yan, M. Li and X. Zhang, An enantioselective aza-Friedel-Crafts reaction of 5-aminoisoxazoles with isatin-derived: N -Boc ketimines, *Org. Biomol. Chem.*, 2021, **19**, 3820–3824.

207 Y. He, M. Lin, Z. Li, X. Liang, G. Li and J. C. Antilla, Direct synthesis of chiral 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines via a catalytic asymmetric intramolecular aza-Friedel-Crafts reaction, *Org. Lett.*, 2011, **13**, 4490–4493.

208 Z. Gao, J. Qian, H. Yang, J. Zhang and G. Jiang, Bronsted Acid Catalyzed Cyclization of Inert N-Substituted Pyrroles to Benzo[f]pyrrolo[1,2- a][1,4]diazepines, *Synlett*, 2021, **32**, 930–934.

209 X. Shen, Y. Wang, T. Wu, Z. Mao and X. Lin, Triply hydrogen-bond-directed enantioselective assembly of pyrrolobenzo-1,4-diazine skeletons with quaternary stereocenters, *Chem. Eur. J.*, 2015, **21**, 9039–9043.

210 H.-X. Chen, Y. Zhang, Y. Zhang, X. He, Z.-W. Zhang, H. Liang, W. He, X. Jiang, X. Chen and L. Qiu, Synthesis of six-membered spirooxindoles via a chiral Brønsted acid-catalyzed asymmetric intramolecular Friedel-Crafts reaction, *RSC Adv.*, 2018, **8**, 37035–37039.

211 J. Seayad, A. M. Seayad and B. List, Catalytic Asymmetric Pictet - Spengler Reaction, *J. Am. Chem. Soc.*, 2006, **128**, 1086–1087.

212 D. Huang, F. Xu, X. Lin and Y. Wang, Highly enantioselective pictet-spengler reaction catalyzed by SPINOL-phosphoric acids, *Chem. Eur. J.*, 2012, **18**, 3148–3152.

213 A. Kim, A. Kim, S. Park, S. Kim, H. Jo, K. M. Ok, S. K. Lee, J. Song and Y. Kwon, Catalytic and Enantioselective Control of the C–N Stereogenic Axis via the Pictet–Spengler Reaction, *Angew. Chem. Int. Ed.*, 2021, **60**, 12279–12283.

214 D. Cheng, H. Wu and S. Tian, Catalytic Asymmetric Pictet-Spengler- Type Reaction for the Synthesis of Optically Active Indolo [3,4-cd][1] benzazepines, *Org. Lett.*, 2011, **13**, 5636–5639.

215 X. Li, D. Chen, H. Gu and X. Lin, Enantioselective synthesis of benzazepinoindoles bearing trifluoromethylated quaternary stereocenters catalyzed by chiral spirocyclic phosphoric acids, *Chem. Commun.*, 2014, **50**, 7538–7541.

216 S. Nakamura, Y. Matsuda, T. Takehara and T. Suzuki, Enantioselective Pictet-Spengler Reaction of Acyclic α-Ketoesters Using Chiral Imidazoline-Phosphoric Acid Catalysts, *Org. Lett.*, 2022, **24**, 1072–1076.

217 S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli and G. Bencivenni, An easy entry to optically active spiroindolinones: Chiral Brønsted acid-catalysed Pictet-Spengler reactions of isatins, *Adv. Synth. Catal.*, 2011, **353**, 860–864.

218 J. J. Badillo, A. Silva-García, B. H. Shupe, J. C. Fettinger and A. K. Franz, Enantioselective Pictet-Spengler reactions of isatins for the synthesis of spiroindolones, *Tetrahedron Lett.*, 2011, **52**, 5550–5553.

219 X.-W. Wang, X. Li, M.-W. Chen, B. Wu and Y.-G. Zhou, Chiral Phosphoric Acid-Catalyzed Pictet-Spengler Reactions for Synthesis of 5′,11′-Dihydrospiro[indoline-3,6′-indolo[3,2-c]qui-nolin]-2-ones Containing Quaternary Stereocenters, *J. Org. Chem.*, 2021, **86**, 6897–6906.

220 C. A. Holloway, M. E. Muratore, R. L. Storer and D. J. Dixon, Direct enantioselective brønsted acid catalyzed N-acyliminium cyclization cascades of tryptamines and ketoacids, *Org. Lett.*, 2010, **12**, 4720–4723.

221 S.-G. Wang, Z.-L. Xia, R.-Q. Xu, X.-J. Liu, C. Zheng and S.-L. You, Construction of Chiral Tetrahydro-β-Carbolines: Asymmetric Pictet–Spengler Reaction of Indolyl Dihydropyridines, *Angew. Chem. Int. Ed.*, 2017, **56**, 7440–7443.

222 Z. L. Xia, C. Zheng, S.-G. Wang and S.-L. You, Catalytic Asymmetric Dearomatization of Indolyl Dihydropyridines through an Enamine Isomerization/Spirocyclization/Transfer Hydrogenation Sequence, *Angew. Chem. Int. Ed.*, 2018, **57**, 2653–2656.

223 Z. Pan, Y. Liu, F. Hu, Q. Liu, W. Shang, X. Ji and C. Xia, Enantioselective Synthesis of Spiroindolines via Cascade Isomerization/Spirocyclization/Dearomatization Reaction, *Org. Lett.*, 2020, **22**, 1589–1593.

224 G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang and J. C. Antilla, Brønsted acid-catalyzed imine amidation, *J. Am. Chem. Soc.*, 2005, **127**, 15696–15697.

225 Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman and J. C. Antilla, VAPOL phosphoric acid catalysis: The highly enantioselective addition of imides to imines, *Chem. Commun.*, 2007, 4477–4479.

226 X. Cheng, S. Vellalath, R. Goddard and B. List, Direct catalytic asymmetric synthesis of cyclic aminals from aldehydes, *J. Am. Chem. Soc.*, 2008, **130**, 15786–15787.

227 M. Rueping, A. P. Antonchick, E. Sugiono and K. Grenader, Asymmetric Brønsted acid catalysis: Catalytic enantioselective synthesis of highly biologically active dihydroquinazolinones, *Angew. Chem. Int. Ed.*, 2009, **48**, 908–910.

228 D.-J. Cheng, Y. Tian and S.-K. Tian, Catalytic asymmetric synthesis of dihydroquinazolinones from imines and 2-aminobenzamides, *Adv. Synth. Catal.*, 2012, **354**, 995–999.

229 D. Huang, X. Li, F. Xu, L. Li and X. Lin, Highly enantioselective synthesis of dihydroquinazolinones catalyzed by SPINOL-phosphoric acids, *ACS Catal.*, 2013, **3**, 2244–2247.

230 Y.-B. Wang, S.-C. Zheng, Y.-M. Hu and B. Tan, Brønsted acid-catalysed enantioselective construction of axially chiral arylquinazolinones, *Nat. Commun.*, 2017, **8**, 15489.

231 Y. He, C. Cheng, B. Chen, K. Duan, Y. Zhuang, B. Yuan, M. Zhang, Y. Zhou, Z. Zhou, Y. Su, R. Cao and L. Qiu, Highly Enantioselective Synthesis of 2,3-Dihydro-1H-imidazo[2,1-a]isoindol-5(9bH)-ones via Catalytic Asymmetric Intramolecular Cascade Imidization−Nucleophilic Addition−Lactamization, *Org. Lett.*, 2014, **16**, 6366–6369.

232 S. Nakamura, T. Wada, T. Takehara and T. Suzuki, Catalytic Enantioselective Synthesis of N,N-Acetals from α-Dicarbonyl Compounds Using Chiral Imidazoline-Phosphoric Acid Catalysts, *Adv. Synth. Catal.*, 2020, **362**, 5374–5379.

233 Y. Kwon, J. Li, J. P. Reid, J. M. Crawford, R. Jacob, M. S. Sigman, F. D. Toste and S. J. Miller, Disparate Catalytic Scaffolds for Atroposelective Cyclodehydration, *J. Am. Chem. Soc.*, 2019, **141**, 6698–6705.

234 N. Man, Z. Lou, Y. Li, H. Yang, Y. Zhao and H. Fu,

Organocatalytic Atroposelective Construction of Axially Chiral N-Aryl Benzimidazoles Involving Carbon-Carbon Bond Cleavage, *Org. Lett.*, 2020, **22**, 6382–6387.

235 Y.-M. Wang, H.-H. Zhang, C. Li, T. Fan and F. Shi, Catalytic asymmetric chemoselective 1,3-dipolar cycloadditions of an azomethine ylide with isatin-derived imines: Diastereo- and enantioselective construction of a spiro[imidazolidine-2,3′-oxindole] framework, *Chem. Commun.*, 2016, **52**, 1804–1807.

236 X. Yuan, X. Wu, P. Zhang, F. Peng, C. Liu, H. Yang, C. Zhu and H. Fu, Axially Chiral Cyclic Phosphoric Acid Enabled Enantioselective Sequential Additions, *Org. Lett.*, 2019, **21**, 2498–2503.

237 Y. Xie, Y. Zhao, B. Qian, L. Yang, C. Xia and H. Huang, Enantioselective N-H functionalization of indoles with α,β-unsaturated γ-lactams catalyzed by chiral Brønsted acids, *Angew. Chem. Int. Ed.*, 2011, **50**, 5682–5686.

238 Y. Cai, Q. Gu and S.-L. You, Chemoselective N-H functionalization of indole derivatives via the Reissert-type reaction catalyzed by a chiral phosphoric acid, *Org. Biomol. Chem.*, 2018, **16**, 6146–6154.

239 J. Yang, Z. He, L. Hong, W. Sun and R. Wang, AsymmetricN-aminoalkylation of 3-substituted indoles by N-protectedN,O-acetals: An access to chiral propargyl aminals, *Org. Biomol. Chem.*, 2020, **18**, 4169–4173.

240 L. Zhang, B. Wu, Z. Chen, J. Hu, X. Zeng and G. Zhong, Chiral phosphoric acid catalyzed enantioselective: N -alkylation of indoles with in situ generated cyclic N -acyl ketimines, *Chem. Commun.*, 2018, **54**, 9230–9233.

241 X.-W. Wang, M.-W. Chen, B. Wu, B. Wang and Y.-G. Zhou, Chiral Phosphoric Acid-Catalyzed Synthesis of Fluorinated 5,6-Dihydroindolo[1,2- c]quinazolines with Quaternary Stereocenters, *J. Org. Chem.*, 2019, **84**, 8300–8308.

242 X.-W. Wang, M.-W. Chen, B. Wu, B. Wang, B. Wan and Y.-G. Zhou, Chiral phosphoric acid-catalyzed regioselective synthesis of spiro aminals with quaternary stereocenters, *Tetrahedron Lett.*, 2021, **65**, 152793.

243 X. Lin, K. Ge, N. He, X. Chen, P. Li, M. Dong and W. Li, Organocatalytic Enantioselective Construction of Acyclic N,N-Acetals via Aza-Addition of Arylamines to Ketimines, *Adv. Synth. Catal.*, 2021, **363**, 4332–4337.

244 G. Li, F. R. Fronczek and J. C. Antilla, Catalytic asymmetric addition of alcohols to imines: Enantioselective preparation of chiral N,O-aminals, *J. Am. Chem. Soc.*, 2008, **130**, 12216–12217.

245 W. Zheng, L. Wojtas and J. C. Antilla, Chiral phosphoric acid catalyzed peroxidation of imines, *Angew. Chem. Int. Ed.*, 2010, **49**, 6589–6591.

246 G. K. Ingle, M. G. Mormino, L. Wojtas and J. C. Antilla, Chiral phosphoric acid-catalyzed addition of thiols to N-acyl imines: Access to chiral N, S-acetals, *Org. Lett.*, 2011, **13**, 4822–4825.

247 L. Shi, B. Zhang, J. Zhang, X. Shi and R. Guo, One-pot multicomponent asymmetric synthesis of α-amidosulfides from thiophenol and N-acylimines generated in situ from α-amidosulfones, *Monatshefte fur Chemie*, 2017, **148**, 375–379.

248 M.-X. Wang, J. Liu, Z. Liu, Y. Wang, Q.-Q. Yang, W. Shan, Y.-H. Deng and Z. Shao, Enantioselective synthesis of chiral α-alkynylated thiazolidones by tandem: S -addition/acetalization of alkynyl imines, *Org. Biomol. Chem.*, 2020, **18**, 3117–3124.

249 R. A. Unhale, N. Molleti, N. K. Rana, S. Dhanasekaran, S. Bhandary and V. K. Singh, Chiral phosphoric acid catalyzed enantioselective addition of thiols to in situ generated ketimines: Synthesis of N,S-ketals, *Tetrahedron Lett.*, 2017, **58**, 145–151.

250 T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, Chiral Brønsted acid catalyzed enantioselective hydrophosphonylation of imines: Asymmetric synthesis of α-amino phosphonates, *Org. Lett.*, 2005, **7**, 2583–2585.

251 P. S. Bhadury, Y. Zhang, S. Zhang, B. Song, S. Yang, D. Hu, Z. Chen, W. Xue and L. Jin, An Effective Route to Fluorine Containing Asymmetric a-Aminophosphonates Using Chiral Bronsted Acid Catalyst, *Chirality*, 2009, **21**, 547–557.

252 Y. Zhao, X. Li, F. Mo, L. Li and X. Lin, Highly enantioselective hydrophosphonylation of imines catalyzed by SPINOL-phosphoric acid, *RSC Adv.*, 2013, **3**, 11895–11901.

253 M. Yamanaka and T. Hirata, DFT study on bifunctional chiral brønsted acid-catalyzed asymmetric hydrophosphonylation of imines, *J. Org. Chem.*, 2009, **74**, 3266–3271.

254 T. Akiyama, H. Morita, P. Bachu, K. Mori, M. Yamanaka and T. Hirata, Chiral Brønsted acid-catalyzed hydrophosphonylation of imines-DFT study on the effect of substituents of phosphoric acid, *Tetrahedron*, 2009, **65**, 4950–4956.

255 F.-Q. Shi and B.-A. Song, Origins of enantioselectivity in the chiral Brønsted acid catalyzed hydrophosphonylation of imines, *Org. Biomol. Chem.*, 2009, **7**, 1292–1298.

256 X. Cheng, R. Goddard, G. Buth and B. List, Direct catalytic asymmetric three-component Kabachnik-fields reaction, *Angew. Chem. Int. Ed.*, 2008, **47**, 5079–5081.

257 N. Momiyama, H. Nishimoto and M. Terada, Chiral brønsted acid catalysis for enantioselective hosomi-sakurai reaction of imines with allyltrimethylsilane, *Org. Lett.*, 2011, **13**, 2126–2129.

258 H.-H. Zhang, Y.-M. Wang, Y.-W. Xie, Z.-Q. Zhu, F. Shi and S.-J. Tu, Organocatalytic chemo-, (E/Z)- and enantioselective formal alkenylation of indole-derived hydroxylactams using o -hydroxystyrenes as a source of alkenyl group, *J. Org. Chem.*, 2014, **79**, 7141–7151.

259 N. Momiyama, H. Okamoto, M. Shimizu and M. Terada, Synthetic Method for 2,2′-Disubstituted Fluorinated Binaphthyl Derivatives and Application as Chiral Source in Design ofChiral Mono- Phosphoric Acid Catalyst, *Chirality*, 2015, **27**, 464–475.

260 N. Momiyama, H. Okamoto, J. Kikuchi, T. Korenaga and M. Terada, Perfluorinated Aryls in the Design of Chiral Brønsted Acid Catalysts: Catalysis of Enantioselective [4 + 2] Cycloadditions and Ene Reactions of Imines with Alkenes by Chiral Mono-Phosphoric Acids with Perfluoroaryls, *ACS Catal.*, 2016, **6**, 1198–1204.

261 Q. X. Zhang, Y. Li, J. Wang, C. Yang, C. J. Liu, X. Li and J. P.

Cheng, B(C6F5)3/Chiral Phosphoric Acid Catalyzed Ketimine–Ene Reaction of 2-Aryl-3H-indol-3-ones and α-Methylstyrenes, *Angew. Chem. Int. Ed.*, 2020, **59**, 4550–4556.

262 H. Ishihara, J. Huang, T. Mochizuki, M. Hatano and K. Ishihara, Enantio- And Diastereoselective Carbonyl-Ene Cyclization-Acetalization Tandem Reaction Catalyzed by Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acids, *ACS Catal.*, 2021, **11**, 6121–6127.

263 J.-H. Xue, M. Shi, F. Yu, X.-Y. Li, W. Ren, L.-N. Fu and Q.-X. Guo, Catalytic Asymmetric Nucleophilic Addition of 3-Vinyl Indoles to Imines, *Org. Lett.*, 2016, **18**, 3874–3877.

264 S. Zhong, M. Nieger, A. Bihlmeier, M. Shi and S. Bräse, Asymmetric organocatalytic synthesis of 4,6-bis(1H-indole-3-yl)-piperidine- 2 carboxylates, *Org. Biomol. Chem.*, 2014, **12**, 3265–3270.

265 C. Retich and S. Bräse, Asymmetric Organocatalytic Synthesis of Bisindoles – Scope and Derivatizations, *Eur. J. Org. Chem.*, 2018, **2018**, 60–77.

266 M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Kŏckritz, A. Pews-Davtyan, N. Nemati and M. Beller, An enantioselective chiral Brønsted acid catalyzed imino-azaenamine reaction, *Org. Lett.*, 2007, **9**, 1065–1068.

267 Y. Wang, Q. Wang and J. Zhu, Organocatalytic Nucleophilic Addition of Hydrazones to Imines: Synthesis of Enantioenriched Vicinal Diamines, *Angew. Chem. Int. Ed.*, 2017, **56**, 5612–5615.

268 D. Uraguchi, K. Sorimachi and M. Terada, Organocatalytic asymmetric direct alkylation of α-diazoester via C-H bond cleavage, *J. Am. Chem. Soc.*, 2005, **127**, 9360–9361.

269 H. Zhang, X. Wen, L. Gan and Y. Peng, Highly efficient asymmetric mannich reaction of dialkyl α-diazomethylphosphonates with N -carbamoyl imines catalyzed by chiral brønsted acids, *Org. Lett.*, 2012, **14**, 2126–2129.

270 R. A. Unhale, M. M. Sadhu, S. K. Ray, R. G. Biswas and V. K. Singh, A chiral Brønsted acid-catalyzed highly enantioselective Mannich-type reaction of α-diazo esters with in situ generated N -acyl ketimines, *Chem. Commun.*, 2018, **54**, 3516–3519.

271 W. Wu, Y. Wang, J. Guo, L. Cai, Y. Chen, Y. Huang and Y. Peng, Asymmetric acyl-Mannich reaction of isoquinolines with α-(diazomethyl)phosphonate and diazoacetate catalyzed by chiral Brønsted acids, *Chem. Commun.*, 2020, **56**, 11235–11238.

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

273 X. Zeng, X. Zeng, Z. Xu, M. Lu and G. Zhong, Highly efficient asymmetric trans-selective aziridination of diazoacetamides and N-Boc-imines catalyzed by chiral brønsted acids, *Org. Lett.*, 2009, **11**, 3036–3039.

274 W. Masamba, Petasis vs. Strecker amino acid synthesis: Convergence, divergence and opportunities in organic synthesis, *Molecules*, 2021, **26**, 1707.

275 M. Rueping, E. Sugiono and C. Azap, A highly enantioselective Brønsted acid catalyst for the Strecker reaction, *Angew. Chem. Int. Ed.*, 2006, **45**, 2617–2619.

276 M. Rueping, E. Sugiono and S. A. Moreth, Metal-free, enantioselective strecker reactions catalyzed by chiral BINOL and TADDOL catalysts, *Adv. Synth. Catal.*, 2007, **349**, 759–764.

277 L. Simón and J. M. Goodman, Mechanism of BINOL-phosphoric acid-catalyzed strecker reaction of benzyl imines, *J. Am. Chem. Soc.*, 2009, **131**, 4070–4077.

278 A. Zamfir and S. B. Tsogoeva, Asymmetric hydrocyanation of hydrazones catalyzed by in situ formed O-silylated BINOL-phosphate: A convenient access to versatile α-hydrazino acids, *Org. Lett.*, 2010, **12**, 188–191.

279 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.

280 K. Shen, X. Liu, Y. Cai, L. Lin and X. Feng, Facile and efficient enantioselective strecker reaction of ketimines by chiral sodium phosphate, *Chem. Eur. J.*, 2009, **15**, 6008–6014.

281 Q. Wang, D.-X. Wang, M.-X. Wang and J. Zhu, Still Unconquered: Enantioselective Passerini and Ugi Multicomponent Reactions, *Acc. Chem. Res.*, 2018, **51**, 1290–1300.

282 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.

283 Y. Su, M. J. Bouma, L. Alcaraz, M. Stocks, M. Furber, G. Masson and J. Zhu, Organocatalytic enantioselective one-pot four-component Ugi-type multicomponent reaction for the synthesis of epoxy-tetrahydropyrrolo[3,4-b] pyridin-5-ones, *Chem. Eur. J.*, 2012, **18**, 12624–12627.

284 J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. (Joelle) Wang, K. N. Houk and B. Tan, Asymmetric phosphoric acid-catalyzed four-component Ugi reaction, *Science*, 2018, **361**, eaas8707.

285 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.

286 Q. Y. Feng, J. Zhu, M.-X. Wang and S. Tong, Organocatalytic double ugi reaction with statistical amplification of product enantiopurity: A linker cleavage approach to access highly enantiopure ugi products, *Org. Lett.*, 2020, **22**, 483–487.

287 M. Terada, K. Soga and N. Momiyama, Enantioselective activation of aldehydes by chiral phosphoric acid catalysts in an aza-ene-type reaction between glyoxylate and enecarbamate, *Angew. Chem. Int. Ed.*, 2008, **47**, 4122–4125.

288 M. N. Grayson, Chiral Phosphoric Acid Catalysis: The Terada Model Revisited, *J. Org. Chem.*, 2021, **86**, 13631–13635.

289 Q.-L. Pei, B.-D. Cui, W.-Y. Han, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, A facile synthesis of 3-hydroxy-3-(trifluoromethyl)-1H-pyrrol-2(3H)-ones with Brønsted acid-catalyzed condensation-cyclization reactions of β-enamino esters and ethyl trifluoropyruvate, *Tetrahedron*, 2014, **70**,

4595–4601.

290 Y.-D. Shao, M.-M. Dong, Y.-A. Wang, P.-M. Cheng, T. Wang and D.-J. Cheng, Organocatalytic Atroposelective Friedländer Quinoline Heteroannulation, *Org. Lett.*, 2019, **21**, 4831–4836.

291 J. Wan, H. Liu, Y. Lan, X. Li, X. Hu, J. Li, H.-P. Xiao and J. Jiang, Catalytic Asymmetric Synthesis of Atropisomeric Quinolines through the Friedländer Reaction, *Synlett*, 2019, **30**, 2198–2202.

292 Y.-D. Shao, D.-D. Han, W.-Y. Ma and D.-J. Cheng, Chiral phosphoric acid catalyzed atroposelective and diastereoselective synthesis of 9-aryltetrahydroacridines, *Org. Chem. Front.*, 2020, **7**, 2255–2262.

293 M. Terada, H. Tanaka and K. Sorimachi, Enantioselective direct aldol-type reaction of azlactone via protonation of vinyl ethers by a chiral brønsted acid catalyst, *J. Am. Chem. Soc.*, 2009, **131**, 3430–3431.

294 G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden and J. Blanchet, Brønsted acid catalyzed asymmetric aldol reaction: A complementary approach to enamine catalysis, *Org. Lett.*, 2010, **12**, 3582–3585.

295 J. Das, F. Le Cavelier, J. Rouden and J. Blanchet, Expanding the scope of the direct regiospecific asymmetric aldol reaction to enones and dienones catalyzed by a BINOL-derived brønsted acid, *Eur. J. Org. Chem.*, 2011, **2011**, 6628–6631.

296 K. Kanomata, Y. Toda, Y. Shibata, M. Yamanaka, S. Tsuzuki, I. D. Gridnev and M. Terada, Secondary stereocontrolling interactions in chiral Brønsted acid catalysis: Study of a Petasis-Ferrier-type rearrangement catalyzed by chiral phosphoric acids, *Chem. Sci.*, 2014, **5**, 3515–3523.

297 H. Wu, Y.-P. He and F. Shi, Recent Advances in Chiral Phosphoric Acid Catalyzed Asymmetric Reactions for the Synthesis of Enantiopure Indole Derivatives, *Synth.*, 2015, **47**, 1990–2016.

298 P. J. Praveen, P. S. Parameswaran and M. S. Majik, Bis(indolyl)methane Alkaloids: Isolation, Bioactivity, and Syntheses, *Synth.*, 2015, **47**, 1827–1837.

299 M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, Bis- and trisindolylmethanes (BIMs and TIMs), *Chem. Rev.*, 2010, **110**, 2250–2293.

300 L. Qin, P. Wang, Y. Zhang, Z. Ren, X. Zhang and C.-S. Da, Direct Asymmetric Friedel-Crafts Reaction of Naphthols with Acetals Catalyzed by Chiral Bronsted Acids, *Synlett*, 2016, **27**, 571–574.

301 L. Cai, Y. Zhao, T. Huang, S. Meng, X. Jia, A. S. C. Chan and J. Zhao, Chiral Phosphoric-Acid-Catalyzed Regioselective and Enantioselective C7-Friedel-Crafts Alkylation of 4-Aminoindoles with Trifluoromethyl Ketones, *Org. Lett.*, 2019, **21**, 3538–3542.

302 L. Zhang, S.-H. Xiang, J. (Joelle) Wang, J. Xiao, J.-Q. Wang and B. Tan, Phosphoric acid-catalyzed atroposelective construction of axially chiral arylpyrroles, *Nat. Commun.*, 2019, **10**, 566.

303 L. Zhang, S.-H. Xiang, J. (Joelle) Wang, J. Xiao, J.-Q. Wang and B. Tan, Publisher Correction: Phosphoric acid-catalyzed atroposelective construction of axially chiral arylpyrroles (Nature Communications, (2019), 10, 1, (566), 10.1038/s41467-019-08447-z), *Nat. Commun.*, 2019, **10**, 518055.

304 J. T. M. Correia, B. List and F. Coelho, Catalytic Asymmetric Conjugate Addition of Indolizines to α,β-Unsaturated Ketones, *Angew. Chem. Int. Ed.*, 2017, **56**, 7967–7970.

305 C. Liu, P. Han, X. Wu and M. Tang, The mechanism investigation of chiral phosphoric acid-catalyzed Friedel-Crafts reactions - How the chiral phosphoric acid regains the proton, *Comput. Theor. Chem.*, 2014, **1050**, 39–45.

306 J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng and J.-A. Ma, A perfect double role of CF3 groups in activating substrates and stabilizing adducts: The chiral Brønsted acid-catalyzed direct arylation of trifluoromethyl ketones, *Chem. Commun.*, 2009, 2356–2358.

307 J. Nie, G.-W. Zhang, L. Wang, D.-H. Zheng, Y. Zheng and J.-A. Ma, Chiral Brønsted-acid-catalyzed enantioselective arylation of ethyl trifluoroacetoacetate and ethyl trifluoropyruvate, *Eur. J. Org. Chem.*, 2009, **2009**, 3145–3149.

308 T. Wang, G.-W. Zhang, Y. Teng, J. Nie, Y. Zheng and J.-A. Ma, Chiral Brønsted acid-catalyzed enantioselective friedel-crafts reaction of 4,7-dihydroindoles with trifluoromethyl ketones, *Adv. Synth. Catal.*, 2010, **352**, 2773–2777.

309 W. Kashikura, J. Itoh, K. Mori and T. Akiyama, Enantioselective Friedel-Crafts alkylation of indoles, pyrroles, and furans with trifluoropyruvate catalyzed by chiral phosphoric acid, *Chem. Asian J.*, 2010, **5**, 470–472.

310 Y. Wang, W. Liu, W. Ren and Y. Shi, Synthesis and Evaluation of 5,5′-Bitetralone-Based Chiral Phosphoric Acids, *Org. Lett.*, 2015, **17**, 4976–4979.

311 M. Biedrzycki, A. Kasztelan and P. Kwiatkowski, High-Pressure Accelerated Enantioselective Addition of Indoles to Trifluoromethyl Ketones with a Low Loading of Chiral BINOL-Derived Phosphoric Acid, *ChemCatChem*, 2017, **9**, 2453–2456.

312 J. Ma and S. R. Kass, Asymmetric Arylation of 2,2,2-Trifluoroacetophenones Catalyzed by Chiral Electrostatically-Enhanced Phosphoric Acids, *Org. Lett.*, 2018, **20**, 2689–2692.

313 G. Li, Y. Yao, Z. Wang, M. Zhao, J. Xu, L. Huang, G. Zhu, G. Bao, W. Sun, L. Hong and R. Wang, Switchable Skeletal Rearrangement of Dihydroisobenzofuran Acetals with Indoles, *Org. Lett.*, 2019, **21**, 4313–4317.

314 X. Deng, Y. Wang, S. Zhang, L. Li, G. Li, G. Zhao and Z. Tang, An organocatalytic asymmetric Friedel-Crafts reaction of 2-substituted indoles with aldehydes: enantioselective synthesis of α-hydroxyl ketones by low loading of chiral phosphoric acid, *Chem. Commun.*, 2020, **56**, 2499–2502.

315 C. L. Hansen, R. G. Ohm, L. B. Olsen, E. Ascic, D. Tanner and T. E. Nielsen, Catalytic Enantioselective Synthesis of Tetrahydocarbazoles and Exocyclic Pictet-Spengler-Type Reactions, *Org. Lett.*, 2016, **18**, 5990–5993.

316 S. Yu, H. Chen, X. Xu, W. Yuan and X. Zhang, Enatioselective Synthesis of Tetrahydrocarbazoles via Chiral Phosphoric Acid Promoted Domino Friedel–Crafts-type Reaction of Indole-3-butanal with Indoles, *J. Heterocycl. Chem.*, 2018,

55, 619–631.

317 D. M. Sedgwick, M. N. Grayson, S. Fustero and P. Barrio, Recent Developments and Applications of the Chiral Bronsted Acid Catalyzed Allylboration of Carbonyl Compounds, *Synth.*, 2018, **50**, 1935–1957.

318 M. Yus, J. C. González-Gómez and F. Foubelo, Catalytic enantioselective allylation of carbonyl compounds and imines, *Chem. Rev.*, 2011, **111**, 7774–7854.

319 P. Jain and J. C. Antilla, Chiral brønsted acid-catalyzed allylboration of aldehydes, *J. Am. Chem. Soc.*, 2010, **132**, 11884–11886.

320 C.-H. Xing, Y.-X. Liao, Y. Zhang, D. Sabarova, M. Bassous and Q.-S. Hu, Asymmetric allylboration of aldehydes with pinacol allylboronates catalyzed by 1,1′-spirobiindane-7,7′-diol (SPINOL) based phosphoric acids, *Eur. J. Org. Chem.*, 2012, **2012**, 1115–1118.

321 P. Barrio, E. Rodríguez, K. Saito, S. Fustero and T. Akiyama, γ-Silylboronates in the chiral Brønsted acid-catalysed allylboration of aldehydes, *Chem. Commun.*, 2015, **51**, 5246–5249.

322 S. Gao and M. Chen, Enantioselective syn- and anti-Alkoxyallylation of Aldehydes via Brønsted Acid Catalysis, *Org. Lett.*, 2018, **20**, 6174–6177.

323 J. Yuan, P. Jain and J. C. Antilla, Bi(cyclopentyl)diol-Derived Boronates in Highly Enantioselective Chiral Phosphoric Acid-Catalyzed Allylation, Propargylation, and Crotylation of Aldehydes, *J. Org. Chem.*, 2020, **85**, 12988–13003.

324 M. N. Grayson, S. C. Pellegrinet and J. M. Goodman, Mechanistic insights into the BINOL-derived phosphoric acid-catalyzed asymmetric allylboration of aldehydes, *J. Am. Chem. Soc.*, 2012, **134**, 2716–2722.

325 M. N. Grayson and J. M. Goodman, Understanding the mechanism of the asymmetric propargylation of aldehydes promoted by 1,1′-Bi-2-naphthol-derived catalysts, *J. Am. Chem. Soc.*, 2013, **135**, 6142–6148.

326 H. Wang, P. Jain, J. C. Antilla and K. N. Houk, Origins of stereoselectivities in chiral phosphoric acid catalyzed allylborations and propargylations of aldehydes, *J. Org. Chem.*, 2013, **78**, 1208–1215.

327 K. Cheng, T. Fan and J. Sun, Chiral phosphoric acid catalyzed enantioselective allylation of aldehydes with allyltrichlorosilane, *Chinese J. Chem.*, 2011, **29**, 1669–1671.

328 Y.-L. Zhang, B.-J. He, Y.-W. Xie, Y.-H. Wang, Y.-L. Wang, Y. C. Shen and Y.-Y. Huang, Enantioselective Isoprenylboration Reaction of Aldehydes Catalyzed by a Chiral Phosphoric Acid, *Adv. Synth. Catal.*, 2019, **361**, 3074–3079.

329 S. Gao and M. Chen, Enantioselective syntheses of 1,4-pentadien-3-yl carbinols via brønsted acid catalysis, *Org. Lett.*, 2020, **22**, 400–404.

330 S. Gao, M. Duan, K. N. Houk and M. Chen, Chiral Phosphoric Acid Dual-Function Catalysis: Asymmetric Allylation with α-Vinyl Allylboron Reagents, *Angew. Chem. Int. Ed.*, 2020, **59**, 10540–10548.

331 Y.-L. Zhang, Z.-N. Zhao, W.-L. Li, J.-J. Li, S. J. Kalita, U. Schneider and Y.-Y. Huang, Catalytic asymmetric aldehyde prenylation and application in the total synthesis of (-)-rosiridol and (-)-bifurcadiol, *Chem. Commun.*, 2020, **56**, 10030–10033.

332 X. Yang, S. Pang, F. Cheng, Y. Zhang, Y.-W. Lin, Q. Yuan, F.-L. Zhang and Y.-Y. Huang, Enantioselective synthesis of 1,3-disubstituted 1,3- dihydroisobenzofurans via a cascade allylboration/oxo-michael reaction of o-formyl chalcones catalyzed by a chiral phosphoric acid, *J. Org. Chem.*, 2017, **82**, 10388–10397.

333 B. E. Hetzler, G. Volpin, E. Vignoni, A. G. Petrovic, G. Proni, C. T. Hu and D. Trauner, A Versatile Bis-Allylboron Reagent for the Stereoselective Synthesis of Chiral Diols, *Angew. Chem. Int. Ed.*, 2018, **57**, 14276–14280.

334 J. Liu and M. Chen, Enantioselective anti- And syn-(borylmethyl)allylation of aldehydes via brønsted acid catalysis, *Org. Lett.*, 2020, **22**, 8967–8972.

335 J. Chen and M. Chen, Enantioselective Syntheses of (Z)-6′-Boryl-anti-1,2-oxaborinan-3-enes via a Dienylboronate Protoboration and Asymmetric Allylation Reaction Sequence, *Org. Lett.*, 2020, **22**, 7321–7326.

336 S. Gao, M. Duan, J. Liu, P. Yu, K. N. Houk and M. Chen, Stereochemical Control via Chirality Pairing: Stereodivergent Syntheses of Enantioenriched Homoallylic Alcohols, *Angew. Chem. Int. Ed.*, 2021, **60**, 24096–24106.

337 P. Jain, H. Wang, K. N. Houk and J. C. Antilla, Brønsted acid catalyzed asymmetric propargylation of aldehydes, *Angew. Chem. Int. Ed.*, 2012, **51**, 1391–1394.

338 L. R. Reddy, Chiral Brønsted Acid Catalyzed Enantioselective Propargylation of Aldehydes with Allenylboronate, *Org. Lett.*, 2012, **14**, 1142–1145.

339 Y. Sasaki, M. Sawamura and H. Ito, Mechanistic insight into the anomalous syn-selectivity observed during the addition of allenylboronates to aromatic aldehydes, *Chem. Lett.*, 2011, **40**, 1044–1046.

340 M. Chen and W. R. Roush, Enantioselective synthesis of anti - And syn -homopropargyl alcohols via chiral Brønsted acid catalyzed asymmetric allenylboration reactions, *J. Am. Chem. Soc.*, 2012, **134**, 10947–10952.

341 M. Chen and W. R. Roush, Correction to Enantioselective synthesis of anti - And syn -homopropargyl alcohols via chiral Brønsted acid catalyzed asymmetric allenylboration reactions, *J. Am. Chem. Soc.*, 2012, **134**, 10947–10952.

342 A. S. Tsai, M. Chen and W. R. Roush, Correction to Chiral Brønsted Acid Catalyzed Enantioselective Synthesis of anti-Homopropargyl Alcohols via Kinetic Resolution- Aldehyde AllenylborationUsing RacemicAllenylboronates, *Org. Lett.*, 2013, **15**, 2325.

343 A. S. Tsai, M. Chen and W. R. Roush, Erratum: Chiral Brønsted acid catalyzed enantioselective synthesis of anti-homopropargyl alcohols via kinetic resolution-aldehyde allenylboration using racemic allenylboronates (Organic Letters), *Org. Lett.*, 2013, **15**, 2325.

344 M. Wang, S. Khan, E. Miliordos and M. Chen, Enantioselective Syntheses of Homopropargylic Alcohols via Asymmetric Allenylboration, *Org. Lett.*, 2018, **20**, 3810–3814.

345 Y. Huang, X. Yang, Z. Lv, C. Cai, C. Kai, Y. Pei and Y. Feng, Asymmetric Synthesis of 1,3-Butadienyl-2-carbinols by the Homoallenylboration of Aldehydes with a Chiral

Phosphoric Acid Catalyst, *Angew. Chem. Int. Ed.*, 2015, **54**, 7299–7302.

346 L. R. Reddy, Chiral Brønsted acid catalyzed enantioselective allenylation of aldehydes, *Chem. Commun.*, 2012, **48**, 9189–9191.

347 M. Wang, S. Khan, E. Miliordos and M. Chen, Enantioselective Allenylation of Aldehydes via Brønsted Acid Catalysis, *Adv. Synth. Catal.*, 2018, **360**, 4634–4639.

348 C. Min, Y. Lin and D. Seidel, Catalytic Enantioselective Synthesis of Mariline A and Related Isoindolinones through a Biomimetic Approach, *Angew. Chem. Int. Ed.*, 2017, **56**, 15353–15357.

349 Y.-C. Zhang, Q. Yang, X. Yang, Q.-N. Zhu and F. Shi, Rational Design of Amine Nucleophiles for Dynamic Kinetic Resolution of Azlactones Leading to Highly Enantioselective Synthesis of Bisamides, *Asian J. Org. Chem.*, 2016, **5**, 914–919.

350 Y. Kwon, A. J. Chinn, B. Kim and S. J. Miller, Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C−N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration, *Angew. Chem. Int. Ed.*, 2018, **57**, 6251–6255.

351 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.

352 L. Wang, J. Zhou, T.-M. Ding, Z.-Q. Yan, S.-H. Hou, G.-D. Zhu and S.-Y. Zhang, Asymmetric N-Hydroxyalkylation of Indoles with Ethyl Glyoxalates Catalyzed by a Chiral Phosphoric Acid: Highly Enantioselective Synthesis of Chiral N,O-Aminal Indole Derivatives, *Org. Lett.*, 2019, **21**, 2795–2799.

353 A. Matsumoto, K. Asano and S. Matsubara, A chiral phosphoric acid catalyst for asymmetric construction of 1,3-dioxanes, *Chem. Commun.*, 2015, **51**, 11693–11696.

354 H.-R. Sun, Q. Zhao, H. Yang, S. Yang, B.-B. Gou, J. Chen and L. Zhou, Chiral phosphoric-acid-catalyzed cascade prins cyclization, *Org. Lett.*, 2019, **21**, 7143–7148.

355 I. Čorić, S. Vellalath and B. List, Catalytic asymmetric transacetalization, *J. Am. Chem. Soc.*, 2010, **132**, 8536–8537.

356 I. Čorić, S. Vellalath and B. List, Correction to: Catalytic asymmetric transacetalization, *J. Am. Chem. Soc.*, 2010, **132**, 12155.

357 Z. Chen and J. Sun, Enantio- and diastereoselective assembly of tetrahydrofuran and tetrahydropyran skeletons with all-carbon-substituted quaternary stereocenters, *Angew. Chem. Int. Ed.*, 2013, **52**, 13593–13596.

358 Z. Sun, G. A. Winschel, A. Borovika and P. Nagorny, Chiral phosphoric acid-catalyzed enantioselective and diastereoselective spiroketalizations, *J. Am. Chem. Soc.*, 2012, **134**, 8074–8077.

359 J.-S. Yu, W.-B. Wu and F. Zhou, The first catalytic asymmetric thioacetalization by chiral phosphoric acid catalysis, *Org. Biomol. Chem.*, 2016, **14**, 2205–2209.

360 J. Kikuchi, H. Aramaki, H. Okamoto and M. Terada, F10BINOL-derived chiral phosphoric acid-catalyzed enantioselective carbonyl-ene reaction: Theoretical elucidation of stereochemical outcomes, *Chem. Sci.*, 2019, **10**, 1426–1433.

361 X. Zeng, K. Ye, M. Lu, P. J. Chua, B. Tan and G. Zhong, Chiral brønsted acid catalyzed enantioselective addition of α-isocyanoacetamides to aldehydes, *Org. Lett.*, 2010, **12**, 2414–2417.

362 R. C. Cioc, P. Schuckman, H. D. Preschel, T. Vlaar, E. Ruijter and R. V. A. Orru, Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide, *Org. Lett.*, 2016, **18**, 3562–3565.

363 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.

