ACDC

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Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications

*Manuel Mahlau and Benjamin List**

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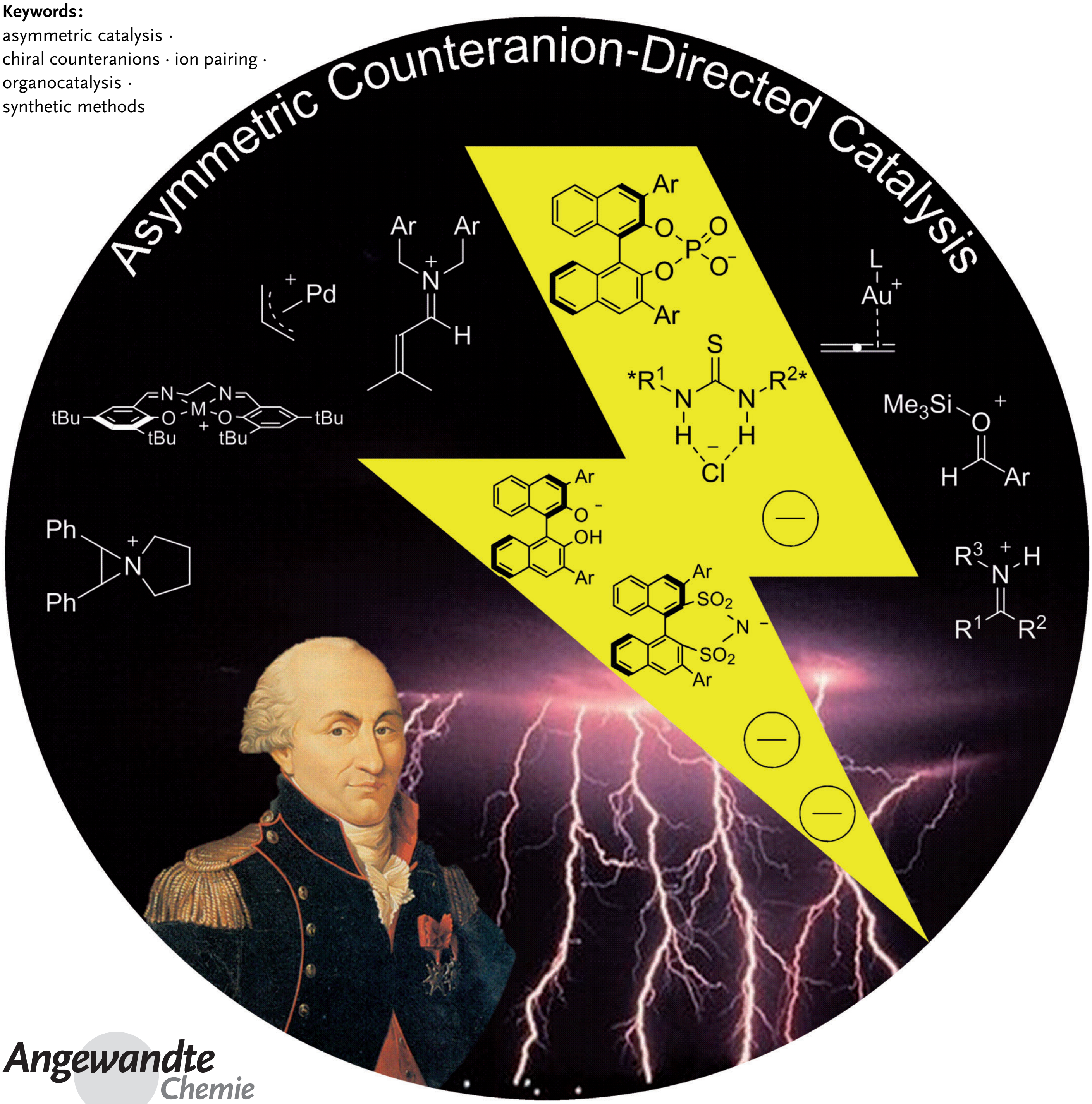

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Recently, the use of enantiomerically pure counteranions for the induction of asymmetry in reactions proceeding through cationic intermediates has emerged as an exciting new concept, which has been termed asymmetric counteranion-directed catalysis (ACDC). Despite its success, the concept has not been fully defined and systematically discussed to date. This Review closes this gap by providing a clear definition of ACDC and by examining both clear cases as well as more ambiguous examples to illustrate the differences and overlaps with other catalysis concepts.

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1. Introduction

Asymmetric catalysis can be realized by using all types of chemical interactions between substrates and catalysts, including covalent bonding (enamine catalysis, metal complexes, etc.) and different types of noncovalent interactions, such as hydrogen bonding or ion pairing. The use of ion pairing in asymmetric catalysis has been realized in enantioselective phase-transfer catalysis, which is well-established for reactions proceeding via anionic intermediates.[1] The underlying idea is that these intermediates are necessarily accompanied by a cation and, if this cation is chiral and a sufficient association can be achieved, reactions can proceed enantioselectively (Figure 1). The idea of inverting the polarity in phase-transfer catalysis to control reactions proceeding via cationic intermediates naturally comes to mind. However, such systems have been elusive until recently. Expanding the concept of controlling reactions involving cationic intermediates beyond phase-transfer catalysis leads to the concept of asymmetric counteranion-directed catalysis (ACDC, Figure 1).[2,3]

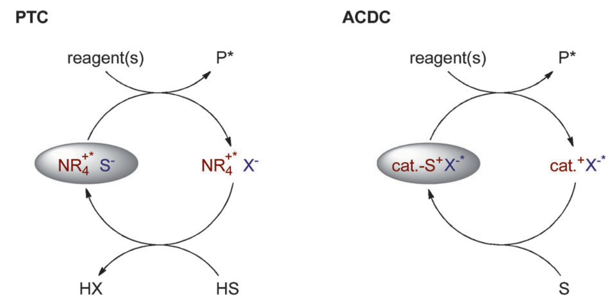

Figure 1. Schematic representation of phase-transfer catalysis with chiral countercations (PTC) and asymmetric counteranion-directed catalysis (ACDC). P = product; S = substrate; X^- = anion.

Early attempts to realize this idea date back to the first years of this century, when several studies of modest success were reported.[4] After the Yamamoto research group disclosed the first examples of highly enantioselective nonenzymatic Brønsted acid catalysis based on their Lewis acid assisted Brønsted acid concept,[5] a breakthrough in this field came in 2004, when the research groups of Akiyama and Terada used binol-based phosphoric acids **4** (see Section 3.1.1, Scheme 1), which had previously been used as ligands in transition-metal and Lewis acid catalysis,[6–8] as organocatalysts for Mannich-type reactions.[9] Although it was later shown that the catalyst used by the Terada research group was a calcium salt, rather than the free acid,[10] these reports marked the beginning of an impressive success story of phosphoric acid derived organocatalysts, which are amongst the most widely used motifs in organocatalysis today.[11]

Our research group has also been active in the area of enantioselective phosphoric acid catalysis, and our early contributions to the field include Brønsted acid catalyzed asymmetric transfer hydrogenations, reductive aminations, and Pictet–Spengler reactions.[12] In this context, we also introduced 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate (TRIP), which is arguably one of the most versatile binol-derived phosphoric acid known to date.[12a,13]

Inspired by the success of binol phosphates as chiral counteranions in asymmetric Brønsted acid catalysis, we hypothesized that it should be possible to expand the concept to the highly enantioselective catalysis of all types of reactions proceeding via cationic intermediates in the stereodetermining step. We named this generalized concept "asymmetric counteranion-directed catalysis" and provided the proof of principle by developing an ACDC-based asymmetric transfer hydrogenation of α,β-unsaturated aldehydes (see Section 3.1.1).

2. What is ACDC?

The term asymmetric counteranion-directed catalysis was coined in 2006 and has since been used to describe reactions that utilize this concept.[14] A precise definition, however, has not been presented to date. As a consequence of the success of this strategy within the last few years, such a definition has become desirable, to allow for the classification of different reactions and comparison with and differentiation from other concepts. ACDC can be described as follows:

Asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding

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[*] M. Mahlau, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: list@mpi-muelheim.mpg.de

through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst.

Some further specifications are required to allow for a systematic application within the different areas of catalysis. One important issue is the role of stabilizing interactions, which often come together with the Coulombic attraction in ion pairs.

Accordingly, Anslyn and Dougherty have provided the following definition of an ion pair:[15]

"An ion pair is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them."

If this definition is strictly followed, the use of the term ion pair would cease to be correct as soon as further interactions between the cation and anion (except for the Coulombic attraction) stabilize the associate. However, the authors also state that other interactions can be overlaid with ion pairing. For example, hydrogen bonds are discussed as a special case of ion pairing between the dipoles of a donor bond and an acceptor atom. This shows that the borders between ion pairing and other interactions are not clear cut and the term ion pair can still be used adequately in such cases. It has also been stated by Marcus and Hefter in the context of the differentiation between ion pairs and complexes, that: "*Once an ion pair is formed, there is no method for determining the origins of the attractive forces holding it together, although we may choose to impose particular models of such forces on it.*"[16]

In many cases it is not possible to determine with reasonable certainty whether a "real" ion pair is involved in a given reaction. On the other hand, the existence of ion pairs is in principle compatible with the presence of further stabilizing interactions. These ambiguities are also reflected in the use of the two related terms "ion-pair catalysis"—which is commonly used to refer to reactions proceeding through ion pairs in the classical sense exclusively—and "asymmetric counteranion-directed catalysis"—*which we define to include all those reactions in which a considerable anion character can be attributed to the component responsible for the asymmetric induction*. Therefore, the term ion pair will be used in the broader fashion, thus allowing for the presence of other stabilizing interactions, as we believe that this facilitates the discussion of the concept at hand.

In Brønsted acid catalysis, for example, ion pairs are often clearly stabilized by hydrogen bonds. For such cases it can be said that the Coulombic attraction within the ion pairs in ACDC may be accompanied by further stabilizing interactions, such as hydrogen bonding, as long as the ionic character of the intermediate does not become negligible. Therefore, enantioselective Brønsted acid catalysis is, in general, included as a specific case of ACDC.

This leads to the realization that there should not be any significant covalent bonding between cation and anion during the selectivity-determining step of the catalytic cycle. Importantly, this does not exclude such covalent interactions involving the relevant anion during other steps of the reaction. In transition-metal catalysis, for example, a resting state or intermediate in which the anion is covalently bound to the metal center is fully compatible with ACDC, as long as this bond is not present during the selectivity-determining step(s) of the reaction.

The application of ACDC to transition-metal catalysis prompts the question of how this is different from the established use of anionic ligands. It is important to note that ACDC and anionic ligands certainly pose two extremes, between which a continuum of real cases exists. Nevertheless, an assignment can be made in many cases by considering which role is predominant during the selectivity-determining step of the reaction. If the anion in question can be considered to be accompanying a cationic active species, which is responsible for the turnover, the reaction is attributed to the concept of ACDC. On the other hand, an anion bound to a metal atom and forming a neutral or still positively charged catalytically active species is considered to be a ligand.

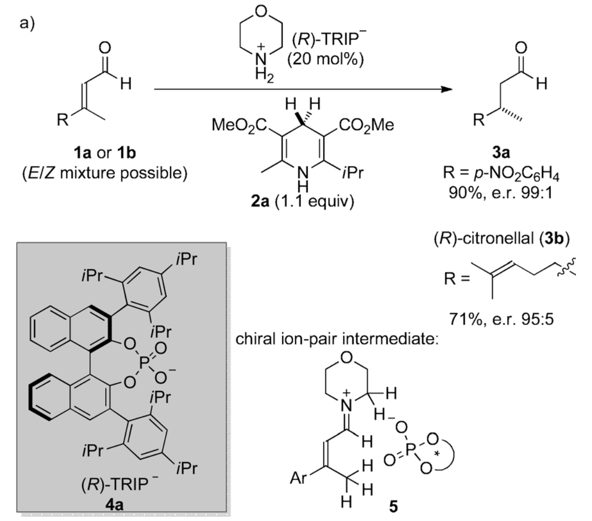
Another case common to both organocatalysis and transition-metal catalysis which requires further attention is the combination of chirality in both the cationic and the anionic moieties of a catalyst. Combined catalyst systems, in which the chiral anion is aided by additional chirality in the cation, are considered to be ACDC as long as the role of the anion meets its definition. Such systems hold particular promise in the design of highly enantioselective catalysts for challenging reactions, where both classical strategies and ACDC alone do not suffice.

In view of these guidelines for the identification of ACDC, it must be pointed out that there will always be catalysts for which no clear assignment can be made. There could also be

Benjamin List was born in Frankfurt, Germany, in 1968. He studied chemistry at the Freie-University Berlin and obtained his PhD in 1997 at the University of Frankfurt. After postdoctoral studies at the Scripps Research Institute he became an Assistant Professor there in 1999. In 2003 he moved back to Germany to take a position as group leader at the MPI für Kohlenforschung in Mülheim. In 2004 he became an Honorary Professor at the University of Cologne and in 2005 became a Director at the MPI. Since 2011 he has also served as managing director of the MPI. His research interests include developing new strategies for organic synthesis.

Manuel Mahlau was born in Madrid, Spain, in 1985. He studied chemistry at the Albert-Ludwigs-Universität Freiburg, where he received his diploma in chemistry in 2010 under the supervision of Prof. Dr. Reinhard Brückner. In 2011 he commenced PhD studies as a Kekulé-fellow of the Fonds der Chemischen Industrie in the group of Prof. Dr. Benjamin List, where he is currently working on new applications of the ACDC concept in Lewis acid catalysis.

cases where a reaction designed to proceed through ACDC turns out to operate through a different pathway or vice versa. The simple lack of information about a specific system will often make definite statements challenging.



Scheme 1. Proof of principle: Catalytic asymmetric transfer hydrogenation with salts of the secondary amine TRIP .[17b]

3. Applications of ACDC

The goal of this section is not to provide a comprehensive overview of ACDC applications, which would in many cases be presumptuous due to the aforementioned ambiguities, but to discuss informative selected cases, with the aim of illustrating the guidelines presented in Section 2. We will treat the areas of organocatalysis, transition-metal catalysis, and Lewis acid catalysis separately, trying to present clear cases of ACDC alongside cases which merit closer inspection to allow for an assignment.

3.1. Applications in Organocatalysis

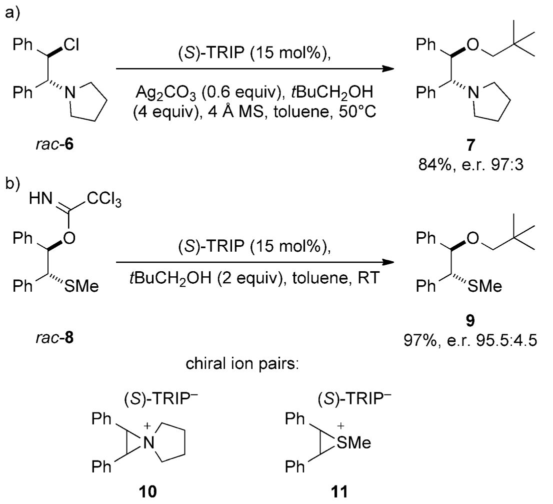
A large number of applications in the early development of ACDC belong to this category, from which the concept also originates. They span from the first examples of highly enantioselective Brønsted acid catalysis to counteranion-controlled asymmetric reactions of quaternary iminium or aziridinium ions.

3.1.1. Proof of Principle—ACDC via Intermediates without Strong Stabilizing Effects

When the concept of asymmetric counteranion-directed catalysis was introduced, an example of "pure" ACDC was required to prove its feasibility as a stand alone concept for the design of enantioselective catalyst systems. We reasoned that such a system could be generated through ion pairing of a secondary amine-derived iminium ion with a chiral counteranion, and chose the catalytic asymmetric transfer hydrogenation of β-disubstituted enals as a benchmark reaction. We prepared a large number of potential catalysts by simply combining secondary amines with binol-derived phosphoric acids and tested these salts as catalysts for the catalytic asymmetric transfer hydrogenation of enals under conditions similar to those using chiral secondary amine catalysts.[17] The morpholine TRIP (**4a-H**) salt was found to be best in terms of activity, selectivity, and substrate generality. Under optimized conditions, this catalyst was applicable to a wide range of enals. For example, the *p*-nitrophenyl-substituted derivative **1a** was reduced to its saturated analogue **3a** in high yield and enantioselectivity (Scheme 1).[17b] Importantly, the reaction was found to be diastereoconvergent, and *E*/*Z* mixtures provided the same enantiomer of the product without loss of selectivity.

The strong ion pairing in this system is evident from the influence of the achiral anion on the enantioselectivity observed in the analogous reaction catalyzed with chiral amines,[17a] and is even more pronounced in the TRIP-based catalyst system, where the achiral reactive iminium ion reacts enantioselectively on the basis of the chiral environment provided by the counteranion (**5**; Scheme 1). It should be pointed out that no additional stabilizing effects are present in the ion-pair intermediate **5**. An obvious hydrogen-bonding stabilization, for example, can be excluded, because of the absence of N-bound hydrogen atoms in quaternary iminium ions. However, weaker C–H···X⁻ hydrogen bonds are likely to be present.[18] Importantly, this system provides the proof of principle for the feasibility of ACDC, as it constitutes a clear case of asymmetric catalysis directed by a chiral counteranion. The potential of ACDC was showcased by the application of the TRIP-based catalyst to the asymmetric transfer hydrogenation of citral (**1b**) to give (*R*)-citronellal (**3b**) in good yield and enantioselectivity. In this case, ACDC proved to be much more powerful than chiral secondary amine catalysis—both the system developed in our research group and the one from MacMillan and co-workers gave only moderate enantioselectivity (e.r. 70:30) with this substrate.[17b]

Subsequently to the introduction of the ACDC concept, the Toste research group realized a reversed-polarity phase-transfer catalysis (Scheme 2a)[19] Here, TRIP together with a stoichiometric amount of silver carbonate was used to abstract chloride from the racemic chloramines *rac*-**6**, thereby generating a chiral ion pair **10** consisting of a quaternary *meso*-aziridinium ion and the TRIP counteranion. Notably, this intermediate could not have been generated by protonation and no obvious hydrogen bonds or other directional interactions stabilize ion pair **10**. The attack of neopentyl alcohol on salt **10** delivered the amino ethers **7** in high yields and enantioselectivities. An analogous *meso*-episulfonium TRIP ion pair **11** was generated from the trichloroacetimidate-substituted racemic sulfide *rac*-**8** (Scheme 2b). This strategy was chosen to avoid the use of silver carbonate, which would likely have bound to the sulfide instead of triggering the desired acetimidate abstraction. In this case, cation formation could be induced by TRIP alone. Even though a Brønsted acid is the active catalyst in this case, ion pair **11** is again devoid of apparent additional attractive interactions, besides the Coulombic force. Further applica-



Scheme 2. Asymmetric ring opening of *meso*-aziridinium and *meso*-episulfonium ions developed by Toste and co-workers.[19] MS = molecular sieves.

tions of reversed-polarity phase-transfer catalysis have since been reported.[20] In addition, related strategies to create other types of cations without the possibility to form any obvious hydrogen bonds have been reported.[21]

3.1.2. Brønsted Acid Catalysis: Hydrogen-Bond-Assisted Ion Pairs

Ever since the seminal reports on chiral Brønsted acid catalysis by the research groups of Akiyama and Terada, the mechanism of these reactions has been of great interest. While Terada and co-workers did not discuss possible mechanisms in their seminal report, the Akiyama research group suggested an ion-pair intermediate for their Mannich-type reaction.[9]

Both research groups later conducted theoretical studies to elucidate the mechanism and the origin of the enantioselectivity in their respective reactions. The study by Gridnev, Terada et al. focused on calculating the different phosphoric acid imine structures formed during the reaction of *N*-Boc-imines with acetylacetone and their characterization by NMR spectroscopy. They concluded that the hydrogen-bonded form **12** (Figure 2) was the relevant intermediate in their reaction and explained the enantioselectivity by comparing the different configurations of this intermediate.

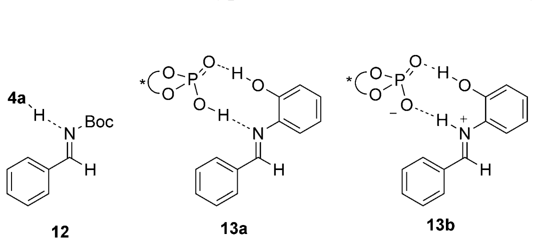


Figure 2. Intermediates calculated for the Mannich-type reactions by the research groups of Akiyama and Terada.[22,23]

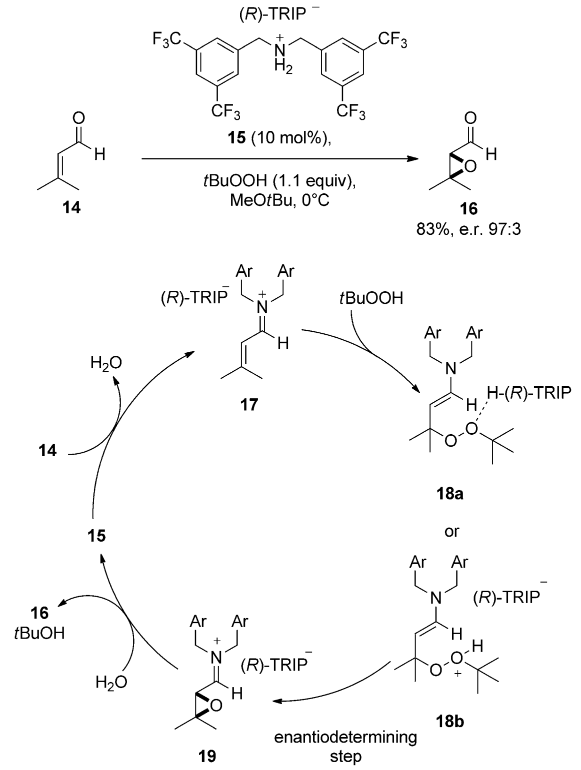
It should be noted, however, that no energies for the corresponding ion pairs or the transition states leading to product formation were presented.[22] In a parallel theoretical study on their Mannich-type reaction, Yamanaka, Akiyama et al. studied several competing reaction pathways and found that the reaction starts with hydrogen-bond association to form **13a**, which equilibrates to ion pair **13b**. They also calculated the respective transition states and concluded "*that the reaction proceeds through the protonation followed by the nucleophilic attack via zwitterionic and nine-membered cyclic TS.*"[23] In this case, the origin of facial discrimination was traced back to the formation of a nine-membered ring involving the Lewis basic oxygen atom of the phosphoric acid and the free hydroxy group of the imine substituent. The second feature essential for organization of the transition state was found to be a π-stacking interaction between said substituent and one of the *p*-nitrophenyl groups on the catalyst. The presence of both hydrogen-bond and ion-pair forms of the catalyst–imine adduct suggested by Yamanaka, Akiyama et al. was recently confirmed by NMR spectroscopic studies by Rueping, Gschwind, and co-workers.[24] The authors studied different adducts formed between diphenylphosphoric acid and aldimines or ketimines. The influence of the substrate, temperature, and concentration on the equilibrium between the hydrogen-bonded adduct and ion pair was also described. The coexistence of both species indicates that reactions may proceed starting from either species and, in analogy to the Curtin–Hammet principle, the decisive factor turns out to be which one is better at forming the transition state leading to the product.

According to the principles presented in Section 2, Brønsted acid catalyzed reactions are classified as ACDC, because the ion pairs are accompanied by hydrogen bonding but the ionic character of the reaction does not become negligible.[11] We first introduced this classification in 2005, and it differentiates between neutral hydrogen-bonding catalysts (such as thioureas or taddol) and stronger Brønsted acid catalysts (e.g. binol-derived phosphoric acids) where ion-pair character can be attributed to the activation mode.[25] A detailed discussion of asymmetric counteranion-directed Brønsted acid catalysis would exceed the scope of this Review. These examples have already been reviewed and can be classified in analogy to the examples discussed here.[11]

3.1.3. ACDC via Intermediates that Allow for Additional Stabilizing Effects

In 2005 Jørgensen and co-workers disclosed a useful diarylprolinol silyl ether catalyzed epoxidation of enals by using hydrogen peroxide as the oxidant.[26] High enantioselectivities were limited to β-monosubstituted enals, and the corresponding β,β-disubstituted analogues generally gave inferior results. As this reaction also proceeds via a quaternary iminium ion intermediate, we reasoned that an alternative catalyst system based on the ACDC concept might be able to overcome this drawback. A systematic optimization of the oxidizing agent, amine, and phosphate component as well as the reaction conditions led to a widely applicable system for the epoxidation of enals (Scheme 3).[27]

Aldehyde **14** could be converted into epoxy aldehyde **16** in good yield and excellent enantioselectivity by applying catalyst **15** derived from dibenzylamine and TRIP together with *tert*-butyl hydroperoxide as the oxidant. Key features of



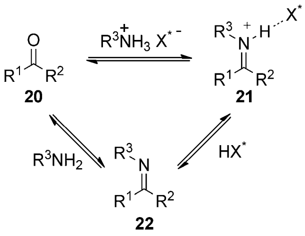
Scheme 3. Asymmetric epoxidation of β,β-disubstituted enals.[27]

this asymmetric counteranion-directed catalytic epoxidation of enals are increased diastereoselectivity (90:10 to 98:2 with the diarylprolinol silyl ether catalyst versus 97:3 to >99:1 through ACDC) and the suitability for β,β-disubstituted enals.

When considering the catalytic asymmetric epoxidation of β-monosubstituted enals, the conjugate addition of *tert*-butyl hydroperoxide to the iminium ion intermediate, and therefore the formation of the β stereocenter, can be viewed as a clear case of ACDC without significant stabilization such as by obvious hydrogen bonds. While this step could be reversible in principle, no indication pointing towards the realization of this pathway was observed during our studies. The involvement of TRIP in the formation of the α stereocenter is clearly proven by the high enantioselectivities obtained with β,β-disubstituted enal **14** bearing two identical substituents. In this case, the initial addition to the chiral iminium–TRIP ion pair does not generate a stereocenter, and the departure of *tert*-butanol from adduct **18** becomes the enantiodetermining step. The two representations **18a** and **18b** suggest that this system is somewhere between hydrogen-bonding catalysis and the formation of an ion pair. This is analogous to the situation typically occurring in Brønsted acid catalysis, which has already been described as a special case of ACDC in Section 3.1.2. Here, however, the same conclusion can also be reached by a different line of thought. The primary product of the cyclization, **19**, is a chiral iminium–TRIP ion pair. This indicates that the transition state leading to **19** will also have ion-pair character. The transition states ultimately leading to the two enantiomers of **16** are made diastereomorphic only by ion pairing with the TRIP anion.

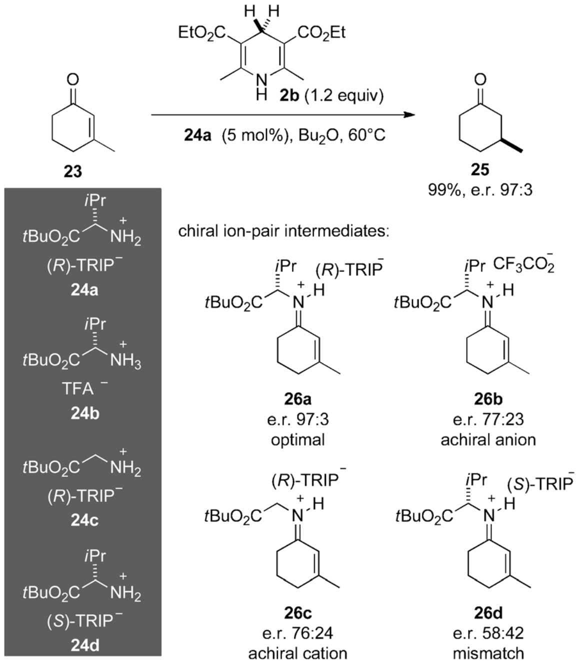
3.1.4. ACDC with Primary Amines

In general, the use of primary ammonium salts with chiral counteranions as catalysts can be regarded as a combination of iminium catalysis and chiral Brønsted acid catalysis (Scheme 4). The role of the primary amine is to engage in the formation of imine **22** from the carbonyl compound **20**. This imine is then activated by the chiral Brønsted acid through protonation to generate **21**. Accordingly, both catalyst components are required.



Scheme 4. ACDC with primary amines.

In 2006, our research group reported a highly enantioselective transfer hydrogenation of α,β-unsaturated ketones based on this activation principle. For example, 3-methylcyclohexenone (**23**) was reduced to saturated ketone **25** in excellent yield and enantioselectivity (Scheme 5).[28] The optimal catalyst was found to be valine ester TRIP salt **24a**. The reduction occurs via intermediate **26a** in this case, which notably contains chiral elements in both the cationic and anionic constituents. According to the guidelines presented in Section 2, such systems are classified as ACDC as long as the role of the anion alone meets the definition. This assignment



Scheme 5. Asymmetric transfer hydrogenation through ACDC combined with catalysis by a chiral primary amine.[28]

can be made by observing the behavior of the two chiral components separately.

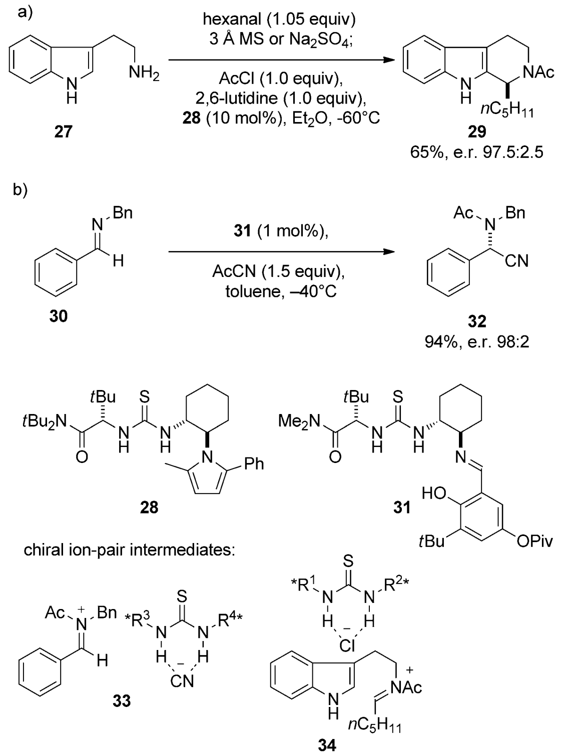
When the same valine derivative was used with the trifluoroacetate counteranion (catalyst **24b**), the results were dramatically inferior (66 % yield, e.r. 77:23) to those obtained with salt **24a**. This reaction proceeds through intermediate **26b** and is controlled exclusively by the chiral primary amine catalyst. Similarly, when TRIP was combined with glycine *tert*-butyl ester to give catalyst **24c**, the reaction was catalyzed with much lower efficiency (66% yield, e.r. 76:24). This reaction proceeds via **26c**, in which the cation is achiral. The asymmetric transfer hydrogenation of α,β-unsaturated ketones is, therefore, an example of combined chiral iminium catalysis and asymmetric counteranion-directed catalysis. It is noteworthy that both parts of the catalyst are close to equal in their influence on the stereochemistry. This leads to a very strong matched/mismatched behavior, and almost racemic product (45 % yield, e.r. 58:42) was obtained when (*S*)-TRIP was used to form the mismatched catalyst **24d**.

In continuation of our studies on asymmetric counteranion-directed epoxidation catalysis we used the strong synergistic effects between chiral primary amine catalysts and enantiopure counteranions to address the long-standing challenges of asymmetrically epoxidizing cyclic enones and α-branched enals.[29] The combination of chiral amine catalysis and ACDC has also been successfully applied to further transformations not discussed in detail here.[30]

3.1.5. *Anion-Binding Thioureas*

Since the seminal reports by the research groups of Wilcox and Hamilton in the early 1990s, thioureas have been known to possess a strong ability to coordinate a variety of anions.[31] Even though thioureas are widely used organocatalysts, most attention has been paid to their ability to activate neutral electrophiles through hydrogen bonding, which may even have led to the misinterpretation of mechanisms in certain cases.[31d]

In 2004, Taylor and Jacobsen reported the acyl-Pictet–Spengler reaction of tryptamine (**27**) and derivatives thereof with different aldehydes to give tetrahydro-β-carbolines, such as **29**, in good yields and enantioselectivities. The reaction is catalyzed by chiral thiourea **28**, and was originally believed to proceed through hydrogen-bonding activation of the acyl–iminium intermediate (Scheme 6a).[32] In 2007, we used structurally related thiourea **31** to catalyze the acyl-Strecker reaction of aldimines. For example, the benzaldehyde-derived imine **30** reacted to give product **32** in high yield and enantioselectivity (Scheme 6b).[33] In this context, the possibility of an anion-binding mechanism involving the chiral ion-pair intermediate **33** was discussed. The Jacobsen research group could then show that their acyl-Pictet–Spengler reaction does indeed involve the formation of the chiral ion-pair intermediate **34**. Inspired by this realization, they used this principle to develop asymmetric addition reactions to oxocarbenium ions.[34] Since then, anion-binding thiourea catalysis has found a variety of applications which have been reviewed elsewhere.[31d]



Scheme 6. Asymmetric anion-binding catalysis with thioureas.[32,33]

The classification of anion-binding catalysis depends on the definition. Anion-binding catalysis is not included in ACDC if the thiourea is viewed as forming a supramolecular complex with the achiral anion (Figure 3A), as the anion remains achiral. Alternatively, the complex of thiourea and the leaving group can be considered to be the anionic part of the reacting ion pair (Figure 3B). If this second point of view is adopted, anion-binding catalysis would be a clear case of ACDC, as the involved intermediates (**33** and **34**) unquestionably have ion-pair character and enantioselectivity is induced by the anionic moiety. As both perspectives on anion-binding catalysis do in our opinion have good justification, it is up to the reader to decide which interpretation to adopt in this case.

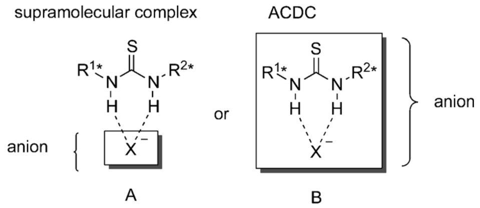


Figure 3. Viewing anion-binding catalysis as supramolecular catalysis (left) or as ACDC is a matter of definition.

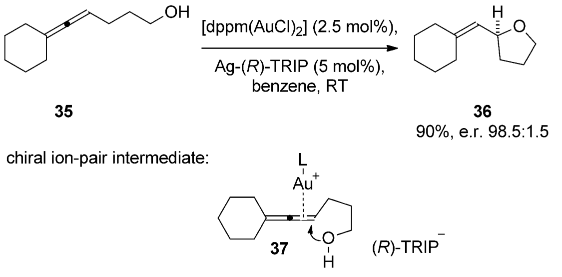
3.2. Applications in Transition-Metal Catalysis

After the generality of the ACDC concept had been demonstrated, its extension beyond the realm of organocatalysis was independently realized by Toste and co-workers as well as our research group, and a number of beautiful applications in transition-metal catalysis have since appeared.[35–37]

3.2.1. Reactions with Complete Metal–Anion Separation

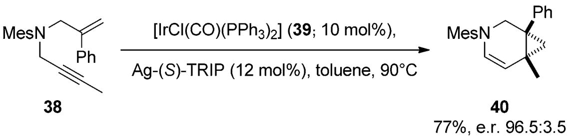
In their report, Toste and co-workers describe three Au-TRIP-catalyzed cyclization reactions, namely the intramolecular hydroalkoxyalation, hydroamination, and hydrocarboxylation of allenes.[35]

The hydroalkoxylation of their model substrate **35** was catalyzed by a combination of an achiral Au complex and a Ag–(*R*)-TRIP salt to give tetrahydrofuran **36** in high yield and excellent enantioselectivity (Scheme 7). These cyclization reactions are archetypical examples of ACDC. Even though tricoordinate Au^I intermediates have been detected, it is generally accepted that Au^I catalysis proceeds via dicoordinated species.[38] In the reaction shown in Scheme 7, the reactive Au complex is generated through ion exchange, which gives AgCl and a Au^I–TRIP salt bearing a phosphine ligand. One of the binding sites of this species has to be available for it to activate the allene moiety as a π acid. As the TRIP anion can not act as a ligand during the relevant steps of the catalytic cycle, it clearly acts as a counteranion. It is likely further involved in hydrogen bonding with the proton on the attacking heteroatom (intermediate **37**). Further applications of chiral counteranions in Au^I chemistry by the Toste research group[39] and others have since been reported.[40]



Scheme 7. Au–TRIP-catalyzed hydroalkoxyalation.[35] dppm = bis(diphenylphosphino)methane.

Recently, an Ir^I-TRIP-catalyzed asymmetric carbocyclization of 1,6-enynes was disclosed. Anion metathesis between Vaska's complex **39** and the Ag–TRIP salt was used to generate an Ir–TRIP ion-pair catalyst which catalyzes the cyclization of 1,6-enynes in good yields and enantioselectivities. For example, **40** was obtained from **38** in 77 % yield and with an e.r. value of 96.5:3.5 (Scheme 8). NMR and IR spectroscopic studies showed that the CO and phosphine ligands stay connected to the Ir center during the entire course of the reaction, while the TRIP anion departs, thereby freeing up the coordination site necessary for catalysis. The enantioselectivity was thus achieved by a chiral counteranion only bound to the catalyst through ion pairing. This pure ACDC situation was also supported by computational studies.[41] The combination of Ir^{III} and TRIP has also been used in hydrogenation and reductive amination reactions by the Xiao research group.[42]



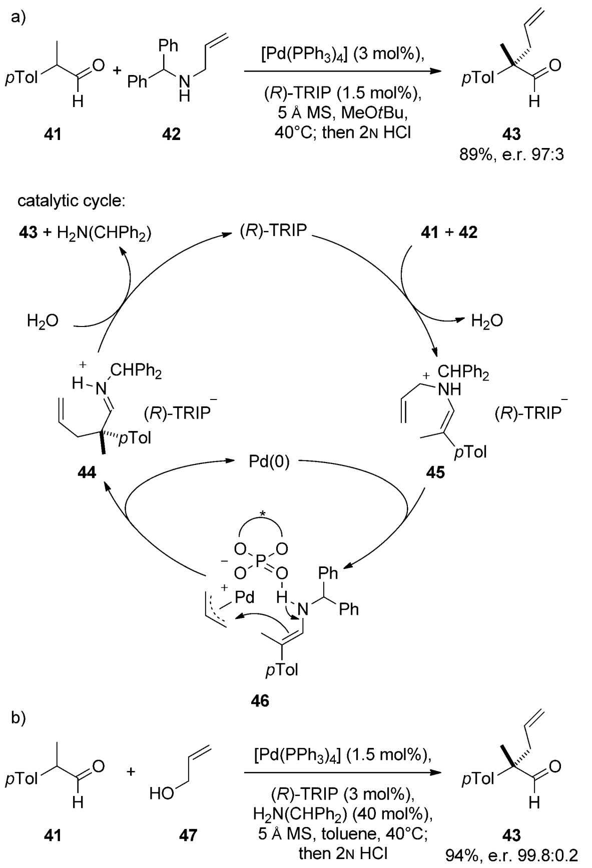
Scheme 8. Ir^I–TRIP-catalyzed carbocyclization of 1,6-enynes.[41] Mes = mesityl.

3.2.2. Ligand or Counteranion—ACDC with Transition Metals

When applying ACDC to transition-metal catalysis, the question arises whether or not the anion simply functions as yet another chiral ligand. This notion must be discounted for two reasons. First, there are clear cases in which the anion responsible for enantioselectivity does not behave as a ligand. Secondly, even in ambiguous cases, the ACDC concept offers a new perspective on the design of catalytic processes, which we consider a value in itself.[6,7]

Our own studies on ACDC in transition-metal catalysis, which were conducted in parallel to the studies by Toste and co-workers on Au catalysis, focused on enantioselective Tsuji–Trost α-allylations of α-branched aldehydes (Scheme 9).[36] Our catalyst system was composed of a Pd^0 source and TRIP in the presence of *N*-benzhydrylallylamine **42** as the allylating agent and promoted the α-allylation of α-branched aldehydes such as **41** in high yield and enantioselectivity (Scheme 9a). The suggested catalytic cycle of this reaction begins with the TRIP-assisted condensation of aldehyde **41** and amine **42** to give enamonium phosphate salt **45**. Reaction of ion pair **45** with Pd gives π-allyl–Pd complex **46**. From here, the enantioselective C−C bond-forming step takes place, thereby liberating the Pd catalyst and iminium phosphate **44**, which upon hydrolysis is converted into the α-allylated aldehyde **43**. In a continuation of this study, we recently developed the first α-allylation of aldehydes by using simple allylic alcohols as allylating agents (Scheme 9b).[43] The reaction involved the same catalyst components as before and benzhydrylamine as an additional catalyst to ensure a well-defined *E* configuration of the nucleophile. Aldehyde **41** thus reacts with allyl alcohol (**47**) to give product **43** in excellent yield and enantioselectivity. Importantly, after TRIP-assisted generation of a π-allyl–Pd complex and enamine formation from **41** and benzhydrylamine, the same intermediate **46** is also formed during the course of this reaction.

To understand the role of TRIP in these transformations, complex **46** will be considered, as it is the intermediate from which the enantiodiscriminating step occurs. The critical question turns out to be whether the interaction between TRIP and Pd is predominantly ionic or covalent in nature. The Tsuji–Trost reaction is generally accepted to proceed via a cationic π-allyl–Pd complex.[44] Even though no detailed

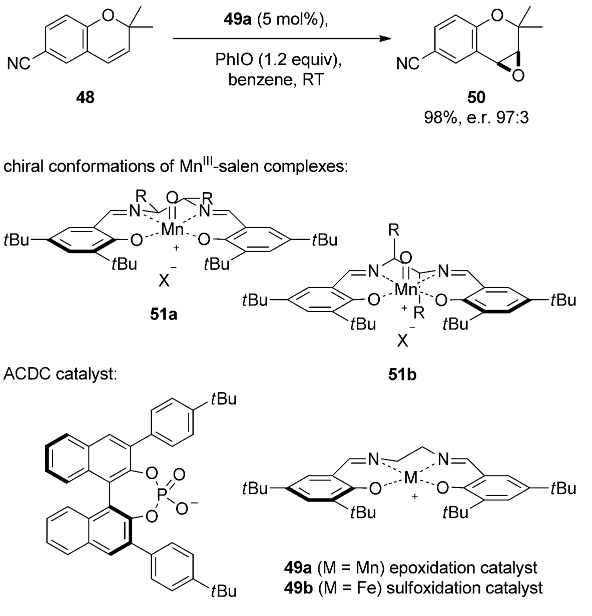


Scheme 9. Pd–TRIP-catalyzed α-allylation of α-branched aldehydes.[36,43]

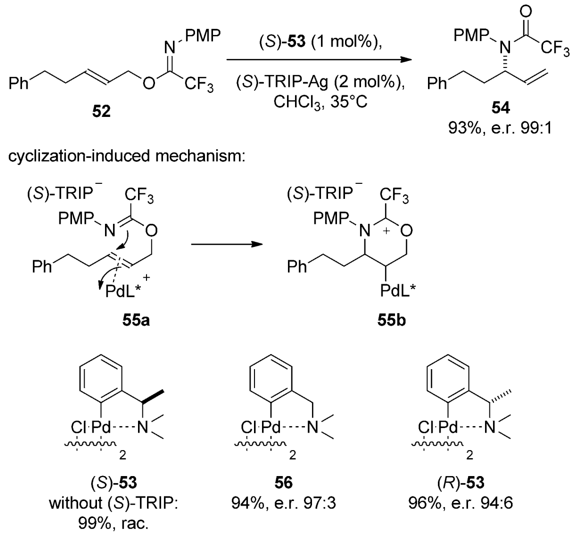
studies on this question have been conducted with our system, in the absence of evidence to the contrary, we assume that intermediate **46** has significant ion-pair character and, therefore, view the reactions shown in Scheme 9 as ACDC.

In 2010, we reported a catalytic asymmetric epoxidation of alkenes (Scheme 10).[45] Our catalyst was based on the Jacobsen–Katsuki epoxidation, in which chiral $\mathrm{Mn^{III}}$–salen complexes are used.[46] These complexes have two possible conformations **51a** and **51b**, of which **51a** is strongly favored when a chiral backbone is used ($R \neq H$). In our studies, the achiral parent compound ($R = H$) was combined with a chiral counteranion to give catalyst **49a**, in which a discrimination between the two enantiomeric conformations of the ligand is induced only by the chiral counteranion.

Ion pair **49a** catalyzes the model reaction of olefin **48** to epoxide **50** in excellent yield and enantioselectivity, and proved to be applicable to a variety of styrene derivatives. Catalyst **49a** is remarkably active and no ligand additives are necessary.[47] This provides further support for the interpretation of the reaction as an example of ACDC, as high activity has previously been found to correlate with weak binding of the anion to the "naked" catalyst.[48] We later expanded the use of this strategy to enantioselective sulfoxidation reactions with catalyst **49b** in the first example of iron ACDC.[49]



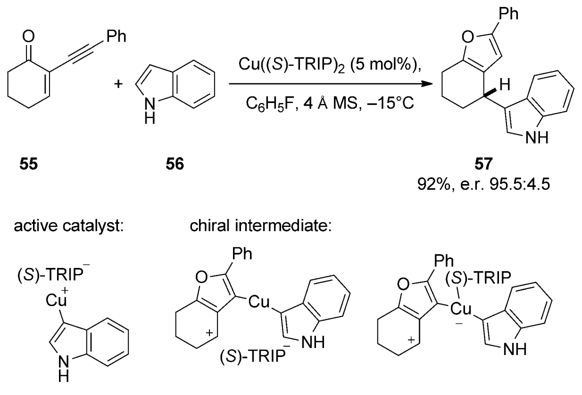
Scheme 10. Mn-catalyzed enantioselective epoxidation of alkenes.[45]



Scheme 11. Counteranion-directed Overman rearrangement.[50] PMP = *p*-methoxyphenyl.

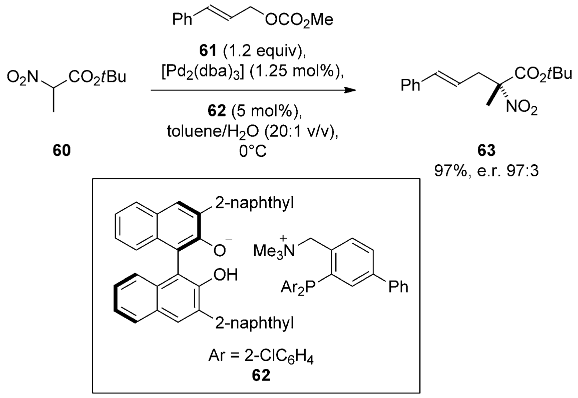
Another example of Pd catalysis is the asymmetric counteranion-directed Overman rearrangement developed by our research group. PMP-protected trifluoroacetimidate **52** rearranged to allyl amide **54** when chiral Pd catalyst (*S*)-**53** and Ag–TRIP were used as catalysts (Scheme 11).[50] The reaction proceeded in high yield and enantioselectivity. The enantioselectivity is almost completely controlled by the chiral counteranion, as shown by the minimal effect when the analogous achiral catalyst **56** or even the opposite enantiomer of the catalyst (*R*)-**53** was used. Furthermore, the "matched" catalyst (*S*)-**53** gave racemic product when used in the absence of the chiral counteranion. The crystal structure of the catalyst formed from Pd complex (*S*)-**53**, imidazol (not present under the reaction conditions), and Ag–TRIP shows the chiral anion to be a Pd ligand in this case. However, during the course of the reaction, intermediate **55b** is formed from complex **55a** according to the well-established cyclization-induced mechanism.[51] The chiral counteranion is not assumed to be a ligand during this enantiodiscriminating step.

Toste and co-workers have developed a Cu^{II}–TRIP-catalyzed cycloisomerization/indole addition sequence. For example, **55** reacted with indole (**56**) to give product **57** in high yield and enantioselectivity (Scheme 12).[52] Mechanistic studies revealed that the active catalyst contains an indole molecule and one chiral anion, which led the authors to suggest complex **58** as the relevant species. The chiral intermediate, from which the enantioselective indole addition takes place, was suggested to be either complex **59a** or **59b**. While a reaction via **59a** would clearly be a case of ACDC, the reaction involving **59b** would just as clearly not be. In this case, an unambiguous classification is, therefore, not possible. However, this reaction nevertheless demonstrates the success of the ACDC strategy, as a Cu^{II} salt with a traditional Lewis basic box ligand failed to catalyze the reaction. It was shown that Ag^{I}–TRIP and Cu^{I}–TRIP salts were also active catalysts for the same transformation, but lower enantioselectivities were obtained in these cases.



Scheme 12. Cu–TRIP-catalyzed cycloisomerization and indole addition.[52]

Very recently, Ooi and co-workers reported a strategy to apply ACDC to reactions proceeding via intermediates where the positive charge is compensated by an anionic nucleophile (Scheme 13).[53] The additional positive charge required to attract a chiral counteranion was added by introducing a quaternary ammonium group into the phosphine ligand. This cation was then paired with a binol-derived monoanion to give ion pair **62**. With this ligand salt on the Pd^{II} catalyst, the reaction of α-nitrocarboxylate **60** to the allyl cation derived from carbonate **61** was catalyzed to give **63** in excellent yield and entantioselectivity. The authors showed through structural modifications of ion-pair ligand **62** that proximity of the anion to the metal center is necessary for high selectivities. Furthermore, it was shown that two equivalents of ion pair **62** are bound to one Pd^{II} cation, as a modest positive nonlinear effect of the ligand concentration was observed, while a first order dependence on the Pd loading was observed, thereby indicating a monomeric Pd species. This reaction design represents a very elegant example of ACDC, as the chiral counteranion is the only source of enantiodiscrimination and presumably remains ionic during the whole course of the reaction. Notably, this strategy can, in principle, be used to apply the ACDC concept to the catalysis of reactions proceeding via neutral species, and substantially broadens the applicability of asymmetric counteranions in transition-metal catalysis and potentially beyond.

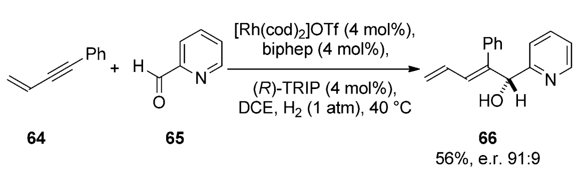


Scheme 13. Asymmetric allylic alkylation of α-nitrocarboxylates.[53] dba = *trans,trans*-dibenzylideneacetone.

3.2.3. *Cooperative and Sequential Catalysis*

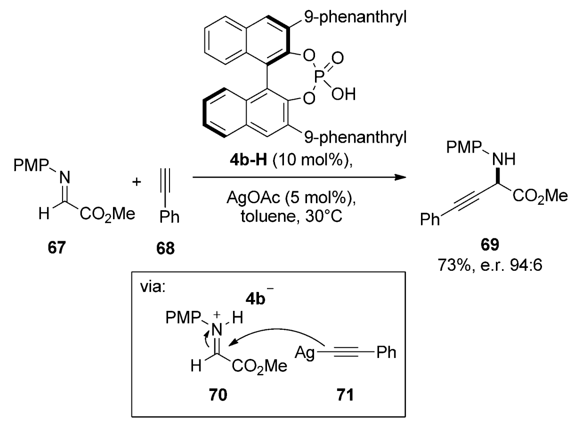
In parallel to the developments in the area of asymmetric counteranion-directed catalysis, the use of several catalytic species in a cooperative or sequential manner have also had considerable success and were reviewed elsewhere.[54] Selected examples will be discussed here to illustrate the interplay between these concepts and ACDC.

The use of transition-metal and Brønsted acid catalysis in a cooperative manner dates back to 2006, when Komanduri and Krische reported the use of an achiral Rh complex and TRIP for the enantioselective reductive coupling between conjugated 1,3-enynes and heteroaryl-substituted aldehydes and ketones (Scheme 14).[55]



Scheme 14. Rh-catalyzed asymmetric reductive coupling.[55] biphep = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl, DCE = 1,2-dichloroethane.

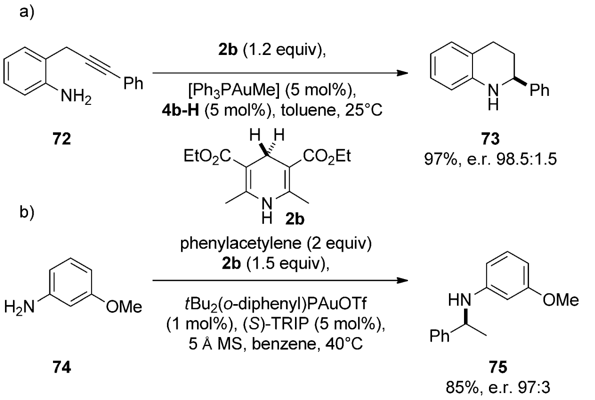
Enyne **64** was coupled with 2-pyridinecarboxaldehyde (**65**) to give allylic alcohol **66** in modest yield and enantioselectivity. Much superior results were obtained with a chiral Rh complex and an achiral acid additive (for example, alcohol **66** was obtained in 91 % yield and e.r. 96:4). Mechanistic studies led to the conclusion that the chiral Brønsted acid activates the substrate by protonation and also showed an alternative ion pairing with the Rh catalyst to be unlikely.



Scheme 15. Asymmetric alkynylation of α-imino esters by cooperative catalysis.[56]

The Rueping research group capitalized on this cooperative catalysis approach in their enantioselective alkynylation of α-imino esters (Scheme 15).[56] Their method relied on the combination of phosphoric acid **4b-H** and silver acetate as catalysts. For example, imine **67** and alkyne **68** were converted into product **69** in good yield and enantioselectivity. The proposed mode of action involves the activation of α-imino ester **67** by acid **4b-H** to form ion pair **70** and the formation of alkynyl–Ag intermediate **71** from silver acetate and terminal alkyne **68**. These two species then react to give product **69** and liberate the two catalysts at the same time. A possible ion exchange of silver acetate to the Ag–**4b** salt in the reaction mixture could not be excluded. This allows for the possibility of **4b** being involved in both catalytic cycles. Since these reports, a variety of cooperatively catalyzed reactions, where ACDC and transition-metal catalysis work in parallel, have appeared.[57]

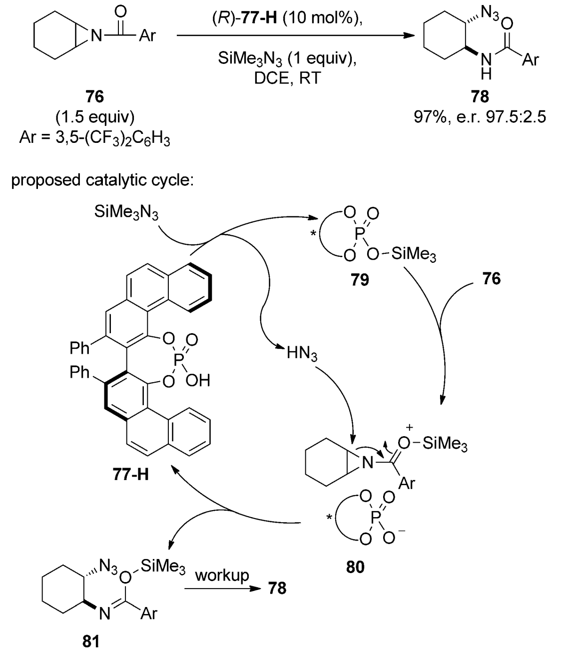
Gong and co-workers reported an Au-catalyzed intramolecular hydroamination and Brønsted acid catalyzed transfer-hydrogenation sequence in which aniline derivatives **72** were transformed into tetrahydroquinolines **73** in excellent yield and enantioselectivity (Scheme 16a).[58] An intermolecular version was simultaneously developed by Liu and Che, who converted aniline derivatives such as **74** into the corresponding secondary amines **75** through reaction with phenylacetylene or derivatives thereof (Scheme 16b).[59] In both cases the Au-catalyzed hydroamination gives an enamine, which is tautomerized and reduced with the chiral binol-derived phosphoric acid catalyst **4b-H** and Hantzsch ester **2b** as the hydride source. The combination of ACDC with other types of catalysis in a sequential manner can lead to a dramatic increase in molecular complexity within a single transformation, and has found numerous applications within the last few years.[60]



Scheme 16. Sequential hydroaminations and asymmetric transfer hydrogenations.[58,59]

3.3. Applications in Lewis Acid Catalysis

Main-group and transition-metal salts with chiral counteranions have also found applications beyond transition-metal catalysis.[61] The first example of asymmetric counteranion-directed Lewis acid catalysis was suggested by Antilla et al. in 2007.[62] They applied the vapol-derived phosphoric acid **77-H** together with $SiMe_3N_3$ for the desymmetrization of *meso*-aziridines (Scheme 17).[8] A variety of cyclic and acyclic substrates including azirinde **76** were converted into the corresponding products **78** in excellent yield and enantioselectivity. On the basis of the critical role of the $SiMe_3$ group, the authors suggested a mechanism beginning with the silylation of **77-H** to give **79** and HN_3. Silylation of azirinde **76** would lead to the formation of intermediate **80**. As an alternative to the chiral ion pair shown, the phosphate anion could also be coordinated to a silicon atom, thereby forming a pentavalent silicon intermediate. However, the representation shown here better indicates the subsequent reactivity. The attack of the azide onto ion pair **80** then regenerates the



Scheme 17. Lewis acid catalyzed desymmetrization of *meso*-aziridines controlled by chiral counteranions.[62]

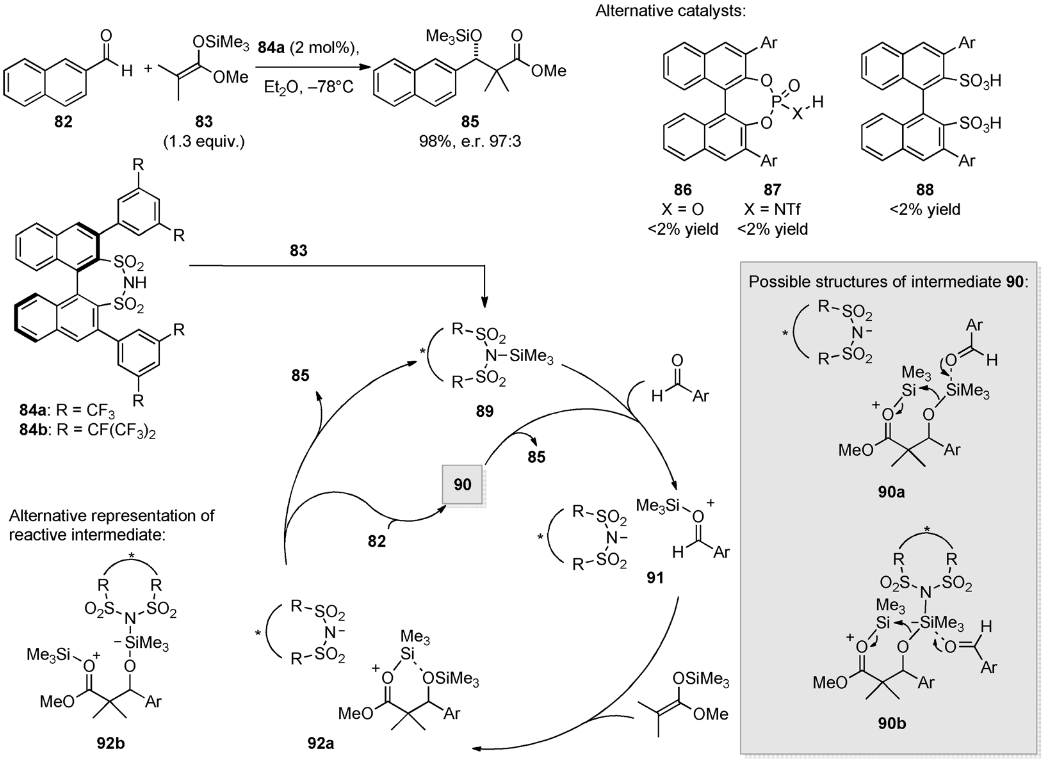
catalyst and gives compound **81**, which is converted into the product **78** during workup.

A major limitation of asymmetric Brønsted acid catalysis has been the need for rather electrophilic substrates, such as imines. The development of catalysts of higher acidity than phosphoric acid diesters has received considerable attention to allow for less-activated substrates, such as ketones. Nakashima and Yamamoto developed binol-derived *N*-triflyl phosphoramides **87**, which are capable of activating ketones for enantioselective attack by nucleophiles.[63] Despite these results, the much sought after activation of aldehydes and olefins with organic Brønsted acid (pre)catalysts remained elusive. As a result of research towards the activation of these challenging substrate classes, we and the Ishihara research group reported the synthesis of the highly acidic binaphthyl-derived disulfonic acid **88** and its application in Brønsted acid catalysis.[64] With the aim of activating aldehydes, we reasoned that the previously unknown cyclic disulfonimide derivatives **84** might show catalytic activity comparable to that of triflimide (Tf_2NH) and at the same time serve as a chiral counteranion. While triflic acid (TfOH) is a stronger Brønsted acid than triflimide, the Lewis acidities of the corresponding silylated species are reversed.[65,66]

We chose to explore this motif for the Mukaiyama-aldol reaction, as Me_3SiNTf_2 was known to catalyze this reaction.[67] Furthermore, previous enantioselective approaches to this reaction have typically suffered non-asymmetricbackground catalysis from an achiral silylium ion.[68] We expected to be able to address this issue by turning the formerly undesired reaction pathway into an enantioselective one, by using the ACDC strategy. Initial studies comparing chiral disulfonimide **84a** to alternative catalysts at room temperature revealed that our new catalyst was active and enantioselective (> 99 % yield and e.r. 90:10), while alternative catalysts such as **86–88** proved to be inactive under these conditions. Under optimized conditions, our model substrate **82** reacted with silyl ketene acetal **83** to give aldol **85** in excellent yield and enantioselectivity (Scheme 18).[69]

This method proved to be applicable to a variety of benzaldehyde and cinnamaldehyde derivatives, and catalyst loadings as low as 0.01 mol % could be used. Mechanistically, the reaction proceeds through an initial silylation of disulfonimide **84a** by silyl ketene acetal **83** to afford the active Lewis acid catalyst **89** (and its O-$SiMe_3$ tautomer). This activation also serves as a self-healing pathway, as the hydrolyzed catalyst formed by trace amounts of water can again be activated by a slight excess of silylacetal **83**. Lewis acid **89** then activates the aldehyde to give ion pair **91**, which is attacked by nucleophile **83** to give intermediate **92a**. The catalytic cycle is completed by the liberation of product **85** with regeneration of the catalyst. The assignment of silylated catalyst **89** (or its O-silylated isomer) as the catalytically active species was confirmed by NMR spectroscopy, which indicated almost instantaneous silylation of acid **84a** by ketene acetal **83**. Furthermore, preformed **89** proved to be active in the presence of the Brønsted acid quencher 2,6-di-*tert*-butyl-4-methylpyridine, which excludes trace amounts of acid **84a** being a possible catalyst.

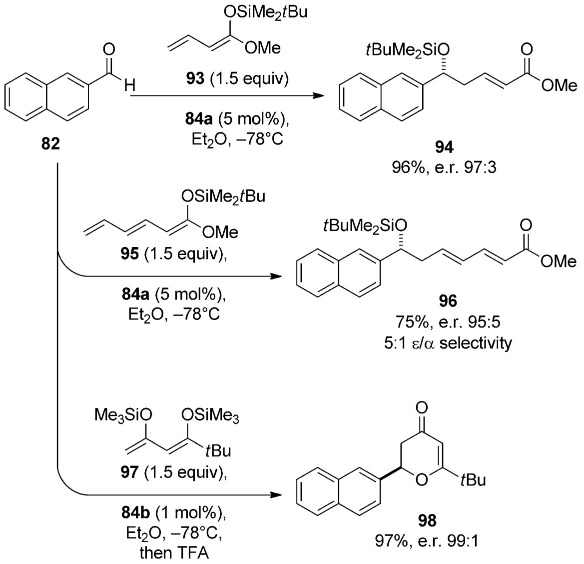
The seemingly obvious classification of this reaction as a case of ACDC on the basis of the involvement of ion pair **91** turns out to be more complicated when the study by Yamamoto and co-workers on triflimide-catalyzed



Scheme 18. Asymmetric counteranion-directed Mukaiyama-aldol reaction.[69]

Mukaiyama-aldol reactions is taken into account. They showed that, in this case, the silicon atom bound to the triflimide remained in the catalyst, while the silyl group of the nucleophile is transferred to a new aldehyde molecule.[70] Yamamoto and co-workers suggested that the effective counteranion could indeed be an adduct formed between the silylated triflimide and a product molecule, which would correspond to **92a** or **92b** in our system (Scheme 18). In this scenario, intermediate **92** first reacts with aldehyde **82** to form a second intermediate **90**. Subsequent liberation of product **85** completes this version of the catalytic cycle. The silylated disulfonimide **89** could, in principle, be considered to be a neutral, Lewis acid which catalyzes the reaction via pentavalent silicon intermediates, instead of an ACDC catalyst. However, the ion-pair representation better shows the polarity of the reaction and was, therefore, favored by Yamamoto and co-workers (and also by us). Despite the dubious nature of the real catalytically active species, we believe that the ionic interpretation involving a chiral counteranion is adequate, thus resulting in this reaction being an example of ACDC.

We further expanded the unique activity and selectivity of our system to the vinylogous and the unprecedented bisvinylogous enantioselective Mukaiyama-aldol reactions (Scheme 19).[71] In the former case, the reaction of 2-naphthaldehyde **82** with nucleophile **93** gave aldol **94** in excellent yield and enantioselectivity as well as complete regioselectivity. The reaction of aldehyde **82** with bisvinylogous nucleophile **95** in turn gave aldol **96** in good yield and equally high enantioselectivity. The moderate ε/α selectivity observed in this case could be rationalized by a computational study. Both reactions could be carried out with a variety of substituted nucleophiles as well as aromatic and conjugated aldehydes, and the synthetic utility of the new bisvinylogous Mukaiyama-aldol reaction was demonstrated by its incorporation into an enantioselective ζ-lactone synthesis.



Scheme 19. Vinylogous and bisvinylogous counteranion-directed Mukaiyama aldol reactions and a hetero-Diels–Alder reaction.[71,72] TFA = trifluoroacetic acid.

Very recently, we expanded our method to asymmetric hetero-Diels–Alder reactions. For example, Diels–Alder product **98** was obtained in excellent yield and enantioselectivity by using dienophile **97** and catalyst **84b**.[72] These initial results suggest that our novel organo-Lewis acid activation mode may be quite general and potentially applicable to various other processes involving reactions of silylated nucleophiles with electrophiles.

4. Summary and Outlook

In this Review we hope to have shown that ACDC is not "just" a hard rock band from Australia or a label for different types of electronic current. This intriguing concept has already been used to design enantioselective reactions in the areas of organocatalysis, transition-metal catalysis, and Lewis acid catalysis. Often better or at least complementary results were obtained compared to more traditional methods. Furthermore, combination with other concepts in catalysis has proven extremely fruitful. For example, the combination of chiral primary and secondary amine catalysis with chiral counteranions has helped to achieve transfer hydrogenations and epoxidations of previously difficult substrate classes. In transition-metal catalysis, the complementarity with traditional ligands enables their replacement or the combination of both sources of asymmetry. Furthermore, the fundamentally different nature of organocatalysis and transition-metal catalysis allows for their coexistence in cooperative or sequential catalysis. ACDC has been used successfully in Lewis acid catalysis to turn an undesired background catalysis into the desired reaction pathway. Even though ACDC is still a very young research field, it has already led to remarkable achievements within the few years since the initial reports. Considering the plethora of reactions proceeding via cationic intermediates that can in principle be catalyzed by using asymmetric counteranion-directed catalysis, exciting new applications of this concept are bound to be developed in the near future. As the critical influence of counteranions has often been neglected in method development, research towards a better understanding of reaction mechanisms will be an essential part of further progress in the field.

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[1] For a recent review on asymmetric phase-transfer catalysis, see T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656–5682.

[2] For earlier reviews presenting examples of ACDC, but not defining the concept or discussing the classification of reactions, see a) J. Lacour, D. Linder, *Science* **2007**, *317*, 462–463; b) L. Ratjen, S. Müller, B. List, *Nachr. Chem.* **2010**, *58*, 640–646; c) M. Mahlau, B. List, *Isr. J. Chem.* **2012**, *52*, 630–638; after the submission of this manuscript, a related review appeared: d) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603–614.

[3] In contrast to their widespread acceptance, the terms “counteranion” and “countercation” to indicate the charge of a counterion has recently been questioned by Lacour and Moraleda (see Ref. [4b]). Despite some arguable ambiguity, we use these terms here anyway, as they are well-suited for the discussion of the concepts treated in this Review and also commonly used in the literature.

[4] For reviews on the application of chiral counteranions in synthesis and catalysis, see a) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373–382; b) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073–7089. For the discussion of these early attempts in the context of ACDC, see the reviews cited in Ref. [2].

[5] For a review, see H. Ishibashi, K. Ishihara, H. Yamamoto, *Chem. Rec.* **2002**, *2*, 177–188.

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