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Unifying Metal and Brønsted Acid Catalysis—Concepts, Mechanisms, and Classifications

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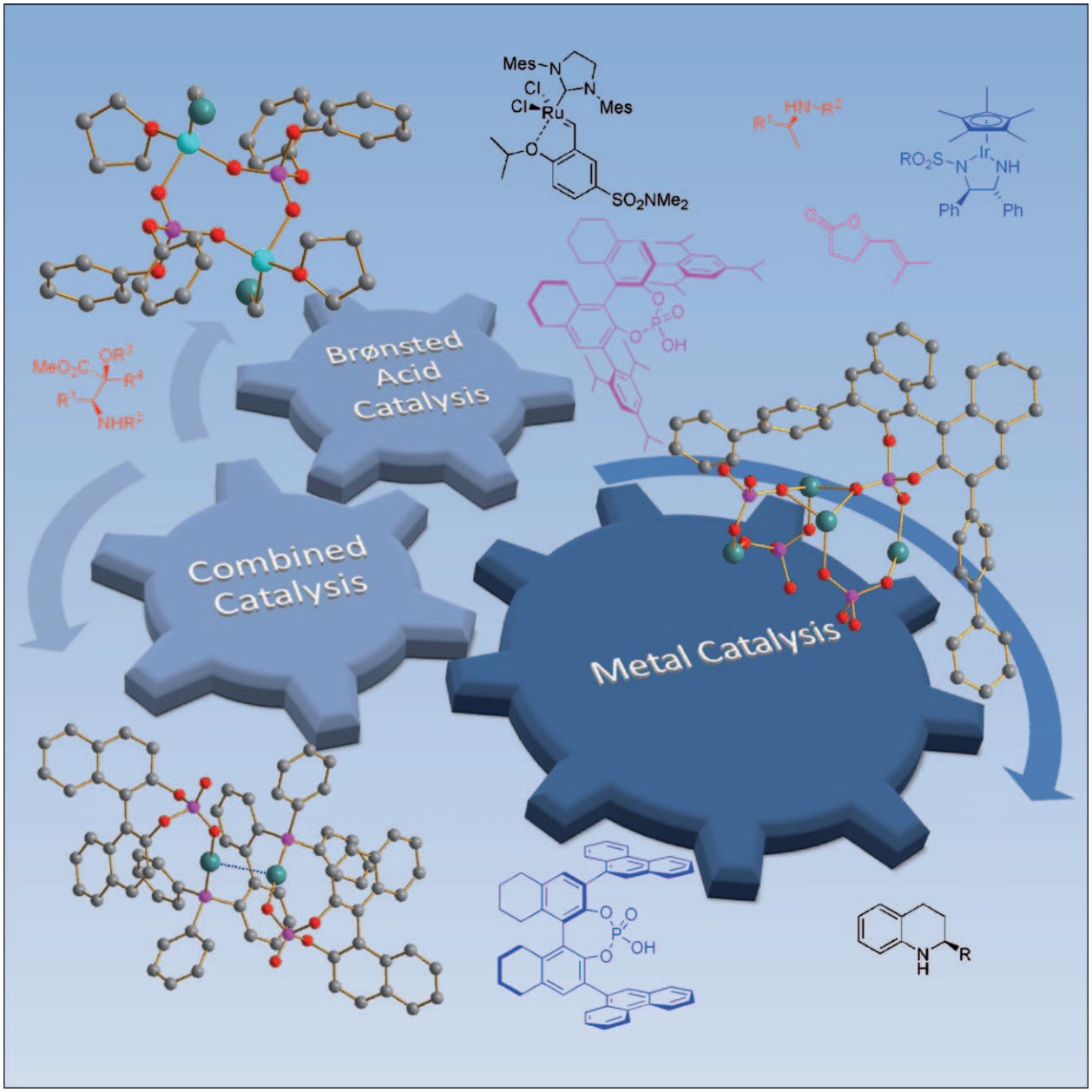

Abstract: Asymmetric catalysis is a key feature of modern synthetic organic chemistry. Traditionally, different combinations of ligands and metals are used to perform highly enantioselective reactions. Since the renaissance of organocatalysis in the early 2000s, tremendous improvement in the field of metal-free catalysis has been achieved. Recently, the combination of transition metals and organocatalysts has allowed the development of new protocols enabling transformations that could not previously be realized. This article aims to present the latest contributions in the field of combined chiral Brønsted acid and metal catalyzed reactions, highlighting the advantages of these catalytic systems as well as describing the uncertainties regarding the molecular structure of the catalytically active species and the reaction mechanisms.

Keywords: asymmetric synthesis · Brønsted acids · combined catalysis · domino reactions · organocatalysis · transition metals

Introduction

Over the past few decades asymmetric transition metal catalysis has emerged as a powerful tool to perform reactions in a highly enantioselective fashion.[1,2] Considerable progress has been made in the field of rational ligand design. However, due to the complex nature of asymmetric catalysis, it is almost impossible to predict the optimal catalyst for a given transformation. Therefore, the development of alternative methods and concepts for performing reactions in a highly selective manner is a major task in modern organic chemistry.

Transition metal catalysts often suffer from being sensitive to air and moisture or are present as contaminants in products. Therefore, many different groups have focused on organocatalysis in which small organic molecules, stable towards air or moisture, are the catalytically active species.[3] Unique to organocatalysis is the substrate activation mode. Whereas transition metal catalysts interact with substrates by coordination, organocatalysts offer the possibility to interact with the substrate either by forming reactive covalent intermediates, such as, enamines or imines in the case of secondary amine catalysis, or by forming hydrogen-bond (Figure 1a and b) or ion-pair complexes (Figure 1c) in the case of Brønsted acid catalysis.[4–6]

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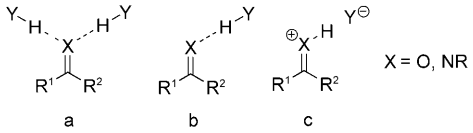
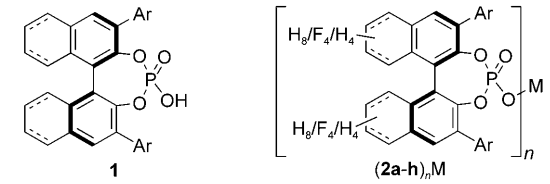


Figure 1. Substrate activation by Brønsted acidic catalysts.

Recently, the combination of organocatalysts and transition metal catalysts has evolved as a new strategy to carry out enantioselective transformations that could not be performed in a traditional way by simply employing one of the two catalysts.[7–9] These transformations not only demonstrate the potential of this merged catalytic approach, but they also show that there are more options to render a reaction highly enantioselective than testing different chiral metal–ligand complexes, organocatalysts, or additives. By using appropriate combinations of an organocatalyst and an achiral or chiral transition metal catalyst, facile ways for reaction optimization can be realized by simply varying one of the two existing catalysts.

This article focuses on reactions that use combinations of chiral Brønsted acids, in particular phosphoric acid diesters (Figure 2), and different chiral and achiral transition metal catalysts. With respect to the mechanism of combined Brønsted acid and transition metal catalyzed reactions, different activation modes can be envisaged. Either a simultaneous activation of both electrophile and nucleophile by the metal and the Brønsted acid can occur or, as in a sequential reaction, first one of the catalysts reacts with the substrate forming an intermediate, which is then activated by the



1a: Ar = 4-Biphenyl, [H_8]-BINOL
1b: Ar = 2,4,6-(iPr)$_3$-Phenyl
1c: Ar = 9-Phenanthryl
1d: Ar = H
1e: Ar = 4-(2-Naphthyl)-Phenyl
1f: Ar = Phenyl
1g: Ar = 4-Cl-Phenyl
1h: Ar = 4-Biphenyl
1i: Ar = 4-tBu-Phenyl
1j: Ar = 9-Anthracenyl

2a: Ar = 4-Biphenyl, [H_8]-BINOL
2b: Ar = 2,4,6-(iPr)$_3$-Phenyl
2c: Ar = H, [F_8]-BINOL
2d: Ar = H
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2f: Ar = 4-Biphenyl
2g: Ar = 4-tBu-Phenyl
2h: Ar = Phenyl

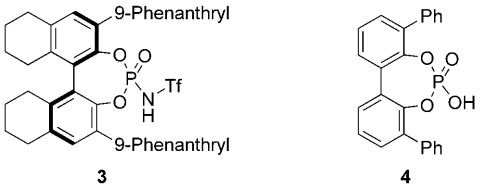


Figure 2. Brønsted acids and metal complexes thereof.

second catalyst for further transformations. The different activation modes of these combined catalytic systems will be discussed.

Phosphoric Acid Diesters—Counterions or Yet Another Ligand?

Before we consider recently reported reactions, important features of chiral phosphoric acid diesters have to be reviewed. Phosphoric acids can either function as Brønsted acid catalysts or interact with the metal catalyst. If interacting with the metal complexes, the acid can act as an anion or as an anionic ligand. Therefore, the role of the acid in the catalytic system is one of the first issues that must be addressed when aiming to understand the reaction mechanism.

A look at the solid-state structure of different metal phosphate complexes found in the Cambridge Crystallographic Database provides evidence for both aforementioned cases. The crystal structure of $[Co(CH_3OH)_4(H_2O)_2][(R)\text{-}\mathbf{1d}]^-[(S)\text{-}\mathbf{1d}]^-\cdot CH_3OH\cdot H_2O$ (**5a**) shows that the octahedral Co atom is surrounded by four methanol and two water molecules with two phosphate moieties associated with each complex through hydrogen bonding and which are not coordinated to the metal.[10,11] Cu and Ni complexes (**5c** and **5d**, respectively) bearing N- and O-ligands (ammonia, methanol, water, 1,2-diethyldiamine) and (*R*)- and (*S*)-BINOL phosphates as counterions have also been described (Figure 3).[12]

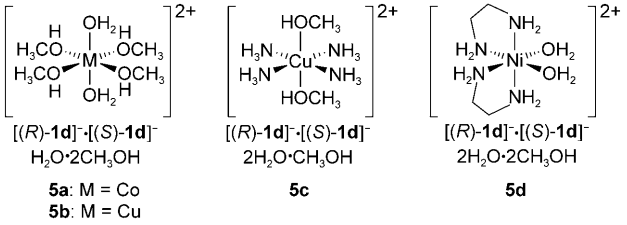


Figure 3. Molecular composition of phosphate salts **5**.

In recent literature, the anions of phosphoric acid diesters are sometimes denoted as counterions that induce enantioselectivity from outside of the cationic catalytic site. Electrostatic interactions between the cationic catalytic active center and the anionic counterion are held liable for the chiral induction.[13]

However, one should not neglect the possibility of the anions of phosphoric acid diesters acting as coordinating ligands and thus inducing chirality in a very similar manner to traditional ligands. In this context and in addition to evidence for ionic interactions, the crystal structure of the chiral phosphoric acid diester silver complex **2a** shows the molecular character of this compound (Figure 4). The tetrameric unit of the silver phosphate provides insight into the coordinating properties of the anion of phosphoric acid diesters. It acts as a bridging ligand between two silver atoms holding the tetramer together. Still, there may be a difference between the solid state and the dissolved state in solution, in which ionic interactions could play an important role. Therefore, extensive studies are required in order to accurately describe these systems. Further insight into the crystal structure of other metal phosphates will be displayed throughout this article.

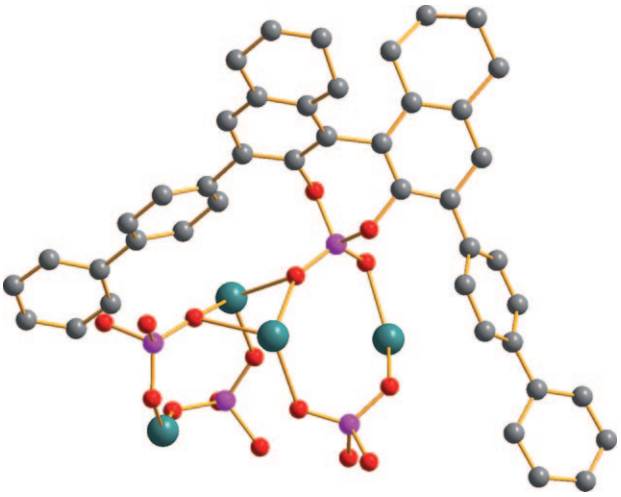


Figure 4. Crystal structure of a chiral phosphoric acid diester silver complex **2a** (hydrogen atoms and backbones of three phosphoric acid diester units are omitted for clarity).

Moreover, there is a fundamental structural difference between the BINOL-based tetrasubstituted chiral phosphate anions and other chiral anions, for example, the non-coordinating chiral tetrasubstituted borate and hexasubstituted phosphorus anions. Whereas in the case of chiral phosphates the negative charge of the anion is shielded only from one side by the binaphthyl backbone, chiral tetra-coordinated borate and hexa-coordinated phosphorus anions possess fully substituted negatively charged central atoms, so that the negative charge is buried in the center of the molecule and is not prone to any interactions with surrounding cations. This is illustrated by the comparison of a space-filling model of the crystal structure of tris(*ortho*-phenylenedioxy)-phosphate (**6**) obtained by Allcock and co-workers[14] (Figure 5, left) and **1a** (Figure 5, right).

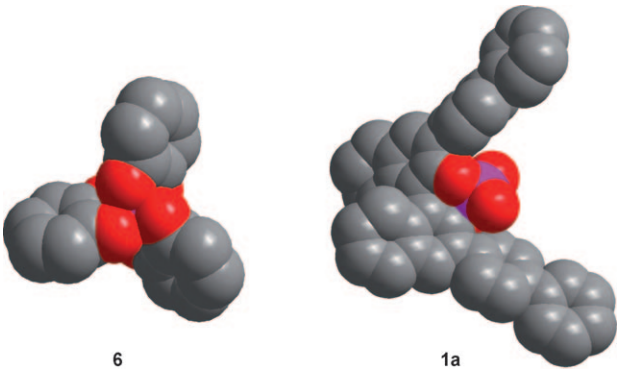


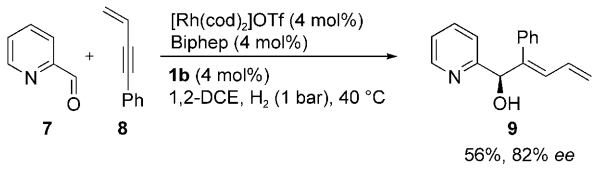
Figure 5. Comparison of space-filling model of a TrisPHAT-anion and a phosphate anion (**1a**).

From a synthetic point of view the synthesis of metal phosphates is more convenient than that of most transition metal complexes. Metal phosphates can easily be obtained by the reaction of phosphoric acid diesters with basic metal compounds, such as silver carbonate or mesitylcopper. Alternatively, metal phosphates can be used in transmetallation reactions to transfer phosphate ions to Au^{I} or lanthanides. Byproducts can easily be removed by filtration or evaporation. Moreover, in contrast to many transition metal complexes, metal phosphates do not require storage under special conditions as they are typically stable to air and moisture.

Dual Catalytic Approaches

The dual catalytic approach takes advantage of simultaneous activation of the electrophile as well as the nucleophile by two different but compatible catalysts. This chapter will outline the development of dual catalytic reactions, starting from the very first example of a combined system consisting of an achiral transition metal and a chiral phosphoric acid diester. Subsequently, improvements of this method will be presented. Chiral dual catalytic systems in which chiral Brønsted acids serve two distinct roles, namely activation of a basic substrate and of a chiral transition metal complex, will also be discussed. Finally, a different activation approach based on the differentiation of the two components of a racemic transition metal complex by chiral Brønsted acids will be described.

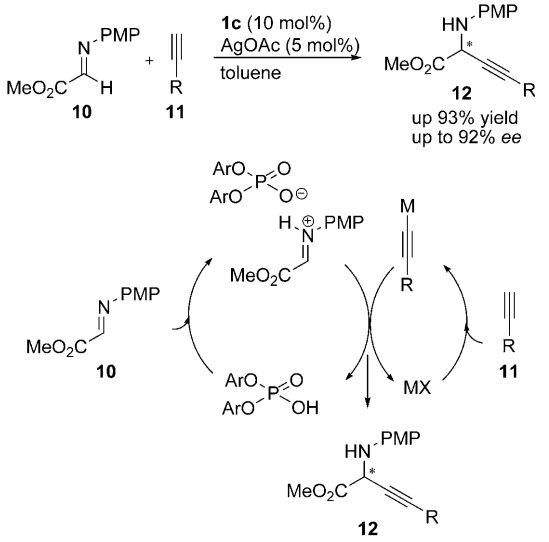
The interplay of a chiral phosphoric acid diester and an achiral transition metal catalyst was first reported in 2006 by Krische and co-workers.[15] In the reductive coupling of pyridine-2-carboxaldehyde (**7**) with 1-phenylbut-3-en-1-yne (**8**), a good level of enantioselectivity could be induced by employing an achiral rhodium catalyst and a chiral phosphoric acid diester (Scheme 1). The enantioselectivity observed in



Scheme 1. Reductive enyne coupling.

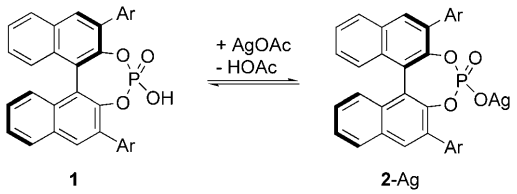
this reaction indicates that the Brønsted acid activated the aldehyde, which enables and controls the subsequent oxidative coupling. This was the only example of combined chiral Brønsted acid and achiral transition metal catalysis and it was used to prove the mechanism of the reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones, which was previously performed with chiral rhodium catalysts and achiral Brønsted acid additives.

The first systematic study of a dual catalytic combined Brønsted acid and transition metal catalyzed reaction was disclosed by Rueping et al. in 2007.[16] The use of an achiral silver salt for the activation of a terminal alkyne and an additional chiral phosphoric acid diester for the parallel activation of an α-iminoester proved to be highly efficient for the addition of terminal alkynes to iminoesters.[17] Consequently, the reaction was performed with excellent stereoselectivity (Scheme 2). Compared to the known metal-catalyzed reactions using chiral copper complexes,[18–21] this dual catalytic concept provides non-proteinogenic β,γ-alkynyl amino acids **12** with a broad substrate scope.



Scheme 2. Proposed reaction mechanism of the Brønsted acid/silver acetate catalyzed alkynylation of α-iminoesters.

Furthermore, the authors draw attention to a different species, which might be formed by the chiral Brønsted acid and silver acetate (Scheme 3). They suggest a counterion-exchange, resulting in the formation of acetic acid and a chiral

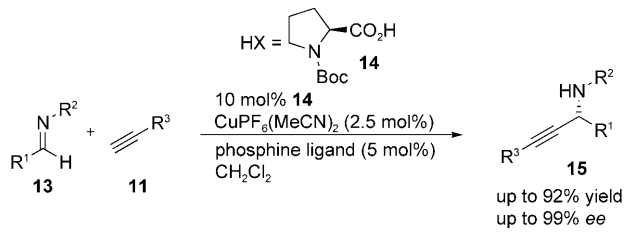


Scheme 3. Possible formation of silver phosphate.

silver phosphate **2-Ag**, which may act as the catalytically active species. Silver phosphate then generates a silver acetylide enclosed by a chiral phosphate anion. Subsequently, the chiral silver acetylide attacks the α-iminoester. Control experiments performed with chiral silver–BINOL complexes in combination with achiral Brønsted acids resulted in similar selectivities, but reduced reactivities.

In 2009 the asymmetric alkynylation reaction again attracted interest in combined transition metal and Brønsted

acid catalysis. In this particular case, amino acids and not phosphoric acids have been used as highly tunable catalysts (Scheme 4). Whereas the imine **13** is activated by the amino



Scheme 4. Asymmetric alkynylation of imines.

acid through hydrogen bonding, the alkyne **11** is activated by an achiral Cu^{I} complex bearing an easily variable monodentate phosphine ligand (Figure 6).[22] This highly modular

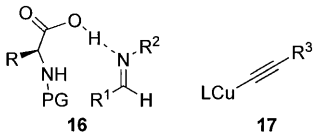


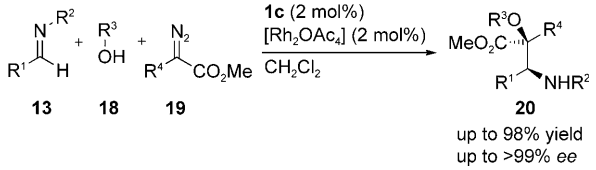
Figure 6. Imine and alkyne activation.

approach displays the potential of combined catalysis, as it implies the use of two catalysts that can readily be optimized in order to obtain high levels of asymmetric induction. For example, with ten amino acids from the "chiral pool" and a library of ten achiral phosphine ligands, 100 different catalyst combinations can be screened in the optimization process. Accordingly, the catalytic system can easily be adjusted for a new substrate. Furthermore, there is no need for thorough chiral ligand synthesis, since the chirality is induced by the N-protected proteinogenic amino acids. Nevertheless, the achiral ligand had considerable influence on the reaction selectivity. Appropriate selection of the phosphine leads to improved enantioselectivity due to steric effects.

The present catalytic approach broadens the scope of asymmetric dual catalytic alkynylation reactions. Whereas in the above case from Rueping, only reactive α-iminoesters **10** could be employed as the electrophile, the present system readily catalyzes the alkynylation of simple aldimines **13**. Furthermore, the system could easily be adapted to different alkyl- and aryl-substituted alkynes and aldimines by simply varying the achiral ligand.

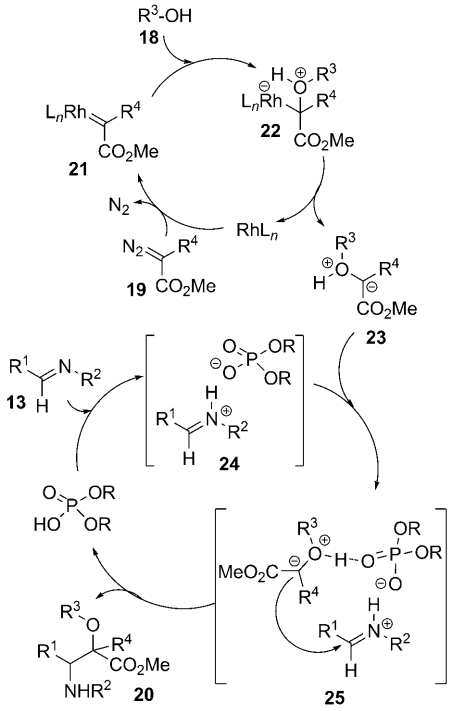
According to kinetic studies the alkynylation reaction has a first-order dependence on the concentration of *N*-Boc-proline, whereas it is of zero order with regard to the concentration of copper. Additional triethylamine completely inhibited the reaction, presumably by blocking the amino acid required for activation. These observations indicate a dual catalytic cycle in which the free amino acid is involved in the rate-limiting step.

Recent reports from Gong, Hu, and co-workers show that the dual catalytic concept is also suitable for multicomponent reactions.[23,24] In a first approach a three-component reaction between diazoacetate, alcohols and aldimines in the presence of an achiral rhodium catalyst and a chiral acid was explored (Scheme 5).[23] Based on the success of Brønsted acids in asymmetric synthesis and the observation that proton donors dramatically accelerate this reaction, the effect of chiral Brønsted acids was investigated. Notably, phosphoric acid diester **1c** not only accelerated this transformation, but also rendered the reaction highly diastereo- and enantioselective.



Scheme 5. Brønsted acid/rhodium acetate dual catalytic three component reaction.

Regarding the mechanism of this dual catalytic reaction, the authors suggest an insertion of the rhodium catalyst into the diazoacetate, forming a metal–carbene complex **21** that is intercepted by the alcohol to form an oxonium–ylide **23** (Scheme 6). This undergoes nucleophilic attack to the imine,



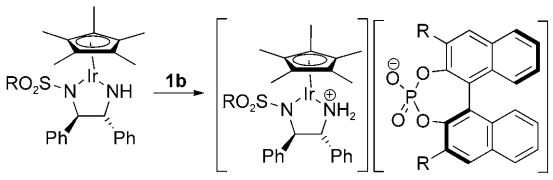
Scheme 6. Proposed reaction mechanism of the asymmetric three component reaction.

which is protonated by the chiral Brønsted acid. Although the authors invoke a cooperative mechanism for this multicomponent reaction, it is in principal a dual catalytic mechanism, in which $[Rh_2(OAc)_4]$ activates the diazoacetate and phosphoric acid diester simultaneously activates the imine.[25]

As an extension of this work, the four-component reaction, using alcohols, amines, aldehydes, and diazoacetate was investigated. In this case imine formation and activation are both promoted by the Brønsted acid.[24]

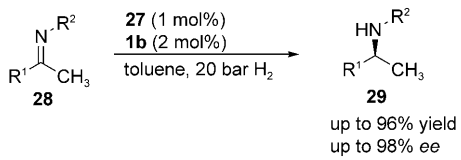
These dual catalytic transformations all have a chiral Brønsted acid catalyst and an achiral transition metal catalyst in common. Xiao and co-workers were the first to report on the interplay of two chiral catalysts. Initial experiments showed that a chiral Ir^{III}–amido complex in conjunction with a phosphoric acid diester forms an efficient catalytic system for the enantioselective hydrogenation of acyclic imines.[26]

Diamine–iridium complexes **26** are known to be highly efficient catalysts for various hydrogenation reactions. In contrast to many different transition metal catalysts containing phosphine ligands, this type of Ir–amido catalysts are air-stable.[27] However, whereas **26a** shows no reactivity in the hydrogenation of imines, upon protonation by Brønsted acids it turns into highly reactive hydrogenation catalysts, such as **27** (Scheme 7).



Scheme 7. Activation of chiral Ir^{III} catalyst by chiral phosphoric acid diester.

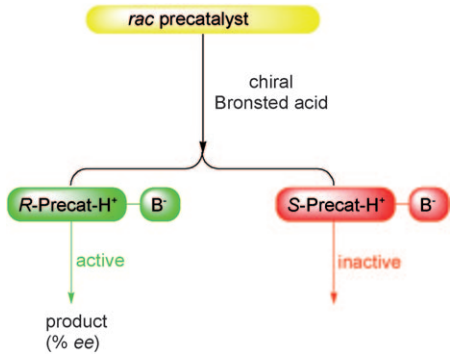
Comparable results were obtained using both a preformed and an in situ generated catalyst. However, the conversion considerably increased when additional Brønsted acid was used in the reaction (Scheme 8). Phosphoric acid diester has a double function in this catalytic system: 1) conversion of the inactive Ir^{III} precatalyst into an active species by forming an iridium–amido–phosphate complex, and 2) activation of the basic imine substrate.



Scheme 8. Enantioselective reduction of acyclic imines.

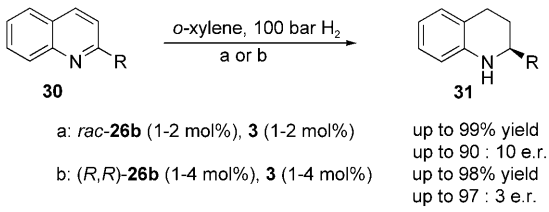
Further improvement consisted of a reductive amination, in which the chiral acid promotes formation of the imine intermediate which is subsequently reduced to the chiral amine in the previously described dual catalytic manner.[28,29]

The concept of chiral Brønsted acid activated, transition metal catalysis has been further developed by Rueping and co-workers. By applying a racemic Ir^{III}–amido complex and chiral Brønsted acid kinetic discrimination was achieved (Scheme 9).[30] The resulting diastereomeric complexes differ in their catalytic properties and it has been shown that by selecting the appropriate chiral Brønsted acid, the resulting matched-case provides higher reactivity and selectivities.



Scheme 9. Brønsted acid differentiated catalysis.

Using this combined Brønsted acid and iridium–amido catalyst the hydrogenation of quinolines could be performed with high selectivities (Scheme 10). This approach to asymmetric catalysis does not require enantiopure transition metal complexes in the screening process. Racemic and thus cheap transition metal catalysts can be used in the optimization process. After finding the optimal metal catalyst and Brønsted acid combination the authors showed that by switching to the corresponding enantiopure transition metal catalyst slightly higher selectivities can be obtained (Scheme 10a, b).



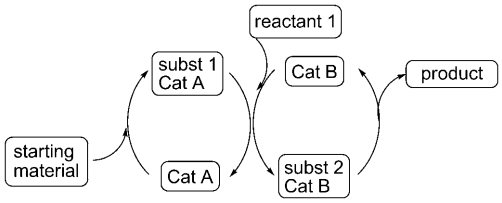
Scheme 10. Brønsted acid differentiated iridium catalyzed reduction of quinolines.

This shows an interesting new facet of combined transition metal and Brønsted acid catalysis as readily accessible racemic transition metal catalysts can be applied in reaction optimizations.

Sequential Catalytic Processes

Sequential, cascade, or domino reactions represent a major field in organic synthesis, since multiple transformations can be carried out in a one-pot fashion, without the need of isolation and purification of the intermediates. Tremendous efforts have been put into developing sequential processes, which all have atom-economy in common. In many of these processes there is little interplay between the catalysts. However, in the case of combined Brønsted acid and transition metal catalyzed reactions one needs to find suitable catalyst combinations that do not poison each other or that would inhibit the catalytic process.

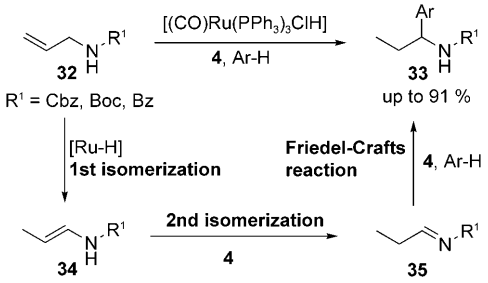
Sequential catalytic processes (Scheme 11) take advantage of multiple consecutive catalytic cycles. The substrate first reacts with catalyst A, the second catalyst B reacts with the



Scheme 11. Sequential catalysis.

product of the first catalytic cycle to provide the final product or an intermediate for subsequent transformations. This is the major difference between sequential catalysis and the previously described dual catalysis.[31–35]

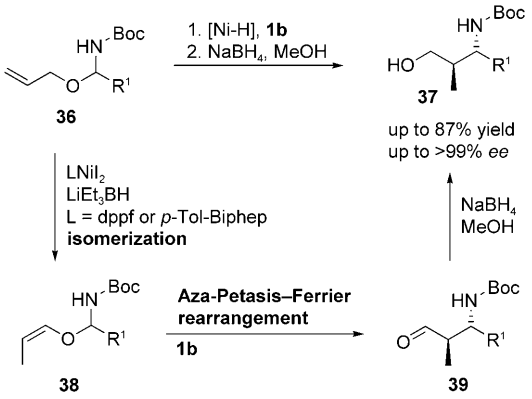
The first example in the field of combined Brønsted acid and transition metal sequential catalysis is from Terada's group and was carried out in a racemic fashion by employing achiral phosphoric acid diesters and achiral Ru catalyst combinations (Scheme 12). The method involves in situ generation of an imine which is subsequently trapped in a Friedel–Crafts reaction.[36]



Scheme 12. Sequential isomerization/Friedel–Crafts reaction.

In the first step allylamide **32** is isomerized by a ruthenium hydride complex forming enamide **34**. Tautomerization of enamide **34** to imine **35** is triggered by phosphoric acid diester **4**, which also serves as the catalyst in the subsequent Friedel–Crafts reaction. The acid-catalyzed tautomerization of enamide to imine is crucial in the course of this reaction. While strong Brønsted acids, such as triflic acid or trifluoroacetic acid, proved to be inefficient, the relatively mild phosphoric acid diesters could efficiently catalyze this transformation. This is probably due to the slow tautomerization of enamide to imine, leading to only low concentrations of the reactive imine being present and, thus, preventing possible side reactions. Whereas no reaction occurs in the absence of ruthenium catalyst, under acid-free conditions isomerization of **32** to enamide **34** takes place. However, the sequential reaction is hampered if no acid is present as imine formation and Friedel–Crafts reaction proceeds only in the presence of acid. Furthermore, an enantioselective version might be obtained by employing chiral phosphoric acid diesters.

A similar reaction sequence using Ni^{II} hydride complexes and additional chiral phosphoric acid diester was examined in the asymmetric aza-Petasis–Ferrier reaction.[37] The Ni^{II} hydride complex, formed in situ from the corresponding NiI_2 complexes, isomerizes allylic alcohol **36** to the *Z*-configured vinyl ether **38** with high levels of diastereocontrol. The enantiospecific acid-catalyzed rearrangement of **38** with consequent reduction of the formed aldehyde **39** furnishes valuable β-amino primary alcohols **37** (Scheme 13).



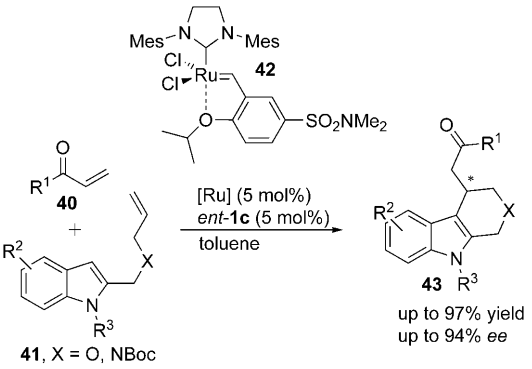
Scheme 13. Sequential isomerization/aza-Petasis–Ferrier rearrangement.

This sequential isomerization/aza-Petasis–Ferrier rearrangement reaction provides valuable β-amino alcohols that cannot be accessed by the typical Mannich reaction. The amino alcohols obtained by the present approach are retrosynthetically derived from aliphatic aldimines which cannot efficiently be used in Mannich reactions since they readily isomerize to the corresponding enamines.

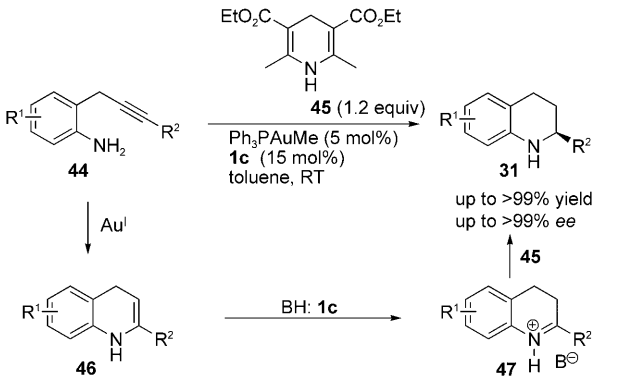
The authors also provide insight into the reaction optimization procedure. Whereas in the dual catalytic approach the reaction is optimized when all components needed for catalysis are present, the steps of the sequential approach can separately be optimized. Accordingly, optimal conditions for a selective isomerization of allyl alcohol **36** were disclosed, irrespective of the optimization of the selective aza-Petasis-Ferrier rearrangement using vinyl ether **38** and

chiral Brønsted acids. With both independently optimized processes in hand the sequential reaction was tested by adding both catalysts to the allyl alcohol **36** to obtain β-amino alcohol **37** in a one-pot reaction.

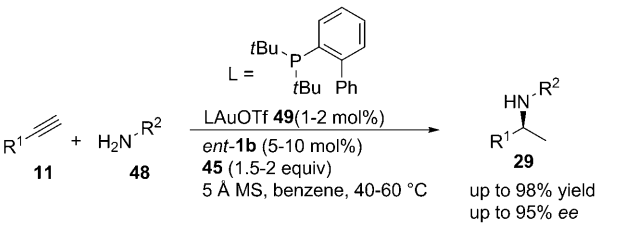
You and co-workers envisioned a cascade reaction which generates an electrophile in the close proximity of an electron-rich arene, which further undergoes Friedel–Crafts reaction (Scheme 14).[38] The cascade was initiated by subject-



Scheme 14. Cross metathesis-Friedel Crafts cascade reaction.



Scheme 15. Sequential intramolecular hydroamination transfer hydrogenation reaction.



Scheme 16. Sequential intermolecular hydroamination transfer hydrogenation reaction.

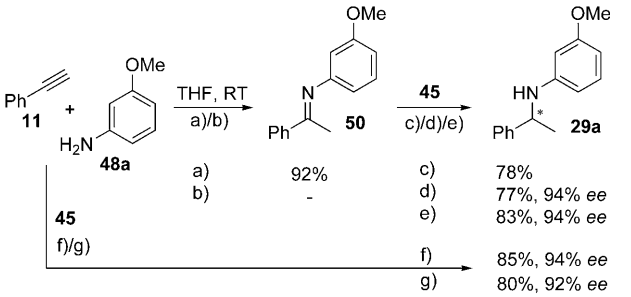
ing vinyl ether **41** (X = O) and phenyl enone **40** to ruthenium-catalyzed cross metathesis[39–41] in the presence of **42** as catalyst.[42–44] Subsequent activation of the obtained indolyl enone by phosphoric acid diester *ent*-**1c** enables an intramolecular Friedel–Crafts reaction and provides **43** in excellent yields and selectivities.

Further development in the area of sequential combined, Brønsted acid, transition metal catalyzed reactions takes advantage of Au^I-catalyzed reactions and successive Brønsted acid catalyzed transfer hydrogenation. To date several reports on the Au-catalyzed[45–47] activation of both double and triple carbon–carbon bonds as well as the subsequent addition of various internal and external nucleophiles have been published.[48–58] In this context the Au^I-catalyzed hydroamination of alkynes provides useful intermediates for consecutive Brønsted acid catalysis.

Che and Gong, independently reported on asymmetric combined Au^I and Brønsted acid catalyzed reactions. Gong and co-workers reported on an intramolecular Au^I-catalyzed hydroamination reaction of 2-(2-alkynyl)anilines **44** providing the appropriate 1,4-dihydroquinolines **46** (Scheme 15).[59] This enamine-like intermediate is isomerized by the Brønsted acid to the corresponding imine **47**, which finally undergoes Brønsted acid catalyzed transfer hydrogenation, yielding tetrahydroquinolines **31** in a highly enantioselective fashion. The method constitutes an alternative to the protocol described by Rueping et al. (Scheme 10).[30]

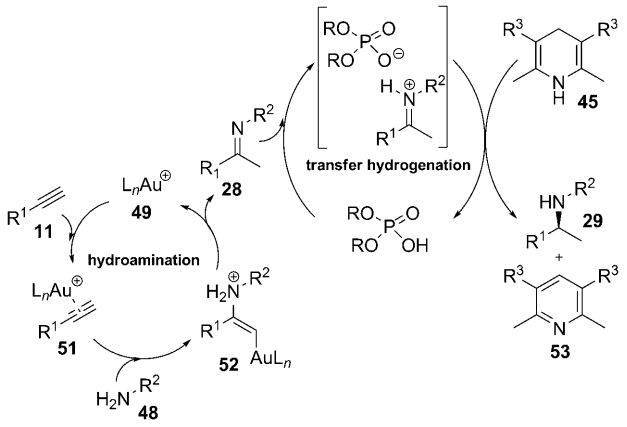
Che and co-workers applied a combination of an achiral Au^I complex and a chiral phosphoric acid diester in an intermolecular hydroamination/transfer hydrogenation cascade reaction of alkynes and anilines (Scheme 16).[60]

Regarding the reaction mechanism, by using ESI-MS spectrometry the authors could show that intermediate **52** is formed after 15 min. Furthermore, they revealed that in the presence of Au^I the hydroamination reaction proceeds smoothly, whereas in the presence of only Brønsted acid the hydroamination is completely inhibited (Scheme 17a, b). Although Au^I complexes can catalyze the transfer hydrogenation of imines, asymmetric transfer hydrogenation only takes place if chiral Brønsted acid is present (Scheme 17c, d). A slightly better yield was obtained in the reduction, when the reaction was performed with a LAuOTf/Brønsted acid combination as compared to the Brønsted acid alone (Scheme 17e vs. d; 83% yield, 94% *ee* vs. 77% yield, 94% *ee*).



Scheme 17. Au^I/Brønsted acid catalyzed hydroamination/transfer hydrogenation reactions. a) [AuCl(L)]/AgBF4 (5 mol%); b) *ent*-**1b**; c) [Au(L)OTf] (5 mol%); d) *ent*-**1b** (10 mol%); e) [Au(L)OTf]/*ent*-**1b** (10 mol%); f) [Au(L)OTf] (1 mol%), *ent*-**1b** (5 mol%), 5Å MS, benzene, 40°C; g) [AuCl(L)]/*ent*-**2b**-Ag (5 mol%), 5Å MS, benzene, 40°C.

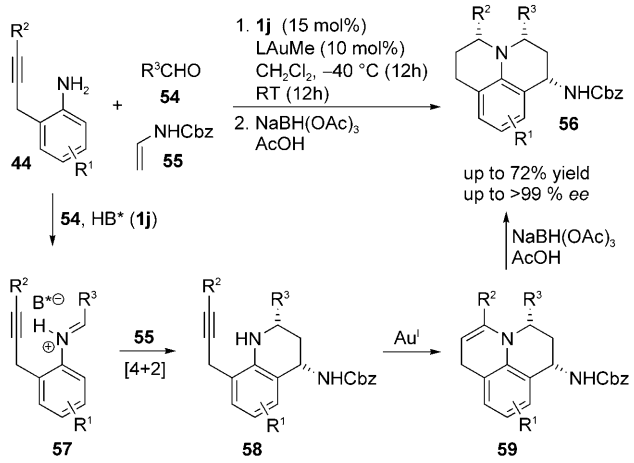
Based on these observations, the authors propose the following reaction mechanism: the Au^I-catalyzed hydroamination reaction furnishes imines that undergo Brønsted acid catalyzed transfer hydrogenation reaction using Hantzsch dihydropyridine as the reducing agent (Scheme 18).



Scheme 18. Reaction mechanism of the intermolecular hydroamination transfer hydrogenation cascade reaction.

Che and co-workers also examined a counterion-exchange, as proposed in the alkynylation reaction by Rueping and co-workers (Scheme 3). Upon using silver phosphate and LAuCl to transmetallate phosphate to Au^I the authors obtained comparable results in the hydroamination/transfer hydrogenation cascade reaction (Scheme 17g vs. f; 80% yield, 92% *ee* using Au phosphate vs. 85% yield, 94% *ee* using LAuOTf and phosphoric acid). Therefore, the formation and involvement of Au phosphate in the catalytic cycle cannot be excluded.

Recently Gong reported a three-component cascade reaction which allows construction of complex heterocyclic compounds **56** with high enantioselectivities (Scheme 19).[61] The sequence takes advantage of two recently introduced reactions: Brønsted acid catalyzed three-component Povarov reaction[62] and Au^I-catalyzed hydroamination. Reaction between *N*-vinylcarbamate (**55**), aldehydes **54** and 2-(2-alkynyl)anilines **44** provides **58**, which are useful synthons for the preparation of julolidine derivatives **56** through Au^I-catalyzed hydroamination and subsequent reduction. Control experiments proved that the free Brønsted acid is the actual catalyst for the Povarov reaction, whereas the in situ formed Au^I phosphate serves as catalyst for the hydroamination reaction.



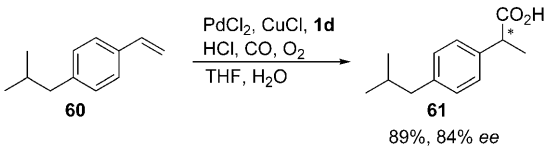
Scheme 19. Synthesis of julolidine derivatives.

A one-pot two-steps procedure for the synthesis of complex N-containing heterocycles was recently reported by Dixon.[63] The sequence makes use of Au^I-catalyzed cycloisomerization of alkynoic acids with consequent addition of amine nucleophiles and chiral Brønsted acid catalysts for promoting the following reactions.

Chiral Transition Metal Phosphates in Catalysis

The question of whether phosphoric acid diesters act as ligands or counterions will be discussed in the section below. In the pioneering work by Alper and Inanaga, phosphoric acid diesters emerged as coordinating ligands to the transition metal centers. Chirality is induced by the coordinating ligand. The term "chiral counterion" associated with chiral phosphoric acid diesters first arose in 2007, when different groups disclosed their pioneering work on "counterion catalysis".

However, Alper and co-workers were the first to apply a transition metal catalyst combined with an additional chiral Brønsted acid in the enantioselective hydrocarboxylation of vinyl arenes (Scheme 20).[64] Although substantial progress

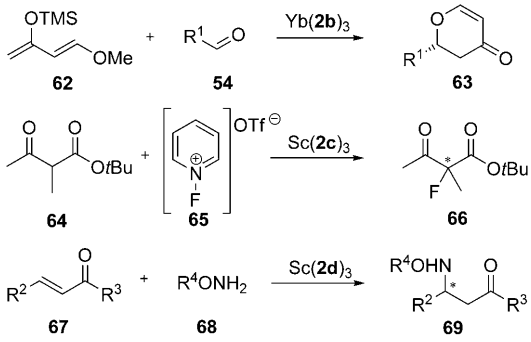


Scheme 20. Hydrocarboxylation of isobutylstyrene.

had been achieved in regioselective hydrocarboxylation reactions of vinyl arenes, no highly enantioselective transformations using chiral ligands or chiral additives had previously been realized. Alper and co-workers were able to demonstrate that the combination of a chiral phosphoric acid diester with $PdCl_2$ gave excellent enantioselectivities in the hydrocarboxylation of styrenes. Important pharmaceuticals such as naproxen and ibuprofen could be isolated with high optical purity. With regard to the reaction mechanism, the authors proposed that chiral phosphoric acid diesters behave as ligands coordinated to palladium.

Inanaga and co-workers reported on rare-earth-metal phosphoric acid diester complexes.[65–71] The synthesis of the latter is carried out by transmetalation of the corresponding

sodium salts to rare-earth-metal trichlorides in hot methanol or water. These rare-earth-metal complexes act as Lewis acidic catalysts in hetero-Diels–Alder reactions,[65–68] asymmetric fluorinations of β-ketoesters[69] and Michael addition reactions[70,71] with phosphoric acid diesters acting as coordinating ligands (Scheme 21).



Scheme 21. Metal phosphate catalyzed reactions developed by Inanaga.

Charette et al. described iodomethylzinc phosphates as powerful reagents for the cyclopropanation of alkenes.[72] Treatment of diphenyl phosphate with diethylzinc and the subsequent addition of diiodomethane provides iodomethylzinc phosphate, which undergoes cyclopropanation reaction in the presence of alkenes. X-ray crystal structure analysis of iodomethylzinc phosphate dimer shows that phosphate anions behave as bridging ligands (Figure 7). The fourth coordination site of zinc is occupied by a molecule of THF.

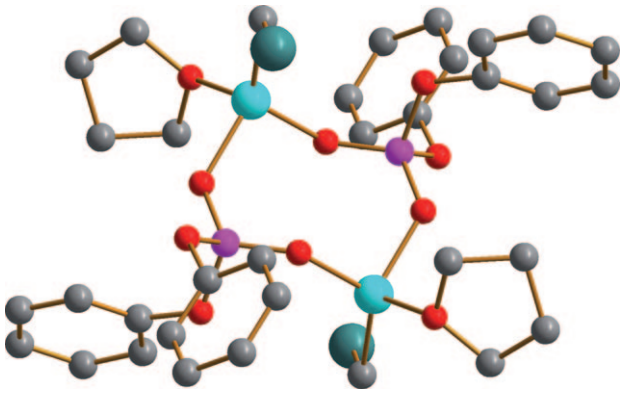
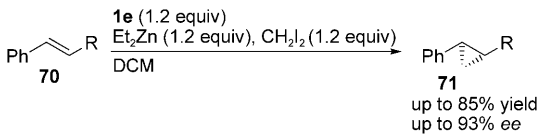


Figure 7. Crystal structure of iodomethylzincphosphate.

An enantioselective version of the reaction was conducted by replacing diphenyl phosphate with the chiral Brønsted acid **1e** (Scheme 22).

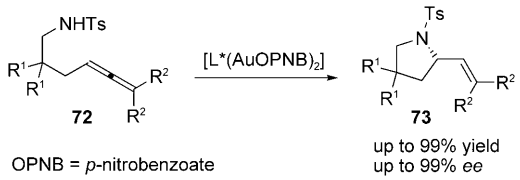
As already mentioned in the previous section achiral Au^I complexes emerged as effective catalysts for the activation of carbon–carbon multiple bonds. However, enantioselective gold catalysis still represents a tremendous challenge in asymmetric synthesis. Since Au^I preferentially exhibits a linear coordination geometry, the chiral environment is far



Scheme 22. Asymmetric cyclopropanation of alkenes.

away from the substrate that is to be activated. Therefore, only a few reports regarding enantioselective Au^I catalysis have been published.[56,57,73–75]

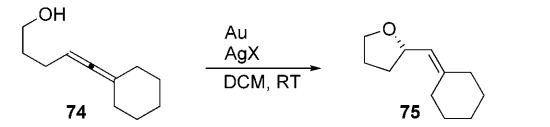
In 2007 Toste and co-workers reported Au^I-catalyzed enantioselective hydroamination reactions using chiral phosphine ligands (Scheme 23). In this study, a remarkable coun-



Scheme 23. Enantioselective hydroamination of allenes.

terion effect was observed. Whereas non-coordinating anions, such as BF_4^-, proved to be inefficient, carboxylate ions render the reaction highly stereospecific.[76]

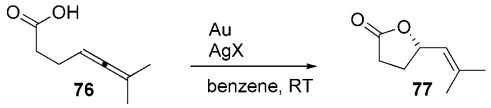
After first examining the effect of chiral ligands and achiral anions, Toste and co-workers turned their attention to systems based on achiral or chiral ligands in combination with chiral phosphate anions. Au phosphate complexes, obtained upon salt metathesis of silver phosphate with AuCl, proved highly efficient in the stereoselective hydroamination, hydroalkoxylation, and hydrocarboxylation of allenes (Schemes 24–26).[77]



Scheme 24. Binuclear Au^I phosphate catalyzed asymmetric hydroalkoxylation.

The high potential of this approach and its adaptability to new challenges is illustrated in the asymmetric hydrocarboxylation and hydroalkoxylation reaction. Whereas complexes bearing chiral ligands and achiral counterions proved to be inefficient in the hydroalkoxylation, complexes incorporating achiral ligands and chiral phosphate anions catalyze this transformation in a highly enantioselective fashion (Scheme 24).

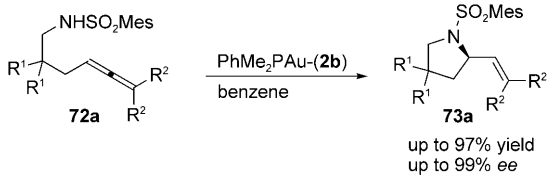
In asymmetric hydrocarboxylations the combinations of chiral ligand/achiral phosphate as well as achiral ligand/chiral phosphate both gave only poor selectivities. However, the matched combination of a chiral ligand and a chiral phosphate renders this reaction highly enantioselective (Scheme 25).



Au = (*S*)-[(AuCl)$_2$(BINAP)]	X = OPNB	38% *ee*
Au = [(AuCl)$_2$(dppm)]	X = **2b**	*ent* 12% *ee*
Au = (*R*)-[(AuCl)$_2$(BINAP)]	X = **2b**	3% *ee*
Au = (*S*)-[(AuCl)$_2$(BINAP)]	X = **2b**	*ent* 82% *ee*

Scheme 25. Binuclear Au^I phosphate catalyzed asymmetric hydrocarboxylation.

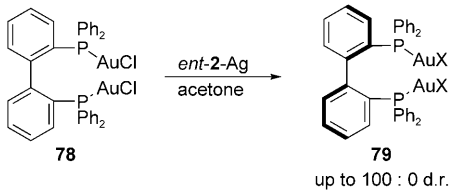
As an extension of this work, the hydroamination of allenes with a system based on an achiral ligand/chiral phosphate combination was investigated (Scheme 26). Notably, with the present system even substrates that exhibited lower selectivity under the initial conditions (Scheme 23) could be efficiently cyclized.



Scheme 26. Au^I phosphate catalyzed asymmetric hydroamination.

The latest achievements in Au^I phosphate-catalyzed allene activations refer to hydroamination and hydroalkoxylation reactions performed with hydrazines and hydroxyamines as internal nucleophiles. The combination of a binuclear Au^I complex, a chiral diphosphine ligand, and an achiral counterion was the key for an efficient asymmetric hydroamination reaction. The reaction provides pyrazolidines, isoxazolidines, and tetrahydrooxazines with high optical purity.[78] In contrast, addition of oxygen nucleophiles to allenes, for example, hydroxylamine in the hydroalkoxylation reaction, requires use of chiral phosphate ions in order to promote a highly selective transformation.

Further evaluation of the interplay of binuclear Au^I complexes that are held together by means of bidentate diphosphine ligands was performed by Mikami and co-workers.[79] The axial chirality of a flexible Biphep racemic ligand coordinated to AuCl could be controlled by applying chiral silver phosphates. Upon anion exchange Biphep exhibits the thermodynamically more stable conformation. Accordingly, excellent diasteroselectivities were observed in this anion controlled dynamic kinetic resolution (Scheme 27). This reaction is highly solvent dependent. Whereas only poor diastereoselectivities can be obtained in weak coordinating solvents, good coordinating solvents, such as acetone, give rise to perfect selectivities. In contrast, use of the silver salts of *N*-triflylphosphoramides in acetone led to decomposition and only if the reaction is carried out in hot benzene does isomerization occur giving a high level of diastereoselectivity (up to 92% *de*). Surprisingly, in this particular case, the preferred conformation of the chiral Biphep moiety is opposite to the one obtained with chiral phosphates.



Scheme 27. Dynamic resolution of atropoisomeric binuclear Biphep Au^I complexes.

Regarding the structure of these complexes, X-ray analysis of **79** (X = 3,3′-diphenyl-(*S*)-1,1′-binaphthyl-2,2′-phosphate) revealed that phosphates act as chiral monodentate ligands (Figure 8). The two Au atoms are connected through aurophilic interaction (Au–Au distance 299 pm), with each Au atom bearing one phosphate ion coordinated through one oxygen atom (bond length Au–O 206 pm). Furthermore, Au is coordinated by two ligands in an almost perfect linear fashion (O-Au-P angles are 177.0 and 177.6° respectively).

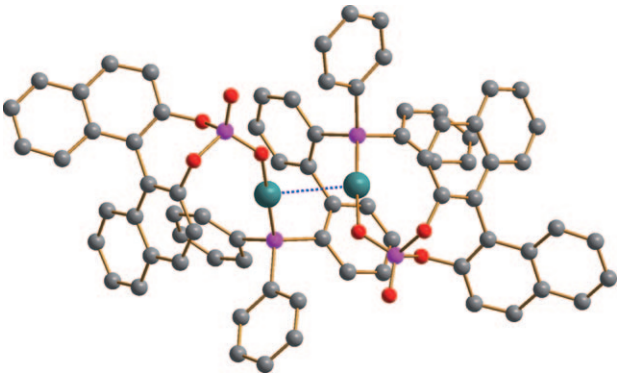
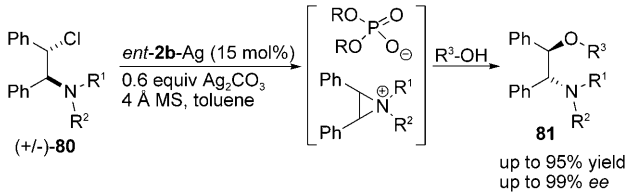


Figure 8. Crystal structure of (*S*)-Biphep-(Au-**2h**)$_2$ (hydrogen atoms and substituents at 3,3' of the BINOL scaffold are omitted for clarity).

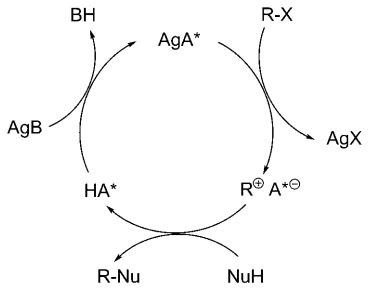
The aurophilic interaction renders this system configurationally stable. Even upon replacement of phosphate with chloride by treating **79** with concentrated hydrochloric acid, no racemization of the axially chiral Biphep ligand occurs. The AuCl complexes resolved thereby were tested in the asymmetric hydroamination reaction. Slightly lower selectivities (up to 91% *ee*) could be observed using the axially chiral Biphep ligand in the reaction developed by Toste and co-workers (Scheme 23).

Apart from the above described applications using combinations of transition metals and chiral Brønsted acids, there is also the possibility to take advantage of other features that are unique to transition metals. Silver can easily abstract halides from organic compounds driven by the formation of insoluble silver halide salts. This can be explored in the formation of aziridines starting from α-halo amines. Use of tertiary amines as internal nucleophiles yields cationic aziridines, which can be brought into a chiral environment by using chiral anions. Subsequent ring opening with an achiral alcohol nucleophile would yield optically active β-amino alcohols.[80] Toste and co-workers successfully applied this concept to the asymmetric ring opening of *meso*-aziridiniumions by employing chiral silver phosphate complexes and additional silver carbonate to regenerate chiral silver phosphate after one catalytic cycle (Scheme 28).[81]



Scheme 28. Asymmetric ring opening of *meso*-aziridiniumions.

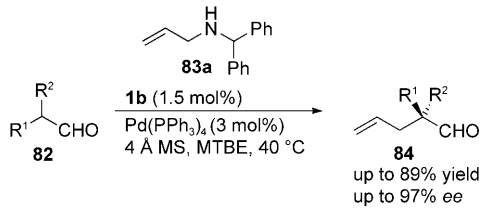
This asymmetric ring-opening reaction is the first example of highly enantioselective, chiral anion, phase-transfer catalysis and provides useful 1,2-aminoalcohols. Chirality is induced by the chiral counterion. The reaction mechanism of this type of phase-transfer catalysis is depicted in Scheme 29.



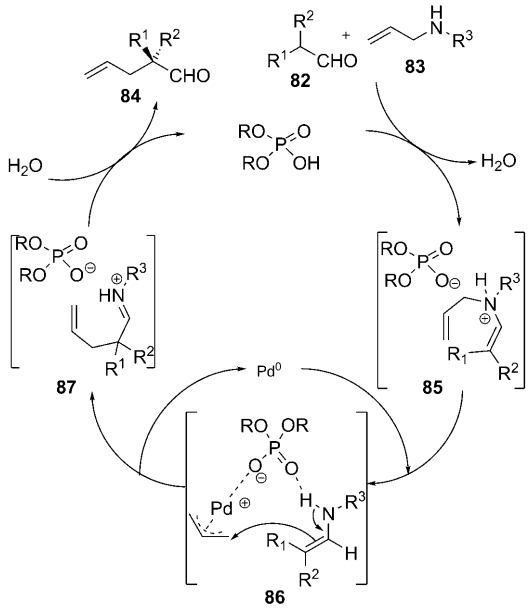
Scheme 29. Chiral anion, phase-transfer catalysis.

Mukherjee and List developed a palladium/Brønsted acid catalyzed α-allylation of α-branched propionaldehydes and secondary allylamines (Scheme 30).[82]

The Brønsted acid first catalyzes imine formation which then undergoes acid-catalyzed tautomerization to form an enamine–phosphate intermediate **85** (Scheme 31). Subsequently a palladium/Brønsted acid catalyzed allyl transfer from the nitrogen to the α-carbon atom takes place. The transfer of allyl from nitrogen to the α-carbon atom only takes place in the presence of palladium and the authors



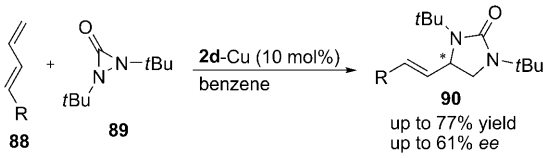
Scheme 30. α-Allylation of propionaldehydes developed by List and co-workers.



Scheme 31. Reaction mechanism of the asymmetric α-allylation.

assume that a cationic π-allyl palladium complex acts as the intermediate. The anion of Brønsted acid **1b** is supposed to align the enamine and the cationic π-allyl palladium complex in close proximity so that the allylation can occur.

Shi and co-workers reported on the copper-catalyzed asymmetric diamination of conjugated olefins.[83] Using chiral copper phosphate complexes, obtained by treating mesitylcopper with the free Brønsted acid, they could carry out a diamination reaction of different olefins with di-*tert*-butyl-diaziridinone as nitrogen source (Scheme 32).



Scheme 32. Copper phosphate catalyzed diamination of olefins.

Different chiral Brønsted acids were converted to their copper complexes (Figure 9); however, only phosphoric acid diesters induced promising enantioselectivity.

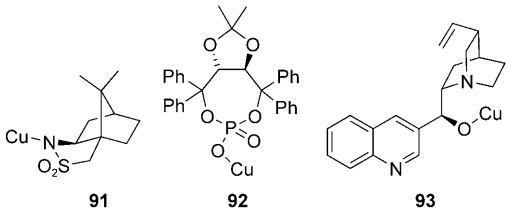
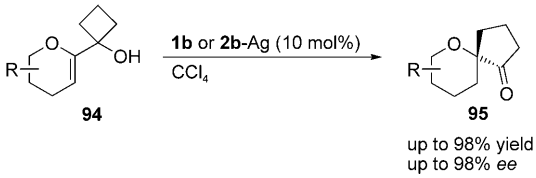


Figure 9. Chiral copper Brønsted acid complexes.

Further development in the transition metal phosphate catalyzed asymmetric transformations was done by Tu and co-workers. Using chiral silver phosphate complexes they performed an enantioselective semipinacol rearrangement of 2-oxo allylic alcohols **94** to provide chiral spiroethers **95** with excellent enantiomeric excesses (Scheme 33).[84] Semi-



Scheme 33. Semipinacol rearrangement of 2-oxo allylic alcohols.

pinacol rearrangement of 2-oxo allylic alcohols can also be achieved with comparable selectivities by the application of the corresponding chiral Brønsted acid. Yet, differences in the catalytic behavior of chiral Brønsted acids and their corresponding metal salts can be observed. Whereas sterically demanding substrates could be activated by the free Brønsted acid, substrates sensitive to acids could efficiently be activated only by the application of the corresponding silver complex.

Latest developments in the field of metal phosphate catalysis concentrate on oxidation reactions. Using a combination of an achiral Mn^{III}–salen complex and a suitable phosphate anion, List and co-workers could efficiently perform the asymmetric epoxidation of various substituted olefins with iodosobenzene as oxidizing agent (Scheme 34).[85]

Although bearing an achiral, C_2-symmetric salene ligand and an achiral anion X, cationic Mn^{III} complexes **99** (Figure 10) are inherently chiral and possess two interconvertible enantiomeric conformations.

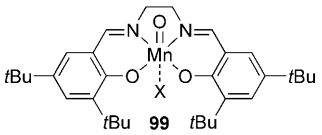


Figure 10. Inherently chiral Mn^{III} complexes **99**.

Therefore, upon interaction of Mn^{I} complex **97** with chiral *ent*-**1i** and PhIO two diastereomeric Mn^{III} complexes **100a** and **100b** will be formed (Figure 11). It was expected that the chiral phosphate anion can differentiate between the two interconvertible conformations and stabilize one, which then performs the catalytic oxidation of olefins.

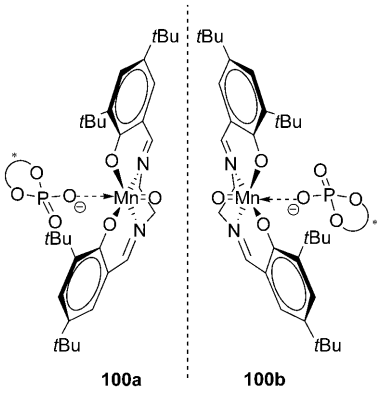
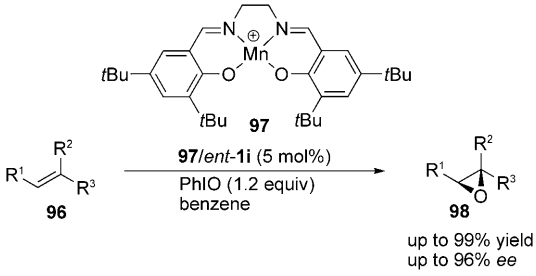
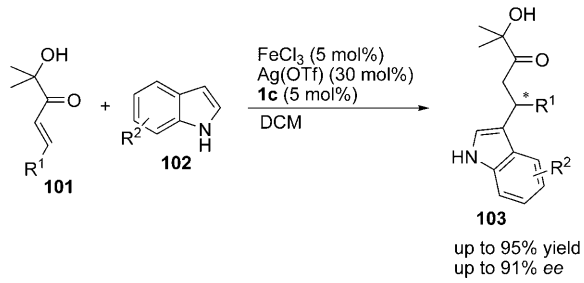


Figure 11. Two possible diastereomeric complexes upon interaction of **97** with *ent*-**1i** and PhIO.

Huang and co-workers recently developed the first iron/Brønsted acid combined asymmetric reaction.[86] The addition of indoles to α′-hydroxyenones could be performed with good enantioselectivities by using cheap $FeCl_3$ and chiral phosphoric acid diesters (Scheme 35). Moreover, additional silver triflate could further improve the selectivity of this reaction. In this transformation, the chiral Brønsted acid has a dual function, on one hand it coordinates to the iron salt, and on the other hand it activates the indole by hy-



Scheme 34. Epoxidation of olefins using an achiral Mn^{III}–salen complex and a chiral phosphate.

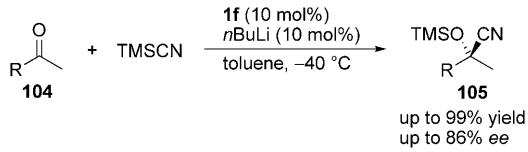


Scheme 35. Iron phosphate catalyzed asymmetric Friedel–Crafts reaction.

drogen bonding interaction. The existence of the iron phosphate complex was supported by ESI-MS spectrometry.

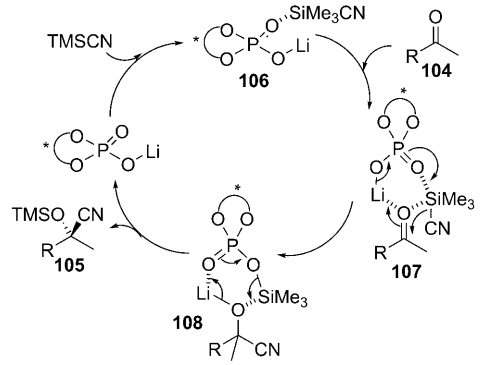
Recently the field of metal phosphate catalyzed reactions has been broadened by reports on the use of main group metal complexes in asymmetric cyanosilylation,[87] Strecker,[88] Friedel–Crafts,[89] Mannich,[90] and Passerini-type[91] reactions.

Ishihara reported the enantioselective cyanosilylation of aromatic ketones by using lithium phosphate complexes.[87] Screening of different conditions allowed identification of optimum parameters for this reaction (Scheme 36).



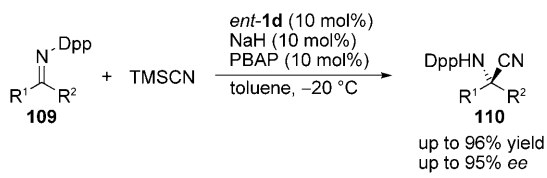
Scheme 36. Lithium phosphate catalyzed asymmetric cyanosilylation of ketones.

The mechanism postulated for this transformation is depicted in Scheme 37. In a first step, the authors proposed activation of TMSCN by lithium phosphate. The six-membered chelate complex **107**, in which the ketone is simultaneously activated by Li and Si, was proposed as the transition state. Attack of cyanide on the *si*-face of the ketone yields an intermediate of type **108**. Subsequently the product is released and the catalyst regenerated.



Scheme 37. Proposed mechanism for the cyanosilylation reaction.

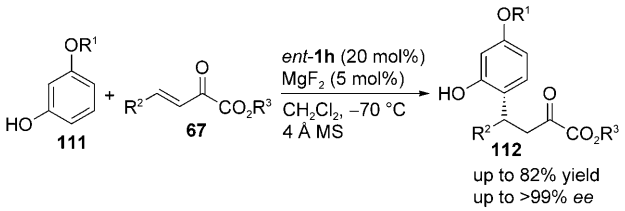
Feng et al. reported the usefulness of sodium phosphates in the enantioselective Strecker reaction (Scheme 38).[88] This hydrocyanation had previously been performed by Rueping using the chiral phosphoric acid as the catalyst.[92]



Scheme 38. Sodium phosphate in the enantioselective Strecker reaction.

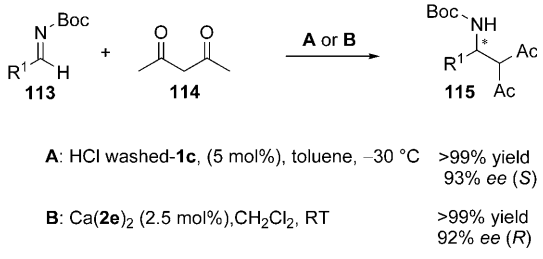
Feng reported that the best results were obtained with sodium salts derived from the simple BINOL phosphoric acid **1d** in the presence of *p*-Bu-*o*-adamantyl phenol (PBAP) as an additive. Use of HCN instead of TMSCN (TMS = trimethylsilyl) as the cyanide source afforded the product in racemic form. Hence, it was concluded that TMSCN is involved in the catalytic cycle and PBAP plays a different role than the generation of HCN from TMSCN.

Luo described the use of Brønsted acids in conjunction with MgF_2 in the Friedel–Crafts reaction of β,γ-unsaturated α-ketoesters (Scheme 39).[89] A 4:1 phosphoric acid:MgF_2 ratio was found to be optimal for a highly enantioselective reaction. Interestingly, no reactions took place when the Brønsted and Lewis acids were individually employed in the reaction. Furthermore, the alkylation of indoles was efficiently performed under the same conditions.



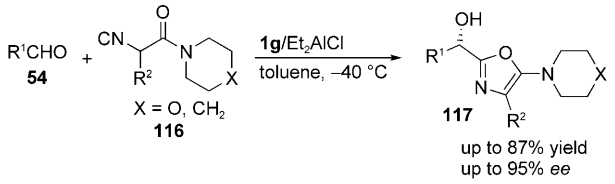
Scheme 39. Phosphoric acid/MgF_2 catalyzed Friedel–Crafts reaction.

Recently Ishihara reported chiral phosphoric acids and their corresponding calcium salts as catalysts in the Mannich reaction between aldimines and 1,3-dicarbonyl compounds.[90] In this context, the free Brønsted acid **1c** and the calcium salt **Ca(2e)$_2$** exhibited comparable activity and selectivity in the reaction between *N*-Boc-benzaldimine (**113**) and acetylacetone (**114**). Interestingly, the product **115** was obtained with comparable, but opposite enantioselectivity (Scheme 40). The two approaches have been subsequently applied to a large range of 1,3-dicarbonyl compounds. The method is particularly useful for the reaction of aldimines with β-ketothioesters in which both systems were highly efficient, affording products with opposite configuration at the chiral amino stereocenter.



Scheme 40. Phosphoric acids and calcium phosphates in the Mannich reaction.

Aluminum phosphates were reported to catalyze the addition of α-isocyanoacetamides to aldehydes, affording the corresponding aminooxazole derivatives with moderate to good levels of selectivity (Scheme 41).[91]



Scheme 41. Aluminum phosphate catalyzed Passerini-type reaction.

Summary and Outlook

The combination of chiral Brønsted acids and achiral or chiral transition metal complexes has received increasing attention in recent years, providing new reaction protocols that furnish important building blocks in a previously unknown fashion. The advantage of combining organocatalysis with metal catalysis was shown in dual catalytic processes in which fast screening is possible by applying Brønsted acids, even those available from the chiral pool. Furthermore, the dual catalytic approach allows simplification of the catalyst evaluation procedure by using one racemic and one chiral catalyst. This allows identification of the optimal combination of the two catalysts for a given transformation. The combination of two different catalysts can also be applied to the in situ generation of highly reactive intermediates. This is nicely illustrated in sequential catalytic processes in which reactive alkyl enamines or enol ethers are generated in situ by a transition metal catalyst and are thus present only in low concentration. In this manner unwanted side reactions can be circumvented. While the reactions are convenient and easy to perform, the nature of the catalytically active species is complex and elaborate studies are required for their structure elucidation. Gaining an understanding of the reaction mechanism at play is essential for further development in this area.[93]

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[1] I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2000**.
[2] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis I–III*, Springer, Berlin, **2000**.
[3] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171.
[4] T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010.
[5] T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758.
[6] M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.
[7] Z. H. Shao, H. B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755.
[8] J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073–7089.
[9] J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373–382.
[10] M. McCann, E. Murphy, *Polyhedron* **1992**, *11*, 2327–2330.
[11] B. Wisser, C. Janiak, *Acta Crystallogr. Sect. E.* **2007**, *63*, m1732–m1733.
[12] T. Dorn, A.-C. Chamayou, C. Janiak, *New J. Chem.* **2006**, *30*, 156–167.
[13] J. Lacour, D. Linder, *Science* **2007**, *317*, 462–463.
[14] H. R. Allcock, E. C. Bissell, *J. Am. Chem. Soc.* **1973**, *95*, 3154–3157.
[15] V. Komanduri, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449.
[16] M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027–7030; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906.
[17] P. de Armas, D. Tejedor, F. García-Tellado, *Angew. Chem.* **2010**, *122*, 1029–1032; *Angew. Chem. Int. Ed.* **2010**, *49*, 1013–1016.
[18] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639.
[19] J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196–11200.
[20] L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275.
[21] G. Blay, L. Cardona, E. Climent, J. R. Pedro, *Angew. Chem.* **2008**, *120*, 5675–5678; *Angew. Chem. Int. Ed.* **2008**, *47*, 5593–5596.
[22] Y. Lu, T. C. Johnstone, B. A. Arndtsen, *J. Am. Chem. Soc.* **2009**, *131*, 11284–11285.
[23] W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783.
[24] X. Xu, J. Zhou, L. Yang, W. Hu, *Chem. Commun.* **2008**, 6564–6566.
[25] In our opinion cooperative catalysis takes place if two different catalysts or multiple active sites of the same catalyst simultaneously interact with the same substrate, thus enhancing its reactivity. Dual catalysis takes place if two different catalysts simultaneously activate independent substrates, thus enabling the reaction.
[26] C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451.
[27] Z. M. Heiden, T. B. Rauchfuss, *J. Am. Chem. Soc.* **2007**, *129*, 14303–14310.
[28] C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969.
[29] M. Klussmann, *Angew. Chem.* **2009**, *121*, 7260–7261; *Angew. Chem. Int. Ed.* **2009**, *48*, 7124–7125.
[30] M. Rueping, R. M. Koenigs, unpublished results.
[31] K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551–564.
[32] A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760.
[33] D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.
[34] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894.
[35] D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076.
[36] K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2008**, *130*, 14452–11453.
[37] M. Terada, Y. Toda, *J. Am. Chem. Soc.* **2009**, *131*, 6354–6355.
[38] Q. Cai, Z.-A. Zhao, S.-L. You, *Angew. Chem.* **2009**, *121*, 7564–7567; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428–7431.
[39] S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
[40] A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.
[41] E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
[42] J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
[43] K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem.* **2002**, *114*, 4210–4212; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.

[44] S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
[45] M. Haruta, *Nature* **2005**, *437*, 1098–1099.
[46] G. J. Hutchings, M. Haruta, *Appl. Catal. A* **2005**, *291*, 2–5.
[47] G. J. Hutchings, M. Brust, H. Schmidbaur, *Chem. Soc. Rev.* **2008**, *37*, 1759–1765.
[48] A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.
[49] A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Catal. Today* **2002**, *72*, 19–27.
[50] A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150–7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990–6993.
[51] A. S. K. Hashmi, R. Salathé, T. M. Frost, L. Schwarz, J.-H. Choi, *Appl. Catal. A* **2005**, *291*, 238–246.
[52] N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759–1774.
[53] A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387–391.
[54] A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936.
[55] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979.
[56] D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403.
[57] D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378.
[58] A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775.
[59] Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183.
[60] X.-Y. Liu, C.-M. Che, *Org. Lett.* **2009**, *11*, 4204–4207.
[61] C. Wang, Z.-Y. Han, H.-W. Luo, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 2266–2269.
[62] H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599.
[63] M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797.
[64] H. Alper, N. Hamel, *J. Am. Chem. Soc.* **1990**, *112*, 2803–2804.
[65] T. Hanamoto, H. Furuno, Y. Sugimoto, J. Inanaga, *Synlett* **1997**, 79–80.
[66] T. Hayano, T. Sakaguchi, H. Furuno, M. Ohba, H. Okawa, J. Inanaga, *Chem. Lett.* **2003**, *32*, 608–609.
[67] H. Furuno, T. Kambara, Y. Tanaka, T. Hanamoto, T. Kagawa, J. Inanaga, *Tetrahedron Lett.* **2003**, *44*, 6129–6132.
[68] H. Furuno, T. Hayano, T. Kambara, Y. Sugimoto, T. Hanamoto, Y. Tanaka, Y. Z. Jin, T. Kagawa, J. Inanaga, *Tetrahedron* **2003**, *59*, 10509–10523.
[69] S. Suzuki, H. Furuno, Y. Yokoyama, J. Inanaga, *Tetrahedron: Asymmetry* **2006**, *17*, 504–507.
[70] H. Sugihara, K. Daikai, X. L. Jin, H. Furuno, J. Inanaga, *Tetrahedron Lett.* **2002**, *43*, 2735–2739.
[71] S. L. Jin, H. Sugihara, K. Daikai, H. Tateishi, Y. Z. Jin, H. Furuno, J. Inanaga, *Tetrahedron* **2002**, *58*, 8321–8329.
[72] M.-C. Lacasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441.
[73] R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391.
[74] N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181.
[75] A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325.
[76] R. L. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453.
[77] G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499.
[78] R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem.* **2010**, *122*, 608–611; *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601.
[79] K. Aikawa, M. Kojima, K. Mikami, *Angew. Chem.* **2009**, *121*, 6189–6193; *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.
[80] The first attempt toward this goal yielded 1,2-aminoalcohols with low yields and selectivities: C. Carter, S. Fletcher, A. Nelson, *Tetrahedron: Asymmetry* **2003**, *14*, 1995–2004.
[81] G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 14984–14985.
[82] S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337.
[83] B. Zhao, H. Du, Y. Shi, *J. Org. Chem.* **2009**, *74*, 8392–8395.
[84] Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724–8726; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572–8574.
[85] S. Liao, B. List, *Angew. Chem.* **2010**, *122*, 638–641; *Angew. Chem. Int. Ed.* **2010**, *49*, 628–631.
[86] L. Yang, Q. Zhu, S. Guo, B. Qian, C. Xia, H. Huang, *Chem. Eur. J.* **2010**, *16*, 1638–1645.
[87] M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776–1780.
[88] K. Shen, X. Liu, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2009**, *15*, 6008–6014.
[89] J. Lv, X. Li, L. Zhong, S. Luo, J.-P. Cheng, *Org. Lett.* **2010**, *12*, 1096–1099.
[90] M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911–3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826.
[91] T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *J. Org. Chem.* **2009**, *74*, 8396–8399.
[92] M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679–2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617–2619.
[93] Added in proofs: During the preparation of this manuscript, a microreview on metal-assisted organocatalysis has appeared, see: C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3025.

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