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The progression of chiral anions from concepts to applications in asymmetric catalysis

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Despite the tremendous advances of the past four decades, chemists are far from being able to use chiral catalysts to control the stereoselectivity of any desired reaction. New concepts for the construction and mode of operation of chiral catalysts have the potential to open up previously inaccessible reaction space. The recognition and categorization of distinct approaches seems to play a role in triggering rapid exploration of new territory. This Review both reflects on the origins as well as details a selection of the latest examples of an area that has advanced considerably within the past five years or so: the use of chiral anions in asymmetric catalysis. Defining reactions as involving chiral anions is a difficult task owing to uncertainties over the exact catalytic mechanisms. Nevertheless, we attempt to provide an overview of the breadth of reactions that could reasonably fall under this umbrella.

Within the broader field of science, organic chemistry is often referred to as a mature field of study. In spite of this, new avenues of inquiry seem to arise with relative frequency. Perhaps we take it for granted that expansions of the field are sparked when one or two chemical laboratories uncover a new reagent, catalyst or underlying mode of reactivity. But this simplistic view, which echoes the romantic notion of a 'Eureka!'-shouting scientist, is clearly not the whole story. In many cases, it may be more illuminating to consider the factors that prompted the chemical community to think about a subject in a different light, thereby revealing new ground ripe for exploration.

Students of asymmetric catalysis are taught that there are a small number of key 'activation modes' that are fundamental to understanding the interaction of catalysts with their targets[1]. Lewis acid catalysis is arguably the most venerable mode, with a vast body of literature dedicated to its study[2]. In this case, the most common scenario is that a Lewis acidic metal combines with a chiral Lewis basic ligand to form a chiral species possessing net Lewis acidity. Coordination of this to a net electrophile such as a carbonyl group generates a chiral complex that is activated towards nucleophilic attack (Fig. 1a). A conceptually analogous activation mode wherein the metal is replaced by a proton is referred to as Brønsted acid catalysis[3]. Formally, once the Brønsted acid has donated its proton to the achiral substrate, a conjugate base remains to provide the chiral environment for the subsequent bond-forming step. This description represents an extreme picture, and in most cases, the proton is effectively 'shared' to a varying extent between the two species through hydrogen-bonding interactions. This model for activation presents challenges for catalyst design because the relatively well-understood principles of tuning the ligand environment of metal centres can no longer be applied; instead, it is the interaction between the conjugate base and conjugate acid that is key to achieving high levels of enantioselectivity in the product.

Despite their relatively weak acidity (pK_a roughly 8–20)[4], chiral urea and thiourea catalysts have been highly effective in this sense, as the relatively strong and directional double hydrogen bonds formed with substrates such as imines provide sufficient electrophilic activation while at the same time providing a highly stereodefined environment (Fig. 1b)[5,6]. Hence these, as well as related TADDOL-derived catalysts[7], are often referred to as chiral hydrogen-bond donor catalysts[3,8].

Of significantly greater acidity (pK_a around 2–4)[9] are chiral phosphoric acids, commonly derived from BINOL (1,1′-bi-2-naphthol). These catalysts have risen to prominence over the past decade because their high acidity permits activation of a broad range of substrates[3,10]. Furthermore, although the single hydrogen bond to the substrate seems to offer a less rigid steric environment, the Brønsted basicity of the phosphoryl oxygen allows simultaneous activation of the electrophile and nucleophile, resulting in extremely high stereocontrol (Fig. 1c)[11].

But the stronger acidity of phosphoric acids and other strong Brønsted acid catalysts[12] leads to an element of mechanistic uncertainty as to whether the electrophile is essentially completely protonated, with enantioselectivity resulting from an electrostatic

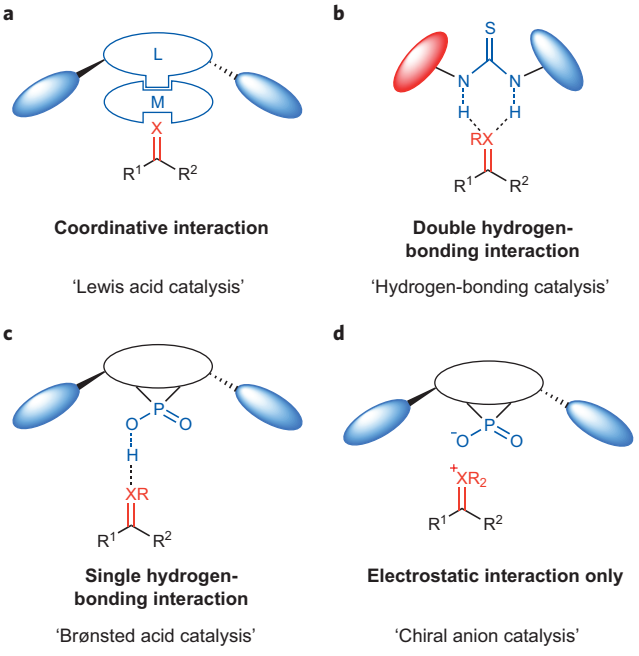

Figure 1 | Representative asymmetric activation modes of a carbonyl group or imine. M, metal; L, ligand.

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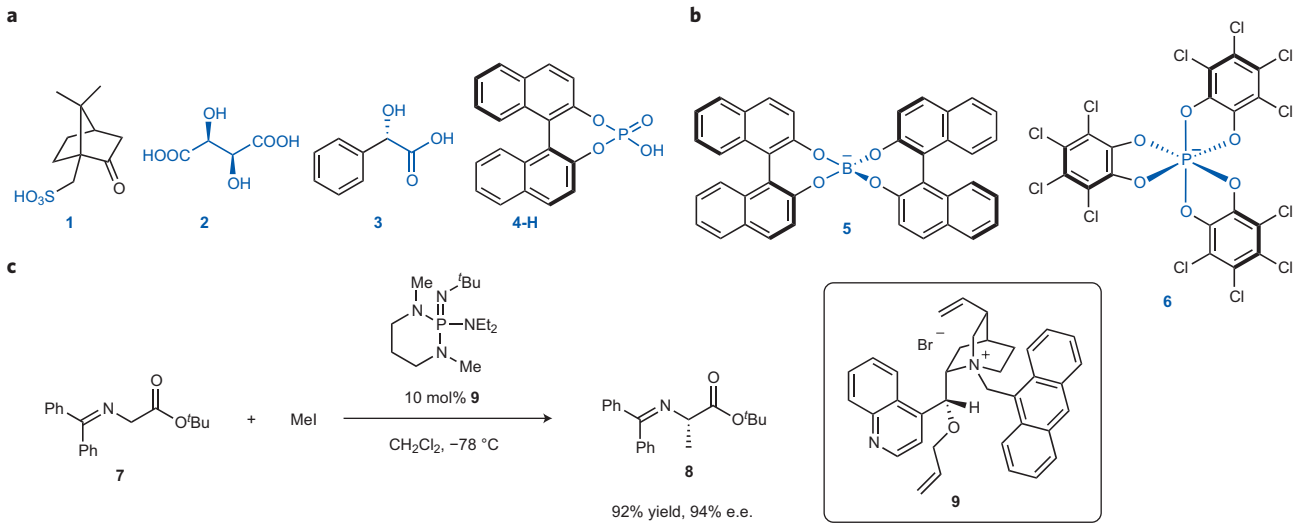

Figure 2 | Early examples of chiral anions and an example of chiral cations in synthesis. a, Chiral acids commonly used in the resolution of racemates. **b**, Examples of non-coordinating chiral anions. **c**, Chiral quaternary ammonium salt-catalysed alkylation under homogeneous conditions. e.e., enantiomeric excess.

ion-pairing interaction with the catalyst, or whether hydrogen-bonding interactions are responsible. Although much evidence has been collected for the hydrogen bond being crucial to the selectivity of these reactions[10,13], the strong acidity means that ion-pairing between a fully protonated substrate and the phosphate counterion cannot be fully excluded[14]. Taking this idea further, a mode of catalysis based on this latter premise of an ion pair linked only by electrostatic interactions can be considered as a separate category from those discussed so far (Fig. 1d). Indeed, the successful realization of such a strategy could constitute a highly general method of introducing asymmetry, for the simple reason that many long-established reactions do in fact proceed by way of cationic intermediates. The youthful but fast-growing field in pursuit of this goal has been referred to as 'chiral counterion catalysis', 'chiral anion-mediated chemistry' or 'asymmetric counteranion-directed catalysis'.

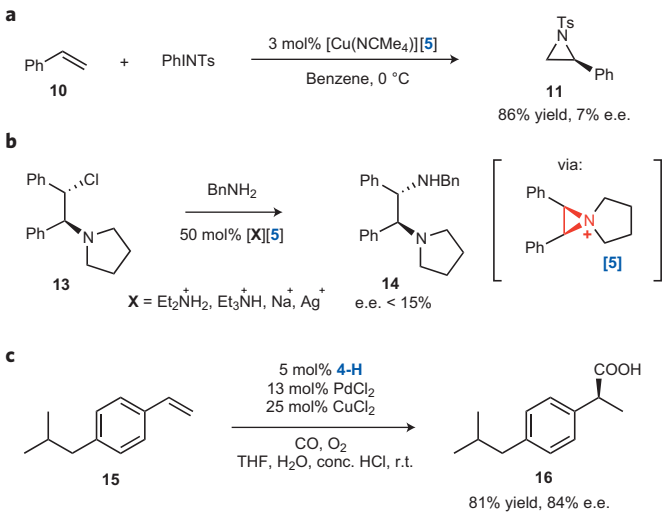

Figure 3 | Early efforts towards asymmetric catalysis using chiral anions. a, Chiral borate anions provide some enantioselectivity in a copper-catalysed aziridination. **b**, Efforts towards asymmetric ring opening of prochiral aziridinium ions using the same chiral borate anion. **c**, Hydrocarboxylation of a styrene using a chiral phosphoric acid in combination with palladium and copper catalysis. Ts, *para*-toluenesulfonyl; Bn, benzyl; THF, tetrahydrofuran; r.t., room temperature.

It must be said that there is some controversy over the very existence of the field under discussion. As alluded to above, for many reactions it is difficult to declare unambiguously that a chiral anion is responsible for the asymmetric induction by virtue of ion-pairing with a substrate or catalyst. There is an undeniable amount of overlap with Brønsted acid catalysis, and grey areas also arise in cases where the anionic species could foreseeably act as a coordinating ligand for a transition metal complex. The lack of clear boundaries may explain the paucity of reviews explicitly addressing the role of chiral anions in catalysis, although several excellent reviews provide a focus on their broader roles in chemistry[15,16]. For asymmetric catalysis, the tendency so far has been to downplay the importance of such notions in favour of more readily defined designations such as Brønsted acid/transition metal co-catalysis[17–19].

Nevertheless, there must be some basis for the increasing number of reports discussing their results in terms of chiral anion catalysis. The conceptualization of a strategy is far from trivial, as it can spur collective thinking about new ways to apply the chemical tool. In this Review, we first offer a point of view on the development of catalysis based on chiral anions and then cover a selection of new transformations that have been devised using the emerging concepts. Recognizing the hazy borders of the field, we have not attempted a comprehensive survey of the reactions that could potentially be encompassed by this categorization, but rather strive to provide an overview.

Early uses of chiral anions and their conjugate acids

Many cornerstones of asymmetric chemistry began as tools for the resolution and spectroscopic analysis of chiral molecules, with applications in catalysis arriving later. Chiral anions are no exception. The resolution of racemates by the formation of diastereomeric salts is, of course, a very old protocol; various acidic compounds from the chiral pool such as camphorsulfonic acid (**1**), tartaric acid (**2**) and mandelic acid (**3**) have been used to resolve basic compounds for the better part of a century (Fig. 2a)[20]. Chiral acids also proved suitable for spectroscopic use, including the determination of the enantioenrichment of a scalemic mixture. Later, synthetic acids like binaphthol-derived phosphoric acid **4-H** were discovered that often provided superior performance for these purposes[21]. The greater flexibility offered by expanding beyond the chiral pool probably aided the progression from these early successes to control over reaction stereoselectivity.

Another important advance was the synthesis and resolution of unreactive chiral anions. The non-coordinating nature of tetrahedral borate and hexacoordinated phosphate anions makes them suitable for tasks that involve ion-pairing with sensitive organometallic complexes or reactive cationic intermediates. Thus, it is not surprising that the borate **5** (refs 22–24) and the phosphate **6** (ref. 25) featured prominently in the early explorations of chiral anion-mediated reactivity (Fig. 2b). The compounds described so far and their derivatives quickly became indispensable for the development of three interrelated areas: transition metal catalysis with chiral anionic ligands, chiral Brønsted acid catalysis, and what might be considered 'true' chiral counterion catalysis. The latter designation is meant to exclude cases where the anion has a covalent, dative or hydrogen-bonding association with the catalyst, reagent or substrate[16].

Chiral cations in phase-transfer catalysis

The ability of chiral species to influence the stereoselectivity of chemical transformations through ion-pairing had already been demonstrated by asymmetric phase-transfer catalysis[26–31]. Highly enantioselective alkylations of enolates ion-paired with chiral quaternary ammonium cations were developed as early as 1984[32,33], so it is curious that ion-pair catalysis with chiral anions lagged rather far behind. The most reasonable explanation, and one that highlights the importance of how we conceive of chemical strategies, is that the intellectual focus was placed on the phase-transfer aspect of the catalysis rather than the chiral ion pair. To this point, a remarkable demonstration that chiral quaternary ammonium ions could aid in asymmetric alkylation of enolates even under homogeneous conditions was recognized as more of a practical improvement than a conceptual one (Fig. 2c)[34]. Even though it took a little longer to arrive, the recent work on catalysis using chiral anions was probably influenced by the shared mechanistic and intellectual features with these types of chiral cation-mediated reactions.

Intellectual foundations of chiral non-coordinating anions

As mentioned above, the synthesis of chiral non-coordinating anions enabled chemists to think about them as discrete chemical entities that could act independently to induce asymmetry. Early work focused on the ability of chiral anions to pair diastereoselectively with supramolecular hosts and organometallic complexes[35,36]. It was not until 2000 that this notion was applied to a catalytic reaction in the investigation of a copper(I)-catalysed aziridination process[37]. Arndtsen and co-workers had observed a marked effect on enantioselectivity when varying the achiral counterion of the cationic Cu(I)–bisoxazoline complexes they used as catalysts. This led them to wonder whether a chiral counterion could influence the reaction stereoselectivity, either alone in or conjunction with a chiral ligand on the metal. The study provided essential validation of this approach as a concept, although rather low enantioselectivity was obtained (Fig. 3a), perhaps preventing its potential from being immediately recognized. Another key study considered chiral anions for a similar but distinct purpose. Rather than pairing with a cationic catalyst, Nelson and co-workers asked whether chiral ions could interact with a prochiral cationic reaction intermediate to achieve an asymmetric transformation[38]. They used the same chiral borate **5** in a ring-opening of *meso*-aziridinium ions such as that derived from **13**, as well as an addition of indole to an iminium ion (Fig. 3b). Again the enantioselectivities were modest (under 15% enantiomeric excess, e.e.), but the study hinted that chiral anions had the potential to be quite general as tools for asymmetric catalysis of reactions proceeding through cationic intermediates. The breakthrough to higher enantioselectivities for both of these strategies—ion-pairing with cationic metal catalysts and reaction intermediates—would have to wait for a repurposing of a different type of structure: chiral phosphate anions.

Chiral phosphates as ligands, Brønsted acids and counterions

In 1990, Alper and Hamel reported an enantioselective hydrocarboxylation of styrenes such as **15** using a palladium/copper/chiral phosphoric acid catalyst system (Fig. 3c)[39]. In this case there was no experimental evidence to support any particular mechanistic role for the chiral acid over another, although the authors suggested that it was acting as a ligand. Although this reaction was an important step in combining metal and phosphoric acid catalysts, it occupies a curious place in the context of subsequent reports because of the unique reaction conditions, specifically the aqueous medium and high concentration of hydrochloric acid. Sometime thereafter, Inanaga and co-workers began exploring rare earth metal complexes with chiral phosphate ligands, which provided high enantioselectivities for a number of Lewis acid-catalysed reactions[40,41]. More recently, Charette and colleagues published a clever

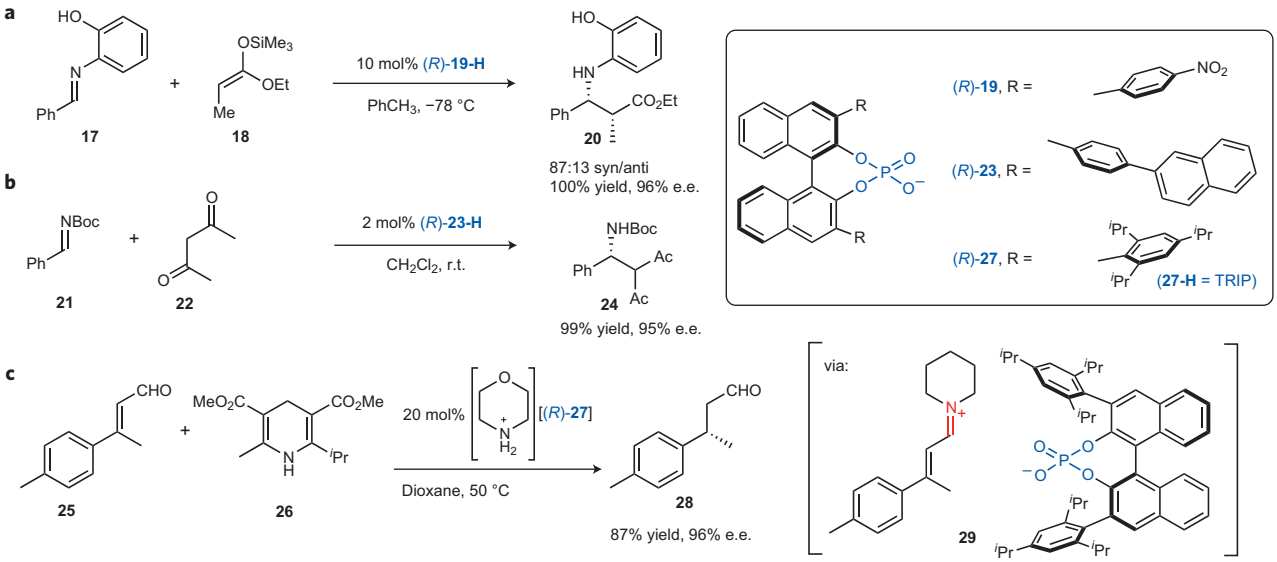

Figure 4 | Some seminal applications of 3,3′-disubstituted BINOL-derived phosphoric acids. a, Asymmetric addition of silyl enol ethers to imines via Brønsted acid catalysis. **b**, Asymmetric addition of acetylacetone to imines by Brønsted acid catalysis. **c**, Asymmetric reduction of enals through chiral anion catalysis. ^{i}Pr, *iso*-propyl; Boc, *tert*-butoxycarbonyl.

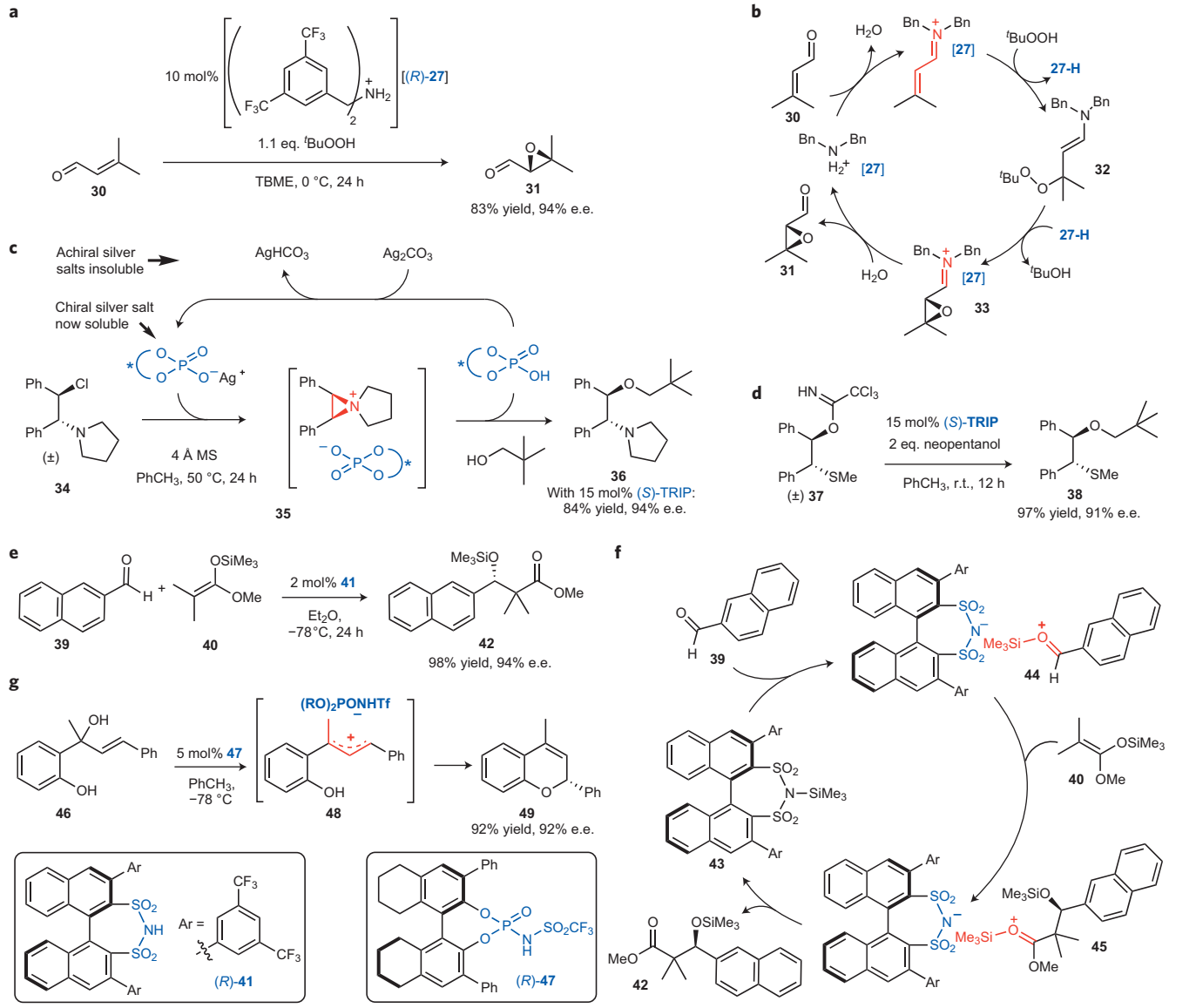

Figure 5 | Examples of asymmetric reactions using chiral counterions derived from Brønsted acid catalysts. a, Epoxidation of enals catalysed by an achiral amine salt of a chiral phosphoric acid. **b**, Proposed mechanism of the epoxidation. **c**, An early example of chiral anion phase-transfer catalysis in which an achiral silver salt remains in the solid phase until it is solubilized by the chiral phosphate catalyst. **d**, The same concept applied to the opening of *meso*-episulfonium ions. **e**, Mukaiyama aldol reaction of aldehydes with silyl ketene acetals catalysed by a chiral BINOL-derived disulfonimide. **f**, Proposed mechanism of the reaction. **g**, Intramolecular allylic substitution using an *N*-triflylphosphoramide catalyst. TBME, *tert*-butyl methyl ether; MS, molecular sieves; Tf, trifluoromethanesulfonyl.

use of substituted binaphthyl-phosphates in an enantioselective Simmons–Smith cyclopropanation[42]. Good asymmetric induction could be achieved even when a catalytic amount of chiral phosphate was used. All of these reports discuss their results in terms of the chiral phosphate acting as a coordinating ligand, and indeed there is no reason to believe that this is not the case. Nevertheless, they have frequently been discussed alongside chiral-anion-mediated reactions. No doubt these and similar examples were important in inspiring developments in ion-pair catalysis; but it is important, although difficult, to distinguish between reactions with different mechanisms so that better predictive patterns can be observed.

Progress in chiral anion chemistry has been closely tied to advances in Brønsted acid catalysis. Although not always mentioned in this context, the work of groups led by Yamamoto and by Ishihara on strong Brønsted acids, including Lewis acid-assisted Brønsted acids (LBAs) and Brønsted acid-assisted Brønsted acids (BBAs), deserves a great deal of credit[43]. For example, the borate **5** originated in its conjugate acid form as a catalyst for asymmetric additions to imines[25]. Yamamoto's various designer acids were among the few highly selective Brønsted acid catalysts for a long time, until seminal reports from Akiyama (Fig. 4a) and Terada (Fig. 4b) and their colleagues demonstrated the utility of 3,3′-bisaryl-substituted binaphthyl phosphoric acids such as **19** and **23** (refs 44,45). The ease of synthesis, structural variation and generality of these catalysts probably accounts for their use by many research groups immediately following these discoveries[46,47].

Also around this time, several groups were investigating the asymmetric conjugate reduction of unsaturated ketones and aldehydes using iminium-based organocatalysis[48]. The utility of chiral phosphoric acids for activating imines probably suggested the possibility of a productive merger between these two types of catalyst. Towards this end, Mayer and List took the step of combining an achiral secondary amine with a chiral phosphoric acid catalyst to achieve the desired asymmetric conjugate reduction of **25** with

excellent enantioselectivity (Fig. 4c)[49]. Because the ionic iminium intermediate (**29**) is fully substituted, there is no obvious way for the phosphate counterion to form a hydrogen bond with the intermediate. This distinction was critical, as it allowed chemists to think about applying chiral phosphates and other anions to reactions beyond activation of Lewis or Brønsted basic substrates like imines and demonstrated that, even in the absence of a handle for hydrogen bonding, these chiral phosphoric acids had the ability to impart excellent enantioselectivities. The authors realized they had an exciting result with widespread implications, going as far as to give the type of catalysis a new name, 'asymmetric counteranion-directed catalysis' (ACDC).

Chiral counterions derived from Brønsted acid catalysts

To extend their concept, Wang and List developed an asymmetric epoxidation of enals, again using an achiral secondary amine in conjunction with chiral phosphoric acids to achieve high enantioselectivities (Fig. 5a)[50]. This study provided an interesting mechanistic question in that substrates such as prenal (**30**) provided excellent enantioselectivities even though, according to the chiral counterion-based mechanism originally envisaged, this would not be expected because the species entering the enantiodetermining step would no longer be ionic (Fig. 5b, **32** to **33**). Instead, the authors invoked a mechanism in which the phosphoric acid is involved in cyclization of the neutral intermediate **32**, leading to the enantioenriched product. Hence the role of the phosphoric acid as a chiral counterion as defined in a mechanistic sense seems less likely, although it certainly constitutes the counterion of the catalyst salt used. This case highlights the difficulties in reaction classification (that is, chiral anion-catalysed) according to mechanism, when exact mechanistic details are often uncertain. Shortly after, the Toste group sought to test further the ability of ion-paired phosphate anions to induce chirality, with their investigation of the asymmetric ring-opening of *meso*-aziridinium and episulfonium ions[51]. As in the initial List report, a particular goal was to use substrates in which hydrogen bonding with the catalyst would be mechanistically improbable. A crucial practical requirement was the introduction of the chiral anion as the sole anion able to pair with the cationic intermediates; their approach was to abstract chloride from a racemic β-chloro tertiary amine using the silver salt of **27** (commonly known as TRIP). To regenerate the silver phosphate without forming undesired achiral aziridinium ion intermediates, they took a new approach in the form of establishing a phase separation between the solution phase (containing substrate and chiral anion catalyst) and the insoluble stoichiometric silver carbonate (solid phase). The latter's insolubility precluded background reaction but did not impede its reaction with the regenerated phosphoric acid (Fig. 5c). Indeed, this system can be thought of as an early example of chiral anion phase-transfer catalysis. Using their catalytic system, the Toste group were able to achieve excellent enantioselectivities in the ring opening of several *meso*-aziridinium ions (such as **34**) with a range of alcohols. When setting about extending this method to the opening of the analogous *meso*-episulfonium ions (such as **37**), the authors recognized that silver would be likely to fail in this case, owing to binding to sulfur, and so they replaced the chloride with a trichloroacetimidate group, a leaving group that could be directly activated by the phosphoric acid catalyst (Fig. 5d). Using a similar desymmetrizing approach, Hennecke and colleagues have achieved moderate but encouraging enantioselectivities by using phosphoric acid catalysts in the asymmetric opening of *meso*-halonium ions, in which chirality is thought to be induced by anion binding in the key *meso*-halonium intermediate[52].

Moving away from the phosphate anion, List and colleagues reported a new Brønsted acid catalyst **41** based on a chiral BINOL-derived disulfonimide motif, and they found that this catalyst was highly effective for the asymmetric Mukaiyama aldol reaction of aldehydes with silyl ketene acetals (Fig. 5e)[53]. The authors assert that their catalyst should be more strongly acidic than analogous phosphoric acids and phosphoramides, and indeed, catalysts based on these functionalities were found to give minimal conversion. Regarding the mechanism, the authors found that the catalyst is rapidly silylated by the silyl ketene acetal; it is this species (**43**) that promotes the aldol reaction and hence a Brønsted-acid-based mechanism is thought not to be in operation (Fig. 5f). Subsequently, the aldehyde **39** is activated through silyl transfer to generate an oxonium ion **44**, which is ion-paired with the conjugate base of the catalyst. Reaction with the silyl ketene acetal produces the product **42** with high enantioselectivity after return of the silyl group to the catalyst. Using a different chiral Brønsted acid motif, Rueping and colleagues have reported an interesting and highly enantioselective *N*-triflylphosphoramide-catalysed intramolecular allylic substitution. This is postulated to proceed by means of a carbocation that is ion-paired with the chiral phosphoramide (**48**; Fig. 5g). The carbocation is generated by dehydration of a racemic allylic alcohol (**46**), and studies using enantiopure allylic alcohols suggest that an S_N2' pathway is not in operation[54]. Lete and colleagues developed a phosphoric acid-catalysed intermolecular addition of indoles to *N*-acyliminium ions, although only moderate enantioselectivities were obtained[55,56]. In this case the *N*-acyliminium ion is generated by dehydration on treatment with the phosphoric acid, and the chiral phosphate counterion in the resulting *N*-acyliminium is proposed to control the addition of the nucleophile. A phosphate ion-paired intermediate produced by dehydration has also been proposed by Gong and colleagues in the apparent S_N1-like enantioselective alkylation of enamides with indolyl alcohols, although in this case hydrogen-bonding interactions to the indole N–H could potentially be involved[57]. Additionally, there have been several reports of chiral phosphoric acid-catalysed reactions that proceed through oxocarbenium ion intermediates. Examples include vinyl ether addition[58], semi-Pinacol rearrangement,[59] transacetalization[60] and most recently spiroacetalization[61].

In some of these transformations, hydrogen bonding of the catalyst to the oxocarbenium ion intermediate has been invoked, although ion-pairing cannot be explicitly ruled out. It is transformations such as these in which the readiness of chemists to think in terms of 'chiral anions' has led to such rewarding new developments. In many cases it may be impossible to say to that there are no possible hydrogen-bonding interactions, especially with such a versatile bifunctional catalyst as TRIP, but it is difficult to deny that thinking of the anion as primary chiral controller has led to a wealth of new chemistry.

Metal catalysis with chiral counterions

Attempting to induce asymmetry by using chiral ions that interact with a metal only through electrostatic interactions, rather than using chiral ligands that coordinate tightly to the metal, seems at first to be an inadvisable strategy. Of course these two extremes are highly idealized, and in reality a continuum of association between ligand and metal can exist. Thus, the task of differentiating a reaction involving a 'true' counterion (that is, electrostatic interactions only) from a weakly coordinating ligand is extremely difficult. In this section we will survey reactions in which the chiral ligand, most commonly a phosphoric acid, can reasonably be regarded as being highly dissociated when compared with a more conventional ligand such as a phosphine. Classification of such reactions becomes more complex still when the phosphoric acid could potentially play a role in hydrogen bonding with an intermediate. Thus this survey should not be regarded as exhaustive, but will attempt to give an overview of the breadth of metals used thus far. Indeed, besides the reports of Alper, Charette and Arndtsen already mentioned, there was a relatively early report from the Krische group involving both metal and phosphoric acid catalysts, although the mechanistic studies and resulting hypotheses suggested that the phosphoric acid catalyst was

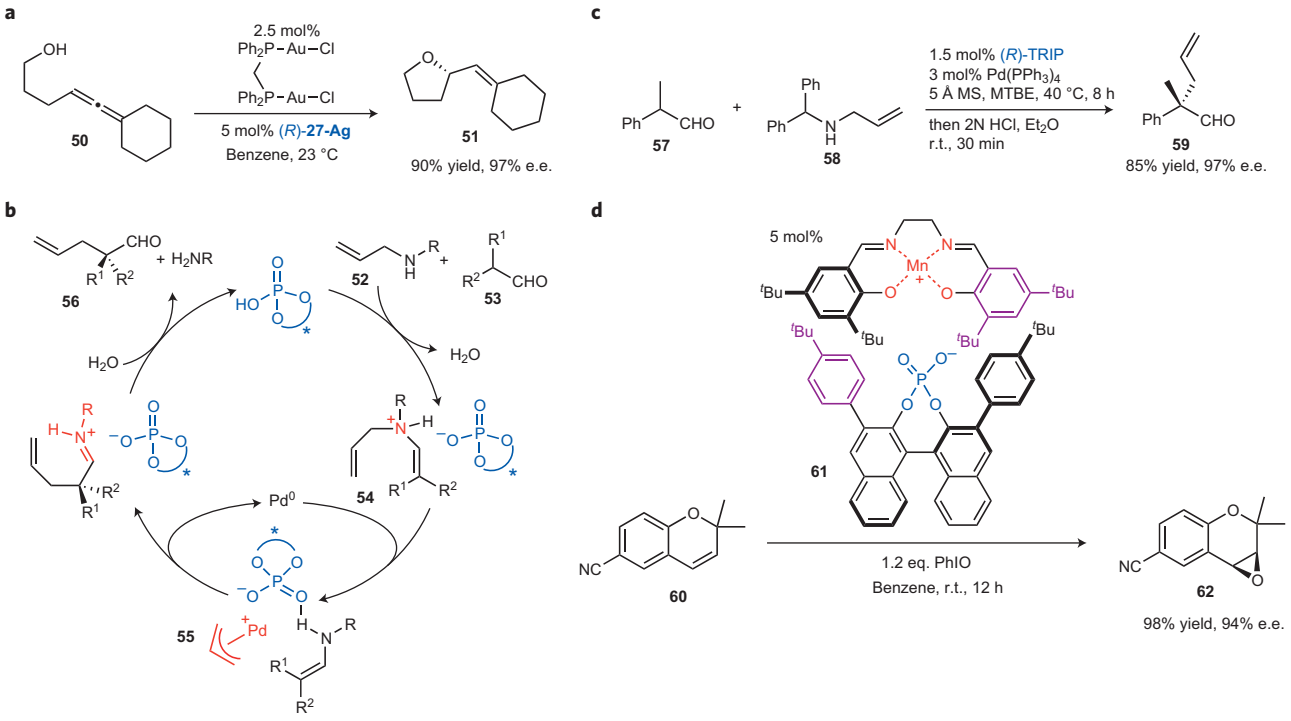

Figure 6 | Examples of asymmetric metal catalysis with chiral anionic counterions. a, Hydroalkoxylation of allenes using a gold catalyst with a chiral phosphate anion. **b**, Mechanistic hypothesis for Tsuji–Trost reaction using a palladium catalyst with chiral phosphate anion. **c**, Successful example of the latter reaction. **d**, Epoxidation of alkenes using a catalyst derived from a cationic achiral Mn–salen complex and a chiral phosphate anion.

playing a role independent of the metal catalyst, rather than as a ligand or counterion[62].

Having developed a host of transformations using cationic gold catalysts[63], Toste and colleagues in 2006 developed a highly enantioselective hydroamination of alkenes using gold catalysts based on chiral diphosphine ligands[64]. In this study, generation of a cationic gold species was crucial for reactivity, and it was observed that the nature of the achiral anion had a significant effect on the enantioselectivity. Although one hypothesis for this effect was based on the required formation of a monocationic over a dicationic gold catalyst, the striking effect of varying the counterion led them to speculate that the anionic counterion could be more profoundly involved in discriminating between the two diastereomeric transition states. Thus when they found that the intramolecular hydroalkoxylation of allenes (**50** to **51**) proceeded with negligible enantioselectivity under the chiral phosphine conditions that had previously succeeded with the analogous hydroamination, the authors considered instead a chiral counterion strategy. Ultimately, using a silver salt of a chiral phosphate (TRIP) in conjunction with an achiral binuclear gold catalyst gave excellent yields and enantioselectivities for the hydroalkoxylation reaction (Fig. 6a)[65]. Tellingly, the highest enantioselectivities were obtained in nonpolar solvents such as benzene, suggesting that strong ion-pairing plays an important role. Chiral anions in conjunction with different ligands on gold have also allowed the addition of several other types of nucleophiles to allenes, including carboxylic acids and hydroxylamines[66,67]. Highlighting the value of thinking in terms of chiral counterions, the Toste group have since published a highly enantioselective hydroamination of dienes in which the sole catalyst is a chiral dithiophosphoric acid[68]. The authors provide strong evidence that this reaction proceeds through a covalent intermediate, but inspiration arose from the possibility of ion-pairing of the dithiophosphate anion with an allylic carbocationic intermediate.

Shortly after Toste's report combining gold catalysis with chiral counterions, a contribution from the List group showcased the potential of marrying a palladium catalyst with a chiral phosphate counterion[69]. They recognized that the Tsuji–Trost reaction, well established as proceeding by means of cationic π-allyl Pd(II) complexes, would be ideally suited for investigation of a chiral anion strategy. Specifically, the authors envisaged a catalytic cycle whereby condensation of a secondary allylamine (**52**) with an α-branched aldehyde (**53**), catalysed by a chiral phosphoric acid catalyst, generates a chiral enammonium phosphate salt (Fig. 6b, **54**). Reaction of this with Pd(0) results in a nucleophilic enamine and an electrophilic cationic π-allyl Pd-complex with its chiral phosphate counterion. This assembly **55**, perhaps assisted by hydrogen bonding to the enamine, would result in stereoselective formation of valuable quaternary allylated stereocenters (**56**). Their hypothesis was proven valid, as use of TRIP in conjunction with a $Pd(PPh_3)_4$ catalyst, both of which were required, allowed allylation of a range of α-branched aldehydes with good to excellent enantioselectivities (Fig. 6c). This elegant work, in combination with the aforementioned work from the Toste group, provided an indication of the potential broad use of chiral anions with metal catalysts. At a similar time, the Rueping group published an enantioselective addition of alkynes to imines using both phosphoric acid and metal catalysis, although the authors' mechanistic proposal suggested that the phosphoric acid was not acting as a ligand or counterion to the metal[70]. Since then, related effects of chiral anions have also been observed in the gold-catalysed additions of alkynes to imines[71].

Using a different metal catalyst, the List group further explored this potential by combining chiral phosphate anions with achiral Mn(III)-salen cations to enable enantioselective epoxidation of alkenes[72]. Their hypothesis stemmed from the observation that in the highly successful Jacobsen–Katsuki epoxidation, the chiral backbone of the salen ligand fixes the complex in one of two possible enantiomorphic conformations. The authors hypothesized that rendering the backbone achiral but introducing a chiral anion could achieve the same end result of favouring one enantiomorphic conformation over the other, this time through ion-pairing. The bulky

C2-symmetric nature of a 3,3′-disubstituted BINOL-derived phosphate anion would effectively mirror and reinforce the chiral microenvironment imparted by the conformationally locked salen ligand. Their hypothesis proved inspired and, although some optimization of the chiral phosphate was required to identify the need for bulky *para*-substituents on the catalyst 3,3′-aryl groups, high enantioselectivities of epoxidized products **62** were obtained (Fig. 6d). In accordance with the proposed ion-pairing mechanism, use of more polar solvents resulted in reduced enantioselectivities. Furthermore, the absolute configuration of the obtained products agreed with their original conformational analysis of the proposed interaction of the phosphate anion with the Mn–salen cation (**61**). The authors also observe that their catalytic system is highly reactive and attribute this advantage to the highly cationic nature of the Mn metal centre, realized through the use of this ion-pairing mode of catalysis. The same group has applied the chiral anion strategy to develop an enantioselective Overman rearrangement, using a similar hypothesis to that in their earlier studies on the Tsuji–Trost reaction: that a chiral phosphate may act as a counterion for a key electrophilic palladium intermediate, thereby inducing asymmetry[73]. Their optimization studies found that palladium chloride-based palladacycle **65** in combination with a chiral silver phosphate was able to induce high enantioselectivity into the products **64** (Fig. 7a), with the enantioselectivity only slightly reduced using the closely related achiral palladacycle **66**. The chiral palladacycle and chiral phosphate displayed a matched/mismatched effect, and in control experiments, palladacycle **65** alone gave high conversion to racemic product and the silver phosphate alone did not catalyse the rearrangement. The authors identified that their active catalyst was likely to be a phosphate-bridged palladium dimer and obtained an X-ray structure of the corresponding monomer complex obtained on treatment with imidazole. Interestingly, they note that the palladium–oxygen bond length of 2.149 Å between the metal and phosphate indicates that the phosphate acts as an anionic ligand rather than a formal counterion. The List group has also reported an improvement of their previous protocol for α-allylation of α-substituted aldehydes. In a preliminary study, they observed that a phosphoric acid catalyst was able to catalyse the allylation of an α-branched aldehyde with an allylic alcohol, but that asymmetric induction was low (e.e. < 10%)[74]. They hypothesized that this could be due to formation of a mixture of *E* and *Z* enols and proposed that use of a primary amine as a third catalyst (after the phosphoric acid and palladium) may *in situ* form the *E*-enamine selectively, a species that should be more reactive than any background enol also formed. Optimization based on this premise led to high enantioselectivities[75]. The same group recently reported a ruthenium-catalysed enantioselective hydrovinylation of alkenes, using cationic Ru complexes with chiral phosphate anions; although high regioselectivity was obtained, enantioselectivities were modest (e.e. <55%)[76].

In the realm of asymmetric hydrogenation, Xiao and colleagues took the step of pairing a chiral cationic iridium complex with a TRIP anion to produce highly enantioselective hydrogenation of imines, both preformed and generated *in situ*, although it is suggested that in the reaction the phosphoric acid is produced and that this will probably induce asymmetry through hydrogen-bonding interactions with the imine substrate[77,78]. Subsequently, Koenigs and Rueping paired racemic iridium complexes with chiral *N*-triflylphosphoramides to realize asymmetric hydrogenation of

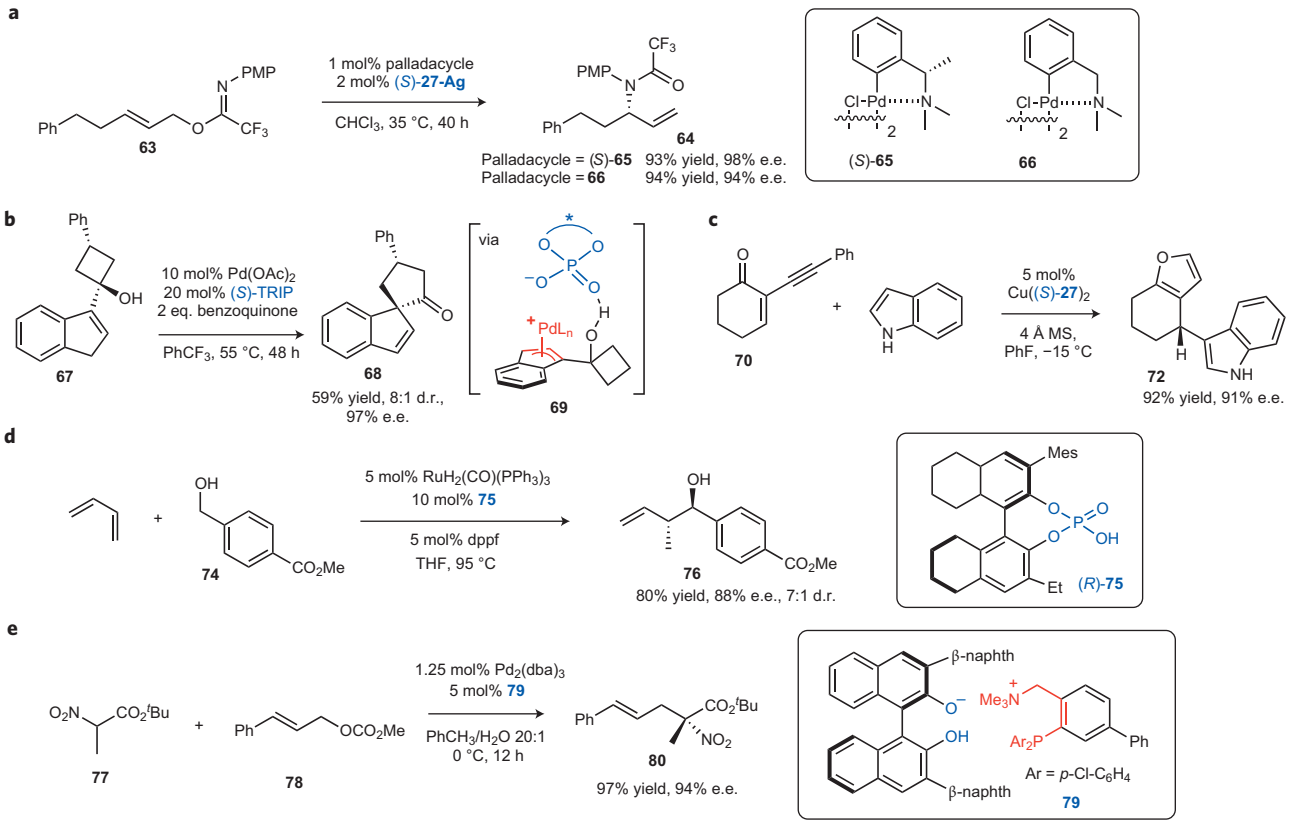

Figure 7 | Further examples of asymmetric metal catalysis with chiral counterions. a, Overman rearrangement using a cationic palladium complex with a chiral phosphate anion. **b**, Semi-Pinacol rearrangement initiated by allylic C–H activation and proceeding through a cationic palladium intermediate paired with a chiral phosphate anion. **c**, Copper-catalysed cycloisomerization/addition reaction in which a chiral phosphate is responsible for the observed enantioselectivity. **d**, Ruthenium catalysis in combination with chiral phosphates for the hydrohydroxyalkylation of butadiene. **e**, Allylic alkylation of α-nitrocarboxylates using catalyst **79** in which a chiral binaphtholate is ion-paired with a quaternary ammonium salt incorporated into a phosphine ligand. PMP, *para*-methoxyphenyl; Mes, 1,3,5-trimethylphenyl; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dba, dibenzylideneacetone; d.r., diastereometric ratio.

quinolones, in which the acid catalyst is proposed to differentiate kinetically between the two enantiomeric iridium complexes[79].

Building on List's prior success of pairing of cationic palladium complexes with chiral phosphates, Chai and Rainey have developed an enantioselective semi-Pinacol rearrangement initiated by Pd(II)-catalysed direct allylic C–H activation (Fig. 7b)[80]. They found that without addition of the phosphoric acid or palladium catalyst, no reaction occurred, and their studies indicate that the reaction proceeds through an allylic C–H activation to produce a cationic π-allyl palladium species **69** which is probably bound to the phosphate through ion-pairing, inducing asymmetry into the subsequent semi-Pinacol rearrangement to give **68**. Copper has also been used in conjunction with anionic phosphate ligands[81] and phosphoric acids[82]. Recently, Toste and colleagues reported an enantioselective cycloisomerization–indole addition reaction using preformed Cu(II)-phosphate catalysts (Fig. 7c)[83]. The reaction was proposed to proceed with the phosphate either ion-pairing with an intermediate or acting as an anionic ligand. Iridium complexes with chiral phosphate counterions have also been successfully used in the carbocyclization of 1,6-enynes[84]. Most recently, Krische and colleagues have combined a ruthenium catalyst with a chiral phosphate counterion to produce enantioselective crotylation of primary alcohols such as **74** through hydrohydroxyalkylation of butadiene (Fig. 7d)[85]. They found that C1-symmetric phosphoric acids, **75** in particular, gave the highest selectivity and propose that these combine with the ruthenium catalyst to give an active ruthenium phosphate species, with the phosphate anion playing a crucial role in providing both enantioselectivity and diastereoselectivity.

Approaching the field from an exciting new angle, Ooi and colleagues have recently reported a highly enantioselective palladium-catalysed allylic alkylation using a phosphine ligand (**79**) that is unconventional in that it bears a quaternary ammonium group that is in turn ion-paired with a chiral binaphtholate anion (Fig. 7e)[86]. A series of control experiments supported the hypothesis that the ion-pairing is crucial for asymmetric induction. Variation of the arrangement of the groups on the phosphine ligand resulted in negligible enantioselectivity, indicating that the coordinative phosphine and ammonium cation moiety must be in precisely the correct orientation. Intriguingly, the free hydroxyl group on the binaphtholate is absolutely necessary for asymmetric induction, suggesting that the hydrogen bonding present in the catalyst (as seen in the X-ray crystal structure) plays an important role. The excellent enantioinduction observed suggests that this metal–ligand-counterion (as opposed to metal-counterion) strategy may provide a successful avenue for future investigation, particularly as it allows for use of a chiral anion approach even when the metal intermediate itself is neutral.

In an intriguing departure from the examples discussed so far, an interesting approach from Belokon and colleagues includes the metal as part of the chiral anion[87]. Potassium cobaltate(III) complexes bearing chiral amino-acid-derived ligands were used as catalysts to obtain encouraging enantioselectivity in the addition of cyanide to benzaldehyde.

The breadth of metals used successfully with chiral anions in such a short period of time attests to the enormous potential of this strategy. It also pays tribute to the immense importance of the BINOL-derived phosphoric acid as a privileged structure providing the basis for these chiral anions, a theme that has run throughout this Review so far. Despite its ubiquity, this motif could only be the tip of the iceberg, with a vast wealth of other chiral anion structures remaining to be explored in combination with metal catalysis.

Chiral anion binding from hydrogen-bonding catalysts

The importance of anion recognition in enzyme mechanisms has been appreciated for some time, but applications in catalysis are only just beginning to emerge[88]. An important contribution from Kotke and Schreiner demonstrated the ability of an achiral thiourea to catalyse the acetalization of aldehydes and ketones at very low catalyst loadings; the authors rationalized this activity with a mechanism in which multiple oxyanion intermediates are stabilized by binding to the thiourea catalyst[89]. They then extended this catalysis to the tetrahydropyranylation of alcohols and performed density functional theory calculations, which suggested that the thiourea catalyst assists first in the generation of the alkoxy nucleophile and subsequently stabilizes the developing oxyanion in the transition state[90]. Given the extensive previous studies using chiral thiourea organocatalysts for imine activation[5], asymmetric catalysis seems to offer an ideal forum to test this intriguing mechanistic hypothesis.

Following from their pioneering work on the use of ureas and thioureas as hydrogen-bond donor catalysts for activation of imines, the Jacobsen group subsequently used similar catalysts to enable enantioselective additions to *N*-acyliminium intermediates in the form of asymmetric Pictet–Spengler[91] and Mannich[92] reactions (Fig. 8a and 8b). Although initially the precise mechanism was unclear, when they expanded the scope to encompass Pictet–Spengler-type cyclizations of β-hydroxylactams promoted by TMSCl (Fig. 8c), they hypothesized that two possible mechanisms could be in operation (Fig. 8d)[93]. Although formal dehydration of **86** and formation of the chlorolactam **89** was found to be fast and irreversible, two possible pathways could potentially follow this. The first, a direct S_N2 displacement of the chloride to give **88** directly, was ruled out by the observation that the reactivity is enhanced in substrates where R is alkyl-substituted. This favours the second option, an S_N1 pathway, whereby the enantiodetermining step is either addition of the indole to the *N*-acyliminium ion (path A, **90** to **91**; or path B, **90** to **92**) or alkyl migration of a plausible spiroindoline intermediate (path A, **91** to **92**). The authors noted, however, that in neither intermediate is there a Lewis basic site for productive binding to the thiourea catalyst. They therefore proposed that that catalyst promotes dissociation of the halide anion leading to a chiral *N*-acyliminium–thiourea complex **90** to which addition occurs, and this hypothesis is supported by pronounced counterion and solvent effects. Thus the chloride counterion is in effect rendered chiral by complexation with the chiral thiourea catalyst, providing substrate activation as well as asymmetric induction.

Having made this conceptual transition from hydrogen-bond activation to chiral-anion abstraction over the course of these investigations, the Jacobsen group set about exploring the exciting possibilities made newly feasible by this insight. Initially, the strategy was extended to analogous Pictet–Spengler reactions involving the pyrrole-based substrates[94]. Seeking to push this further, they next examined additions of silyl ketene acetals onto chiral oxocarbenium ions generated from 1-chloroisochromans and found that excellent enantioselectivities could be obtained using similar thiourea catalysts[95]. This concept has since been extended successfully to a number of systems. A particularly elegant example includes polycyclizations that proceed through *N*-acyliminium intermediates and proposed anion binding[96]. In this case, thiourea catalysts with large aromatic substituents were required for high enantioselectivity. This was proposed to be due to the ability of these extended catalysts to stabilize π-cation interactions in the reaction intermediates. Furthermore, the novel ion-pairing mechanism has enabled the interception of non-heteroatom stabilized carbocations with high enantioselectivities, allowing the enantioselective alkylation of α-arylpropionaldehydes (Fig. 8e)[97]. In this case the authors found that a thiourea catalyst bearing a primary amine (**95**) was required for both high reactivity and enantioselectivity, suggesting that the reaction proceeds by means of enamine intermediate **97**. Mechanistic studies showed that an S_N2 pathway for attack on the bromodiarylmethane was highly unlikely relative to an S_N1 pathway. Furthermore, the thiourea component was essential, strongly suggesting that the electrophile was activated by a halide abstraction

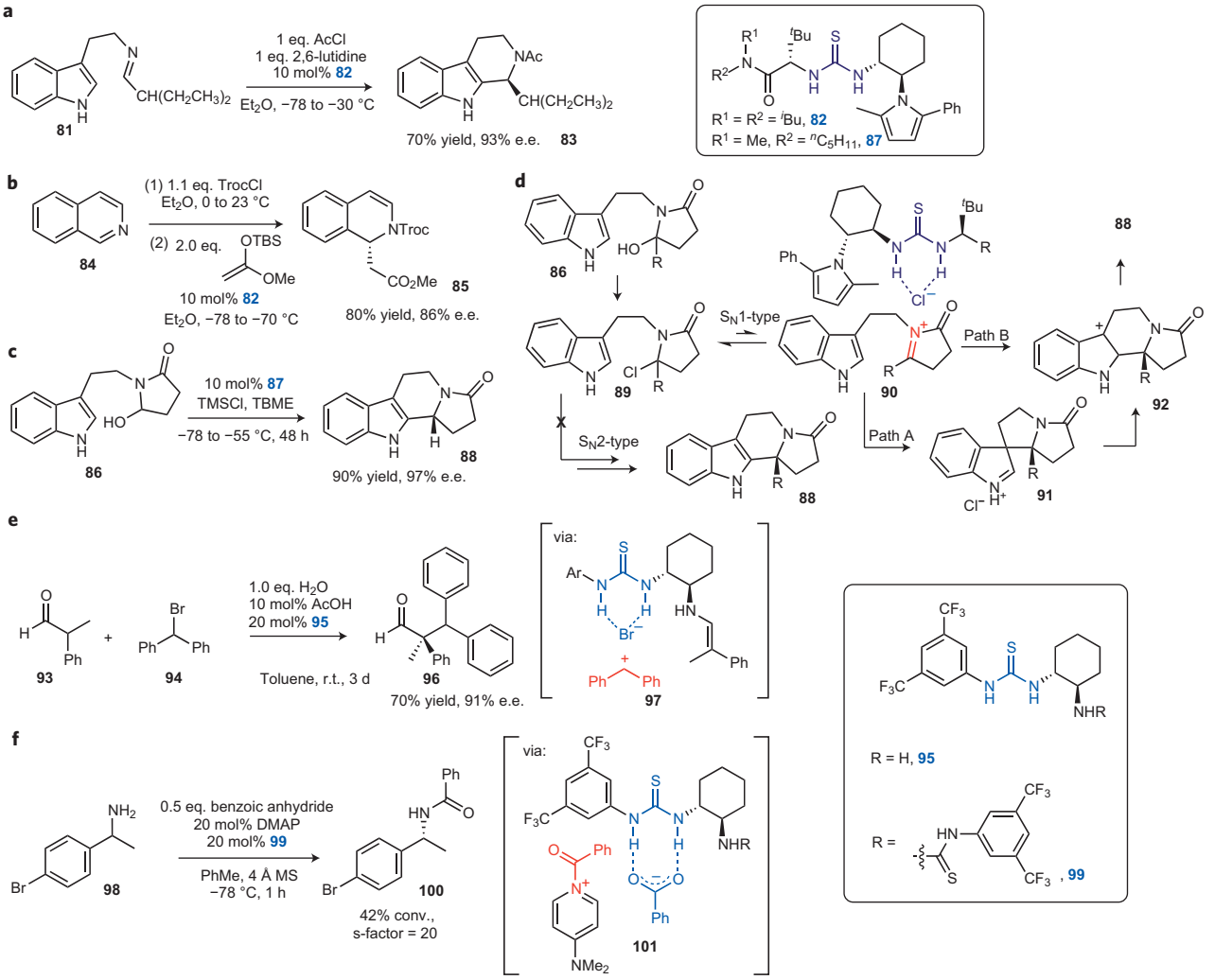

Figure 8 | Examples of asymmetric catalysis by chiral anion binding from hydrogen-bonding catalysts. a, Thiourea-catalysed Pictet–Spengler reaction. **b**, Thiourea-catalysed intramolecular Mannich reaction. **c**, Thiourea-catalysed Pictet–Spengler-type cyclization of β-hydroxylactams. **d**, Possible mechanistic pathways in the latter reaction showing the hypothesized intermediate **90**. **e**, Alkylation of α-arylpropionaldehydes using this concept of chiral anion binding. **f**, Kinetic resolution of primary amines using chiral anion binding to a benzoate anion in intermediate **101**. Ac, acetyl; TMS, trimethylsilyl; Troc, 2,2,2-trichloroethoxycarbonyl; TBS, *tert*-butyldimethylsilyl; DMAP, 4-dimethylaminopyridine.

leading to a chiral ion pair, in line with previous studies, now involving a carbocation. The same group recently reported enantioselective acylation of silyl ketene acetals through fluoride anion binding, providing a further example of how clever catalyst design can produce a highly effective template for the reactants[98].

The Seidel group has used similar putative anion-binding to chiral thiourea catalysts to achieve kinetic resolutions of primary amines. Their approach draws inspiration from nucleophilic desymmetrization using chiral DMAP-derived catalysts[99], but turns this on its head by making the DMAP-component achiral and instead using a chiral counterion. They found thiourea catalyst **99** to give selectivity factors (*s*-factors) of 7.1 to 24 for the kinetic resolution of a range of benzylic amines (such as **98**) and postulated that the benzoate anion of the acylated DMAP intermediate binds with the catalyst resulting in chiral ion pair **101** (Fig. 8f)[100]. By using a slightly modified catalyst, they were subsequently able to extend this methodology to propargylic amines and additionally to lower the catalyst loading from 20 mol% to 5 mol%, with *s*-factors ranging from 12 to 56 (ref. 101). Proving the generality of the concept, this catalyst was also highly effective in the desymmetrization of *meso*-diamines by monobenzoylation, providing products with enantiomeric excesses of up to 95% (ref. 102). The same group recently reported an elegant transformation in which *O*-acylated azlactones are transformed into the corresponding *C*-acylated products using their dual catalysis approach, in this case with the substrate becoming the anion upon acyl transfer, chirality being induced by interaction with the anion-binding thiourea catalyst[103].

The contribution of thiourea anion-binding catalysis to the chiral anion story is a particularly good illustration in that it demonstrates the value of making the intellectual jump, brought about through mechanistic insight, to thinking in terms of chiral anions; in this case, it has led to chemistry that might otherwise have been considered infeasible.

Chiral anion phase-transfer catalysis

Previously discussed work from the Toste group (Fig. 5c) had demonstrated that asymmetric induction through ion-pairing could be combined with a strategy in which a stoichiometric achiral promoter in the solid phase remains isolated from the reactants that occupy the liquid phase. This draws comparisons with better-established variants of phase-transfer catalysis in which a lipophilic chiral cation salt mediates the reaction between a reagent in organic solution and an activated anionic substrate in the aqueous or solid phase. In this case, ion-pairing of the latter with the cationic catalyst

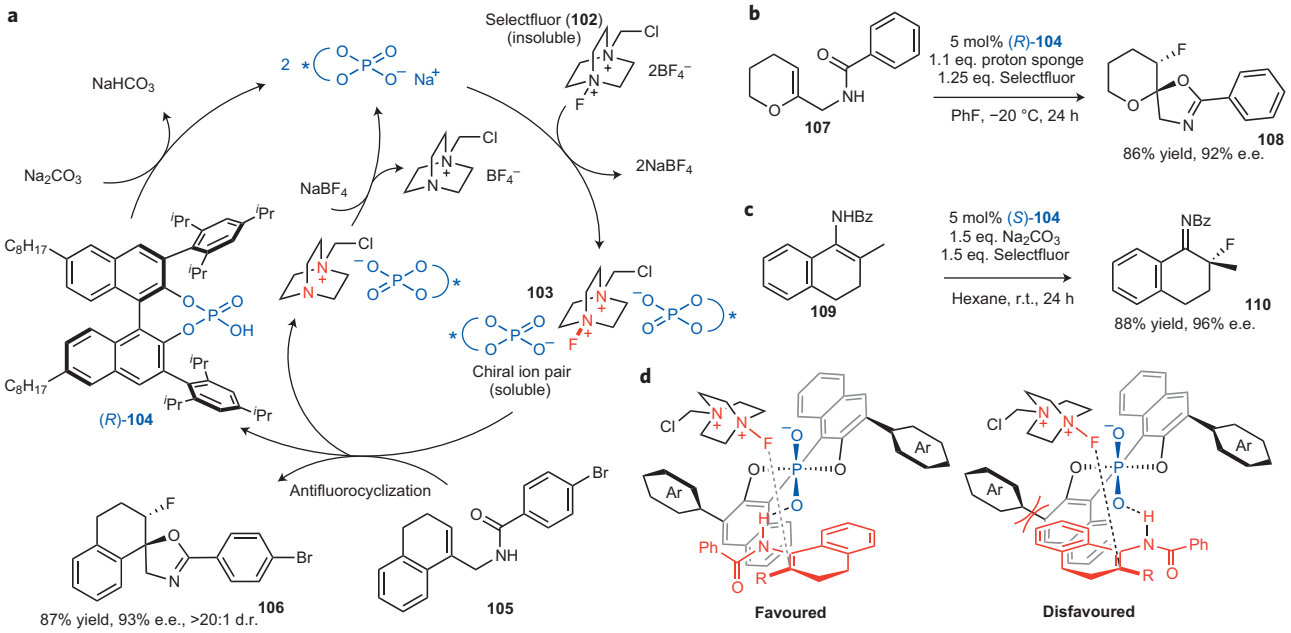

Figure 9 | Examples of the use of chiral anions in asymmetric phase-transfer catalysis. a, Proposed catalytic cycle for the fluorocyclization of dihydronaphthalene derivatives showing the proposed chiral Selectfluor species after double anion exchange (**103**). **b**, Fluorocyclization of an enol ether using this concept. **c**, Fluorination of enamides using chiral anion phase-transfer catalysis. **d**, Proposed model to rationalize the absolute stereochemistry observed in the latter transformation. Bz, benzoyl.

solubilizes it in the organic phase while providing a chiral environment for the ensuing reaction[31]. Very recently, Toste and colleagues have reported an even more analogous inversion of this familiar paradigm. In their work, an achiral anionic reagent is sequestered in the solid phase and is only able to be brought into bulk solution containing the substrate by the action of a chiral, anionic phase-transfer catalyst[104]. Specifically, they selected Selectfluor (**102**), a cationic electrophilic fluorinating reagent, as a suitable reagent that is insoluble in nonpolar solvents but may be both solubilized and rendered chiral by the *in situ* replacement of its BF_4^- counterions with lipophilic, chiral anions to give **103** (Fig. 9a). TRIP derivatives amply fulfilled the latter requirements, and Toste and colleagues found that by using the nonpolar fluorobenzene as solvent and 5 mol% of a TRIP catalyst modified by the addition of lipophilic alkyl chains (**104**), they could achieve high enantioselectivities in the fluorocyclization of enol ether **107** (Fig. 9b). They were able to extend this effectively to less electron-rich alkenes such as dihydronaphthalene **105** (Fig. 9a), and a completely unactivated alkene also participated in the fluorocyclization with moderate enantioselectivity. Evidence for the association of two chiral anions with Selectfluor, as depicted in the proposed catalytic cycle, was acquired from observation of a significant nonlinear effect. A second report from the Toste group using this chiral anion phase-transfer strategy allows the fluorination of cyclic enamides such as **109** with high levels of enantioselectivity (Fig. 9c)[105]. Their protocol allows isolation of the stable *N*-benzoyl imine products that can be readily manipulated to motifs valuable in pharmaceutical synthesis, such as chiral β-fluoroamines and α-fluoroketones. The authors propose a model that accounts for the absolute stereochemistry observed by analogy with modelling studies carried out on prior phosphoric acid-catalysed reactions of enamides (Fig. 9d)[11]. They propose that the phosphate anion is able to form an ion pair with Selectfluor on one oxygen atom, while simultaneously activating the enamide through hydrogen bonding with the second. The enamide would reside so as to put the bulk of the tetralone in an 'open' quadrant, with the amide group occupying a 'closed' quadrant. Additionally, they speculate that the high tolerance of the reaction towards substitution on the enamide (Fig. 9d, R) may reflect that these positions point away from the catalyst and thus have no effect on catalyst–substrate binding. These transformations arguably provide examples of catalysis whereby the chiral anion is playing an indisputably 'anionic' role in binding with the reagent, although the catalyst probably binds with the substrate itself through a more familiar hydrogen-bonding mode. More generally, this is just one of many possible permutations in which the chiral anion may operate and, while highlighting the complexities of classification, also emphasizes the broad potential applications of chiral anions in asymmetric catalysis.

Conclusion

This Review has summarized both the origins of and recent progress in the development of catalytic reactions involving chiral anions. Notwithstanding the parallel development of thiourea-based chiral anion binding catalysts, the realization of highly effective Brønsted acid catalysts, primarily in the form of BINOL-derived phosphoric acids, for enantioselective addition to imines was undoubtedly a trigger point for recent rapid development of the field. This class of catalysts has proved remarkably versatile as undisputed counterions in their own right, as anionic ligands for a broad range of transition metals, and most recently as anionic phase-transfer catalysts. It has not only provided organic chemists with a highly stereodefined, bifunctional anionic catalyst platform, but it also crucially encouraged its users to think in term of ion pairs, even though hydrogen bonding is still regarded as an important factor in these reactions. As noted above, rigorously defining whether an anionic interaction is involved the enantiodetermining step of a specific reaction may not always be possible. But this does not detract from the fact that the ion-pair conceptualization has driven chemists to expand the boundaries of the capabilities of these catalysts. The discovery of new chemical reactions is arguably driven by hypothesis, and the ultimate legitimacy of the initial hypothesis may be inconsequential to the discovery of exciting new modes of reactivity or selectivity. We hope that this short Review will further stimulate collective thinking on new approaches for stereocentre-forming reactions involving cationic intermediates, reagents and catalysts.

References

1. Walsh, P. J. & Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis* (University Science Books, 2008).
2. Yamamoto, H. *Lewis Acids in Organic Synthesis* (Wiley-VCH, 2000).
3. Akiyama, T. Stronger Brønsted acids. *Chem. Rev.* **107,** 5744–5758 (2007).
4. Jakab, G., Tancon, C., Zhang, Z., Lippert, K. M. & Schreiner, P. R. (Thio)urea organocatalyst equilibrium acidities in DMSO. *Org. Lett.* **14,** 1724–1727 (2012).
5. Taylor, M. S. & Jacobsen, E. N. Asymmetric catalysis by chiral hydrogen-bond donors. *Angew. Chem. Int. Ed.* **45,** 1520–1543 (2006).
6. Vachal, P. & Jacobsen, E. N. Structure-based analysis and optimization of a highly enantioselective catalyst for the Strecker reaction. *J. Am. Chem. Soc.* **124,** 10012–10014 (2002).
7. Huang, Y., Unni, A. K., Thadani, A. N. & Rawal, V. H. Hydrogen bonding: Single enantiomers from a chiral-alcohol catalyst. *Nature* **424,** 146–146 (2003).
8. Doyle, A. G. & Jacobsen, E. N. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **107,** 5713–5743 (2007).
9. Christ, P. *et al.* pKa values of chiral Brønsted acid catalysts: phosphoric acids/amides, sulfonyl/sulfuryl imides, and perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.* **17,** 8524–8528 (2011).
10. Terada, M. Chiral phosphoric acids as versatile catalysts for enantioselective transformations. *Synthesis* 1929–1982 (2010).
11. Simón, L. & Goodman, J. M. A model for the enantioselectivity of imine reactions catalyzed by BINOL-phosphoric acid catalysts. *J. Org. Chem.* **76,** 1775–1788 (2011).
12. Hatano, M., Maki, T., Moriyama, K., Arinobe, M. & Ishihara, K. Pyridinium 1,1′-binaphthyl-2,2′ disulfonates as highly effective chiral brønsted acid–base combined salt catalysts for enantioselective Mannich-type reaction. *J. Am. Chem. Soc.* **130,** 16858–16860 (2008).
13. Simón, L. & Goodman, J. M. Theoretical study of the mechanism of Hantzsch ester hydrogenation of imines catalyzed by chiral BINOL-phosphoric acids. *J. Am. Chem. Soc.* **130,** 8741–8747 (2008).
14. Fleischmann, M., Drettwan, D., Sugiono, E., Rueping, M. & Gschwind, R. M. Brønsted acid catalysis: hydrogen bonding versus ion pairing in imine activation. *Angew. Chem. Int. Ed.* **50,** 6364–6369 (2011).
15. Lacour, J. & Hebbe-Viton, V. Recent developments in chiral anion mediated asymmetric chemistry. *Chem. Soc. Rev.* **32,** 373–382 (2003).
16. Lacour, J. & Moraleda, D. Chiral anion-mediated asymmetric ion pairing chemistry. *Chem. Commun.* 7073–7089 (2009).
17. Shao, Z. & Zhang, H. Combining transition metal catalysis and organocatalysis: a broad new concept for catalysis. *Chem. Soc. Rev.* **38,** 2745–2755 (2009).
18. Zhong, C. & Shi, X. When organocatalysis meets transition-metal catalysis. *Eur. J. Org. Chem.* **2010,** 2999–3025 (2010).
19. Rueping, M., Koenigs, R. M. & Atodiresei, I. Unifying metal and Brønsted acid catalysis—concepts, mechanisms, and classifications. *Chem. Eur. J.* **16,** 9350–9365 (2010).
20. Eliel, E. L., Mander, L. N. & Wilen, S. H. *Stereochemistry of Organic Compounds* (Wiley-Interscience, 1994)
21. Jacques, J., Fouquey, C. & Viterbo, R. Enantiomeric cyclic binaphthyl phosphoric acids as resolving agents. *Tetrahedron Lett.* **12,** 4617–4620 (1971).
22. Lacour, J., Ginglinger, C., Grivet, C. & Bernardinelli, G. Synthesis and resolution of the configurationally stable tris(tetrachlorobenzenediolato) phosphate(v) ion. *Angew. Chem. Int. Ed.* **36,** 608–610 (1997).
23. Lacour, J., Ginglinger, C. & Favarger, F. Asymmetric recognition of TRISPHAT anion. Unusually high difference in reactivity of the pseudoenantiomers of cinchona alkaloids. *Tetrahedron Lett.* **39,** 4825–4828 (1998).
24. Shevchenko, I. V., Fischer, A., Jones, P. G. & Schmutzler, R. The unusual oxidation of a 1,5,2,4-diazadiphosphorinan-6-one with tetrachloro-ortho-benzoquinone. *Chem. Ber.* **125,** 1325–1332 (1992).
25. Ishihara, K., Miyata, M., Hattori, K., Tada, T. & Yamamoto, H. A New chiral BLA promoter for asymmetric aza Diels–Alder and aldol-type reactions of imines. *J. Am. Chem. Soc.* **116,** 10520–10524 (1994).
26. Maruoka, K. *Asymmetric Phase Transfer Catalysis* (Wiley-VCH, 2008).
27. Ojima, I. *Catalytic Asymmetric Synthesis* (Wiley-VCH, 2000).
28. Maruoka, K. & Ooi, T. Enantioselective amino acid synthesis by chiral phase-transfer catalysis. *Chem. Rev.* **103,** 3013–3028 (2003).
29. Lygo, B. & Andrews, B. I. Asymmetric phase-transfer catalysis utilizing chiral quaternary ammonium salts: asymmetric alkylation of glycine imines. *Acc. Chem. Res.* **37,** 518–525 (2004).
30. O'Donnell, M. J. The enantioselective synthesis of alpha-amino acids by phase-transfer catalysis with achiral Schiff base esters. *Acc. Chem. Res.* **37,** 506–517 (2004).
31. Ooi, T. & Maruoka, K. Recent advances in asymmetric phase-transfer catalysis. *Angew. Chem. Int. Ed.* **46,** 4222–4266 (2007).
32. Dolling, U. H., Davis, P. & Grabowski, E. J. J. Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-indacrinone via chiral phase-transfer catalysis. *J. Am. Chem. Soc.* **106,** 446–447 (1984).
33. Hughes, D. L., Dolling, U. H., Ryan, K. M., Schoenewaldt, E. F. & Grabowski, E. J. J. Efficient catalytic asymmetric alkylations. 3. A kinetic and mechanistic study of the enantioselective phase-transfer methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone. *J. Org. Chem.* **52,** 4745–4752 (1987).
34. O'Donnell, M. J., Delgado, F., Hostettler, C. & Schwesinger, R. An efficient homogeneous catalytic enantioselective synthesis of α-amino acid derivatives. *Tetrahedron Lett.* **39,** 8775–8778 (1998).
35. Owen, D. J. & Schuster, G. B. Induced circular dichroism in cyanine borate penetrated ion pairs. *J. Am. Chem. Soc.* **118,** 259–260 (1996).
36. Lacour, J., Jodry, J. J., Ginglinger, C. & Torche-Haldimann, S. Diastereoselective ion pairing of TRISPHAT anions and tris(4,4′-dimethyl-2,2′-bipyridine)iron(II). *Angew. Chem. Int. Ed.* **37,** 2379–2380 (1998).
37. Llewellyn, D. B., Adamson, D. & Arndtsen, B. A. A novel example of chiral counteranion induced enantioselective metal catalysis: the importance of ion-pairing in copper-catalyzed olefin aziridination and cyclopropanation. *Org. Lett.* **2,** 4165–4168 (2000).
38. Carter, C., Fletcher, S. & Nelson, A. Towards phase-transfer catalysts with a chiral anion: inducing asymmetry in the reactions of cations. *Tetrahedron* **14,** 1995–2004 (2003).
39. Alper, H. & Hamel, N. Asymmetric synthesis of acids by the palladium-catalyzed hydrocarboxylation of olefins in the presence of (R)-(−)- or (S)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate. *J. Am. Chem. Soc.* **112,** 2803–2804 (1990).
40. Inanaga, J., Sugimoto, Y. & Hanamoto, T. Achiral and chiral lanthanide(III) salts of superacids as novel Lewis acid catalysts in organic synthesis. *New J. Chem.* **19,** 707–712 (1995).
41. Hanamoto, T., Furuno, H., Sugimoto, Y. & Inanaga, J. Asymmetric hetero Diels–Alder reaction catalyzed by chiral ytterbium(III) phosphate{Yb[(R)-(−)-BNP]$_3$}: remarkable ligand effect on the enantioselectivity. *Synlett* **1,** 79–80 (1997).
42. Lacasse, M. C., Poulard, C. & Charette, A. B. Iodomethylzinc phosphates: powerful reagents for the cyclopropanation of alkenes. *J. Am. Chem. Soc.* **127,** 12440–12441 (2005).
43. Yamamoto, H. & Futatsugi, K. 'Designer acids': combined acid catalysis for asymmetric synthesis. *Angew. Chem. Int. Ed.* **44,** 1924–1942 (2005).
44. Akiyama, T., Itoh, J., Yokota, K. & Fuchibe, K. Enantioselective Mannich-type reaction catalyzed by a chiral Bronsted acid. *Angew. Chem. Int. Ed.* **43,** 1566–1568 (2004).
45. Uraguchi, D. & Terada, M. Chiral Bronsted acid-catalyzed direct Mannich reactions via electrophilic activation. *J. Am. Chem. Soc.* **126,** 5356–5357 (2004).
46. Terada, M. Binaphthol-derived phosphoric acid as a versatile catalyst for enantioselective carbon–carbon bond forming reactions. *Chem. Commun.* 4097–4112 (2008).
47. Yang, J. W., Hechavarria Fonseca, M. T., Vignola, N. & List, B. Metal-free, organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes. *Angew. Chem. Int. Ed.* **44,** 108–110 (2005).
48. Ouellet, S. G., Tuttle, J. B. & MacMillan, D. W. Enantioselective organocatalytic hydride reduction. *J. Am. Chem. Soc.* **127,** 32–33 (2005).
49. Mayer, S. & List, B. Asymmetric counteranion-directed catalysis. *Angew. Chem. Int. Ed.* **45,** 4193–4195 (2006).
50. Wang, X. & List, B. Asymmetric counteranion-directed catalysis for the epoxidation of enals. *Angew. Chem. Int. Ed.* **47,** 1119–1122 (2008).
51. Hamilton, G. L., Kanai, T. & Toste, F. D. Chiral anion-mediated asymmetric ring opening of meso-aziridinium and episulfonium ions. *J. Am. Chem. Soc.* **130,** 14984–14986 (2008).
52. Hennecke, U., Müller, C. H. & Fröhlich, R. Enantioselective haloetherification by asymmetric opening of meso-halonium ions. *Org. Lett.* **13,** 860–863 (2011).
53. García-García, P., Lay, F., García-García, P., Rabalakos, C. & List, B. A powerful chiral counteranion motif for asymmetric catalysis. *Angew. Chem. Int. Ed.* **48,** 4363–4366 (2009).
54. Rueping, M., Uria, U., Lin, M-Y. & Atodiresei, I. Chiral organic contact ion pairs in metal-free catalytic asymmetric allylic substitutions. *J. Am. Chem. Soc.* **133,** 3732–3735 (2011).
55. Aranzamendi, E., Sotomayor, N. & Lete, E. Brønsted acid catalyzed enantioselective α-amidoalkylation in the synthesis of isoindoloisoquinolines. *J. Org. Chem.* **77,** 2986–2991 (2012).
56. Gómez-SanJuan, A., Sotomayor, N. & Lete, E. Enantioselective intramolecular α-amidoalkylation reaction in the synthesis of pyrrolo[2,1-a]isoquinolines. *Tetrahedron Lett.* **53,** 2157–2159 (2012).
57. Guo, Q-X. *et al.* Highly enantioselective alkylation reaction of enamides by Brønsted-acid catalysis. *Org. Lett.* **11,** 4620–4623 (2009).
58. Terada, M., Tanaka, H. & Sorimachi, K. Enantioselective direct Aldol-type reaction of azlactone via protonation of vinyl ethers by a chiral Brønsted acid catalyst. *J. Am. Chem. Soc.* **131,** 3430–3431 (2009).
59. Zhang, Q-W. *et al.* Brønsted acid catalyzed enantioselective semipinacol rearrangement for the synthesis of chiral spiroethers. *Angew. Chem. Int. Ed.* **48,** 8572–8574 (2009).

60. Čorić, I., Vellalath, S. & List, B. Catalytic asymmetric transacetalization. *J. Am. Chem. Soc.* **132,** 8536–8537 (2010).
61. Čorić, I. & List, B. Asymmetric spiroacetalization catalysed by confined Brønsted acids. *Nature* **483,** 315–319 (2012).
62. Komanduri, V. & Krische, M. J. Enantioselective reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones via rhodium-catalyzed asymmetric hydrogenation: mechanistic insight into the role of Brønsted acid additives. *J. Am. Chem. Soc.* **128,** 16448–16449 (2006).
63. Shapiro, N. D. & Toste, F. D. A reactivity-driven approach to the discovery and development of gold-catalyzed organic reactions. *Synlett* 675–691 (2010).
64. LaLonde, R. L., Sherry, B. D., Kang, E. J. & Toste, F. D. Gold(I)-catalyzed enantioselective intramolecular hydroamination of allenes. *J. Am. Chem. Soc.* **129,** 2452–2453 (2007).
65. Hamilton, G. L., Kang, E. J., Mba, M. & Toste, F. D. A powerful chiral counterion strategy for asymmetric transition metal catalysis. *Science* **317,** 496–499 (2007).
66. LaLonde, R. L., Wang, Z. J., Mba, M., Lackner, A. D. & Toste, F. D. Gold(I)-catalyzed enantioselective synthesis of pyrazolidines, isoxazolidines, and tetrahydrooxazines. *Angew. Chem. Int. Ed.* **49,** 598–601 (2010).
67. Aikawa, K., Kojima, M. & Mikami, K. Synergistic effect: hydroalkoxylation of allenes through combination of enantiopure BIPHEP–gold complexes and chiral anions. *Adv. Synth. Cat.* **352,** 3131–3135 (2010).
68. Shapiro, N. D., Rauniyar, V., Hamilton, G. L., Wu, J. & Toste, F. D. Asymmetric additions to dienes catalysed by a dithiophosphoric acid. *Nature* **470,** 245–249 (2011).
69. Mukherjee, S. & List, B. Chiral counteranions in asymmetric transition-metal catalysis: highly enantioselective Pd/Brønsted acid-catalyzed direct alpha-allylation of aldehydes. *J. Am. Chem. Soc.* **129,** 11336–11337 (2007).
70. Rueping, M., Antonchick, A. P. & Brinkmann, C. Dual catalysis: a combined enantioselective Brønsted acid and metal-catalyzed reaction—metal catalysis with chiral counterions. *Angew. Chem. Int. Ed.* **46,** 6903–6906 (2007).
71. Campbell, M. J. & Toste, F. D. Enantioselective synthesis of cyclic carbamimidates via a three-component reaction of imines, terminal alkynes, and p-toluenesulfonylisocyanate using a monophosphine gold(I) catalyst. *Chem. Sci.* **2,** 1369–1378 (2011).
72. Liao, S. & List, B. Asymmetric counteranion-directed transition-metal catalysis: enantioselective epoxidation of alkenes with manganese(III) salen phosphate complexes. *Angew. Chem. Int. Ed.* **49,** 628–631 (2010).
73. Jiang, G., Halder, R., Fang, Y. & List, B. A highly enantioselective Overman rearrangement through asymmetric counteranion-directed palladium catalysis. *Angew. Chem. Int. Ed.* **50,** 9752–9755 (2011).
74. Jiang, G. & List, B. Palladium/Brønsted acid-catalyzed α-allylation of aldehydes with allylic alcohols. *Adv. Synth. Cat.* **353,** 1667–1670 (2011).
75. Jiang, G. & List, B. Direct asymmetric α-allylation of aldehydes with simple allylic alcohols enabled by the concerted action of three different catalysts. *Angew. Chem. Int. Ed.* **50,** 9471–9474 (2011).
76. Jiang, G. & List, B. Enantioselective hydrovinylation via asymmetric counteranion-directed ruthenium catalysis. *Chem. Commun.* **47,** 10022–10024 (2011).
77. Li, C., Wang, C., Villa-Marcos, B. & Xiao, J. Chiral counteranion-aided asymmetric hydrogenation of acyclic imines. *J. Am. Chem. Soc.* **130,** 14450–14451 (2008).
78. Li, C., Villa-Marcos, B. & Xiao, J. Metal–Brønsted acid cooperative catalysis for asymmetric reductive amination. *J. Am. Chem. Soc.* **131,** 6967–6969 (2009).
79. Rueping, M. & Koenigs, R. M. Bronsted acid differentiated metal catalysis by kinetic discrimination. *Chem. Commun.* **47,** 304–306 (2011).
80. Chai, Z. & Rainey, T. J. Pd(II)/Brønsted acid catalyzed enantioselective allylic C–H activation for the synthesis of spirocyclic rings. *J. Am. Chem. Soc.* **134,** 3615–3618 (2012).
81. Zhao, B., Du, H. & Shi, Y. Cu(I)-catalyzed diamination of conjugated olefins with tunable anionic counterions. a possible approach to asymmetric diamination. *J. Org. Chem.* **74,** 8392–8395 (2009).
82. Yazaki, R., Kumagai, N. & Shibasaki, M. Direct catalytic asymmetric conjugate addition of terminal alkynes to α, β-unsaturated thioamides. *J. Am. Chem. Soc.* **132,** 10275–10277 (2010).
83. Rauniyar, V., Wang, Z. J., Burks, H. E. & Toste, F. D. Enantioselective synthesis of highly substituted furans by a copper(II)-catalyzed cycloisomerization-indole addition reaction. *J. Am. Chem. Soc.* **133,** 8486–8489 (2011).
84. Barbazanges, M. *et al.* Enantioselective IrI-catalyzed carbocyclization of 1,6-enynes by the chiral counterion strategy. *Chem. Eur. J.* **17,** 13789–13794 (2011).
85. Zbieg, J. R., Yamaguchi, E., McInturff, E. L. & Krische, M. J. Enantioselective C–H crotylation of primary alcohols via hydrohydroxyalkylation of butadiene. *Science* **336,** 324–327 (2012).
86. Ohmatsu, K., Ito, M., Kunieda, T. & Ooi, T. Ion-paired chiral ligands for asymmetric palladium catalysis. *Nature Chem.* **4,** 473–477 (2012).
87. Belokon, Y. N. *et al.* Potassium and silver chiral cobaltate(III) complexes as precatalysts for asymmetric C–C bond formation. *Tetrahedron* **19,** 822–831 (2008).
88. Zhang, Z. & Schreiner, P. R. (Thio)urea organocatalysis: What can be learnt from anion recognition? *Chem. Soc. Rev.* **38,** 1187–1198 (2009).
89. Kotke, M. & Schreiner, P. R. Acid-free, organocatalytic acetalization. *Tetrahedron* **62,** 434–439 (2006).
90. Kotke, M. & Schreiner, P. R. Generally applicable organocatalytic tetrahydropyranylation of hydroxy functionalities with very low catalyst loading. *Synthesis* **5,** 779–790 (2007).
91. Taylor, M. S. & Jacobsen, E. N. Highly enantioselective catalytic acyl-Pictet–Spengler reactions. *J. Am. Chem. Soc.* **126,** 10558–10559 (2004).
92. Taylor, M. S., Tokunaga, N. & Jacobsen, E. N. Enantioselective thiourea-catalyzed acyl-Mannich reactions of isoquinolines. *Angew. Chem. Int. Ed.* **44,** 6700–6704 (2005).
93. Raheem, I. T., Thiara, P. S., Peterson, E. A. & Jacobsen, E. N. Enantioselective Pictet–Spengler-type cyclizations of hydroxylactams: H-bond donor catalysis by anion binding. *J. Am. Chem. Soc.* **129,** 13404–13405 (2007).
94. Raheem, I. T., Thiara, P. S. & Jacobsen, E. N. Regio- and enantioselective catalytic cyclization of pyrroles onto N-acyliminium ions. *Org. Lett.* **10,** 1577–1580 (2008).
95. Reisman, S. E., Doyle, A. G. & Jacobsen, E. N. Enantioselective thiourea-catalyzed additions to oxocarbenium ions. *J. Am. Chem. Soc.* **130,** 7198–7199 (2008).
96. Knowles, R. R., Lin, S. & Jacobsen, E. N. Enantioselective thiourea-catalyzed cationic polycyclizations. *J. Am. Chem. Soc.* **132,** 5030–5032 (2010).
97. Brown, A. R., Kuo, W-H. & Jacobsen, E. N. Enantioselective catalytic alpha-alkylation of aldehydes via an S_N1 pathway. *J. Am. Chem. Soc.* **132,** 9286–9288 (2010).
98. Birrell, J. A., Desrosiers, J-N. & Jacobsen, E. N. Enantioselective acylation of silyl ketene acetals through fluoride anion-binding catalysis. *J. Am. Chem. Soc.* **133,** 13872–13875 (2011).
99. Wurz, R. P. Chiral dialkylaminopyridine catalysts in asymmetric synthesis. *Chem. Rev.* **107,** 5570–5595 (2007).
100. De, C. K., Klauber, E. G. & Seidel, D. Merging nucleophilic and hydrogen bonding catalysis: an anion binding approach to the kinetic resolution of amines. *J. Am. Chem. Soc.* **131,** 17060–17061 (2009).
101. Klauber, E. G., De, C. K., Shah, T. K. & Seidel, D. Merging nucleophilic and hydrogen bonding catalysis: an anion binding approach to the kinetic resolution of propargylic amines. *J. Am. Chem. Soc.* **132,** 13624–13626 (2010).
102. De, C. K. & Seidel, D. Catalytic enantioselective desymmetrization of meso-diamines: a dual small-molecule catalysis approach. *J. Am. Chem. Soc.* **133,** 14538–14541 (2011).
103. De, C. K., Mittal, N. & Seidel, D. A Dual-catalysis approach to the asymmetric Steglich rearrangement and catalytic enantioselective addition of *O*-acylated azlactones to isoquinolines. *J. Am. Chem. Soc.* **133,** 16802–16805 (2011).
104. Rauniyar, V., Lackner, A. D., Hamilton, G. L. & Toste, F. D. Asymmetric electrophilic fluorination using an anionic chiral phase-transfer catalyst. *Science* **334,** 1681–1684 (2011).
105. Phipps, R. J., Hiramatsu, K. & Toste, F. D. Asymmetric fluorination of enamides: access to α-fluoroimines using an anionic chiral phase-transfer catalyst. *J. Am. Chem. Soc.* **134,** 8376–8379 (2012).

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Competing financial interests

The authors declare no competing financial interests.