CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Catalytic Enantioselective Formation of C−C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update

Shū Kobayashi,*[,†] Yuichiro Mori,[†] John S. Fossey,[‡] and Matthew M. Salter[†]

[†]Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K.

CONTENTS

1. Introduction 2626
2. Scope of the Current Review 2627
3. Addition of Stabilized Carbon Nucleophiles (Mannich- and Nitro-Mannich-type Reactions) 2627
   3.1. The Direct and Indirect Mannich-type Reaction 2627
   3.2. Addition of Stabilized Carbon Nucleophiles to C═N Catalyzed by Transition Metals 2627
      3.2.1. Metal-Catalyzed Asymmetric Direct Mannich and aza-Henry-type Reactions 2627
      3.2.2. Indirect Asymmetric Mannich and Aza-Henry-type Reactions Catalyzed by Transition Metals 2636
   3.3. Mannich and Aza-Henry-type Reactions Mediated by Organocatalysts 2645
      3.3.1. Reactions Mediated by Proline Derivatives 2645
      3.3.2. Catalytic Asymmetric DMTR Mediated by Chiral Brønsted Acids 2650
      3.3.3. Chiral Thiourea Catalysts 2654
      3.3.4. Cinchona Alkaloids as Chiral Bases 2657
      3.3.5. Catalytic Asymmetric DMTR Mediated by Phase-Transfer Catalysts 2659
4. Aza-Friedel−Crafts Reactions 2659
   4.1. Aza-Friedel−Crafts Reactions Mediated by Transition Metal Catalysts 2659
   4.2. Aza-Friedel−Crafts Reactions Mediated by Organocatalysts 2662
5. Aza-Morita−Baylis−Hillman (AMBH) Reactions 2665
6. Asymmetric Catalytic Addition of Nonstabilized Organometallic Nucleophiles 2668
   6.1. Transition Metal-Catalyzed Arylation of Imines with Aryl Metal Nucleophiles 2669
   6.2. Addition of Alkali and Alkali-Earth Metal Nucleophiles to Imines 2669
   6.3. Addition of Alkyl and Aryl Zinc Reagents to Imines Promoted by Transition Metals 2671
   6.4. Catalytic Asymmetric Allylation of Imines and Hydrazones 2678
   6.5. Strecker Reactions 2682
   6.6. Formation of Aziridines 2687
7. Cycloaddition Reactions of Imines and Hydrazones 2688
   7.1. Diels−Alder Reactions 2688
   7.2. Formal [2 + 2] Aza Cycloaddition Processes 2694
8. Conclusion 2695
Author Information 2695
Biographies 2695
Acknowledgment 2696
References 2697

1. INTRODUCTION

Chiral molecules containing asymmetric carbon centers bonded with nitrogen are ubiquitous in nature and also form important structural fragments in both natural and man-made biologically active molecules where they frequently exercise a profound influence in determining the nature and intensity of their bioactivities. As a result, much attention has been devoted to the study of methods for the stereoselective generation of nitrogen-bonded chiral centers,[1] among the most thoroughly investigated being addition reactions to C═N functionalities. Many of these approaches make use of *diastereoselective* processes involving the addition of chiral nucleophiles or chiral C═N electrophiles to the corresponding achiral reaction partner. While such methods constitute valuable additions to the toolbox of the synthetic chemist, they suffer from the obvious drawbacks that (a) stoichiometric or superstoichiometric quantities of the chiral source are required to complete the reaction and (b) the chiral auxiliary component must be removed from the final product and recycled (often with a poor rate of recovery). In this context, *catalytic enantioselective* addition reactions offer an attractive solution, because they, in principle, permit the generation of large amounts of asymmetric material for the investment of a small quantity of the chiral source.

In the case of catalytic enantioselective mediation of reactions involving aldehydes and ketones such as Diels−Alder,[2]

Received: July 1, 2010
Published: March 15, 2011

dx.doi.org/10.1021/cr100204f | *Chem. Rev.* 2011, 111, 2626–2704

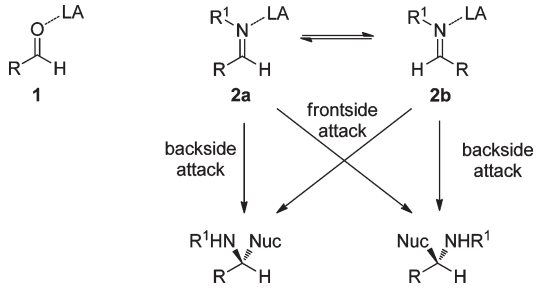


Figure 1. Coordination modes, selectivities, and C═N isomerization.

Strecker,[3] aldol, allylation, and reduction reactions, much progress has been made. However, the closely related reactions involving C═N electrophiles such as imines, oximes, and hydrazones are far less well understood. This is partially due to the relative difficulty of studying the latter reaction due to the increased conformational flexibility of the metal-coordinated form of imines compared with those of carbonyl compounds. While Lewis acids coordinate to aldehydes *syn* to the hydrogen atom[4] (**1**, Figure 1) and are assumed to adopt a rigid transition arrangement, the corresponding imines may coordinate in either a *syn* **2a** or *anti* **2b** fashion by equilibration of (*Z*)−(*E*) geometries[5] thereby opening the possibility of plural reaction manifolds and hence lowering stereoselectivities. Furthermore, in many metal-catalyzed additions to imines, the Lewis acid may be trapped by coordination to the basic nitrogen atom of the starting material or the new amine formed in the reaction, rendering it inactive.

That is not to say, however, that protocols for these reactions have not been developed, indeed it was the emergence of just such procedures that prompted one of us to publish a review[6] of catalytic enantioselective addition reactions to imines involving the addition of nucleophiles to imines under the influence of substoichiometric quantities of metal complexes and chiral ligands almost 10 years ago. In the intervening decade, a number of important developments in this area, most notably the rise of organocatalytic reactions and protocols for the direct addition of active methylene and methine nucleophiles have been revealed, which, in our opinion, render the production of an update of our original review both timely and desirable.

2. SCOPE OF THE CURRENT REVIEW

In dealing with a synthetic topic of the breadth and importance of the addition reactions of C═N systems, discipline is required in selection, and exclusion, of material in order to produce a work that is informative to the reader but not unfathomable. In preparing this review therefore, we have found it necessary to impose the following restrictions. The present work covers the period from the end of 1998, subsequent to the completion of our previous review but prior to its publication, to the beginning of 2009 and surveys the literature on the addition of carbon nucleophiles to imines and hydrazones under the influence of metallic and nonmetallic promoters and substoichiometric quantities of a chiral source. By definition therefore, achiral procedures and diastereoselective reactions in which one of the reacting species bears a chiral auxiliary are necessarily excluded. The reduction reactions of imines and hydrazones are of great importance but have been deliberately placed outside the scope of this review for reasons of manageability, and readers are directed to alternative summaries available elsewhere.[7] In addition, due to the publication of the excellent review on the Strecker reaction by Gröger,[3] the section concerning the cyanation of imines only covers the literature from mid-2002 to the present. For a comprehensive treatment of asymmetric propargylation of C═N compounds, readers should consult the review of the area by Tomioka.[8]

3. ADDITION OF STABILIZED CARBON NUCLEOPHILES (MANNICH- AND NITRO-MANNICH-TYPE REACTIONS)

3.1. The Direct and Indirect Mannich-type Reaction

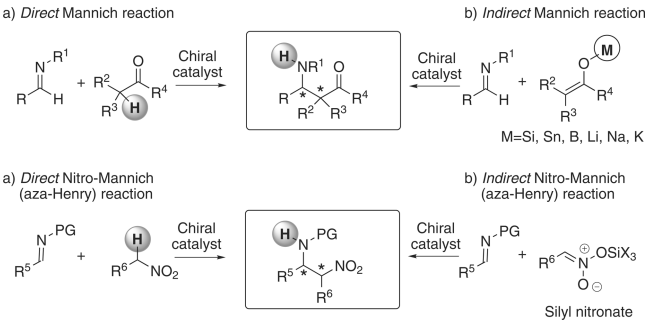
The Mannich reaction between a Schiff base and a nucleophile, first introduced in the early part of the 20th century,[9] is one of the most powerful reactions known to chemists for the construction of nitrogen-containing compounds.[10] In the classical intermolecular Mannich reaction (the so-called direct reaction), three components, an aldehyde, an amine and an α-acidic carbonyl compound, react directly to form a *β*-amino carbonyl compound (Mannich base). Despite the potential of this reaction, the relatively low acidity of aldehyde or ketones means that harsh conditions and long reaction times are required, which frequently leads to undesired side reactions. Additionally, early procedures suffered from a serious limitation in that generally only formaldehyde could be used as a nonenolizable aldehyde precursor of the iminium ion. The development of methods for the indirect Mannich reaction involving the synthesis and use of isolable and highly reactive enolate surrogates such as silyl enol ethers and ketene silyl acetals (the so-called Mukaiyama reagents) have obviated the problems associated with the original procedure.[11]

For the purposes of this review, we use the term *direct Mannich-type reaction* (DMTR)[12] to describe a process in which the *parent carbonyl compound* is converted into the nucleophilic species *in situ* either via naturally occurring equilibrium or by interaction with a substoichiometric amount of the reaction promoter. Common classes of reagents meeting these criteria include aldehydes, ketones, esters, nitroalkanes, and 1,3-combinations thereof (malonates, cyanomalonates, nitromalonates, *β*-ketoesters, *β*-diketones, etc.). By contrast, the *indirect Mannich-type reaction (IMTR)* is defined as the corresponding process utilizing an activated derivative of the carbonyl compound that is generated stoichiometrically either *in situ* or by prior preparation and isolation, which undergoes addition to the electrophile under the influence of a substoichiometric quantity of the reaction promoter. This definition encompasses common reagents such as preformed boron enolates, tin enolates, or silyl enol ethers, ketene silyl acetals, silyl nitronates, and alkali metal enolates generated stoichiometrically by the action of a strong base on the parent carbonyl precursor (Scheme 1).

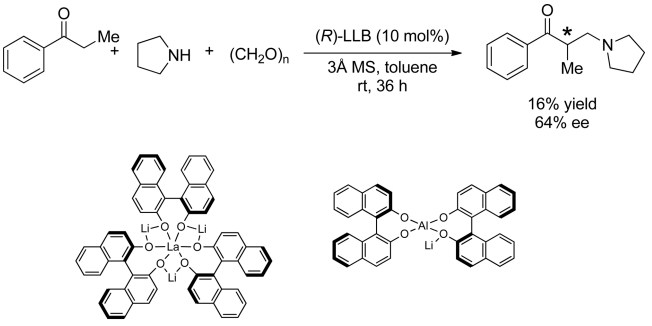
3.2. Addition of Stabilized Carbon Nucleophiles to C═N Catalyzed by Transition Metals

3.2.1. Metal-Catalyzed Asymmetric Direct Mannich and aza-Henry-type Reactions. As outlined above, the so-called direct Mannich-type reaction has many advantages over the indirect procedure especially from the standpoint of atom economy[13−15] and the fact that the nucleophilic component can be used in its native state without the need for prior generation, isolation, and purification of activated derivatives. A direct corollary to this is the generally rather low reactivity of the would-be nucleophilic component as nucleophiles in their unmodified state, which must be overcome before the reaction can

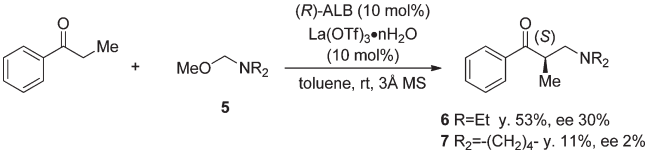
Scheme 1. The Direct and Indirect Mannich and Nitro-Mannich Reactions



Scheme 2. Shibasaki's DMTR with Rare-Earth Metal Catalysts



Scheme 3. Use of (*R*)-ALB and Co-catalyst in the DMTR

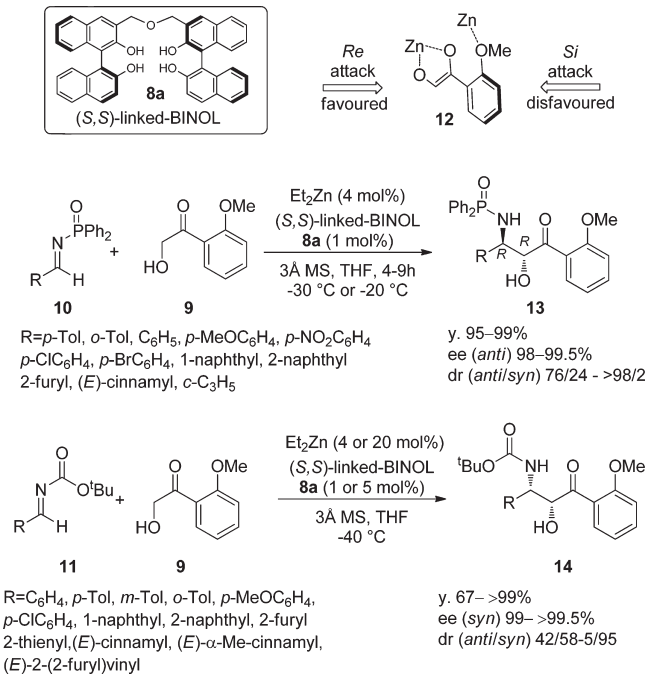


proceed. Therefore, activation of the nucleophilic component is the leading problem in the accomplishment of the DMTR.

The first example of the direct asymmetric catalytic Mannich-Type reaction, reported in 1999 by Shibasaki and co-workers,[16] involved the functionalization of propiophenone with formaldehyde and pyrrolidine in a three-component reaction catalyzed by (*R*)-LaLi$_3$tris(binaphthoxide) complex, **3** (Scheme 2), which had previously been applied to good effect in the analogous direct aldol[17] and nitroaldol[18] reactions. Initial trials afford the desired adduct in low chemical yield and enantioselectivity (5% and 6% respectively); however it was found that addition of molecular sieves to remove water lead to a dramatic improvement in enantioselectivity (64%).

In the same paper, the authors described the used of (*R*)-LLB and (*R*)-AlLibis(naphthoxide) [(*R*)-ALB],[19] **4**, to promote the closely related direct Mannich-type reaction between isolated hemiaminal ethers **5** and propiophenone. They found that neither catalyst functioned well by itself [12% yield, 25% ee with (*R*)-LLB; 6% yield, 16% ee with (*R*)-ALB] but that in the case of (*R*)-ALB, use of M(OTf)$_3\cdot n$H$_2$O (Ln = Sc, Yb, La) as cocatalyst gave the desired addition product with better enantioselectivity and in dramatically improved yield (Scheme 3). The best results were obtained with La(OTf)$_3\cdot n$H$_2$O although anhydrous La(OTf)$_3$ did not perform well as the cocatalyst.

Scheme 4. Highly *anti*- and *syn*-Selective Catalytic Asymmetric Direct Mannich-type Reaction of *N*-Diphenylphosphinoyl Imines and *N*-Boc Imines, Respectively, Promoted by Zn/(*S*,*S*)-linked-BINOL Species



Shibasaki et al. reported a catalyst system formed from diethyl zinc and (*S*,*S*)-linked BINOL ligand **8a**[20] for the direct addition of α-hydroxy aromatic ketones **9** to *N*-diphenylphosphinoyl imines **10**. The reaction proceeded under very mild conditions with a wide range of nonenolizable *N*-diphenylphosphinoyl (Dpp) imine substrates in the presence of 1 mol % of the ligand, to afford the corresponding *N*-protected α-hydroxyl-*β*-amino ketones in excellent yield and enantioselectivity as almost exclusively the *anti* isomer. The presence of a methoxy group at the *ortho*-position of the α-hydroxyl ketone was found to be essential for the realization of high enantioselectivities (Scheme 4). Furthermore it was found that by raising the temperature to 0 °C and extending the reaction time to 24 h, it was possible to reduce the catalyst loading to 0.02 mol % with no significant erosion of yield or enantio- and diastereoselectivity [98% yield, 97% ee (*anti*), 98/2 *anti*/*syn*].[21] Shortly after this, the same authors demonstrated that the same catalyst efficiently promoted the analogous reaction with *N*-*tert*-butoxycarbonyl (Boc) imines **11** to give the corresponding addition product in a highly *syn*-selective manner.

The influence of protecting groups on the stereochemical course of an asymmetric catalytic reaction allowing the use of a single catalyst to access both *syn* and *anti* diastereomers had been noted previously by Kobayashi et al. during their studies on the catalytic asymmetric indirect Mannich reactions of α-oxygenated silyl ketene acetals;[22] however the use of substituents on the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

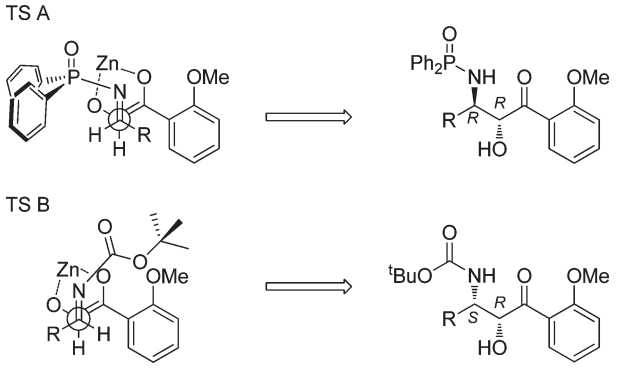


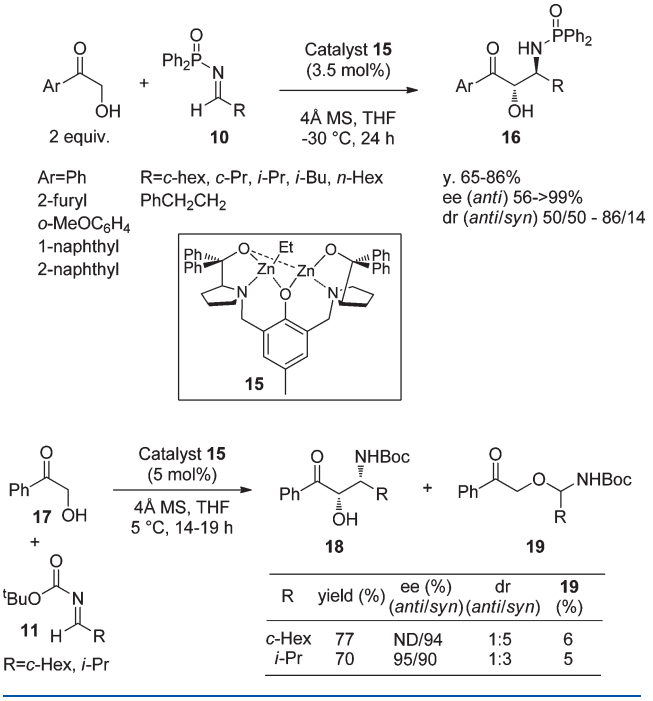
Figure 2. Transition states in the Zn/linked-BINOL catalyzed DMTR.

imine nitrogen atom to exercise stereocontrol over the reaction was unprecedented. The authors invoked the participation of a binuclear zinc enolate **12** in the reaction. In addition, the fact that the absolute stereochemistry [(*R*)] at the ketone α-carbon was the same regardless of the nature of the group attached to the imine nitrogen led the authors to conclude that the catalyst exercised strong stereofacial control over the approach of the reacting species, favoring attack on the *re* face, but that the exact spacial orientation of the imine in the transition state differed depending on the nature of the protecting group on the imine nitrogen. The authors proposed that in the case of the *N*-Dpp-imines, the reaction proceeded via transition state A, which minimizes interactions between the ketone aromatic ring and the bulky phosphinoyl phenyl groups delivering the (2*R*,3*R*) addition product. For *N*-Boc imines, the greater bulk of the imine R group relative to the *tert*-butoxycarbonyl group of the carbamate protecting group was believed to force the path describe by transition state B affording the corresponding (2*R*,3*S*) adduct (Figure 2).

Studies of reaction kinetics revealed a complicated picture in which both reactions were first-order with respect to the catalyst; in the case of the *N*-Dpp-imines, the reaction was almost zero order with respect to the imine and first-order in ketone, whereas in the case of the *N*-Boc reactions the reverse was found to be true, indicating that the rate-limiting step differs depending on the imine used. The authors postulated that the catalytic species is actually a heptanuclear Zn/linked-BINOL/ketone oligomer[23] in which zinc phenoxide can serve as a Brønsted base and zinc ions act as a Lewis acid for the activation of the imine component. Further investigation revealed a short induction period in the case of the reactions involving the *N*-Dpp-imines although experiments ruled out a significant role for asymmetric autocatalysis in the reaction and high catalyst efficiency was noted for both reactions (TON up to 4920).

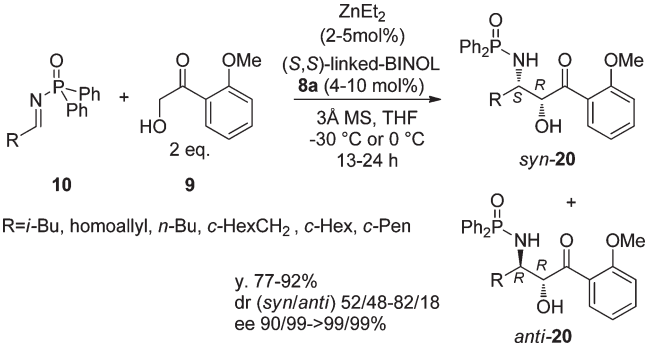
Although capable of promoting the DMTR in very high yield and with impressive levels of both enantio- and diastereocontrol, the systems so far described only promoted addition to imines formed from aldehydes that are not readily enolizable. This shortcoming in the methodology was addressed by Trost et al. who applied the (*S*,*S*)-dinuclear zinc catalyst **15**, originally developed for the catalytic asymmetric aldol reaction[24] to the DMTR with Dpp- and *N*-Boc imines.[25] They demonstrated the utility of this system in catalyzing the addition of α-hydroxy aryl ketones to a range of Dpp-imines derived from aliphatic aldehydes **10** to give the corresponding *anti* addition products in good yield and diastereoselectivity and very good to excellent enantioselectivity [dr up to (*anti*/*syn*) 86/14, ee up

Scheme 5. Trost's Dinuclear Zinc Catalyst in the DMTR of Alkyl Dpp- and N-Boc-Imines



R	yield (%)	ee (%) (*anti*/*syn*)	dr (*anti*/*syn*)	**19** (%)
c-Hex	77	ND/94	1:5	6
i-Pr	70	95/90	1:3	5

Scheme 6. DMTR with Aliphatic Imines Promoted by Zn/Linked-BINOL Catalysts



to >99%] (Scheme 5). Use of the antipode of the catalyst afforded the corresponding products with the reverse absolute stereochemistry with essentially identical yield and stereoselectivity. Furthermore it was found that the analogous reaction using aliphatic *N*-Boc imines **11** derived from both cyclic and acyclic aliphatic aldehydes also proceeded smoothly to give the expected *syn* amino alcohol products with good yield and diastereostereoselectivity and very high enantioselectivity along with a small quantity of the hemiaminal byproduct (Scheme 5).

Shortly after this report, Shibasaki et al. disclosed that linked BINOL ligands in combination with Zn(II) can also effect the direct catalytic asymmetric addition of α-hydroxy aryl ketones to aliphatic imines (Scheme 6).[26] Although diastereoselectivities were modest, a point ascribed to the low facial selectivity of the catalyst for aliphatic imines, both chemical yield and ee were good to excellent. It was found to be important to use a

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

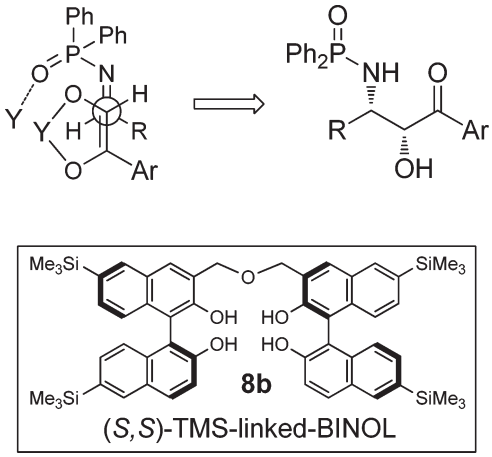
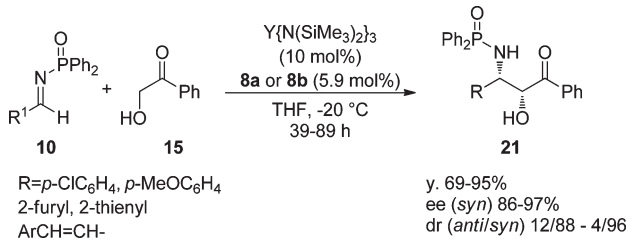
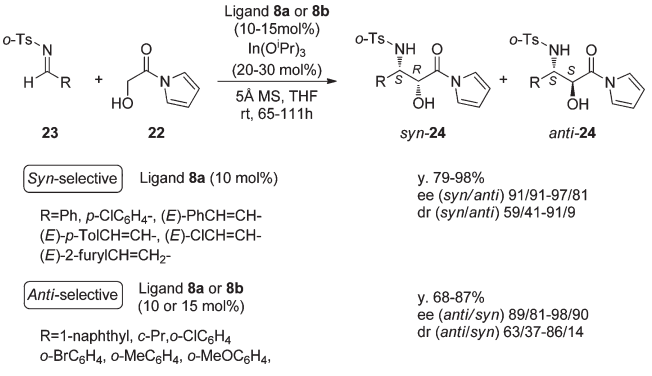


Figure 3. Proposed TS for *syn*-selective addition of Dpp-imines to α-hydroxy ketones.

Scheme 7. *Syn*-Selective DMTR of Dpp-Imines Catalyzed by Y/TMS Linked-BINOL Catalyst



Scheme 8. DMTR of *N*-(2-Hydroxyacetyl)pyrroles Promoted by In(O^{i}Pr)/Linked-BINOL Catalysts



$NaHCO_3$/DCM biphasic system for the generation of the imines from phosphinoyl sulfonyl precursors, which procedure afforded the imines in sufficient purity that they could be used directly in the Mannich reaction.

In another twist to the story, Shibasaki and co-workers have reported that an yttrium-based catalyst formed from linked BINOL **8a** catalyzes the addition of Dpp-imines to α-hydroxy aryl ketones to give the addition product *with high levels of syn selectivity*. By use of this combination, direct Mannich-type products were obtained in good to excellent yield and enantioselectivity although long reaction times were necessary (Scheme 7). The authors attribute the remarkable switch in

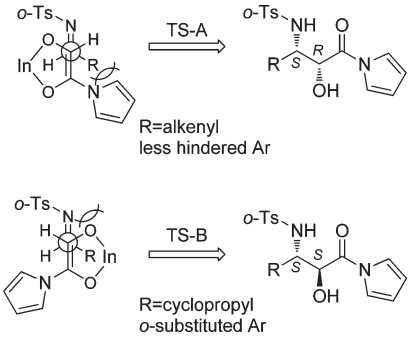


Figure 4. Transition state for the DMTR of *N*-(2-hydroxyacetyl)-pyrroles.

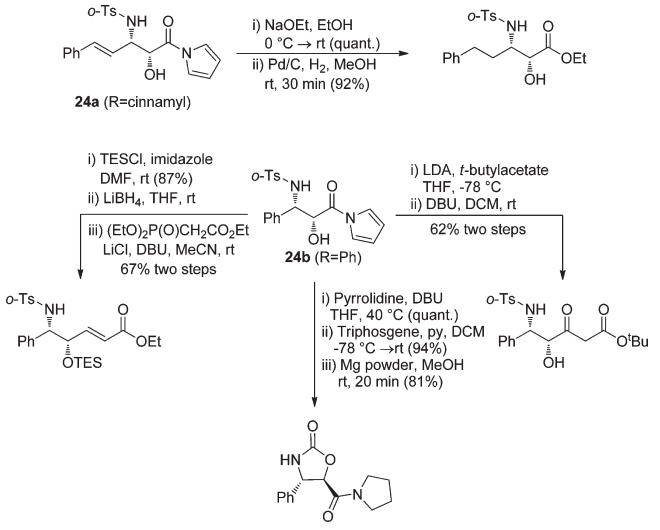
diastereoselectivity compared with the related Zn/linked-BINOL system to the higher oxophilicity of yttrium, which favors a transition state in which the phosphonium group on the imine nitrogen adopts an *s-cis* arrangement and is coordinated to the metal center via the phosphonium oxygen atom leading to an acyclic transition state (Figure 3), which minimizes gauche interactions between the imine and the yttrium enolate.[27]

The same authors have also disclosed that a combination of either the parent (*S*,*S*) linked-BINOL **8a** or ligand **8b** and In(O^{i}Pr)$_3$ permits the use of *N*-(2-hydroxyacetyl)pyrroles as nucleophiles in the DMTR with *N*-*o*-Ts imines (Scheme 8).[28] The reactions proceed smoothly at room temperature to give the desired products in good to excellent yield and very high enantioselectivity. Although the imines that could be used in the reaction were limited to those derived from nonenolizable ketones (aryl, vinyl, and cyclopropyl), the diastereochemical course of the reaction was found to depend strongly on the substitution pattern of the imine R substituent. Whereas vinylic imines and those with unsubstituted or *para*-substituted benzenes gave the *syn* diastereomer with high selectivity (*syn*/*anti* up to 91/9), naphthyl and *ortho*-substituted aryl groups as well as cyclopropyl favored the *anti* product (*anti*/*syn* up to 86/14). Furthermore, in contrast to the DMTR involving α-hydroxy ketones described above, in this instance, the *syn* or *anti* diastereomers (2*R*,3*S*) or (2*S*,3*S*) were established by variation of the asymmetric center at the keto α-carbonyl, whereas the stereogenic center at the nitrogen *ipso* position was always *S*. The authors ascribed the sensitivity of the diastereomeric course of the reaction to competing steric interactions between the pyrrole ring and the imine R group (Figure 4, TS-A) and that between the imine nitrogen and the α-O-In group of the coordinated *N*-(2-hydroxyacetyl)pyrrole (Figure 4, TS-B). They reasoned that the former interaction (TS-A) would be less destabilizing with R = alkenyl or unhindered aryl, favoring formation of the *syn*-product in these cases. However, in the case of R = *o*-Ar, these interactions would become prohibitive, forcing the reaction down the pathway described by TS-B, affording the *anti* product. The fact that both diastereomers were obtained in high enantiomeric excess with the same absolute stereochemistry at the *N*-appended stereogenic centers showed that the catalyst exerted strong enantiofacial control over the reaction.

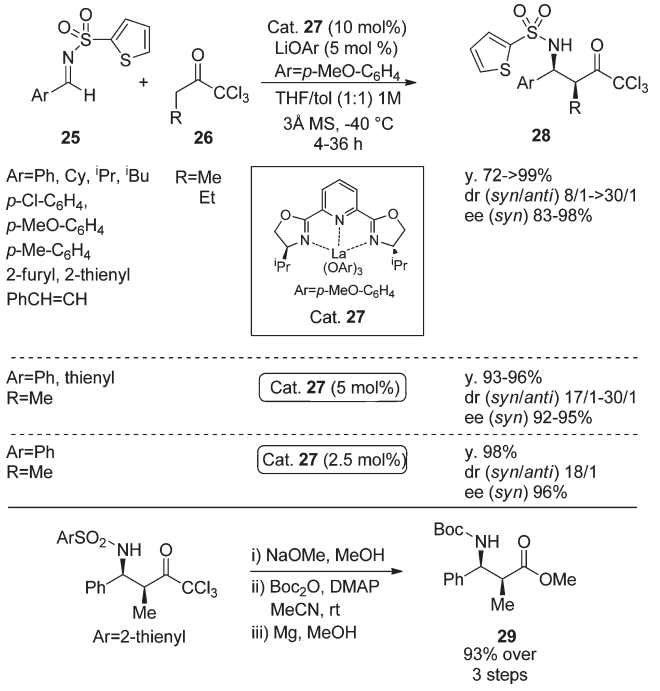
Although reaction times required by this protocol were rather long and the catalyst loading a little high in comparison with other methods, the presence of the acyl pyrrole functionality allowed smooth conversion of the addition products into a range of synthetically versatile derivatives by standard functional group interconversions (Scheme 9).

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 9. Transformation of Addition Products from the DMTR of *N*-(2-Hydroxyacetyl)pyrroles

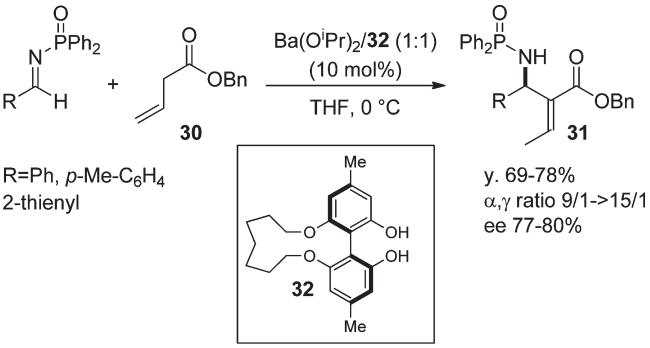


Scheme 10. The Catalytic Asymmetric DMTR of 1,1,1-Trichloroketones



The direct Mannich-type reaction is not limited to the addition of α-hydroxy carbonyl nucleophiles however. The closely related reaction of 1,1,1-trichloromethyl alkyl ketones with *N*-tosyl imines under simple lithium phenoxide catalysis was described[29] and has been followed up by an asymmetric version.[30] Shibasaki and co-workers found that the reaction with this nucleophile and Carretero-type *N*-thienylsulfonyl imines **25** could be promoted by La(III)-pybox catalysts affording the corresponding β-trichloro ketones **26** in excellent yield and stereoselectivity as predominantly the *syn* diastereomer (Scheme 10). Catalyst loading was successfully reduced to

Scheme 11. Ba-Catalyzed DMTR of β,γ-Unsaturated Esters with *N*-Dpp Imines



2.5 mol % in certain cases. The products of the reaction could be readily transformed into synthetically important intermediates, for example, hydrolysis of the trichloroketone moiety followed by protecting group interconversion afforded α-methyl-β-amino ester **29** in excellent yield. A vinylogous Mannich-type reaction of γ-butenolides with *N*-diphenylphosphinoyl imines was also investigated. A chiral lanthanum pybox Lewis acid/Brønsted acid/amine combination was effective in delivering the corresponding dihydrofuranyl phosphinic amides in excellent yields and enantiomeric excesses.[31]

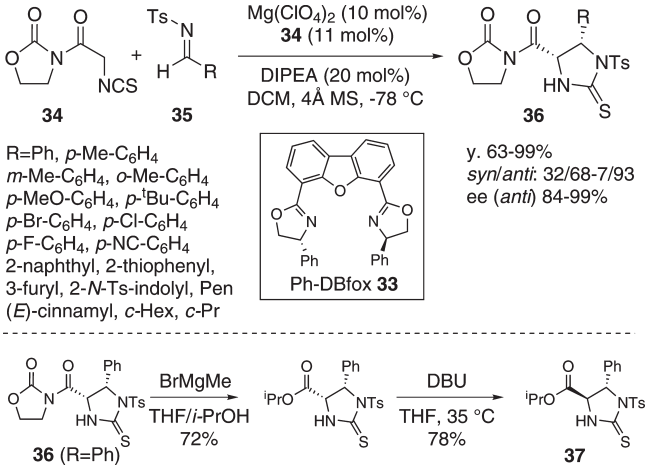
The DMTR of β,γ-unsaturated esters to *N*-Dpp imines catalyzed by $Ba(O^iPr)_2$[32] and either 2,2′-binaphthyl or tethered biaryl diol ligand **32** gave the corresponding adduct in reasonable yield and ee.[33] The racemic reaction catalyzed by $Ba(p\text{-MeO-}C_6H_4O)_2$ worked well, delivering the addition products in high to very high yields with almost complete control over the geometry of the newly formed olefin, as predominantly the α-adduct; four examples of the asymmetric version of the reaction were reported (Scheme 11). Despite the high regioselectivity of the reaction, yields and enantioselectivities were modest; however this concept opens up a potentially valuable and flexible route to nonracemic aza-Morita−Baylis−Hillman-type products.

The application of alkali-earth metal salts in the DMTR has been extended by Willis and co-workers to include Mg(II).[34] Using a combination of $Mg(ClO_4)_2$ and Ph-DBFOX **33**, they achieved the condensation of isothiocyanate-substituted oxazolidinone **34** with a range of *N*-tosyl imines derived from both aromatic and aliphatic aldehydes to give selectively the products of *anti*-Mannich addition, which spontaneously cyclized to the corresponding thioureas **36** (Scheme 12). Their success is particularly of note as DMTRs with carboxylic acid surrogate nucleophiles are rare.[33] Best yields and selectivities were obtained with 10 mol % catalyst, reduction of loading to 5 mol % impacting enantioselectivity. An attractive feature of the process, in addition to mild conditions and excellent yields and enantioselectivities, is the fact that adducts can be isolated in a protected but reactive form, which facilitates their easy conversion to *syn*-Mannich adducts **37** via transformation to the corresponding isopropyl esters and base-catalyzed epimerization.

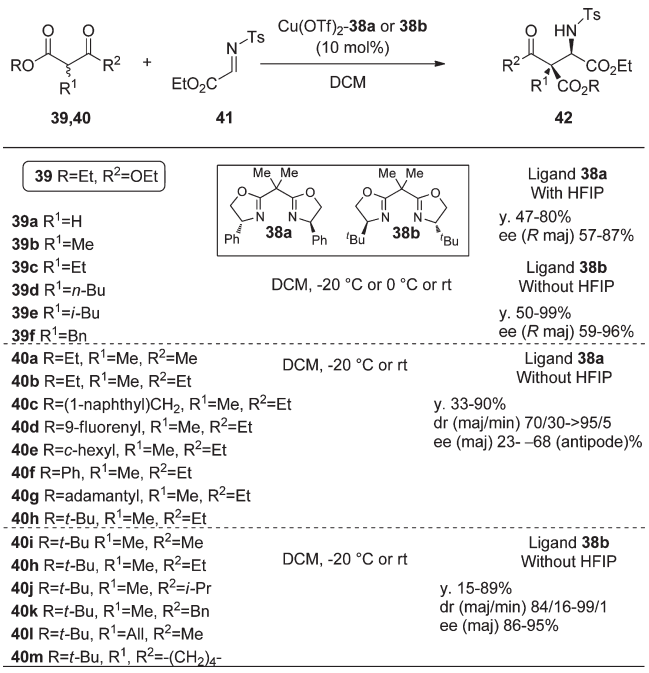
The catalytic asymmetric direct addition of malonates and β-keto esters to imines have been demonstrated by Jørgensen et al.[35] Using a combination of $Cu(OTf)_2$ and bisoxazoline ligands **38a,b**, they succeeded in promoting the reaction of a variety of diethyl derivatives **39a−f** and substituted β-keto esters **40a−l** to the highly activated *N*-tosyl-α-imino ester **41** derived from *p*-toluenesulfonamide and ethyl glyoxylate in high yield but

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 12. Willis' Mg(II)-Catalyzed Enantioselective DMTR with Isothiocyanate Oxazolidinones



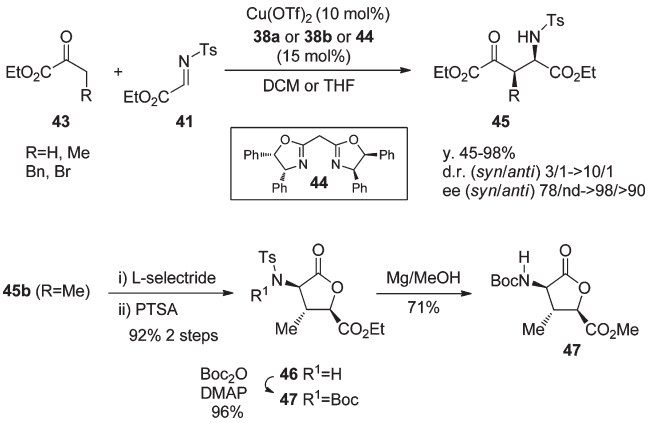
Scheme 13. Cu(II)-Box-Catalyzed DMTR of Malonates and β-Keto Esters



with very low levels of enantioselectivity. Addition of 1.5 equiv of hexafluoroisopropanol (HFIP) was found to improve the enantioselectivity in the case of addition with Cu(OTf)$_2$/(*R*)-Ph-Box **38a** (Scheme 9, R = EtO, R^1 = H, R^2 = Et; without HFIP, yield 95%, ee 39%; with HFIP, yield 63%, ee 80%) but not in the case of Cu(OTf)$_2$/(*S*)-^{t}Bu-Box **38b** (Scheme 13). Overall, the additions of β-keto esters using (*S*)-^{t}Bu-Box gave the best results in terms of enantioselectivity.

In the case of the addition of malonates, the absolute stereochemistry of the major isomer was determined as being (*R*,*R*) by converting the adduct from the addition of diethyl malonate to **41** into *N*-tosyl-diethyl aspartic acid and comparison with an authentic sample. Intriguingly, it was found that both (*R*)-Ph-Box **38a** and (*S*)-^{t}Bu-Box **38b** gave the addition products *as the same*

Scheme 14. Direct Catalytic Asymmetric Addition of Pyruvates to Glyoxal Imine 41



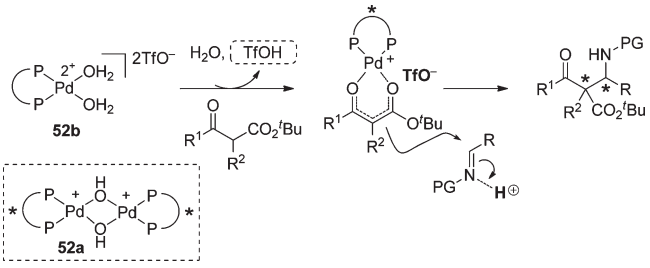


Figure 5. Sodeoka's palladium dihydrate catalyst system for the DMTR of β-keto esters.

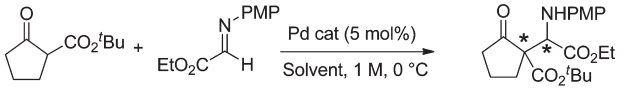
enantiomer despite the ligands themselves having the opposite sense of chirality. In addition, in the β-keto ester series, changing the nature of the ester from that derived from a primary or secondary alcohol to a tertiary alcohol led to a reversal of stereoselectivity.

The combination of Cu(OTf)$_2$/Box has been used to activate pyruvate esters **43** toward direct Mannich-type reactions.[36] The reaction proceeded smoothly under mild conditions affording the corresponding *N*-tosyl-α-amino esters **45** with high *syn* selectivity and good to excellent enantioselectivity. In practice, it was necessary to reduce the 2-oxo group with L-selectride and isolate the product as lactone **46** in order to avoid epimerization at the labile C-3 center. Exchange of protecting groups gave the synthetically useful *N*-Boc-α-amino lactone **47** (Scheme 14).

Sodeoka et al. have introduced a Pd(II) dihydrate-based catalyst system,[37] which activates β-keto esters toward addition to imines via the intermediate corresponding palladium enolate (Figure 5).[38] The catalyst promoted smooth addition of *tert*-butyl cyclopentanone-2-carboxylate **48** to the imine **49** formed from *p*-anisidine and ethyl glyoxylate with a range of bidentate phosphorus ligands **50a,b** and **51a,b** to give the desired products in good to excellent yield and with good to excellent diastereo- and enantioselectivity (Scheme 15). A key feature of the catalyst system is the simultaneous activation of the β-keto ester nucleophile by the palladium Lewis acid and Brønsted acid activation of the imine by an equivalent of triflic acid, which is liberated on coordination of the β-keto ester by the catalyst. Use of the catalyst formed from (*R*)-BINAP **50a** and the dinuclear palladium source **52a**, which does not proceed with the formation of triflic acid, only provided the addition product in 23% yield as opposed to the 77% yield that was obtained using the analogous **52b**/(*R*)-BINAP system. A survey of substrate scope in the

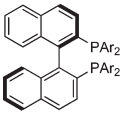
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 15. DMTR of *N*-PMP Ethyl Glyoxylate Imine with *tert*-Butyl Cyclopentanone-2-carboxylate

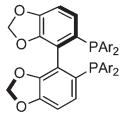


48 49

Ligand	Solvent	Yield (%)	d.r. (maj/min)	ee maj (%) ee min (%)
50a	DMF	74	96/4	97/87
50a	THF	77	83/17	98/97
50b	THF	96	83/17	97/91
51a	THF	89	81/19	99/98
51b	THF	63	98/2	93/50

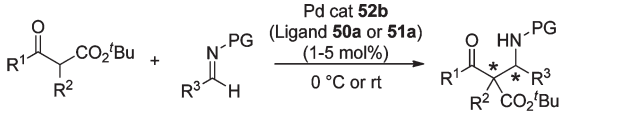


50a Ar = C_6H_5
(*R*)-BINAP
50b Ar = *p*-MeC_6H_4
(*R*)-Tol-BINAP



51a Ar = C_6H_5
(*R*)-SEGPHOS
51b Ar = *m,m*-$Me_2C_6H_3$
(*R*)-DM-SEGPHOS

Scheme 16. Substrate Scope in the DMTR of β-Keto Esters Catalyzed by Pd(II) Dihydrate Catalysts

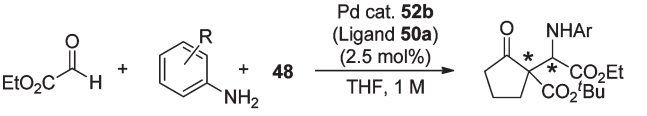


53a R^1-R^2 = $(CH_2)_3$
53b R^1-R^2 = $(CH_2)_4$
53c R^1=R^2= Me

54a PG=PMP, R^3=Ph
54b PG=Boc, R^3=*p*-Me-C_6H_4
54c PG=Boc, R^3=2-furyl
54d PG=Ts, R^3=*p*-Cl-C_6H_4
54e PG=Ts, R^3=CH=CHPh

y. 61-99%
d.r. (maj/min) 50/50->95/5
ee (maj/min) 86/55-99/99

Scheme 17. Three-Component DMTR of β-Keto Esters and Imines



R=*p*-MeO, Ar=PMP, rt, 3 h
y. 61%
dr (maj/min) 70/30
ee (maj/min)% 96/96

R=*m*-Cl, Ar=*m*-Cl-C_6H_4, -20 °C, 72 h
y. 85%
dr (maj/min) 95/5
ee (maj/min)% 98/88

reaction revealed that the combination of **52b** and ligands **50a** or **51a** efficiently promoted the addition of both cyclic and acyclic β-keto esters to a range of activated imines to give the corresponding α-amino esters in good to excellent yield and, except in the case of the addition of **53a** and **54b** catalyzed by $Pd(OH_2)_2$-$(OTf)_2$/**50a** [dr 50/50, ee (maj/min) 99/95], with very high diastereo- and enantioselectivity (Scheme 16).

Sodeoka and co-workers also found that their system effectively facilitated the three-component DMTR of *tert*-butylcyclopentanone-2-carboxylate and the imine formed *in situ* from ethyl glyoxylate and either *p*-anisidine or *m*-chloroaniline with moderate to good yield and high selectivity (Scheme 17).

Derivatization of the major product obtained from the reaction between **53a** and **54a** and comparison with literature data

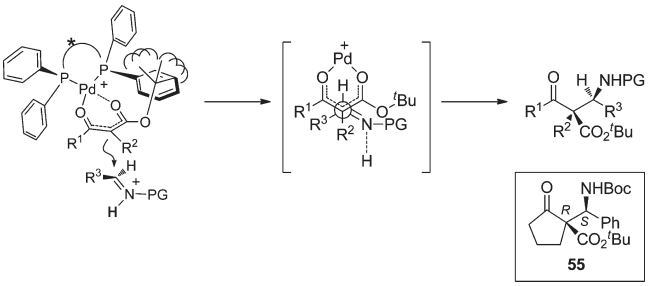
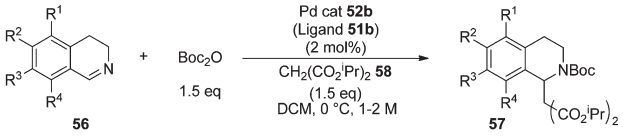


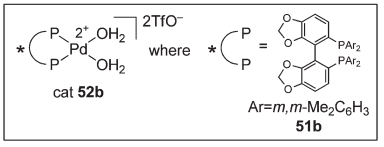
Figure 6. Proposed transition state.

Scheme 18. Addition of Malonate Esters to Dihydroisoquinolines



R^1 / R^2 / R^3 / R^4
56a H / H / H / H
56b H / H / MeO / H
56c H / R^2-R^3=OCH_2O / H
56d H / MeO / MeO / H
56e MeO / H / H / MeO
56f MeO / MeO / H / H
56g H / H / Me / H
56h H / H / Br / H

y. 57-98%
ee 81-97%



revealed the absolute and relative stereochemistry to be (*R,S*) *syn* (**55**, Figure 6). This in turn led the authors to propose an open transition state,[11a] in which the proton-activated imine unit approaches from the *re* face of the cationic Pd-enolate with excellent facial selectivity (Figure 6).

Sodeoka and co-workers have also shown that their catalyst system is capable of promoting the smooth direct addition of malonates to a wide range of dihydroisoquinolines under very mild conditions (0 °C) in generally good to excellent yield and with very good to excellent enantioselectivity (Scheme 18).[39] Although the reaction proceeded in a range of protic and aprotic solvents, dichloromethane was found to give the best results.

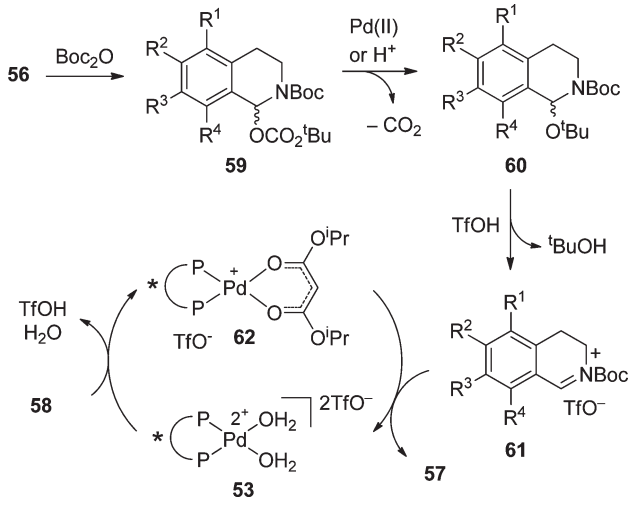
The authors noted that the order of addition in the reaction was extremely important. Stirring a mixture of dihydroisoquinoline **56a** and diisopropyl malonate **58** in the presence of catalyst **52b** in THF for 24 h did not yield any of the desired product. However, pretreatment of the dihydroquinolone with Boc_2O followed by addition of the catalyst and **58** gave the addition product in 94% (38% ee) in 2 h. This observation led the authors to suggest a mechanism in which reaction of the dihydroisoquinolone **56** with Boc_2O occurs first to give the *N*-Boc-*tert*-butylcarbonate **59**, which, under the influence of Lewis or Brønsted acid catalysis loses carbon dioxide generating *N,O*-acetal intermediate **60**. Subsequent triflic acid-catalyzed elimination of *tert*-butanol then gives *N*-Boc iminium ion **61**, which reacts with the palladium enolate of the malonate **62** and then gives the observed addition product **57** (Scheme 19).

The utility of the reaction was further enhanced by the discovery that tetrahydroisoquinolone **63** could be made to undergo the corresponding catalytic asymmetric decarboxylative addition reaction in the presence of DDQ (Scheme 20).[40−42]

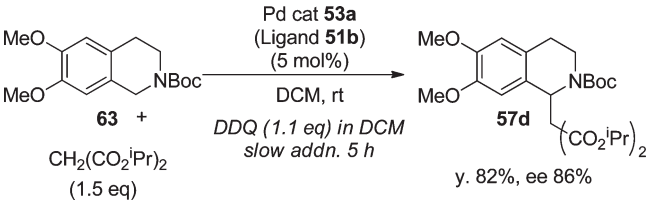
Glycine imino alkyl esters **64** have been widely used as glycine cation and anion synthons and have found extensive application

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 19. Proposed Mechanism for the Direct Mannich-type Addition of Malonates



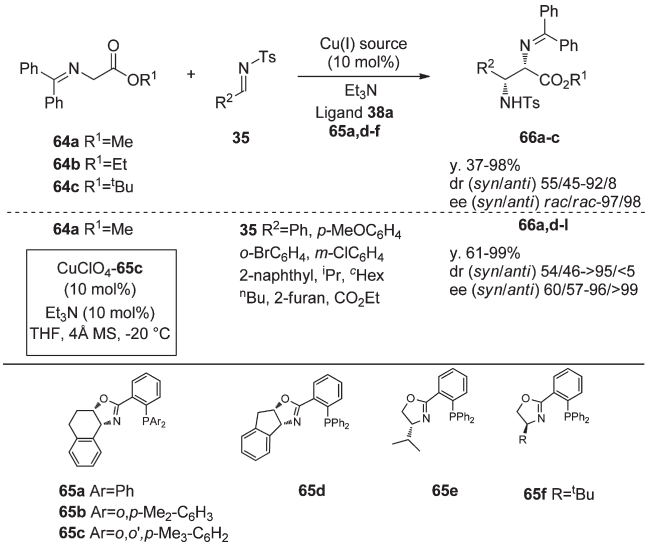
Scheme 20. Dehydrogenative Direct Addition of Malonate to Tetrahydroisoquinoline



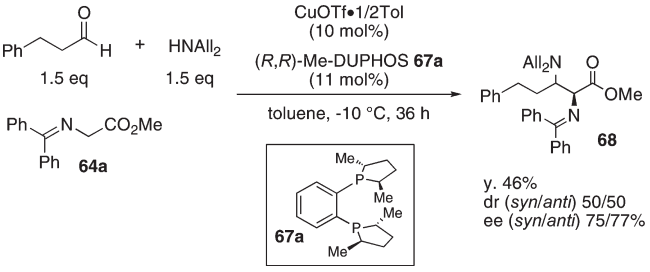
as starting materials for the synthesis of natural and non-natural amino acids.[43] The activation of these species with transition metal catalysts for use in the catalytic asymmetric direct addition to imines has been realized by Jørgensen and co-workers.[44] They examined catalysts based on $CuClO_4$, $CuPF_6$, and $AgClO_4$ with ligands (*S*)-BINAP (*S*)**50a**, (*S*)-Tol-BINAP (*S*)-**50b**, and Box-type ligands **38a** and *N*,*P*-ligands **65a**−**g** in the reaction of glycine imino esters $Ph_2C{=}NCH_2CO_2R$, **64**, and *N*-*p*-tosyl-*C*-phenyl imine, **35** (Scheme 21). A combination of $CuClO_4$ (10 mol %), and *N*,*P*-ligand **65c** in THF was found to give optimum results. Increasing steric bulk of the ester led to improved diastereoselectivity but at the expense of enantioselectivity. The reaction was general over a range of *C*-alkyl and *C*-aryl imines giving the 1,2-diamine addition products in very good to excellent yield and with good to excellent stereoselectivities. NMR spectroscopic studies indicated that, contrary to the behavior observed in other systems,[45] only the glycine-derived component is coordinated to the catalyst and that it undergoes deprotonation to give the Cu(I)-stabilized imino glycine alkyl ester anion, which forms the neutral complex. Semiempirical modeling studies suggested a tetrahedral geometry at the metal center of the complex with the ligands directing reaction to the *Si* face of the complex.

As part of their investigation of the direct catalytic asymmetric three-component Mannich reaction, Kobayashi and co-workers described a Cu(I)-catalyzed protocol for the addition of methyl *N*-benzylidine glycinates to iminium ions formed *in situ* from aldehydes[46] and secondary amines (Scheme 22).[47] In the absence of a chiral catalyst, the reaction provided the addition products in good to excellent yield and very high diastereoselectivity,

Scheme 21. Catalytic Enantioselective Addition of Glycine Imino Ester Derivatives to *N*-Tosyl Imines



Scheme 22. Three-Component Direct Asymmetric Catalytic Mannich Reaction



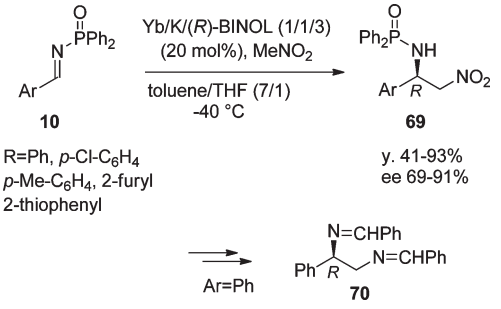
whereas the corresponding asymmetric catalytic addition proceeded in modest yield and enantioselectivity with little or no discrimination in the formation of diastereomers.

The nitro-Mannich reaction (also known as the aza-Henry reaction), in which nitro compounds undergo addition to C=N functionalities, has also been the subject of scrutiny.[48] The first recorded example of a direct catalytic asymmetric nitro-Mannich reaction was published by Shibasaki and co-workers in 1999, in which they used a novel Yb/K heterobimetallic complex of BINOL and [YbK(binaphthoxide)$_2$] to promote the addition of nitromethane to *N*-diphenylphosphinoyl aryl imines (Scheme 23).[49] Although the substrate scope described was limited, yields and enantioselectivities were moderate to high, and the reaction proceeded under very mild conditions (−40 °C). The absolute configuration of the product obtained using the catalyst formed from (*R*)-BINOL was determined as being *R* by conversion of one of the products (Ar = Ph) to the double Schiff base **70**.

Catalyst preparation studies indicated an optimal Yb/K/BINOL ratio of 1/1/3, which in turn led the authors to propose a catalyst structure in which Yb straddles 2 equiv of BINOL, one oxygen atom of each of which is also coordinated to the potassium ion. A third BINOL molecule is thought to hydrogen bond to the main catalyst assembly (structure **A**, Figure 7) and that this is in equilibrium with structure **B**. However, an aggregated complex (structure **C**) could not be ruled out.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 23. The Direct Asymmetric Catalytic Nitro-Mannich Reaction



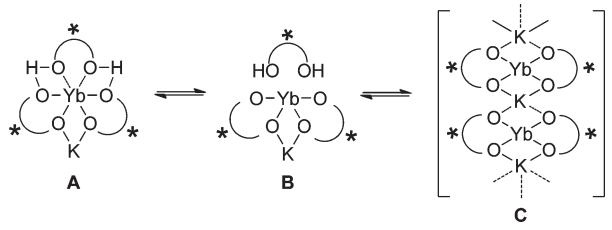


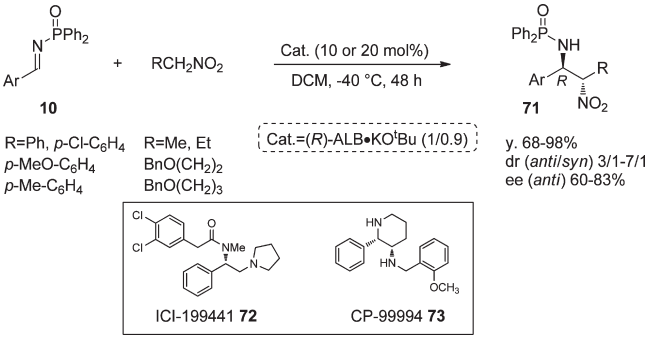
Figure 7. Proposed catalyst structures for the Yb/K/BINOL catalyst.

Shibasaki et al. quickly followed up their initial report by the first enantio- and diastereoselective catalytic nitro-Mannich reaction, this time utilizing a combination of their (*R*)-AlLibis(naphthoxide) [(*R*)-ALB **4**] and KO^{t}Bu (1/0.9 ratio) to effect smooth addition of several nitro alkanes to *N*-diphenylphosphinoyl imines **10** giving the secondary nitro addition product **71** in good to excellent yield and moderate to good enantioselectivity with a moderate to good preference for the *anti* diastereomer (Scheme 24).[50] Neither (*R*)-ALB by itself nor YbKH$_2$[(*R*)-bisnaphthoxide]$_3$ were effective in promoting the reaction. The synthetic utility of both catalyst systems was demonstrated by the authors by their subsequent use in the preparation of the biologically important compounds ICI-199441, **72** (using YbKH$_2$[(*R*)-bisnaphthoxide]$_3$), and CP-99994, **73** [using (*R*)-ALB].[51]

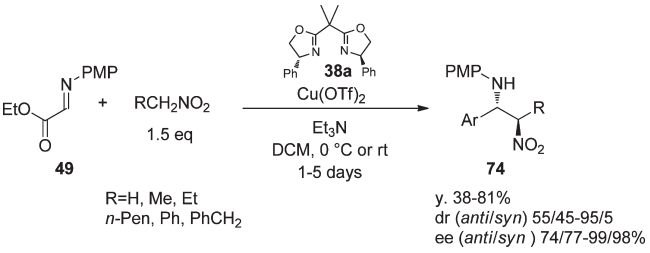
Almost concurrent with this disclosure, Jørgensen et al. independently reported the catalytic enantio- and diastereoselective nitro-Mannich reaction of nitro alkanes with *N*-*p*-methoxyphenyl imino ester **49**, catalyzed by simple catalysts formed from Cu(II) salts and Box-type ligands **38a**, **38b**, and **44**.[52] The procedure is operationally convenient in that it may be carried out under ambient conditions without the need for dry solvent. Chemical yields and enantioselectivities were generally very good to excellent, although the dr was variable, again with a preference for the *anti*-product (Scheme 25). At room temperature, the reactions were complete after 24 h; however at the lower temperature of 0 °C needed to obtain the highest selectivities, very long reaction times were required (5 days). Addition of secondary or tertiary amines to the system (triethylamine was found to give best results) led to increased yields although the quantity of the amine and timing of addition was found to be important.

The same group reported a mixed Lewis acid−Brønsted base protocol for the direct aza-Henry reaction of activated nitroalkanes.[53] Using a 1:1 combination of quinine and the chiral Lewis acid catalyst derived from Cu(OTf)$_2$ and (*S*)-Ph-Box **38a**, they achieved the addition of nitroacetate **75** to *N*-PMP imino

Scheme 24. Catalytic Enantio- And Diastereoselective Direct Nitro-Mannich Reaction



Scheme 25. Cu(II)-Box Catalyzed Asymmetric Direct Nitro-Mannich Reaction

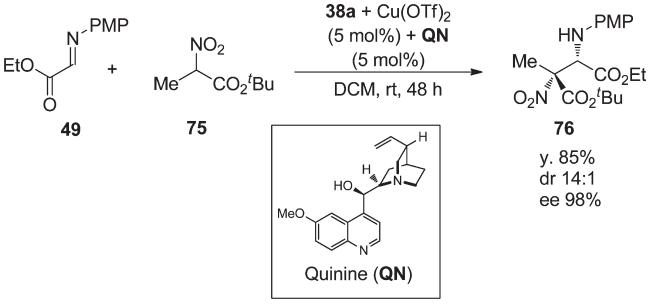


ester **49** to give synthetically valuable quaternary diesters **76** in high yield and excellent diastereo- and enantioselectivity with as little as 5 mol % catalyst (Scheme 26). Other cinchona alkaloids gave inferior results leading the authors to claim molecular recognition behavior between the Brønsted base and Lewis acid moieties.

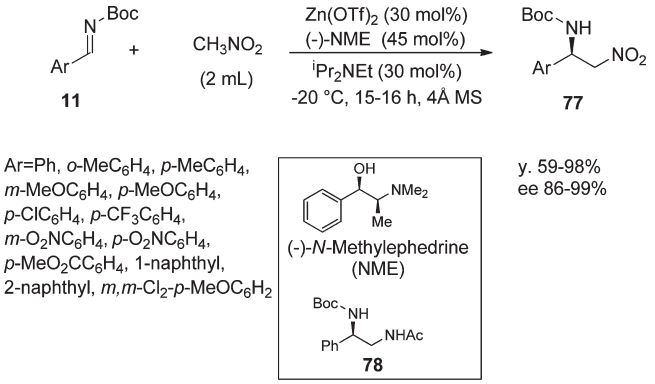
In addition to these protocols, zinc-based systems for the asymmetric catalytic nitro-Mannich reaction have been reported. In the first of these, Palomo et al., following on from their work on the catalytic asymmetric Henry reaction,[54] applied the combination of Zn(OTf)$_2$ and (−)-*N*-methylephedrine to the addition of nitromethane to a range of *N*-protected arylimines (Scheme 27).[55] Initial studies showed *tert*-butoxycarbonyl to be the nitrogen protecting group of choice. Accordingly the authors demonstrated that a range of *N*-Boc imines **11** would undergo smooth addition with nitromethane to deliver the corresponding (*R*)-β-nitro amines in good to excellent yield and enantioselectivity. The absolute configuration was established by the conversion of one of the products **77a** (Ar = Ph) into the known diamine **78**. Subsequent to this, the groups of Trost[56] and Qian[57] reported that the Trost Zn/ligand system **15**, developed for the aldol, nitro aldol, and Mannich reactions (*vide supra*), could also be applied to the aza-Henry reaction of *N*-carbamate imines and *N*-sulfonyl, *N*-PMP, and *N*-DPP imines, respectively (Scheme 28). In the first case, Trost demonstrated the addition of nitromethane and other nitroalkanes to a range of common *N*-Boc and *N*-Moc imines in moderate to high yields and very good enantiomeric excesses. Additionally, the reaction with problematic α,β-unsaturated imines was shown to proceed smoothly. In the case of addition to *N*-sulfonyl imines, the addition of 1 equiv (with respect to the catalyst) of triphenylphosphine oxide was necessary for smooth reaction.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 26. Creation of Quaternary Carbon Centers by Aza-Henry Reaction



Scheme 27. Zn(II)/Ephedrine-Catalyzed Asymmetric Direct Nitro-Mannich Reaction

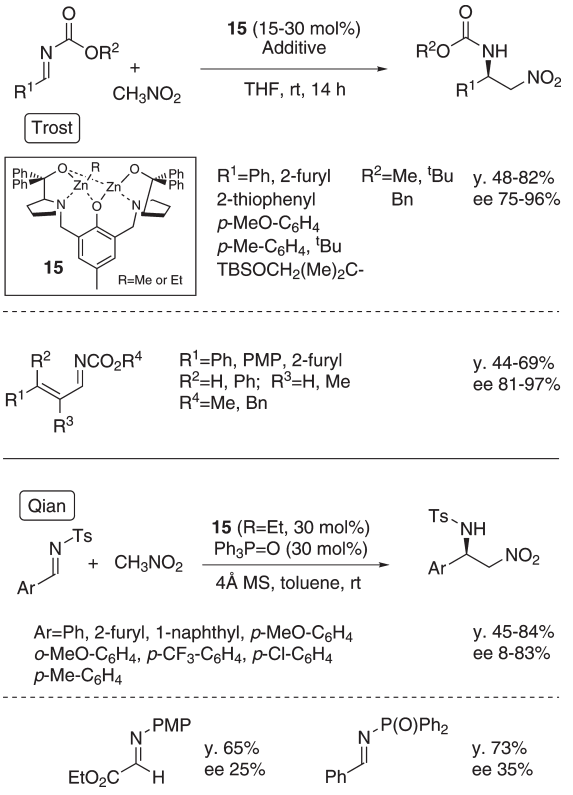


In all the examples shown above, the enantioselective diastereomeric version of the reaction proceeds with a strong preference for the *anti* diastereomer. Shibasaki et al. have reported the first example of a *syn*-selective enantioselective catalytic direct aza-Henry reaction using a new type of Cu(II)/Sm(III)−salen-type bimetallic catalyst system **79** (Scheme 29).[58] Chemical yields and enantioselectivities were very good to excellent, and in all cases the diastereoselectivity was >20/1 in favor of the *syn* product. The combination of metals was arrived at after extensive optimization studies of pairings of the M^{2+} metal ions Cu(II), Zn(II), Mg(II), Ni(II), and Rh(II) with a range of lanthanoid metals. The inclusion of both Cu(II) and Sm(III), as well as the 1:1:1 ratio of metals and ligand, was vital for efficient and selective turnover of the reaction. Addition of a hindered phenol was found to improve the enantioselectivity of the reaction, it is believed by stabilizing the monomeric form of the catalyst. A barium-catalyzed sequence furnishing isomerized aza-Morita−Baylis−Hillman-type products in up to 80% ee with biaryldiol axially chiral ligands has also been described.[33]

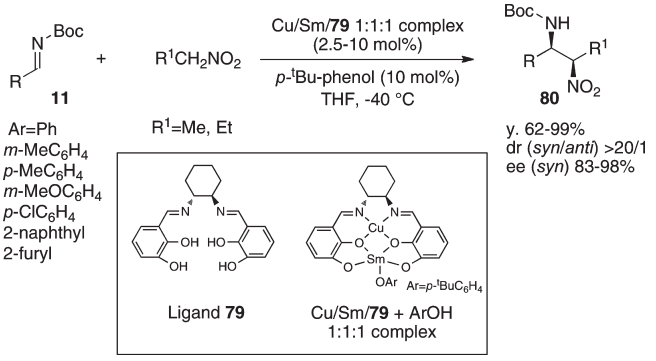
In addition, Shibasaki has revealed a number of excellent chiral catalytic systems for the direct Mannich-type reaction based on lanthanide pybox,[59] nickel-binaphthyl conjugates,[60,61] and rare earth chiral constructs.[62] Feng and co-workers performed aza-Henry reactions effectively catalyzed by chiral bis-*N*-oxide complexes of copper;[63,64] the same group also reported chiral bis-*N*-oxide scandium complexes in related IMTR.[65]

3.2.2. Indirect Asymmetric Mannich and Aza-Henry-type Reactions Catalyzed by Transition Metals. As noted in the previous section, the most challenging point of the direct

Scheme 28. Trost's Binuclear Zn Catalyst System in the Direct Nitro-Mannich reaction



Scheme 29. *syn*-Selective Direct Asymmetric Catalytic Aza-Henry Reaction



Mannich-type reaction is the activation of the pronucleophile species. In the indirect Mannich-type reaction, this problem is addressed by first converting the pronucleophile into a more active derivative, typically the corresponding silyl enol ether. Needless to say, the disadvantages of this approach are the exact opposites of the advantages associated with the direct Mannich-type reaction: increase in the number of reaction, purification, and isolation steps and poor atom efficiency due to the removal and nonrecovery of protecting groups (normally alkyl or aryl silanes) incorporated into the nucleophile.

At the time of publication of our previous review, the catalytic asymmetric indirect Mannich-type reaction was emerging as an important technique. In the intervening decade, advances in the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

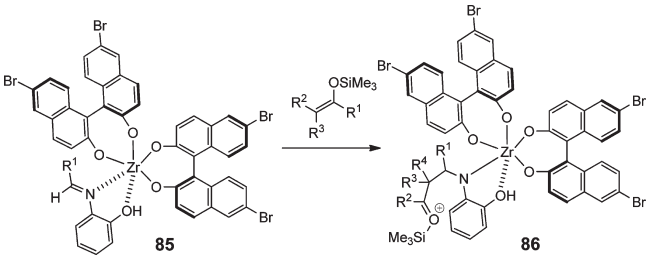
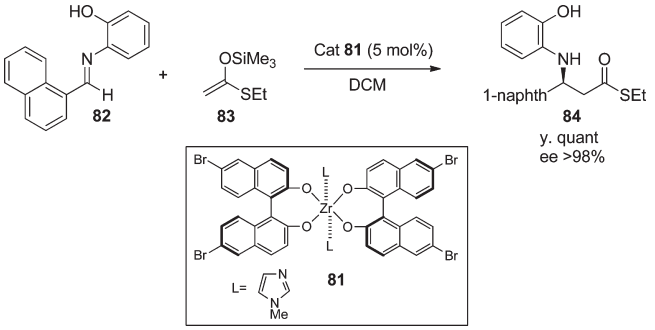


Figure 8. Intermediates in Kobayashi's 6,6′-disubstituted-BINOL/Zr-(IV) catalyzed IMTR.

Scheme 30. 6,6′-Disubstituted-BINOL/Zr(IV) Catalysts in the IMTR of Imines and Silyl Ethers

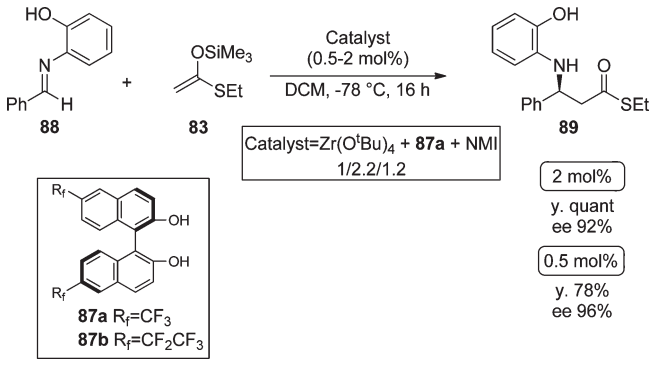


number and synthetic scope of catalysts along with improvements in the understanding of catalyst structure and mechanism, including multimetallic[66] and dual activation catalyst strategies,[67] mean that the catalytic asymmetric IMTR can now be considered an established technique in organic synthesis.

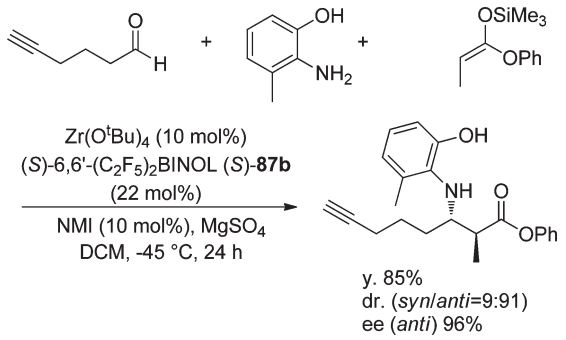
3.2.2.1. Metal-1,1-Binapthol-Derived Catalysts. Following their earlier report of the first genuinely catalytic asymmetric Mannich reaction, utilizing Lewis acids formed from 1:2 complexes of zirconium(IV) and 2,2′-binaphthyl (BINOL)-derived ligands,[68] Kobayashi and co-workers introduced a series of improved and highly activated catalysts for the reaction. Importantly, they discovered that 2:1 combinations of 6,6′-disubstituted-BINOLs and $Zr(O^tBu)_4$ act as extremely effective catalysts in the reaction, especially in presence of stabilizing imidazole ligands (e.g., *N*-methyl imidazole (NMI), 2-methyl imidazole, or 1,2-dimethyl imidazole (DMI)). The NMI or DMI is believed to play an important role in stabilizing the bis-BINOL Zr monomer relative to oligomeric forms. NMR spectroscopic studies indicated that the catalyst was highly symmetrical in nature and from this the structure of the catalyst **81** formed with NMI was deduced to involve equatorial binding of the BINOL moieties with NMI occupying the apical positions. The new catalyst species readily promoted the IMTR of *N*-(2-hydroxy)phenyl imines and silyl enol ethers, silyl ketene acetals, and silyl ketene thioacetals giving the desired addition products in excellent yield and enantioselectivities (Scheme 30). Addition of NMI or DMI to these catalyst systems is crucial for the realization of high selectivities: without it almost no stereoinduction was observed.[69]

The hydroxy group of the imine *N*-substituent was found to be essential for the realization of high enantioselectivities, which suggested bidentate coordination of the imine to the catalyst. The coordinated species is believed to involve the equatorial−apical flipping of one of the BINOL moieties in the complex to

Scheme 31. IMTR Catalyzed by 6,6′-Bistrifluoromethyl-BINOL/Zr(IV)



Scheme 32. Three-Component Reaction in the Synthesis of Onchidin

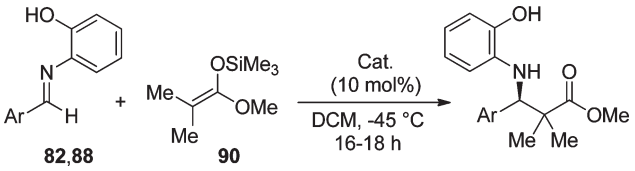


facilitate binding of the imine-generating structure **85**. Attack on the *Si* face of the imine affords the *O*-silylated N−Zr bonded complex **86**, the presence of which in the catalytic cycle was supported by a crossover experiment. Subsequent O → N migration of the silyl group releases the product and regenerates the catalyst (Figure 8). In the same paper, the authors reported an even more active catalyst constructed from the novel 6,6′-bis(trifluoromethyl)-BINOL ligand **87a** and $Zr(O^tBu)_4$, which was found to catalyze the related IMTR with high enantioselectivity and very low loading (0.5 mol %) (Scheme 31). A related catalyst prepared using 6,6′-bis(pentafluoroethyl)-BINOL **87b** was used in a highly *anti*-selective three-component IMTR adding propionate units to imines in good yield and excellent selectivity.[70] This technology was used in the group's synthesis of cytotoxic marine depsipeptide onchidin (Scheme 32)[71] and has also been extend to an equally selective hafnium variant.[72]

The synthetic utility of this class of catalyst was further enhanced by the discovery that preparation of the catalyst formed from **87b**, $Zr(O^tBu)_4$, and NMI in the presence of 5 Å MS in benzene at 80 °C followed by removal of solvent gave a chiral ZrMS adsorbed catalyst system that could be stored almost indefinitely in air (up to 13 weeks) without any significant loss of activity for the Mannich-type reaction of **88** and $Me_2C{=}C(OMe)OSiMe_3$, **90**, in DCM at −45 °C (yield quant, ee 90%; after 13 week storage yield 99%, ee 90%, Table 1, entries 1,2).[73] By comparison, the corresponding freshly prepared catalyst system suffered significant deterioration in activity after storage in air for 24 h. The catalyst system showed equivalent substrate scope to that of the IMTR promoted by the freshly prepared

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Table 1. Comparison of Activity of Stable Chiral Zr or Hf/BINOL Catalysts



entry	catalyst	Ar	comment	additive (mol %)	yield (%)	ee (%)
1	**87b** 6,6′-C_2F_5 ZrMS	Ph	freshly prepared	NMI (20)	quant.	90
2	**87b** 6,6′-C_2F_5 ZrMS	Ph	13 weeks storage	NMI (20)	99	90
3	**87b** 6,6′-C_2F_5 Zr powder	Naph	freshly prepared	none	quant.	89
4[a]	**87b** 6,6′-C_2F_5 Zr crystal	Naph	freshly prepared	none	80	85
5	**87c** 6,6′-Br Zr powder	Ph	freshly prepared	none	86	85
6	**87c** 6,6′-Br Zr powder	Ph	6 months storage	none	92	85
7	**87c** 6,6′-Br Hf powder	Naph	freshly prepared	NMI (10)	93	85
8	**87c** 6,6′-Br Hf crystal	Naph	freshly prepared	none	67[b]	85

[a] 20 mol % catalyst was used. [b] 132 h.

catalyst system. Addition of extra NMI was found to be crucial for efficient reactivity in all case. Other molecular sieves (4 Å, 5 Å) also afforded active catalysts, but enantioselectivities were maximized by the use of 3 Å MS. Furthermore, it was shown that the ZrMS catalyst could be recovered and reused up to three times with no adverse effect on yield.

In their investigation of methods for the preparation of more stable and amenable catalysts, Kobayashi et al. discovered that the catalyst formed from a 2:1 mixture of **87c** (6,6′-Br_2-BINOL) or **87b** (6,6′-$(C_2F_5)_2$-BINOL) and $Zr(O^tBu)_4$ could be precipitated from DCM solution as a powder by the addition of hexane, which showed high activity as a catalyst for the IMTR (Table 1, entries 3,5). The loading could be reduced to as little as 1−2 mol % without significant erosion of performance. Furthermore, the catalysts retained their activity for up to 6 months even when stored under air (Table 1, entry 6). By use of *N*-benzyl imidazole (NBI) in place of NMI and variation of the crystallization procedure, crystals suitable for X-ray structure determination were obtain and showed a $Zr_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$ solid state structure in which no NBI was incorporated. The single-crystal catalysts also worked well in the IMTR even in the absence of externally added NMI (Table 1, entry 4).[74] An analogous hafnium-based system has been reported by the same authors (Table 1, entry 7,8).[72] The system is similarly robust and performs comparably to the other air-stable catalysts in the IMTR, although reactions using the powdered form require the external addition of 10 mol % NMI. The single crystal form of the catalyst was found to be $Hf_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$ in direct analogy to the zirconium case.

Martin and co-workers used a BINOL/Ti(IV) system to catalyze the vinylogous Mannich-type reaction.[75] In their work, they discovered that a simple 2:1 combination of the parent 2,2′-binaphthyl ligand **87d** (R = H) and $Ti(O^iPr)_4$ at 20 mol % loading catalyzed the addition of siloxyfurans **91** to *N-ortho*-hydroxyphenyl aromatic imines giving the corresponding β-amino lactones **92** in moderated yield and good diastereoselectivity.

A highly efficient and practical method for catalytic asymmetric, silver-catalyzed, vinylogous Mannich reactions was conceived by Snapper and Hoveyda;[76] they extended the scope to challenging alkyl-substituted aldehydes[77] and later reported excellent reaction outcomes for vinylogous addition to α-ketoimine esters with chiral silver catalysis.[78]

The presence of the chiral ligand also influenced the diastereoselection, because in the absence of BINOL, the reactions proceeded to give close to 1:1 ratios of racemic diastereomers (Scheme 33).

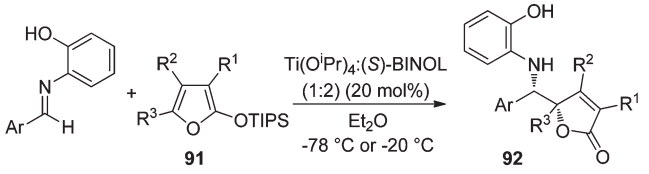
A variant of the zirconium-based catalyst system has been introduced by Wulff and co-workers. They used a 2:1:1.2 combination of $(Zr(O^iPr)_4/^iPrOH)$/(*S*)-VAPOL (**93**)/NMI in the IMTR of **88** and **90** giving the desired adduct as the *R* isomer.[79] Although the reaction proceeded reasonably well under the Kobayashi conditions (DCM, −45 °C, 10 h), the loadings were high (20 mol %) and both yields and selectivities were modest (Table 2, entry 1) although much better results were obtained in toluene. In toluene, selectivities were insensitive to temperature with high ee's being maintained across almost a 100 °C temperature range (Table 2, entries 2−4). The higher temperature allowed a decreased catalyst loading with the added bonus of raising chemical yields without significantly damaging the high levels of selectivity afforded by the catalyst. Using this strategy, the authors found it was possible to reduce catalyst loading to 0.5 mol % before yields became unreasonably low (60%) although enantioselectivity was still acceptable (85% at 41 °C). Most strikingly, the authors noticed that in this case the *S* isomer of the ligand afforded the *R* addition product in contrast to the analogous 6,6′-disubstituted BINOL catalysts where the *R* catalyst delivers the *R*-product (*vide supra*).

In further investigations, the authors employed molecular modeling to show that choice of the imine *N*-substituent was crucial for superior docking into the chiral pocket of the Zr/VAPOL catalyst. They identified imines derived from 2-amino-*o*,*p*-dimethylphenol as being the most suitable and demonstrated that with this system enantioselectivity could be maintained at high levels even up to 100 °C in toluene with as little as 2 mol % catalyst and showed that this protocol could be successfully applied to a range of common aromatic imines giving the addition product in high yields and enantioselectivities (Scheme 34).

The stereochemical model for the reaction using 2:1 BINOL/metal catalysts put forward by Kobayashi assumes that equatorial−apical flipping within the C_2-symmetric complex of BINOL ligand A (Figure 9, Flip A) creates a chiral pocket into which the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 33. Ti(IV)−BINOL Catalyzed Vinylogous Mannich-type Reactions of Siloxyfurans

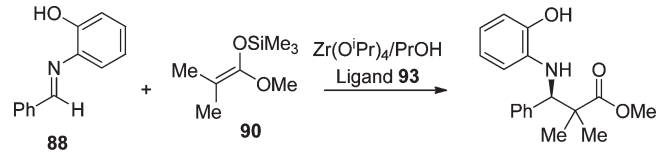


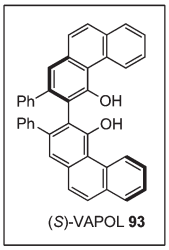
Ar=Ph, *p*-Cl-C_6H_4, *p*-NO_2-C_6H_4, *p*-MeO-C_6H_4, 1-naphthyl, pyridyl

R^1, R^2, R^3=H, Me

y. 50-80%
dr (*syn*/*anti*) 66/34-96/4
ee (*syn*) 28-54%

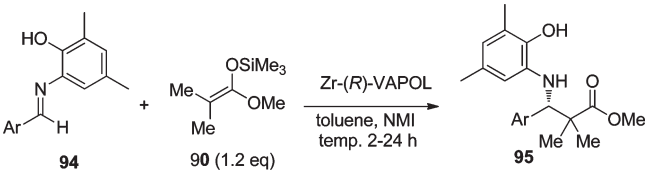
Table 2. Wulff's Zr/VAPOL-Based Catalyst System for the IMTR





Entry	Conditions	y. (%)	ee (%)
1	20 mol% cat. -45 °C, 10 h DCM	50	80
2	20 mol% cat. -45 °C, 20 h, tol	92	91
3	20 mol% cat. 25 °C, 15 h tol/DCM 15:1	94	89
4	2 mol% cat. 40 °C, 6 h tol/DCM 15:1	100	86

Scheme 34. IMTR of Several Imines with the Zr/VAPOL System at High Temperatures



Ar=Ph	20 mol% cat. 25 °C up to 100°C	y. 91-100% ee 98.0-98.5%
	5 mol% cat., 100°C	y. 90%, ee 98.4%
	2 mol% cat., 100°C	y. 95%, ee. 98.5%
Ar=*p*-Cl-C_6H_4, *p*-MeO-C_6H_4, *m*,*p*-MeO-C_6H_3, 1-naphthyl	2 mol% cat., 100°C	y. 83-90% ee. 93.0-99.8%%

bidentate imine substrate can bind. The absolute stereochemistry of the product points to subsequent *si*-face attack on the bound ligand.[80] An additional, nonproductive pathway involves the flipping of BINOL B (Flip B), which generates a nonstereoselective ligand−metal complex leading to loss of stereoinduction in the reaction. In order to address this, Kobayashi et al. developed novel linked bis-BINOL methane (BBM) ligands, **96**,[81] and tridentate

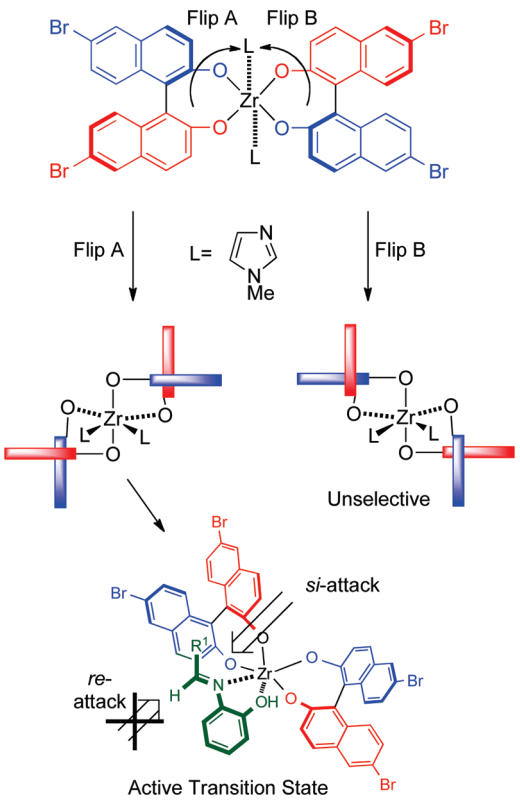


Figure 9. Proposed stereochemical model of the 6,6′-disubstituted-BINOL/Zr(IV) catalyzed IMTR.

BINOL−phenol mixed ligands, **97a**−**k**. Catalysts formed from a 1:1.5 mixture of $Zr(O^tBu)_4$/ligand functioned very efficiently as in the IMTR of silylated nucleophiles and a range of common imine electrophiles under very mild conditions (Scheme 35).[82]

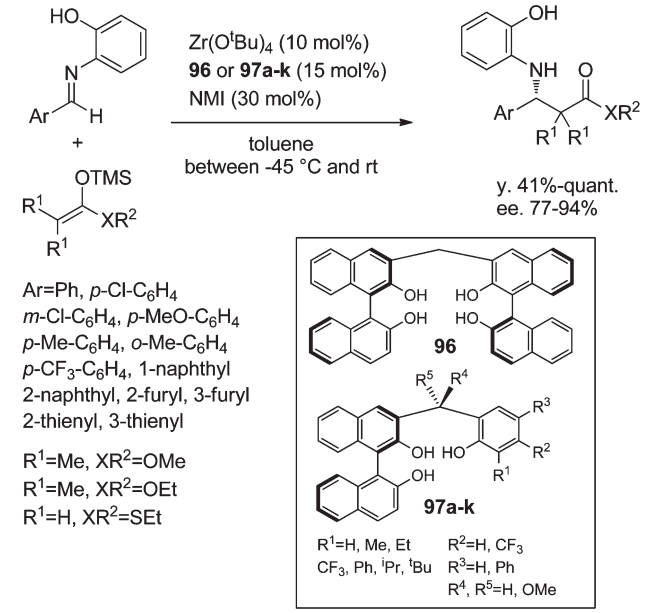
The authors conducted a detailed NMR spectroscopic study of the catalyst prepared using **97c** (R^1 = ^{i}Pr, R^2−R^5 = H) and found that at least three species were present in solution of which only one, a monomeric 1:1 complex of Zr and the tricoordinated ligand, is believed to be the active species in equilibrium with bridged dimer. The relative proportions of each of these solution complexes could be manipulated by varying the relative proportions of metal source and ligand.[83] The same tridentate BINOL-based ligands were also found to form a very active catalyst when combined with niobium(V) salts. Here again, the ^{i}Pr-substituted **97c** performed best, giving the desired Mannich adduct in the reaction between imine, formed from nonenolizable aldehydes and *o*-anisole, and silyl ketene acetals in comparable yield and superior enantioselectivities compared with the analogous Zr(IV) system (Scheme 35).[84] In this case, NMR spectroscopic studies indicated that the catalyst species is composed of a 2:2 dinuclear niobium−ligand complex stabilized by alkoxide ligands.

Concurrent with their development of 2:1 BINOL/Zr catalysts, the group of Kobayashi also introduced a catalyst system consisting of complexes of Zr(IV) and 3,3′-disubstituted BINOLs **98a**−**d** (Scheme 36).[85] They found that the presence of substituents at the 3-position allowed the formation of 1:1 ligand/metal structures and do not require the addition of NMI.

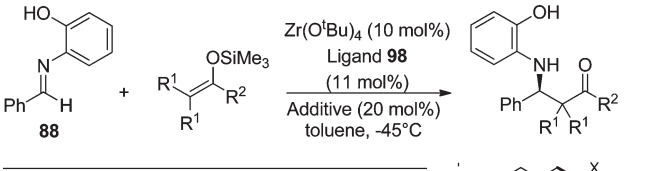
The catalyst effectively promoted the IMTR of ketene silyl acetals and ketene silyl thioacetals with imine **88**. Here again the presence of the *ortho*-hydroxy group on the imine *N*-substituent was found to be crucial for the realization of high selectivities

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 35. Use of BBM and Tridentate Linked BINOL Ligands with Zr(IV) and Nb(V)



Scheme 36. Equimolar Zirconium/3,3′-BINOL Lewis Acids in the IMTR



R1	R2	Ligand	Additive	y. (%)	ee (%)
Me	OMe	**98a**	PrOH	63	23
Me	OMe	**98b**	PrOH	95	70
Me	OMe	**98c**	PrOH	99	69
Me	OMe	**98d**	PrOH	99	44
Me	OMe	**98c**	H_2O	94	95
H	SEt	**98c**	H_2O	60	79

leading the authors to conclude that the imine binds to the catalyst in a bidentate fashion similar to that invoked for the 2:1 BINOL/metal catalysts. It was noted that the products of the IMTR were obtained in high ee as exclusively the *R* enantiomer whereas use of the same catalyst in the corresponding aldol reaction afforded the *S* isomer, that is, the opposite sense

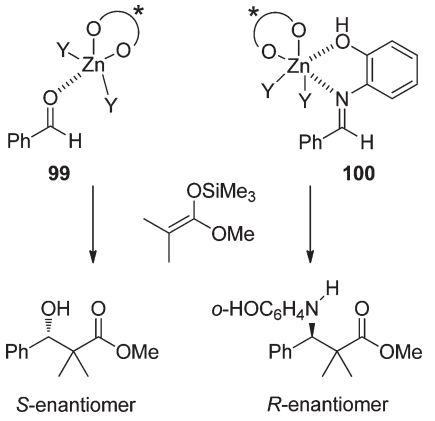
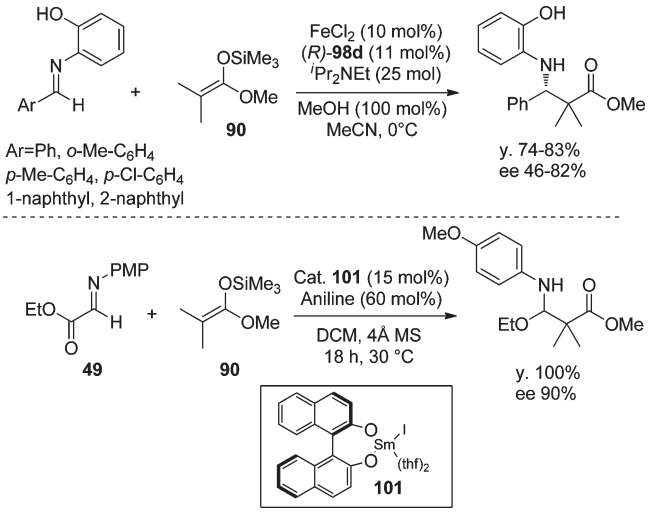


Figure 10. Binding geometries in the 1:1 Zr/BINOL-catalyzed asymmetric IMTR and aldol reaction.

Scheme 37. The IMTR Catalyzed by Fe(II) and Sm(III)/BINOL Catalysts



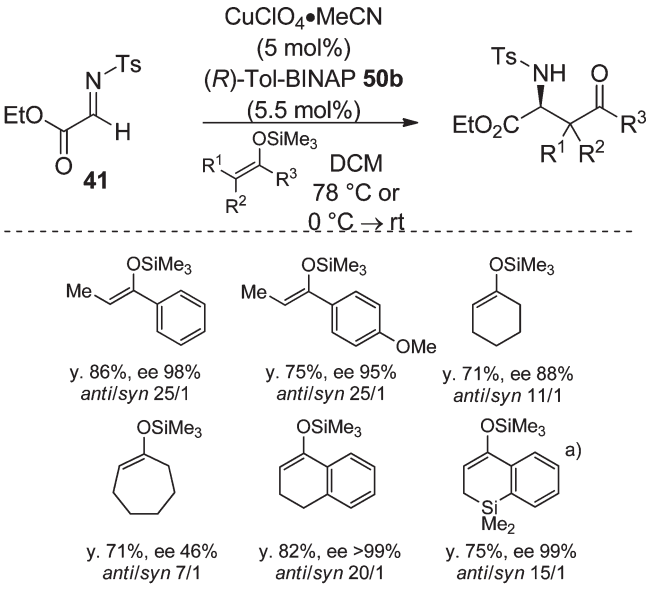
induction was imparted by the complex. Differences in binding geometries were invoked to explain the reversal in enantioselectivities of these two reactions (Figure 10).

The 3,3-disubstituted BINOL ligands can also be used to form catalysts in combination with Fe(II) and Sm(III) (Scheme 37). In the first case, Kobayashi et al. screened a number of (*R*)-3,3′-disubstituted-BINOL ligands with $FeCl_2$ as the metal source and found that a 1:1.1 mixture of the metal and 3,3′-I_2-BINOL gave optimum results. Although yields and selectivities were moderate compared with the analogous zirconium system, a reversal of selectivity was observed as use of the *R*-ligand gave the *S* product in direct contrast to the (*R*)-Br_2-BINOL/Zr(IV) system.[86] Subsequently, Collin and co-workers disclosed that a 1:1 combination of $SmI_3(thf)_3$ and (*R*)-1,1-binaphthol could be used to promote the IMTR of silyl ketene acetal **90** in good to excellent yield and up to 82% ee.[87] They examined a range of amine additives and described a rather complex reaction system in which rates of addition of the silyl ketene acetal and catalyst maturation effects played an important role.

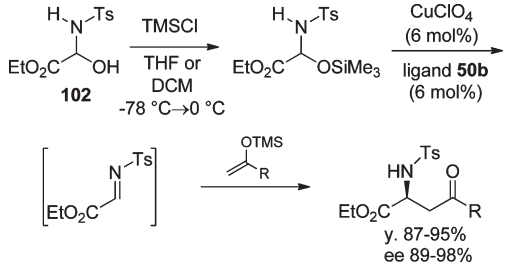
Tin BINOL derived catalysts were reported by Izumiseki et al. where an *in situ* generated ethoxide bromide catalyst furnished Mannich-type adducts from alkenyl trichloroacetates in up to 98% ee.[88]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 38. IMTR of Silyl Enol Ethers and Imine 41 Catalyzed by Cu(I)/Tol BINAP



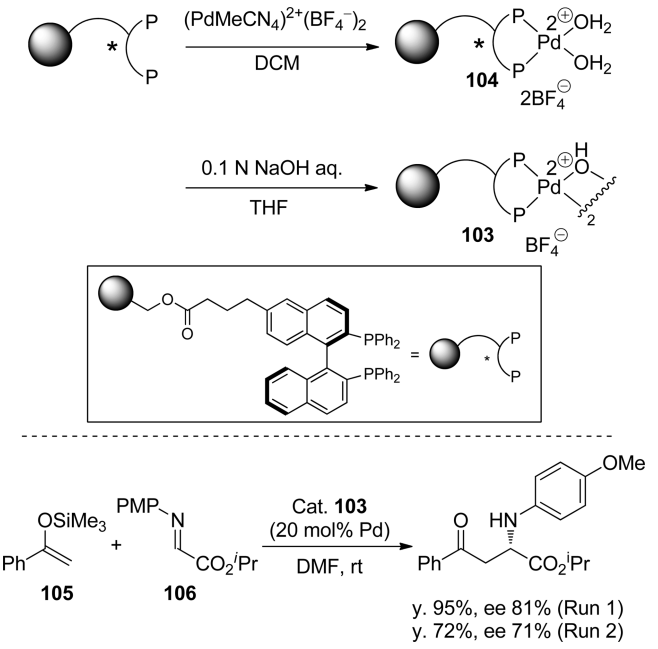
Scheme 39. Lectka's One-Pot Imine Generation-IMTR Protocol



3.2.2.2. Metal−Phosphine-Derived Catalysts. Early examples of Pd(II)−phosphine-based catalyst systems for the Mannich reaction were described almost simultaneously by Sodeoka[89] and Lectka[90] in the late 1990s. Although both methods used similar combinations of Pd(II) with BINAP-type ligands, Lectka also examined the use of Cu(I) and Ag(I) as the Lewis acid component. In their original report, Lectka et al. demonstrated the addition of *Z*-enol silanes to highly activated α-imino esters in excellent yield and selectivity. Subsequently they demonstrated that the corresponding *E*-enolates formed from cyclic systems are also amenable nucleophiles in the reaction promoted by Cu(I)/Tol-BINAP catalysts (Scheme 38).[91] One limitation of procedures using very reactive α-imino esters as electrophiles is the difficulty experienced in their synthesis and handling. Usefully, Lectka et al. discovered that generation of the imines *in situ* from the corresponding *N*,*O*-hemiaminals [HNX-C(OR)CO_2Et], **102**, could be effected by the Cu(I)/BINAP system in the presence of enolsilanes and that the subsequent IMTR could take place in high yield and enantioselectivity in one-pot (Scheme 39).[92]

Following their early success with dimeric palladium aquo phosphine catalysts Sodeoka and co-workers have developed a protocol for the use of solid phase catalysts using commercially

Scheme 40. Preparation of Immobilized Pd(II) Catalysts and Its Use in the IMTR



available polymer-bound BINAP and Pd(II) (Scheme 40).[93] They found it necessary to utilize a dimeric catalyst species **103** rather than the monomeric **104** because use of the latter was unsuccessful (although catalyst **104** did promote the analogous aldol reaction). Accordingly, the addition of enol silane **105** to α-imino ester **106** occurred smoothly in good yield albeit it with comparatively low enantioselectivity. The catalyst complex could be recovered and reused although both yield and ee were adversely affected in subsequent runs.

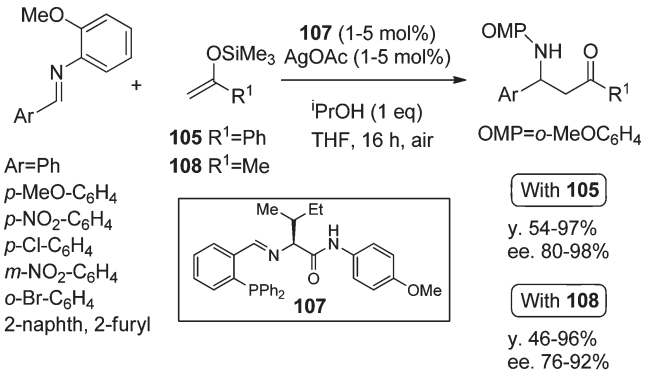
Hoveyda and co-workers have applied their novel mixed P−N ligand system **107** to the IMTR catalyzed by Ag(I).[94] The system catalyzed the addition of a range of aliphatic, aromatic, and olefinic enol silanes to *o*-methoxyphenyl imine giving the desired *β*-amino ketones in very high yield and good enantioselectivity (Scheme 41).

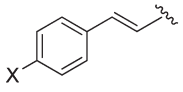
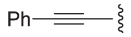
The catalyst was also effective for the three-component IMTR between *o*-anisidine, aliphatic aldehydes, and acetone silyl enol ether (yield 41−60%, ee 92−94%). Removal of the protecting group could be effected under mild oxidizing conditions using $PhI(OAc)_2$ without compromising the stereochemical integrity of the amine chiral center. Using their three-component protocol, the authors described a short synthesis of (−)-sedamine (Scheme 42).

A problem frequently encountered in the development of Mannich-type reactions is the difficulty associated with the removal of protecting groups from the nitrogen atom in the newly formed amine product. Although both oxidative and reductive methods have been applied, these often require harsh conditions, which can lead to reduced chemical and optical yields of the free amine products. With this in mind, Carretero et al. have developed an effective procedure for the IMTR based on the addition of enol silanes to *N*-(2-thienyl)sulfonamides catalyzed by a complex of Cu(I) and a ferrocenyl *P*,*S* ligand system.[95] Screening a number of *N*-sulfonyl protecting groups identified *N*-2-thienyl imine **109** as giving best results when exposed to ketene silyl thioacetals in the presence of the catalyst formed

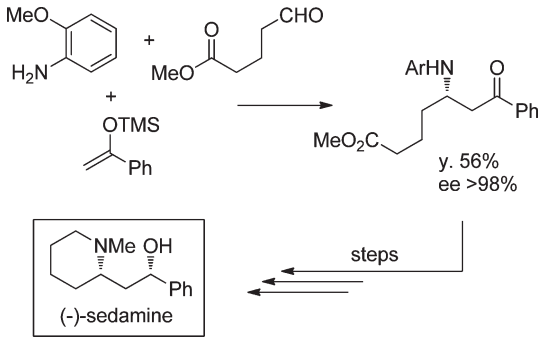
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 41. Hoveyda's Peptidic P,N-Ag(I) Catalyst System in the IMTR



Imine Ar	X	R^1	AgOAc (mol%)	temp. (°C)	Yield (%)	ee (%)
	H	Ph	1	4	51	90
	H	Me	1	4	77	89
	MeO	Ph	3	22	74	96
	MeO	Me	5	22	47	90
	NO_2	Ph	3	-5	>98	92
	NO_2	Me	3	-5	74	90
	-	Ph	1	4	93	92
	-	Me	3	-5	91	88

Scheme 42. Three-component IMTR Leading to the Synthesis of (−)-Sedamine

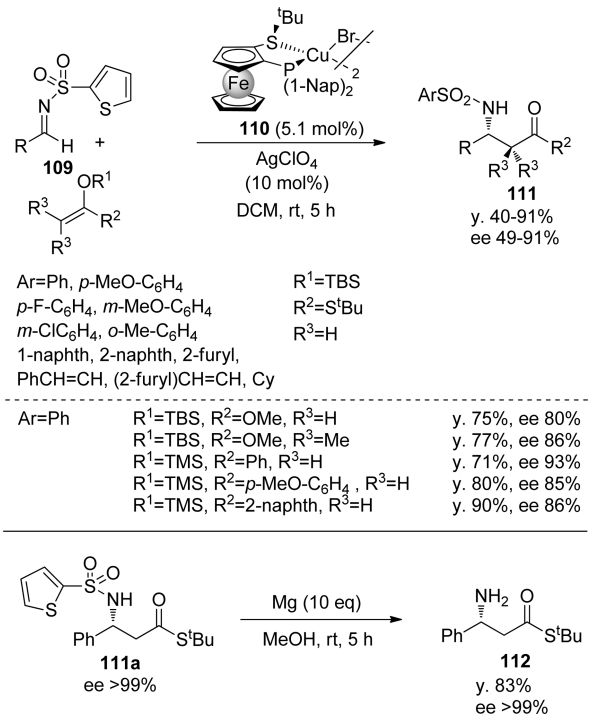


from the ligand **110** and CuBr in the presence of an equimolar mixture of $AgClO_4$ at ambient temperature (Scheme 43).[96]

Although yields and enantioselectivites varied considerably between substrates, the scope of the reaction was broad and allowed the use of imines formed from alkenyl and alkylaldehydes. Use of CuCl also produced a viable catalyst, but results were poorer than for the CuBr system. An attractive feature of the protocol is that the *N*-(2-thienyl)sulfonamide group can be readily removed under very mild conditions (10 equiv of Mg, MeOH, rt, 5 h) to afford the free amine with high conversion and no loss of stereochemical integrity, the same catalyst was also employed in vinylogous asymmetric Mannich reactions with good effect.[97] Yuan et al. developed a silver-catalyzed vinylogous Mannich reaction employing chiral phosphine−Schiff base ligands.[98]

An axially chiral phosphine oxazoline ligand was used in combination with a silver(I) source for the highly enantioselective reaction of aldimines with trimethylsiloxyfuran under mild conditions.[99]

Scheme 43. Use of *P,S*-Ligand/Cu(I) Catalyst Systems in the IMTR

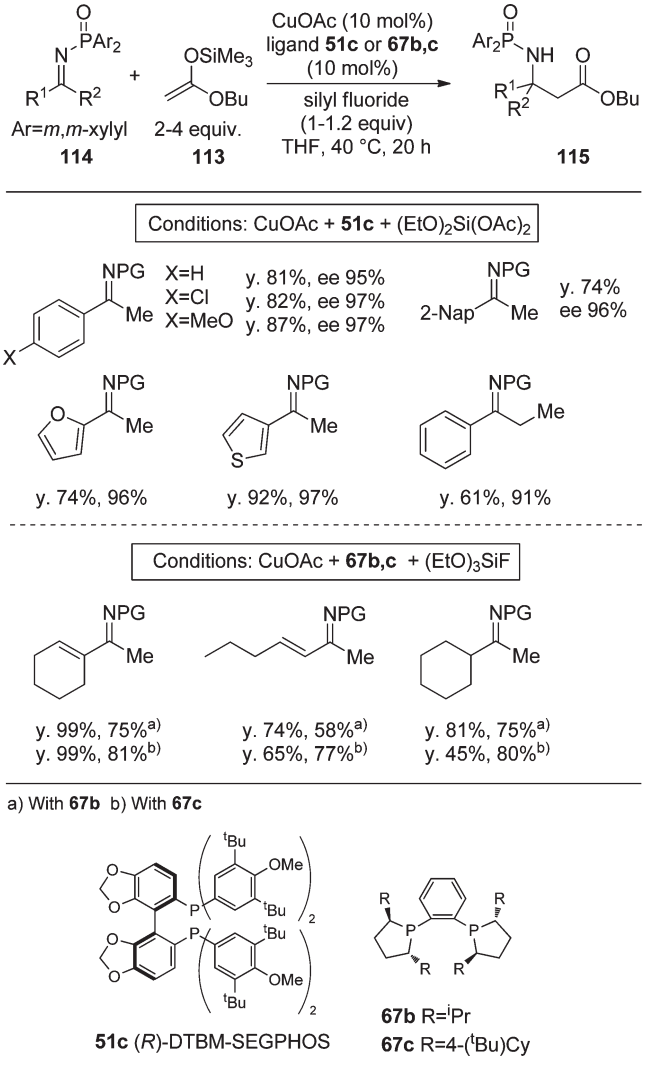


An important development in Mannich-type reaction chemistry was disclosed by the group of Shibasaki where they demonstrated a general method for the catalytic asymmetric IMTR using *N*-bisarylphosphinoyl ketoimines as electrophiles.[100,101] Following on from their work on the analogous catalytic asymmetric aldol reaction of ketones,[102] they used either CuOAc/DTBM SEGPHOS **51c** or CuOAc/DUPHOS (**67b**, ^{i}Pr, or **67c**, 4-*tert*-butylcyclohexyl) catalysts to effect the addition of silyl ketene acetal **113** to a range of *N*-bisarylphosphinoyl ketoimines **114** derived from aryl or alkenyl alkyl ketones giving the corresponding *N*-protected tertiary amine products **115** in high to very high yields and good to excellent enantioselectivities (Scheme 44). The nature of the alkoxy silyl fluoride additive was found to be crucial for the promotion of rapid regeneration of the catalyst by *N*-silylative release of it from the copper amide species generated in the reaction and the realization of rapid catalyst turnover. Use of $(MeO)_2SiF_2$ as the silylating agent gave good results; however synthesis of the $(MeO)_2SiF_2$ was nontrivial. The readily available $(EtO)_2Si(OAc)_2$ fortunately gave comparable performance. The authors also demonstrated that the *N*-bisxylylphosphinoyl protecting group could be removed efficiently to give corresponding tertiary β-amino acid after hydrolysis in high yield (Scheme 45).

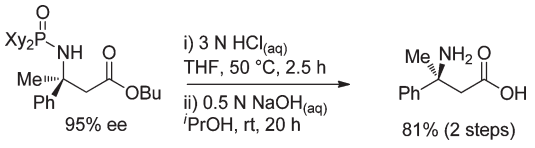
Another P−N ligand metal combination employed isopropyl phosphinoferrocenyl oxazoline (iPr-Phosferrox[103]) in a highly selective reaction of imines with protected glycine, where it was possible to switch the diastereoselectivity of the product through judicious ligand tuning.[104]

3.2.2.3. Other Metal−ligand Combination Catalysts. Another protocol for the IMTR of enol silanes to ketoimines has been introduced by Jørgensen et al. In this, they used Zn/pyBOX **116** catalysts to promote addition of silylketene acetals to tethered *N*-carbamoyl α-ketimino esters **117** giving the tertiary

Scheme 44. Shibasaki's IMTR with *N*-Bisxylylphosphinoyl Ketoimines



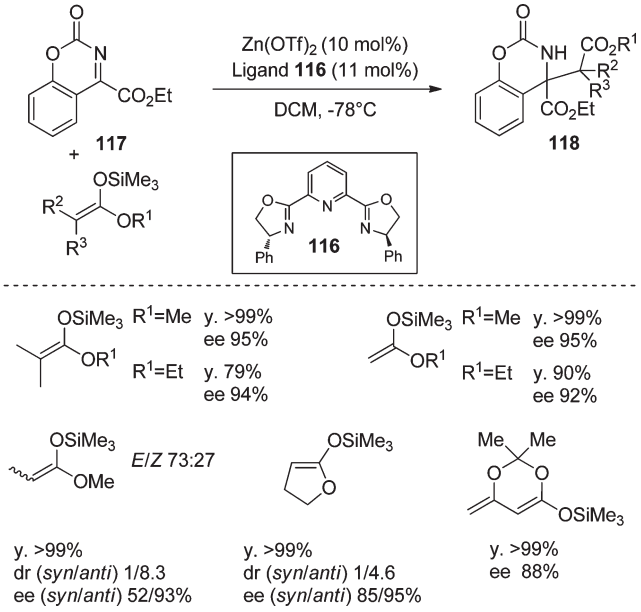
Scheme 45. Deprotection of Tertiary β-Amino Esters



β-amino esters **118** in high yield and excellent enantioselectivity (Scheme 46).[105]

NMR spectroscopic titration experiments suggested that the active catalyst species is a 1:1 Zn/pyBOX complex, which exists in equilibrium with the corresponding 1:2 Zn/pyBOX dimer. Additional support for this postulate came from the observation of a strong nonlinear effect between ligand and product ee. The relative amounts of these two species were found to be strongly dependent on the metal/ligand ratio as well as the presence of additives. Addition of 1 equiv of water with respect to zinc was found to stabilize the monomeric form such that it persisted even in the presence of more than 1 equiv of the ligand. These results

Scheme 46. Jørgensen's Zn-pyBOX-Catalyzed IMTR of Ketimino Esters



led the authors to conclude that the active catalyst species consists of a monomeric ligand/zinc aquo species.

Jørgensen has reported the IMTR of cyclic Danishefsky diene **119** with *N*-tosyl imino ester **41** catalyzed by $CuClO_4$/(*R*)-Tol-BINAP **50b** giving the adduct *anti*-**120** selectively. None of the corresponding aza-Diels−Alder product was obtained (Scheme 47).[45]

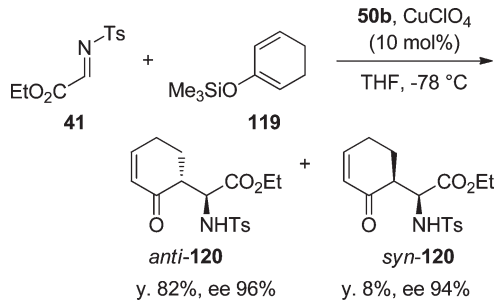
In other work by Kobayashi et al., metal−diamine ligand catalyst systems were developed that permit the addition of methyl and silyl enol ethers to *N*-acyl glyoxylate imines **121a**−**c** in good yield and stereoselectivity (Scheme 48).[106] In the first case, the nature of the *N*-acetyl side chain dictated the nature of the metal source and the conditions used: imines bearing methyl and long-chain alkyl groups **121a,b** required Cu(OTf)$_2$/diamine **122a** at 0 °C, whereas the more reactive *N*-benzoyl imine **121c** underwent smooth reaction even at −78 °C with a Cu(I)/phosphine catalyst.[107]

The corresponding reaction with readily removable *N*-protecting groups (Boc, Cbz, and Troc) was also reported by the same authors.[108] Although formally an IMTR, the mechanism of the reaction is thought to resemble a [4 + 2] cycloaddition: the Mannich adduct was not observed in the crude reaction mixture, and instead vinyl ether **125** and an unidentified product were detected prior to quenching the reaction. Hydrogen transfer within **125** was postulated to lead to compound **126**, which gave the final Mannich adduct **127** on hydrolysis. The synthetic utility of this approach was demonstrated by a short synthesis of HPA-12, **124**, and its analogues, which are thought to be involved in specific inhibition of sphingomyelin in mammalian cells.[109]

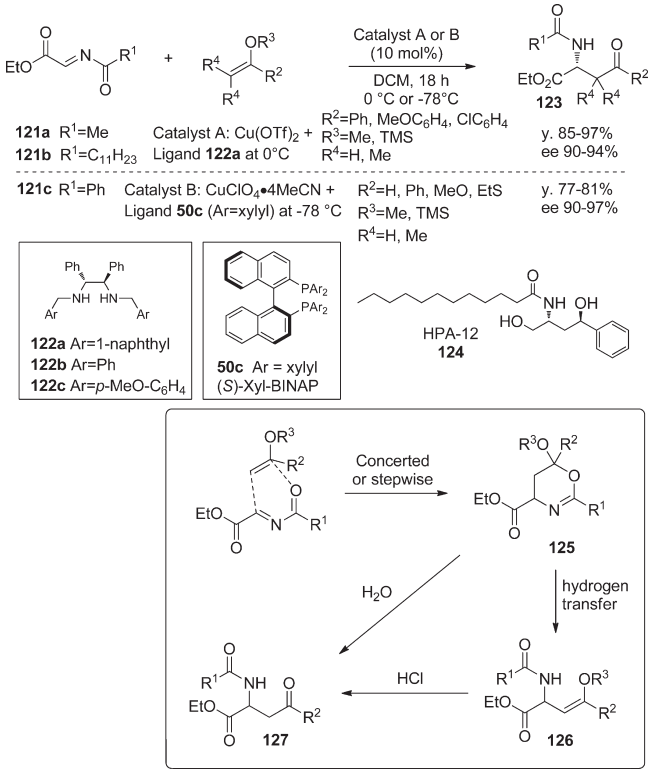
The same combination of Cu(OTf)$_2$ and diamine ligands **122a**−**c** were used to promote the addition of enamides **128** to several *N*-acyl imino esters **129** giving the corresponding β-amino imines **130**. Yields and enantioselectivities in the reaction were generally high to excellent except in the case of piperidino and morpholino enamines **131** and **132**, which delivered only racemic products. The resultant *N*-acyl imino esters could be further transformed either by hydrolysis to the corresponding ketones **133** or by reduction with LiAlH(O^{t}Bu)$_3$/LiI selectively

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 47. IMTR of with Cyclic Danishefsky Diene 119

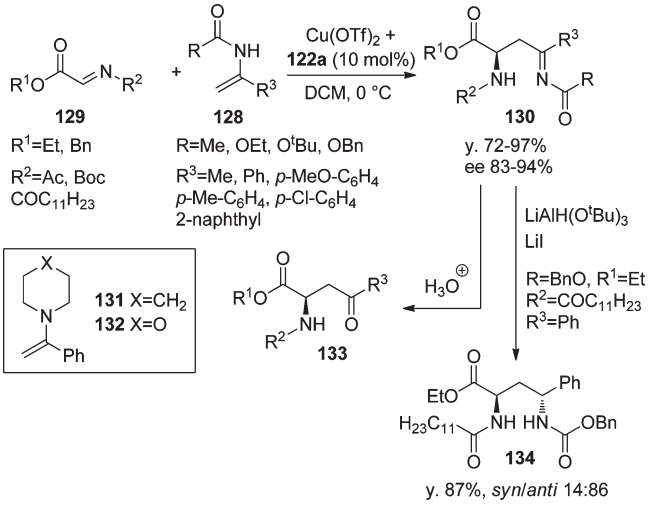


Scheme 48. Addition of Enol Ethers to Imines with Chiral Cu Catalysts



to the *anti* diamine **134** (Scheme 49).[110] The flexibility and synthetic utility of this methodology was further demonstrated by the report of the IMTR of simple enol silanes with *N*-Troc-α-iminophosphonates **135**.[111] A wide range of enol silanes of aryl methyl ketone added smoothly to the electrophile in the presence of 10 mol % of the catalyst formed from **122a** and $Cu(OTf)_2$ to give the desired adduct in good yield and excellent selectivity (Scheme 50). It was found that the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was important for efficient catalyst turnover: The authors proposed a bidentate coordination **137** of the phosphonyl imine, which undergoes nucleophilic attack by the silyl enol ether from an open transition state giving adduct **138** protonation/desilylation of which with HFIP liberates the product and returns the catalyst. In the absence of the additive, the reaction was very slow and *N*-silylated adduct **139** was obtained as the major product. The authors also described the use of their methodology to synthesize

Scheme 49. Catalytic Asymmetric IMTR of *N*-Acyl Enamines and α-Imino Esters



140 and **141**, phosphonyl analogues of kynurenine 3-hydroxylase inhibitors FCE 28833, **142**, and *m*-NBA, **143**, respectively.

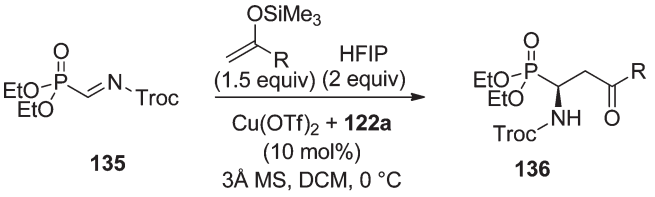
Shortly thereafter in related work, the same group introduced a method for the asymmetric catalytic indirect Mannich-type reaction of hydrazones in aqueous solvent systems.[112] The authors found that a combination of ZnF_2 and diamine ligand **122b** facilitated the addition of silyl enol ethers to (*E*)-ethyl 2-(2-(phenylcarbonyl)hydrazono)ethanoate **144** giving the desired adducts in moderate to good yield and with high to very high diastereo- and enantioselectivites. Unusually for a Lewis acid catalyzed process, water was not only tolerated but was found to be essential for efficient reaction. The authors also found that the addition of a small amount of triflic acid (1 mol %) led to dramatically improved yields. It is noteworthy that use of (*E*) or (*Z*) enol ethers gives stereospecifically the *syn* or *anti* product, respectively. The reaction is believed to proceed by dual Lewis acid (Zn^{2+})/Brønsted base (F^-) activation in which rapid catalytic turnover of the TMSF regenerates the ZnF_2 *in situ*. The pathway is not thought to involve a zinc enolate species (Scheme 51).

Acylation of the appropriate initial adduct followed by reduction and cleavage of the N−N bond with SmI_2 again gave ready access to **127**.

In contrast to the direct nitro-Mannich (aza-Henry) reaction, the corresponding *indirect* procedure involving the addition of preformed nitronates to imines is much less well-known. The first example of the catalytic asymmetric aza-Henry reaction of nitronates that did not require the addition of external base was described by Jørgensen in 2001.[113] Using a range of BOX-type ligands and Cu(I) or Cu(II) sources, they were able to catalyze the addition of silyl nitronates to a range of imino esters (PMP, Ph, Ts) in good to very high yield and up to >98% ee at −100 °C (Scheme 52). Very low reaction temperatures were necessary due to a rapid uncatalyzed background reaction that persisted even down to −78 °C. Having established the absolute configuration of the product obtained using (*R*)-Ph-Box as *R,R* (90% ee), the authors proposed a mechanism involving dual coordination of both the imino ester substrate and the nitronate followed by Lewis acid catalyzed loss of TMS from the latter to give a cyclic transition state **151** from which the addition proceeded to afford the observed product (*R*)-**150**. Anderson and co-workers have

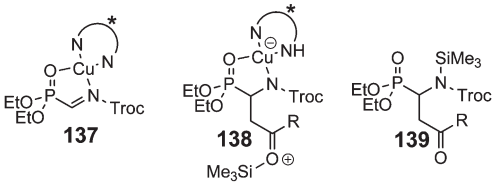
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

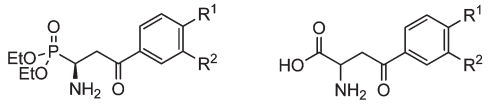
Scheme 50. Catalytic Asymmetric IMTR of *N*-Troc Phosphonyl Imines



R	y. (%)	ee (%)	R	y. (%)	ee (%)
Ph	86	91	*m,p*-Cl_2-C_6H_3	83	92
p-Me-C_6H_4	82	85	1-naphthyl	79	92
p-Cl-C_6H_4	71	91	2-naphthyl	84	87
p-Br-C_6H_4	86	86	*m*-NO_2-C_6H_4	88	94
p-I-C_6H_4	80	89	Me	70	89
p-MeO-C_6H_4	82	76	S^{t}Bu[a]	69	90

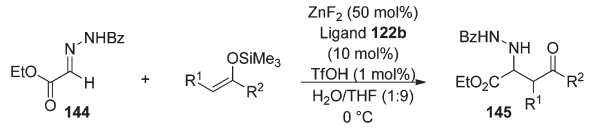
a) TES enol ether





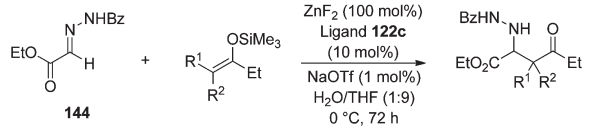
140 R^1=R^2=Cl ee >99%
141 R^1=H, R^2=NO_2 ee>99%
142 R^1=R^2=Cl FCE 28833
143 R^1=H, R^2=NO_2 *m*-NBA

Scheme 51. Addition of Enol Ethers to Hydrazones with Metal Diamine Catalysts



R^1=H, R^2=*p*-Me-C_6H_4
R^1=H, R^2=*p*-MeO-C_6H_4
R^1=H, R^2=*p*-Cl-C_6H_4
R^1=Me, R^2=Ph
R^1=Me, R^2=^{i}Pr

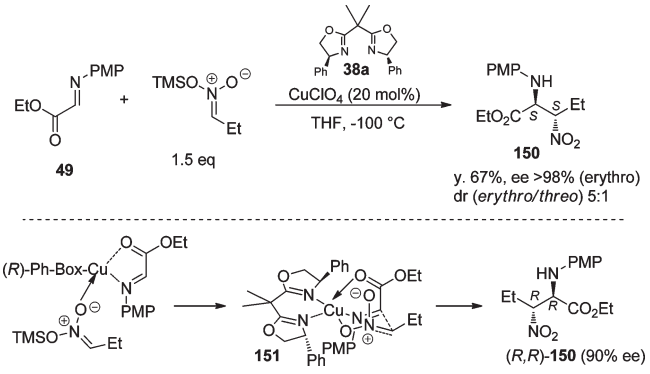
y. 30-91%
dr (*syn*/*anti*) 90/10-96/4
ee (*syn*) 88-91%



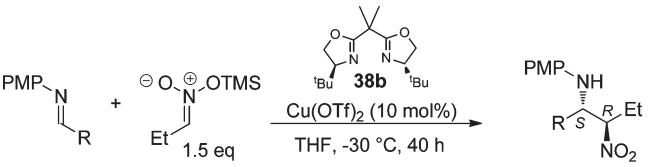
146 (*E*) R^1=H, R^2=Me *E*/*Z* 76:24
147 (Z) R^1=Me, R^2=H *E*/*Z* 1:99
148 y.98%, (*syn*/*anti*) 13:87, ee 88/91
149 y. 65%, (*syn*/*anti*) 77:23, ee 86/81

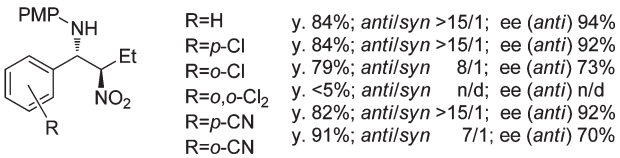
also examined the reaction with *N*-PMP imines using a similar but subtly different combination of (*S*,*S*)-*tert*-butyl-Box **38b** with $Cu(OTf)_2$ as the Lewis acidic source.[114] Using this system, they achieved generally very good yields and selectivities in the reaction with aldimines, but the corresponding reaction with ketimines proceeded hardly at all. An attractive point of this method is the relatively low catalyst loading (10 mol %) and more amenable temperatures (−30 °C) (Scheme 53).

Scheme 52. Catalytic Asymmetric Addition of Nitronates to Imines with Cu(I) Catalysts

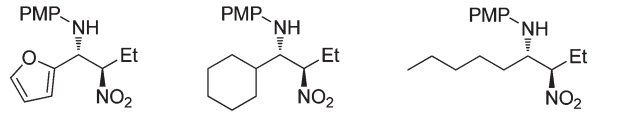


Scheme 53. Catalytic Asymmetric Addition of Nitronates to Imines with Cu(II) Catalysts





R=H	y. 84%; *anti*/*syn* >15/1; ee (*anti*) 94%
R=*p*-Cl	y. 84%; *anti*/*syn* >15/1; ee (*anti*) 92%
R=*o*-Cl	y. 79%; *anti*/*syn* 8/1; ee (*anti*) 73%
R=*o*,*o*-Cl_2	y. <5%; *anti*/*syn* n/d; ee (*anti*) n/d
R=*p*-CN	y. 82%; *anti*/*syn* >15/1; ee (*anti*) 92%
R=*o*-CN	y. 91%; *anti*/*syn* 7/1; ee (*anti*) 70%



y. 89%
anti/*syn* 11/1
ee (*anti*) 94%

y. 88%
anti/*syn* >15/1
ee (*anti*) 87%

y. 88%
anti/*syn* 1/1
ee (*anti*) 86%

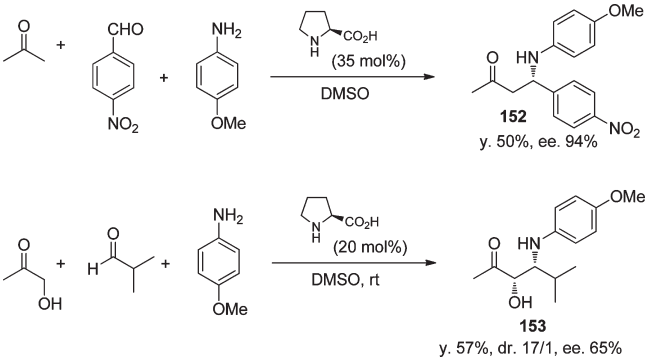
3.3. Mannich and Aza-Henry-type Reactions Mediated by Organocatalysts

The field of organocatalysis is currently one of the fastest growing areas of organic synthesis and is one that extends its tendrils into almost every aspect of our science.[115−117] Although dating as far back as the era of Liebig, the concept was formally mooted in the 1920s by Langenbeck who described "organic catalysis" and was then reintroduced under its current moniker by MacMillan and others in 2000. For the purposes of this review, a distinction will be drawn depending on the catalyst structure: proline derivatives, chiral Brønsted acids, chiral thioureas, and cinchona alkaloids.

3.3.1. Reactions Mediated by Proline Derivatives. Although the catalysis of the direct asymmetric aldol reactions[118,119] by proline was a well-established process, its use in the analogous direct Mannich-type reaction leading to the formation of β-amino ketones with excellent enantioselectivity was first reported by List in the year 2000 (Scheme 54).[120,121] Although yields were only moderate and catalyst loading was high (35 mol %), the reaction could be made to operate with both aromatic and

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 54. Organocatalytic Asymmetric DMTR under Proline Catalysis



aliphatic aldehydes and unsubstituted as well as α-hydroxy ketones. The proposed mechanism of the reaction involved the intermediacy of an enamine generated in equilibrium with the iminium species formed from the condensation of the proline with the more reactive aldehyde partner (Figure 11). Although in the original paper, the authors proposed the interaction of a *Z*-imine to explain the strong *syn* preference of the reaction, this was later modified[122] to the *E*-imine shown and contrasted with the proposed transition state for the corresponding aldol reaction. Although the intermediacy of the enamine **156** forms part of the generally accepted mechanism for proline-catalyzed reactions, this has been challenged by Seebach, who provided strong evidence for the involvement of the oxazolidinone **157** as an important intermediate in the reaction,[123] and further computational studies, which are in agreement with some observed results, have been reported.[124]

The initial report by List was followed by a flurry of publications by Barbas,[125] List,[115h−j,126] Jørgensen,[115f,127] Córdova,[128] and Hayashi[129] all of whom reported important developments in substrate scope and catalyst structure. Given the rapidly developing nature of the field, it is unsurprising that organocatalysis has been the subject of numerous reviews and highlight articles. Organocatalyzed addition of nucleophiles to the C═N functionality has, in the years since our preceding review, been a subject discussed within other work in 2004,[130] and asymmetric organocatalyzed Mannich reactions were summarized in a *Tutorial Review*, which appeared in late 2007.[131] With Buckley[132] along with Zu and Lu[133] providing preceding summaries detailing current advances and a range of excellent examples appearing during the preparation of this manuscript,[134] the most salient and pertinent reports are detailed to provide perspective.

As outlined above, the proline-catalyzed asymmetric DMTR is a convenient and flexible route to a wide range of *β*-amino carbonyl compounds, which are generated in good yield and excellent enantioselectivity as overwhelmingly the *syn* diastereomer. Although Barbas and Córdova had previously demonstrated that (*S*)-methoxymethylpyrrolidine (SMP) could be used to obtain the relevant *anti* system with good diastereoselectivity in the reaction of aldehydes with α-imino esters (Scheme 55), yields and enantioselectivities were moderate and reliable methods for the synthesis of the corresponding *anti* diastereomer with high enantioselectivity remained a problem. Elegant solutions to this problem have been reported by the groups of Maruoka[135] and Barbas.[136] Employing protected prolinols as catalysts, first reported by Karlsson and Högberg,[137] is reasoned to inhibit the

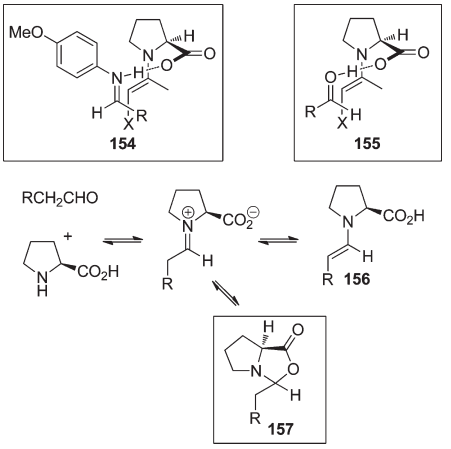
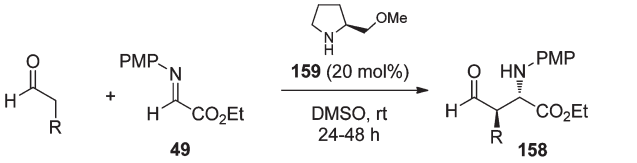


Figure 11. Proposed transition states for the organocatalytic DMTR **154** and aldol **155** reaction.

Scheme 55. *anti*-Selective Organocatalytic Asymmetric DMTR



formation of unreactive hemiaminal intermediates (discussed later, Figure 14).

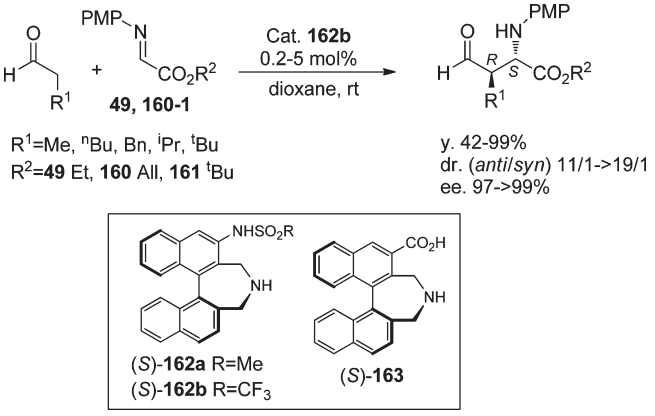
In the first of these, Maruoka and co-workers employed their axially chiral amine system originally designed as catalysts for the direct asymmetric aldol reaction[138] in the addition of aldehydes to preformed α-imino ester **49**, **160-1** (Scheme 56). Acetaldehyde was utilized as a highly effective nucleophile in a closely related reaction, catalyzed by **162b** in a following report.[139]

The highest diastereoselectivities were obtained using trifluoromethanesulfonamide catalyst **162b**, which gave far better yields than **162a** and better diastereomeric ratios than catalyst **163** [R^1 = ^{i}Pr, R^2 = Et, **162b** (*anti*/*syn*) >20/1 versus **163** (*anti*/*syn*) 1/1.1]. This was rationalized by considering that in the case of **162b** stronger H-bonding between the imine and the trifluoromethanesulfonamide side group permits only the *syn*-enamine arrangement leading to the generation of *anti*-addition products, whereas the comparatively weaker H-bond between the imine and remote carboxylic acid permits both the *syn* and *anti* enamine arrangements with concomitant loss of diastereoselectivity (Figure 12).

By contrast, Barbas et al. postulated that the *syn* selectivity of proline-catalyzed systems lay in the steric biasing of intermediate enamine **156** into the *S-trans* conformation, leading to reaction at the *re* face of the enamine giving the *cis* addition product, due to interactions between the enamine hydrogen and the proline acid group that disfavor the *S-cis* arrangement (Figure 13, left side).[136] They reasoned that a designed catalyst giving an enamine such as **164** in which a blocking group has been introduced at the 5-position of the pyrrolidine ring and the acid group moved to

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 56. *anti*-Selective Asymmetric Organocatalyzed DMTR



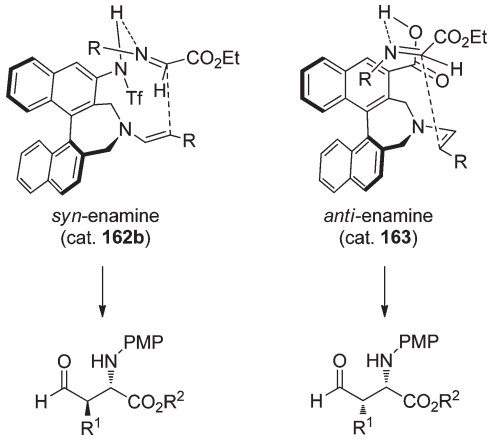


Figure 12. Proposed transition state for Maruoka's *anti*-selective organocatalytic DMTR.

the 3-position should lead to the reaction again on the *re*-face of the enamine but proceeding by a different *S-trans* conformation, this time giving the *anti*-addition product (Figure 13, right side).

The required catalyst was synthesized in six steps from (*R*)-4-hydroxyl-L-proline and used in the reaction of α-imino ester **49**, **165**, or **166** and unmodified aldehydes affording the required addition products in good to excellent yield and excellent diastereo- and enantioselectivity (Scheme 57). Computational studies carried out to estimate the relative contributions to the *anti*-selectivity of the 5-methyl and 3-carboxylic acid group indicated that the methyl group contributed about 1 kcal mol^{-1} toward *anti*-diastereoselectivity. Although this route provided an ingenious solution to the problem of *anti*-selectivity of reaction involving aldehyde donors, the analogous reactions with ketones were extremely slow. This obstacle was overcome by using the less sterically hindered 5-desmethyl derivative **168**, which efficiently catalyzed the reaction of α-imino esters with a range of linear and cyclic ketones in protic solvent medium (Scheme 58).[140]

Proline-catalyzed Mannich reactions to *N*-Boc-imine electrophiles have been exploited by a number of researchers including Enders,[141] List,[142] and Córdova,[143] the latter of whom used this methodology to synthesize the side chain of Taxotere.[144] Utilization of dihydroxyacetone derivatives as nucleophiles in proline-catalyzed Mannich reactions facilitates highly selective delivery of a functional

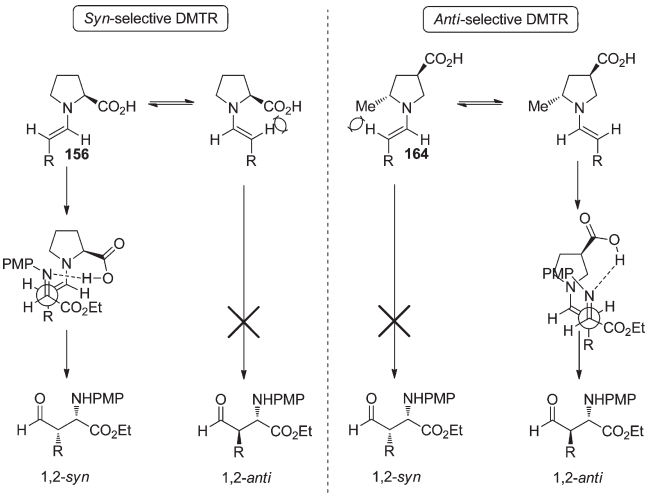


Figure 13. Conformations in the Barbas *anti*-selective organocatalytic asymmetric DMTR.

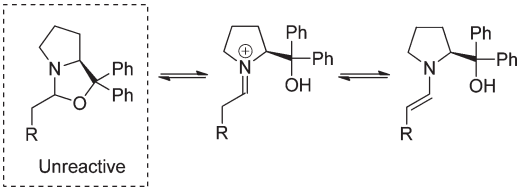


Figure 14. Formation of unreactive hemiaminal species.

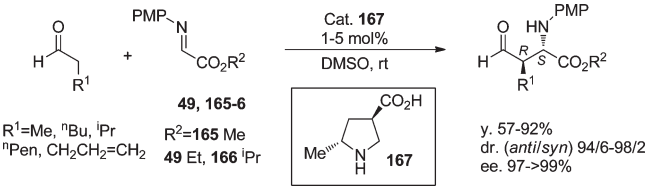
C_3 unit for further elaboration toward complex sugar motifs. Among the pioneers in this field the work of Westermann,[145] Barbas,[146] Córdova,[147] and Enders[148] stands out; imino sugars were also directly available.[149]

The theme of modifying the proline motif to provide second generation amino-organocatalysts has been an important development in organocatalysis. Although the original proline system afforded addition products with excellent yields and selectivities, the low solubility of the catalyst necessitated the use of very polar or protic solvents such as DMSO or ^{i}PrOH, which are difficult to remove and may be incompatible with some functionalities. A partial solution to this was put forward by Barbas et al. who investigated the effect of solvent on the organocatalytic DMTR using ketone donors and found that running the reaction in an ionic liquid ([bmim]BF_4) gave improved yields with lower (5 mol %) catalyst loadings. Furthermore in the reaction with cyclohexanone the catalyst/ionic liquid solution could be recovered and reused up to 4 times with only a small drop in yield and no effect on selectivity (Scheme 59).[150]

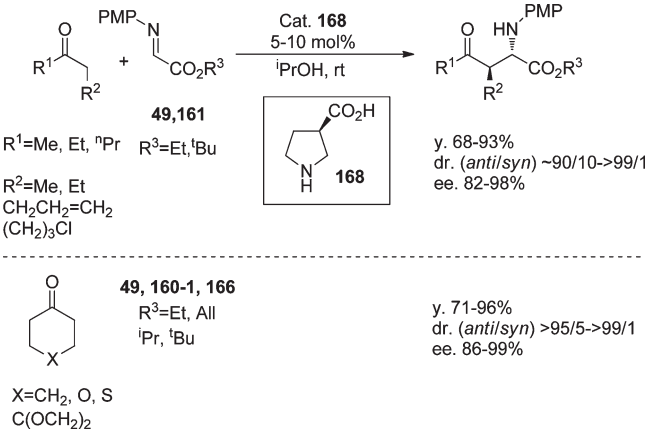
In an effort to address this, the groups of Ley[151] and Wang[152] have introduced a series of *N*-sulfonyl triflamides **169a**−**c** as new proline-derived organocatalysts with superior solubility in organic solvents for asymmetric catalytic DMTR with unmodified ketone donors. Very high yields and stereoselectivities were maintained across a wide range of organic solvents (DMSO, $CHCl_3$, DMF, THF, MeCN, EtOAc, $MeNO_2$, dioxane) in a *syn* selective reaction. These developments came hot on the heels of 5-pyrrolidin-2-yltetrazole **170** of Ley et al.,[153] which was introduced as a highly effective proline substitute that may be used for organocatalytic ketone-donor DMTR in nonpolar organic solvents with no loss of enantioselectivity (Scheme 60). A number

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 57. Barbas' *anti*-Selective Organocatalytic DMTR



Scheme 58. *Anti*-Selective Organocatalytic DMTR with Ketone Donors

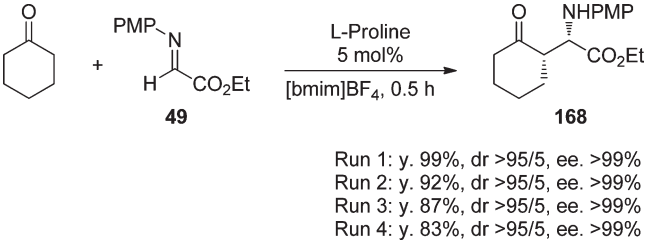


of linear and cyclic ketones were tested in the reaction using common laboratory less-polar solvents (e.g., THF, MeCN, DCM) giving the *syn*-products in good yield and excellent enantio- and diastereoselectivity. Proline was not effective under the same conditions. The authors proposed an intimately bonded chairlike transition state **171** to explain the observed high enantio- and diastereoselectivities.

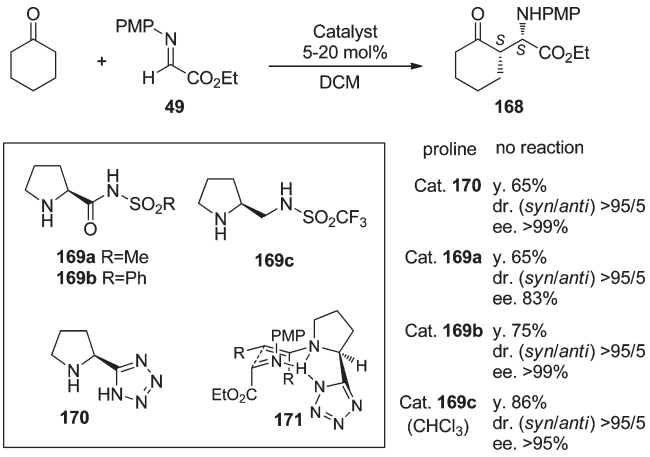
The Ley tetrazole has been employed in the three-component asymmetric organocatalytic DMTR of α-amino and α-azido ketones with activated imines (Scheme 61).[154] The authors noted a dependence of regiochemistry on the nature of the α-nitrogen substituent where in the presence of **170** in DMSO, α-azido methyl ketone **172** underwent addition on the same carbon as the azide giving the *syn*-α-azido-*β*-amine **173**, whereas the corresponding α-phthimidoacetone reacted via the methyl group α to the ketone giving the *β*-amine **174** with complete regioselectivity. The same tetrazole was one of a number of compounds **170** and **175**−**177** that were examined by Córdova et al. as catalysts for their three-component ketone α-aminomethylation protocol using formaldehyde as the iminium carbonyl precursor (Scheme 62).[155] In comparison to the parent proline, the derived catalysts all performed poorly in terms of enantioselectivity under the conditions applied, although no results of reactions carried out in solvents known to be optimal for second generation proline catalysts were disclosed. The proline-catalyzed reaction, however, displayed a wide substrate scope with both linear and cyclic ketones undergoing the reaction smoothly to give the corresponding aminomethylation products in high yield and excellent enantiomeric excess, consistent with results obtained in their earlier studies on the three-component cross-Mannich reaction.[12,128]

Mauksch et al. first commented on an intriguing phenomenon,[156] which was later investigated by Amedjkouh and Brandberg wherein

Scheme 59. Organocatalyzed DMTR in [bmim]BF_4



Scheme 60. Organocatalytic DMTR Catalyzed by Proline Derivatives



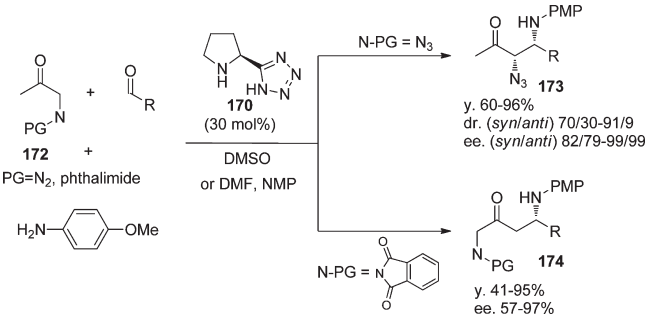
an intriguing variation of the reaction that furnishes compound **168** in excellent ee and yield was investigated, providing strong evidence for an autocatalytic process.[157]

The α-aminomethylation of aldehydes was independently reported by Chi and Gellman[158] and Córdova and co-workers,[159] in which chiral amine catalyzed reactions between aldehydes and a formaldehyde-derived imine precursor proceeded with high chemo- and enantioselectivity (up to 98% ee after *in situ* reduction).

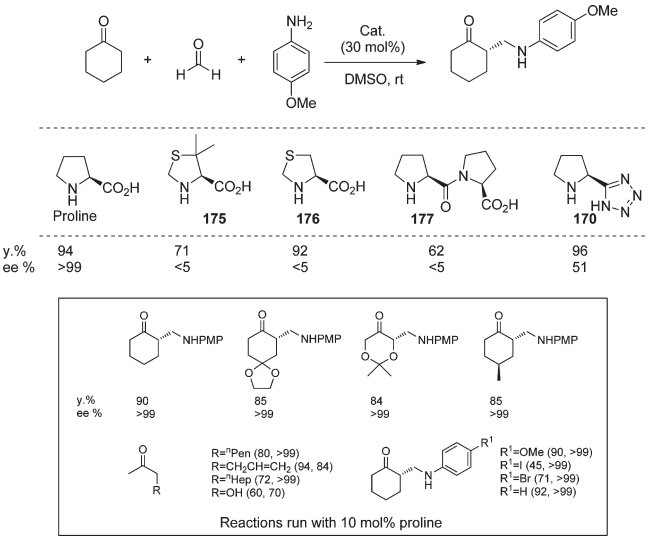
Hayashi and co-workers have also studied the proline-catalyzed cross-Mannich reactions of aldehydes (Scheme 63) and in particular the observation that that the cross-Mannich of two different aldehydes in the presence of *p*-anisidine proceeds at temperatures as low as −20 °C whereas the analogous aldol reaction requires a minimum temperature of 4 °C. Competition experiments led the authors to conclude that aldimines are approximately 7 times more reactive in the Mannich reaction than aldehydes in the corresponding direct aldol reaction.[160] Calculations indicated that the higher relative reactivity of aldimines is determined by the highly asynchronous transfer of the proline carboxylic acid proton and C−C bond formation, which activates the electrophile more efficiently than in the aldol reaction where proton transfer and new C−C bond formation are almost simultaneous. The authors also noted that use of water freezing techniques were found to permit the use of substrates not normally applicable to the cross-Mannich reaction. The same group also demonstrated the synthetic utility of their methodology with formal total syntheses of nikkomycins B and B_x.[161]

Linear α- or *β*-amino acids and their derivatives have been investigated as organocatalysts in the three-component DMTR by

Scheme 61. Dependence of Regiochemistry on Protecting Group in the Organocatalytic DMTR



Scheme 62. Catalysts in the α-Aminomethylation of Ketones

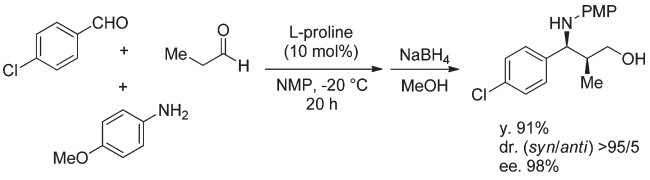


the groups of Córdova and Cheng.[162−165] Use of common amino acids serine, leucine, isoleucine, phenylalanine, valine, and aspartate in the coupling of cyclohexanone with *p*-nitrobenzaldehyde and *p*-anisidine gave the desired *S,S-syn* adduct in moderate yield and moderate to high enantio- and diastereomeric excess.

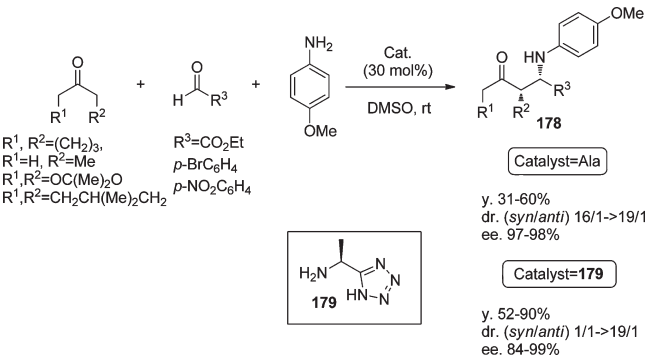
The authors found that alanine and its tetrazole derivative **179** gave best results in the three-component reaction of *p*-anisidine with a wide range of ketones and aldehyde coupling partners (Scheme 64). Although proline exhibits reactivity and generality that has led to its being defined as a "universal catalyst" its reliance on strong H-bonds to activate both the aldehyde nucleophile and the electrophile,[166] delivering high enantioselectivities, has limited its use to those substrates capable of forming such interactions. In an effort to overcome this problem and broaden still further the substrate scope in the reaction, Jørgensen and co-workers examined bulky bisphenylprolinol derivatives[167] **180a−c** as catalysts (Scheme 65).[168] In their studies, they opted to protect the prolinol hydroxyl group as its TMS ether in order to shut down the formation of the unreactive hemiaminal in the proposed catalytic cycle (Figure 14).

Of the catalysts examined, the bis-(3,5-bis(trifluoromethyl) phenyl) substituted system gave the best results, supplying the desired adducts in good yield and excellent enantioselectivities. Significantly, the products were obtained preferentially as the *anti*

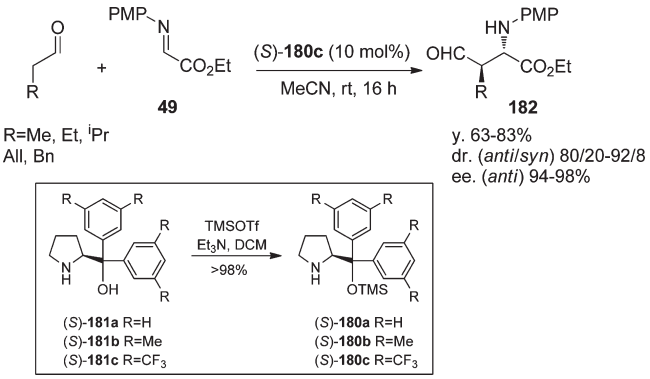
Scheme 63. The Proline-Catalyzed Cross-DMTR with Aromatic and Aliphatic Aldehydes



Scheme 64. Linear Amino Acid Derivatives As Organocatalysts in the DMTR



Scheme 65. Bulky *O*-TMS Prolinol-Derived Organocatalysts in the Asymmetric DMTR

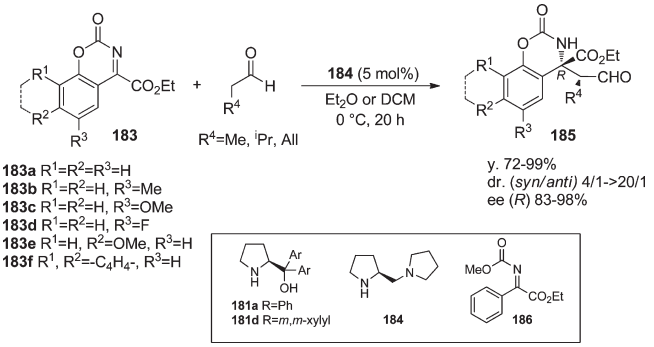


form with moderate to high diastereoselectivity and with the opposite diastereoisomer that was obtained with simple proline. More recently Córdova widened the substrate scope and reported improved diastereo- and enantioselectivity under slightly modified conditions.[169]

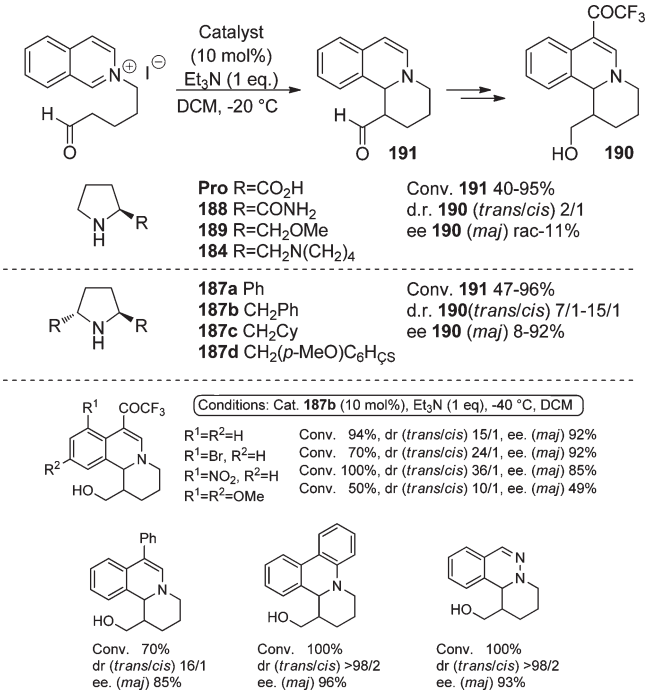
Jørgensen and co-workers made use of modified proline derivatives in carrying out the first organocatalytic asymmetric DMTR to ketoimines **183**.[170] Screening of a number of promoters, **181a,d** in addition to proline and proline methyl ester, identified bispyrrolidine **184** as being the catalyst of choice. A range of substituents on the ketoimine aromatic ring were tolerated including electron-withdrawing (*p*-F) and donating groups (*p*-OMe), and the desired products were obtained in excellent yield and stereoselectivity. Significantly, the reaction with the corresponding untethered *N*-carbamate ketoimine **186** did not proceed under the same conditions (Scheme 66).

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 66. Organocatalytic DMTR of *N*-Carbamoyl Ketoimines



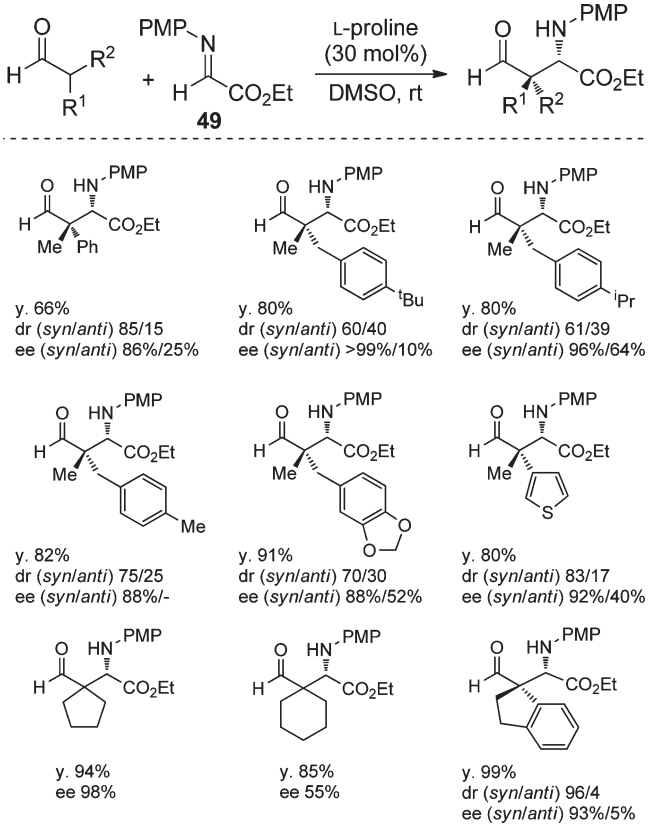
Scheme 67. Organocatalyzed Asymmetric Direct Mannich-type Annulations



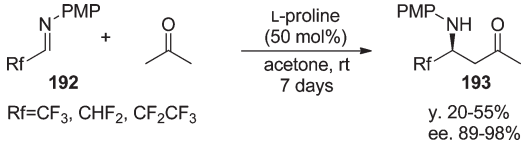
The same group also examined ligand **181a** as a potential catalyst for direct Mannich-type annulations.[127] In this case however, it was ineffective, as were a number of related proline-derived species. However, structurally related C_2-symmetric systems gave good results with 2*S*,5*S*-2,5-dibenzyl pyrrolidine **187b** being the catalyst of choice giving the desired annulated product in good yield and high diastereo- and enantioselectivity. Instability of the initial annulated product necessitated a derivatization sequence that gave the corresponding trifluoroacetylated alcohols **190**, which were sufficiently stable to allow full characterization (Scheme 67). While the preformation of trigonally protected imines provides access to versatile and often orthogonally protected products their synthesis can often be nontrivial. In this connection, Gianelli et al. found that *in situ* generation of the imine by an elimination protocol was effective.[171]

In addition to modifications of catalyst structure, a number of important developments in substrate scope of the organocatalytic

Scheme 68. Organocatalytic DMTR with Branched Aldehyde Donors



Scheme 69. Use of Fluorinated Imines in the Organocatalytic DMTR



asymmetric DMTR have been reported. Barbas et al. demonstrated the utility of branched aldehyde donors in the reaction catalyzed by proline, leading to the rapid and efficient generation of a range of molecules containing quaternary carbon centers (Scheme 68).[172]

The organocatalyzed DMTR of fluoroalkyl *N*-PMP imines **192** with acetone, affording synthetically important α-fluorinated amines **193**, has also been demonstrated (Scheme 69).[173]

Jiang et al. discovered that proline derivative catalyzed reactions could be assisted by the addition of chiral Brønsted acids .[174] Other variations include choice of solvent such as ionic liquids employed by Liu et al. with good effect.[175,176]

3.3.2. Catalytic Asymmetric DMTR Mediated by Chiral Brønsted Acids. The development of chiral highly active Brønsted acids[177] is a rapidly growing area in organocatalysis.[178] Some of the most effective examples are those derived from phosphoric acid/BINOL esters[179] **194a**−**e** and **195a**−**c** (Figure 15) or phosphoric acid/BINAL amides **196**. These possess both Brønsted acidic and Lewis basic sites and are thought to form

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

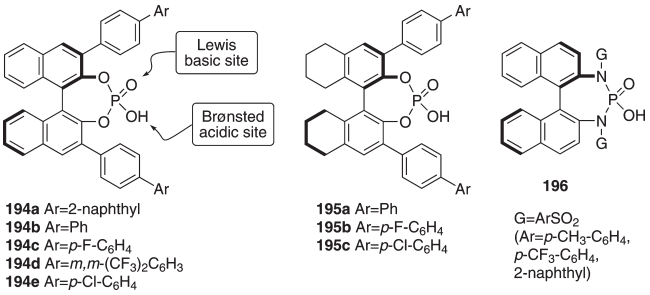
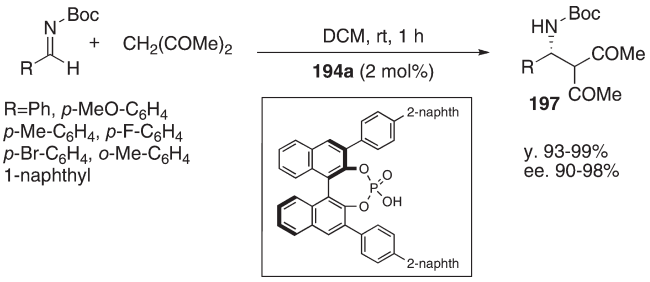


Figure 15. Chiral phosphoric acid and phosphoramide Brønsted acid catalysts.

Scheme 70. Terada's Chiral Brønsted Acid Catalyzed Asymmetric DMTR



strong H-bonds with the electrophile, which serves the dual purpose of activating the electrophile and fixing it within the chiral pocket formed by the binaphthyl ligand.[180]

In this context, Terada has used highly hindered phosphoric acids of type **194** to promote the addition of acetylacetone to aromatic *N*-Boc imines, giving the β-amino diketone product in excellent yield and enantiomeric excess (Scheme 70).[181] Four chiral phosphoric acids were examined in the reaction with best results being obtained with that bearing very bulky 4-(β-naphthyl)phenyl side groups. The reaction could be scaled up to 1 g and catalyst loading could be cut to 1 mol % giving the product (R^1 = Ph) in 94% yield although the reaction time was doubled. The authors reported efficient recovery of the catalyst (>80%). Following this, they described computational (B3LYP/6-31g(d,p) level) and NMR studies aimed at elucidating the nature of the transition state.[182] The authors examined transition states for the interaction of both *cis* and *trans* **11** (R^1 = Ph) and the chiral phosphoric acid **194b** (Ar = Ph). Their results indicated that the stereoselectivity of the reaction originated from a transition state alignment in which hydrogen bonding of the P(O)OH moiety to the imine nitrogen holds the latter in a chiral pocket in which one face is strongly shielded by the biphenyl side group (Figure 16). The bulk of the *N*-protecting group was found to be crucial for restricting rotation about the H-bond with nitrogen, less bulky groups than *tert*-butyl giving lower selectivity. Use of related phosphorodiamidic acids **196** in the reaction gave high yields but much lower levels of selectivity.[183]

The same group used this class of catalyst to promote the Mannich-type reaction between preformed imines and enecarbamates in an organocatalytic process complementary to the metal-mediated protocol introduced by Kobayashi.[110,184] In this case, the 9-anthracyl version, **194f**, of the catalyst proved to be most efficacious, delivering the desired addition products **198** of a range of *N*-carbamoyl enamines **126a**−**d** to *N*-benzoyl imines **199** ,which

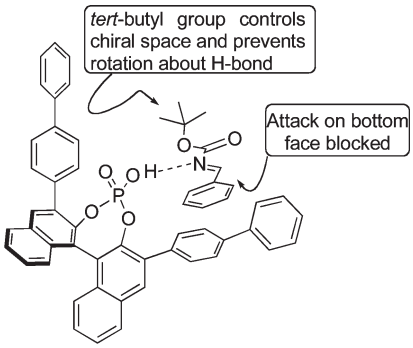
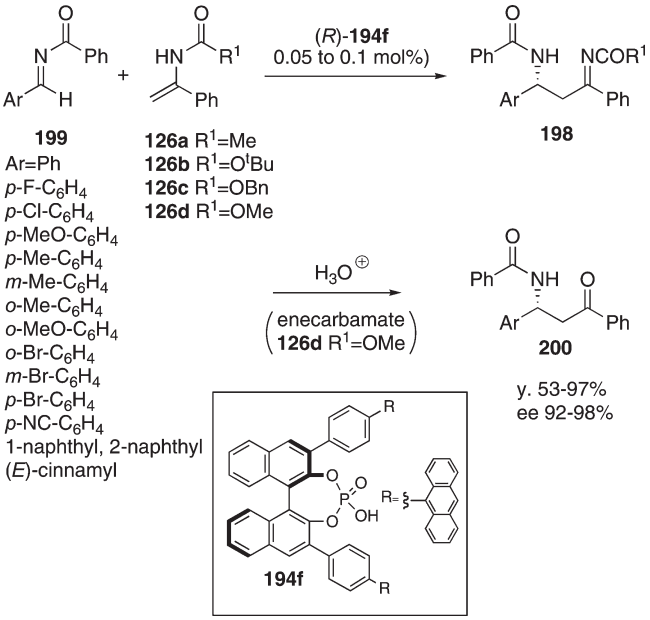


Figure 16. Postulated transition state for DMTR with chiral phosphoric acids.

Scheme 71. Catalytic Enantioselective Mannich Addition of Enecarbamates to Imines Promoted by Chiral Phosphoric Acids

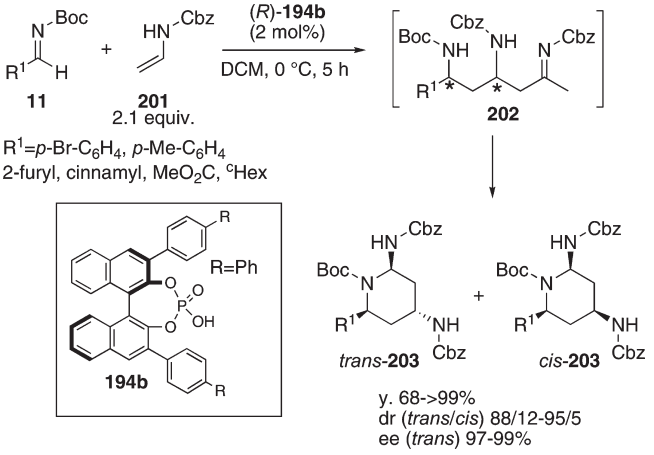


were subjected to hydrolysis to give the corresponding ketones **200** in 53−97% yield and excellent enantiomeric excesses (92−98% ee) at very high S/C (substrate to catalyst) ratios (up to 2000:1) (Scheme 71).[185]

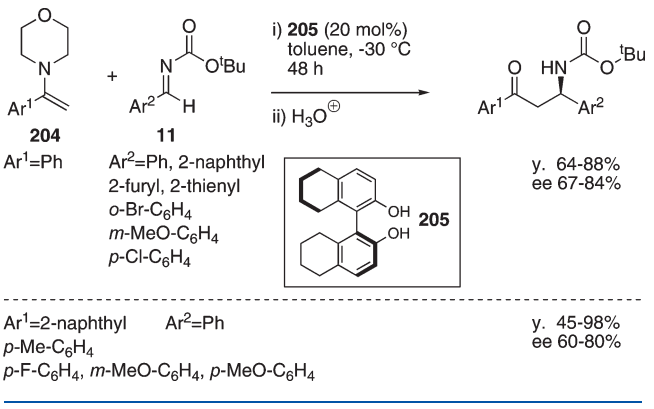
Terada and co-workers reported a method for the synthesis of enantioenriched piperidines via the chiral phosphoric acid-catalyst Mannich reaction of α-unsubstituted *N*-Cbz enecarbamates and *N*-Boc imines (Scheme 72).[186] The propensity of these systems to undergo multiple additions of the enecarbamate has limited their use in synthesis; however by judicious choice of catalyst (phosphoric acid **194b**) and conditions, Terada effected the addition of 2 equiv of the *N*-Cbz enamine **201** with excellent stereocontrol to form tandem adduct **202**, which underwent spontaneous cyclization to the piperidine products *trans*-**203** and *cis*-**203**. Only two of the possible four diastereomers were produced with the *trans*-isomer being strongly favored with the ratio being decided by substrate control rather than by the catalyst. Other related catalysts [**194f**, **194g** (R = H), and **194h** (R = *m*,*m*-$Ph_2C_6H_3$)] also promoted the reaction in similar excellent yield and enantioselectivities but with slightly inferior

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 72. Synthesis of Enantioenriched Piperidines by Organocatalyzed Mannich Reaction of Primary *N*-Cbz Enamide and *N*-Boc Imines



Scheme 73. Dixon's H_8-BINOL-Mediated Mannich Reaction of Enamines and *N*-Carbamoyl Imines

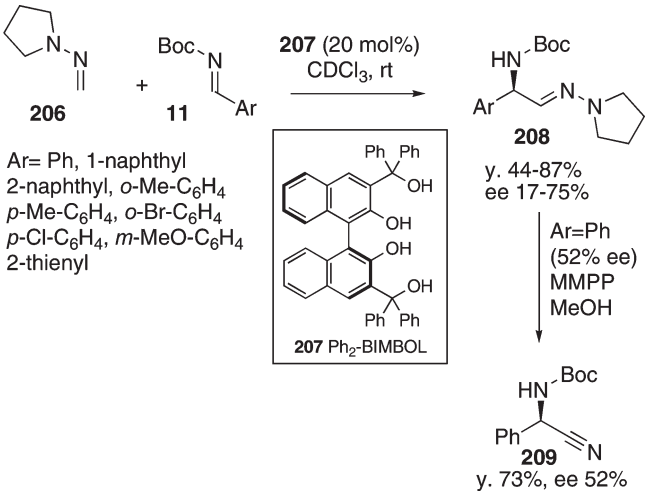


diastereoselectivities. Derivatives of **201** could be used as electrophile precursors (similar to asymmetric copper-catalyzed reactions of Kobayashi and co-workers[187]) for reaction with 2,4-pentanedione with moderate ee.[188]

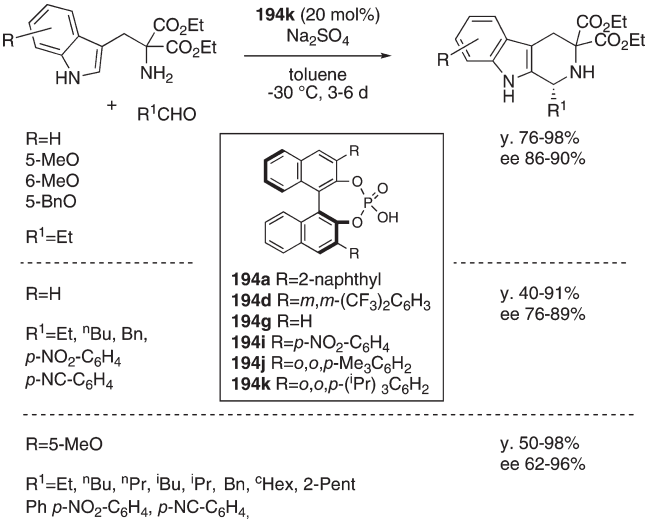
A related organocatalytic procedure, although not one involving phosphoric acids, has been introduced by Dixon et al. They used simple BINOL catalysts to promote the addition of enamines with *N*-carbamoyl imines **11** facilitating rapid access to the *N*-protected β-amino ketones in fair to good yield and reasonable enantioselectivity (Scheme 73). From the wide range of catalysts surveyed, commercially available H_8-BINOL **205** was found to be the most active although 20 mol % catalyst loadings were required for efficient reaction.[189]

The report followed on from the same group's discovery that methyleneaminopyrrolidine **206** can be used as a nucleophile for Mannich additions to *N*-Boc arylamines in the presence of binaphthol-type catalysts of which 3,3′-bis(diphenylmethanol)-2,2′-binaphthol (Ph_2-BIMBOL) **207** was found to be the most active. Application of this system gave the corresponding (*R*)-α-amino hydrazones **208** in fair to good yield and moderate enantioselectivities, which could be converted in one step to the Strecker-type products **209** (Scheme 74).[190]

Scheme 74. Mannich-type Addition of Methyleneaminopyrrolidine to Imines



Scheme 75. Asymmetric Catalytic Pictet–Spengler Reaction Promoted by Chiral Phosphoric Acids

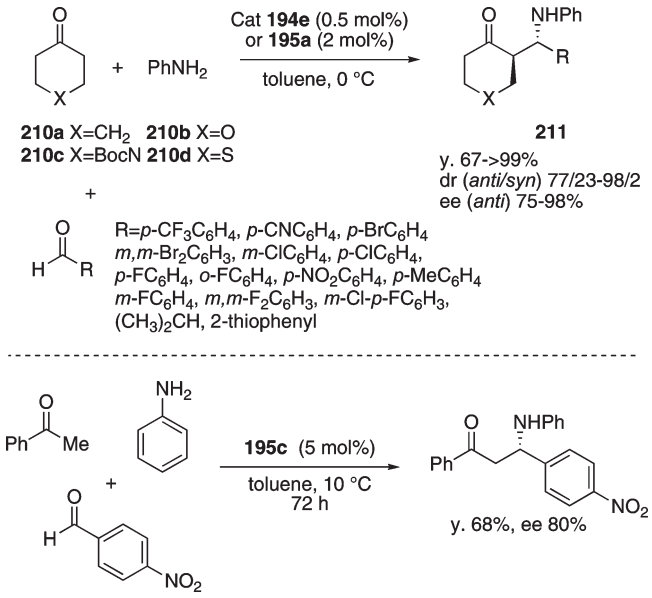


An elegant variation of the chiral phosphoric acid-catalyzed Mannich addition has been reported by List and co-workers in the guise of a two-component catalytic asymmetric Pictet–Spengler reaction. They screened a range of 3,3′-disubstituted BINOL phosphoric acids **194** before selecting **194k** as the favored catalyst. Exposure of a range of substituted *gem*-diester indole precursors to aliphatic and aromatic aldehydes to 20 mol % of the catalyst under dehydrating conditions (Na_2SO_4) afforded the desired tricyclic addition products in generally good yield in up to 96% ee (Scheme 75).[191]

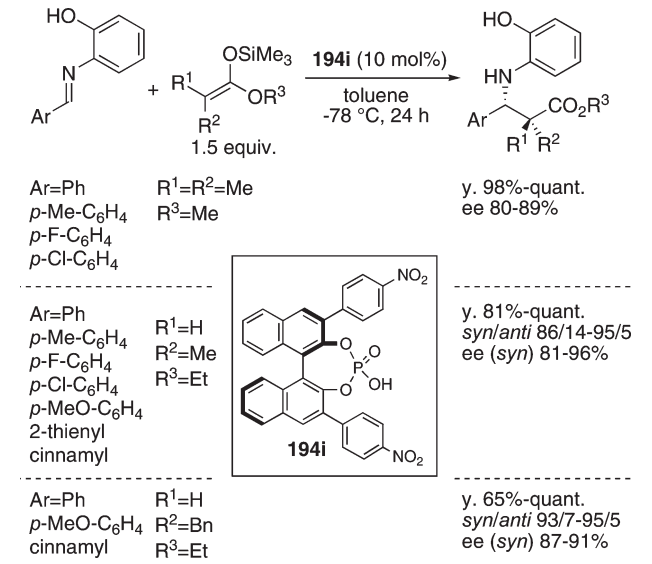
Gong et al. described a three-component catalytic asymmetric DMTR between ketones **210**, anilines, and electron-poor aldehydes under the influence of a range of chiral phosphoric acids **194a–e** and **195a–c** (Scheme 76).[180] Most effective catalysis was observed with the use of **194b** and cyclohexylbiphenyl **195a** although higher loading was required in the case of the latter. Linear aliphatic and aromatic ketones were also amenable to the reaction, in what was the first reported organocatalytic DMTR

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 76. Three-Component DMTRs Catalyzed by Chiral Phosphoric Acids



Scheme 77. Organocatalyzed IMTR Promoted by Chiral Phosphoric Acid 194i



with aromatic ketone donors, although this required the use of more forcing conditions and higher loadings.

Novel organocatalyzed approaches to the IMTR have also been reported. Akiyama and co-workers have described a highly stereoselective procedure for the addition of silyl ketene acetals to *N*-(*ortho*-hydroxy)phenyl imines catalyzed by 3,3′-bis(*para*-nitro)phenyl-2,2′-binaphthol phosphoric acid **194i**. Both the enantioselective and diastereoselective reaction proceeded in high to quantitative yield and with high to very high selectivity (Scheme 77).[192] The presence both of the *ortho*-hydroxy group on the imine nitrogen aryl substituent and the NO_2 substituent in the catalyst were required for high selectivities, leading the authors to postulate that the stereoselection in the reaction arises

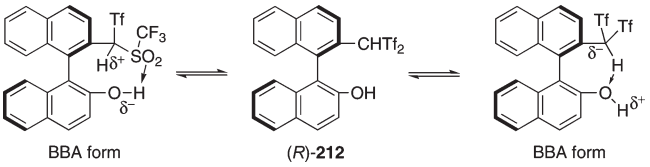
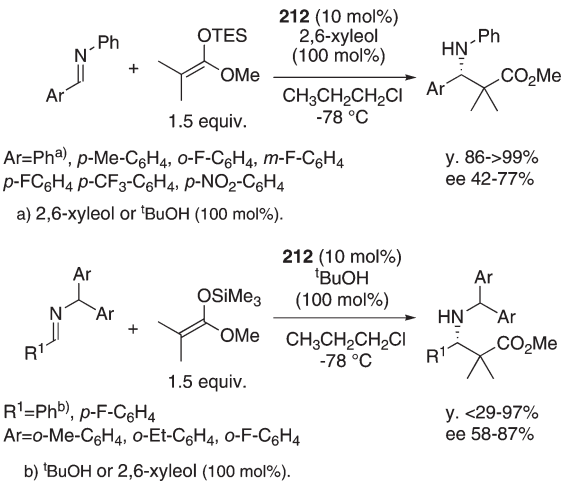


Figure 17. Postulated mechanism of BBA activation.

Scheme 78. IMTR Promoted by BBA Catalysts



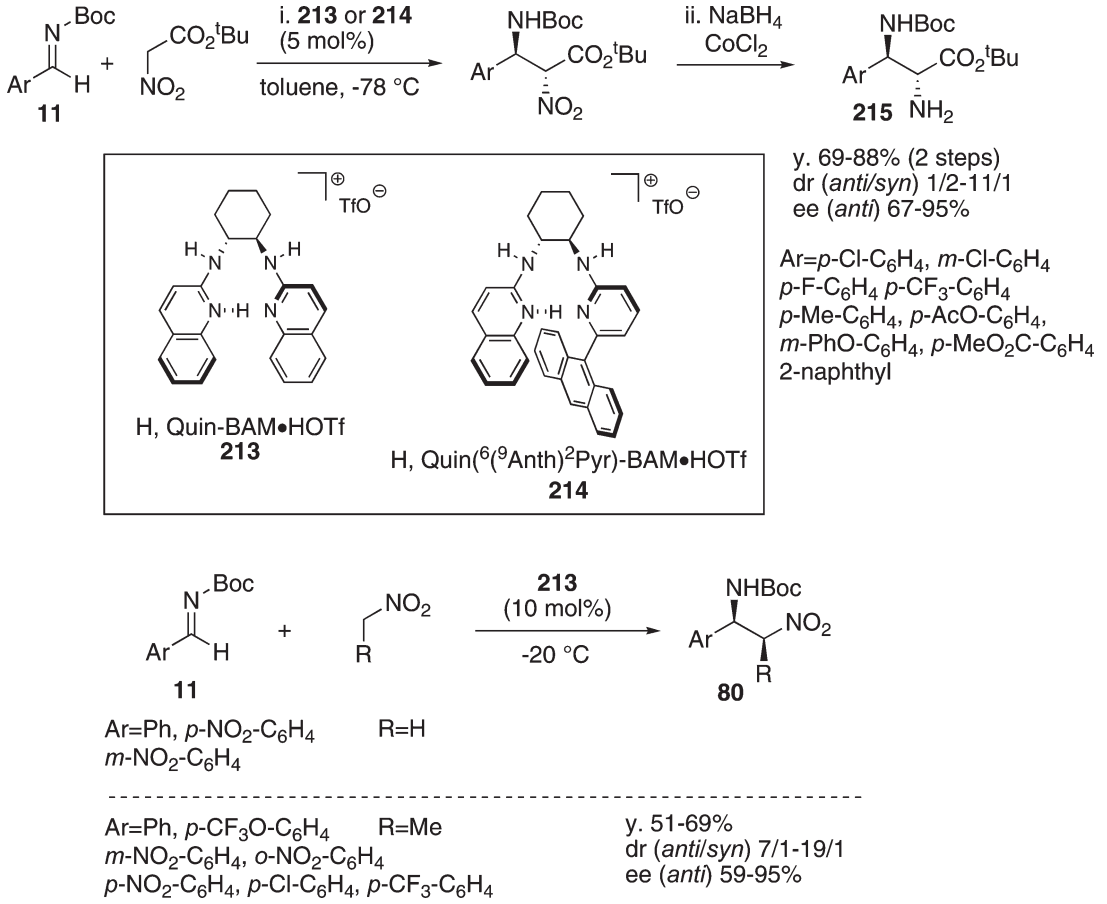
from a tight ion pair formed by protonation of the imine by the phosphoric acid, which serves as a chiral counterion, which was discussed in more detail in a later paper.[192a] Akiyama and co-workers used the same imine in vinylogous IMTRs, although slightly modified phosphoric acid structures were employed.[193] However, Sickert and Schneider performed successful vinylogous IMTRs on a PMP imine in >90% ee and proposed a catalytic cycle.[194,195]

In a report by Rueping et al., addition of an achiral Brønsted acid to a chiral phosphoric acid catalyzed reaction enabled acetophenone to be employed as a nucleophile.[196] The same group also reported a chiral phosphoric acid catalyzed aza-Henry reaction.[197]

An alternative approach to the issue of Brønsted acid catalyzed IMTR has been taken by Yamamoto, who introduced the concept of Brønsted acid-assisted chiral Brønsted acids (BBA) for the addition of silyl ketene acetals to *N*-aryl and *N*-benzhydryl imines, using chiral 2-bis(trifyl)methyl-2′-hydroxy-1,1′-binaphthyl **212**. Based on the observation that the acidity of bis(trifyl)methane is practically the same as or higher than the corresponding sulfonic acid, they envisaged that hydrogen bonding between the bis(trifyl)methyl proton and the neighboring OH oxygen would lead to catalyst structural rigidity and increases acidity for the OH proton, both of which factors would lead to high yields and selectivities (Figure 17).[198] While yields were good to excellent in most cases, enantioselectivities were generally on the moderate side for this type of protocol (Scheme 78). Optimum conditions for the reaction differed slightly depending on the nature of the imine electrophile, but in both cases, imines derived from electron-deficient aldehydes gave best results. Addition of a hindered alcohol (2,6-xylenol or *tert*-butanol) was necessary for smooth progression of the reaction, and the alcohol is believed to scavenge the silyl group

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 79. DMTR of Nitroacetic Acid Esters Using H Quin-BAM·HOTf-type Chiral Acids



liberated from the silyl ketene acetal, which otherwise acts as a Lewis acid to catalyze a nonselective background reaction.

Johnston et al. have introduced novel chiral Brønsted acid catalysts H,Quin-BAM·HOTf **213** and H,Quin(^{6}(^{9}Anth)^{2}Pyr)-BAM·HOTf **214**[199,200] for the addition of nitroacetic acid esters to *N*-Boc imines (Scheme 79).[201] The use of the former gave the addition product with good to high ee's but almost no diastereoselectivity, whereas the more hindered anthryl-substituted acid gave diastereomeric ratios as high as 11:1 in favor of the *anti* product and average enantioselectivities in the 85−95% range. The products were isolated after reduction to avoid epimerization at the nitroester center. The *anti*-diastereoselection was a result of kinetic control of addition, because submitting the *anti*-nitroamine product to the catalyst at room temperature leads to erosion of the *anti*/*syn* ratio.

In a separate report, the same authors described the analogous aza-Henry reaction (Scheme 79)[202] in which H,Quin-BAM·HOTf **213** (10 mol %) successfully promoted the addition of nitromethane and nitroethane to a range of *N*-Boc imines to give the β-amino nitro compounds in up to 95% ee and excellent dr.

3.3.3. Chiral Thiourea Catalysts. Thiourea-based systems also have strong credentials as highly active and selective organocatalysts. The groups of Jacobsen[203,204] and Takemoto[205,206] and others[207,208] have reported the use of systems such as **216a,b**, **217a, b**, **218a,b**, **219** (Figure 18), and amino thioureas for a range of transformations including the Mannich and the nitro-Mannich reactions. Jacobsen and co-workers used catalyst **216a** to promote the indirect Mannich-type reaction of *N*-Boc imines with silyl ketene acetals.[209] The reaction proceeded under extremely mild conditions in toluene with a range of different imine substrates to give the corresponding β-amino esters. Although the reaction proceeded in good yield at ambient temperature, ee's were only moderate. Use of lower temperature (−40 °C) led to enhanced enantioselectivity by suppression of a nonselective background reaction (Scheme 80). Subsequently the same authors found thiourea **217b**[210] to be the most effective catalyst for enantio- and diastereoselective direct nitro-Mannich reactions of *N*-Boc imines of nonenolizable aldehydes. In these studies, a wide range of imines underwent smooth addition with nitroethane to give predominantly the *syn*-β-nitro amine in good to excellent yield and very high stereoselectivities (Scheme 81). At almost the same time, the group of Takemoto[211] reported a detailed study of the scope of the thiourea-catalyzed aza-Henry reaction in which they paid particular attention to the nature of the nitrogen protecting group on stereoselectivity (Scheme 82). They discovered that the absolute stereochemistry of the newly formed stereogenic center was strongly dependent on the nature of the nitrogen protecting group; acyl or carbamate protection gave the *R* enantiomer, whereas *N*-DPP imines gave the *S* enantiomer. In further studies, *tert*-butoxycarbonyl was identified as the nitrogen protecting group of choice, and it was shown that a wide range of suitably protected aromatic imines undergo smooth aza-Henry reaction with nitromethane in good yield and excellent enantioselectivity.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

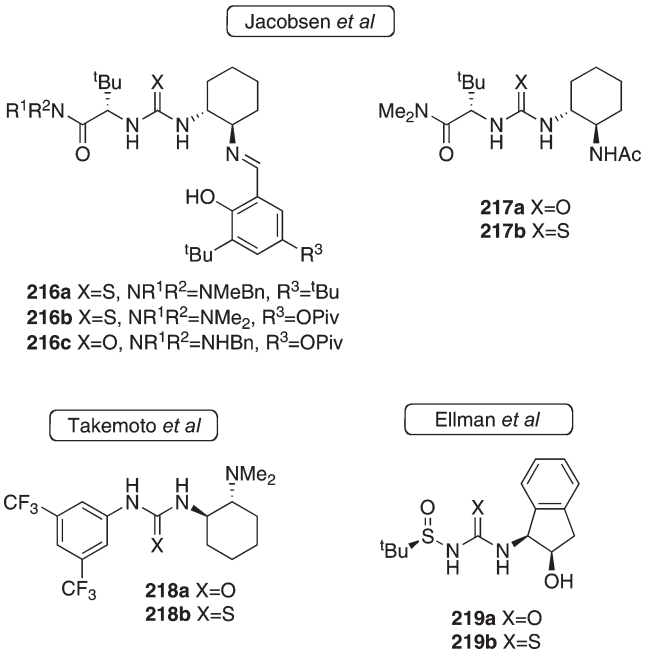
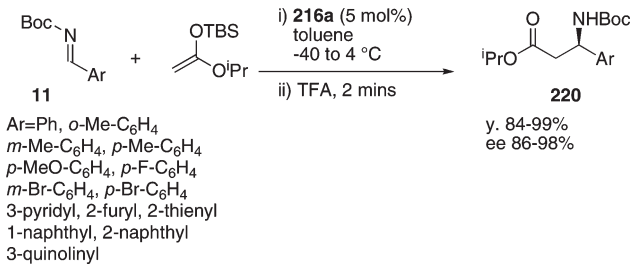
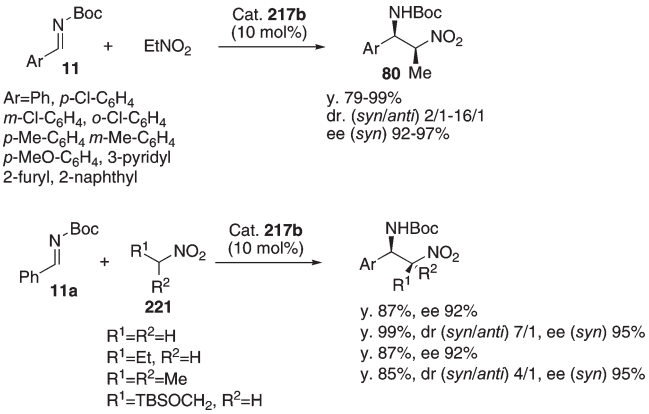


Figure 18. Thiourea- and amide-based Brønsted acid organocatalysts.

Scheme 80. Thiourea-Catalyzed Indirect Mannich-type Reaction with Silyl Ketene Acetals

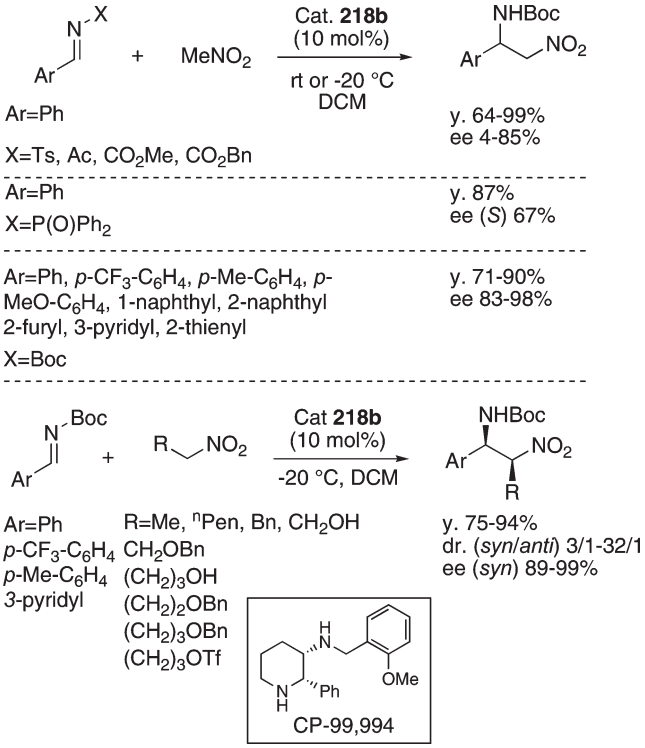


Scheme 81. Jacobsen's Thiourea-Catalyzed Asymmetric Nitro-Mannich Reaction



The corresponding enantio- and diastereoselective reactions with a variety of nitroalkanes also proceeded readily and with good selectivity. In the same report, Takemoto et al. also demonstrated the synthetic utility of their methodology by a short and efficient preparation of NK-1 receptor agonist CP-99,994. The thiourea system is believed to act via a templated Brønsted acid effect in which the substrates are both coordinated and activated by dual hydrogen bonding to the urea NH groups. In considering the mechanism of the reaction, the authors suggested two possible pathways: coordination and deprotonation of the nitroalkane followed by displacement by the imine and the C−C bond-forming step (route a) or prior coordination/activation of the imine followed by coordination/deprotonation of the nitro compound and the C−C bond formation (route b Figure 19).[212]

Scheme 82. Takemoto's Thiourea-Catalyzed Asymmetric Nitro-Mannich Reaction



Ellman and co-workers have revealed a new class of *N*-sulfinyl urea catalyst **219** for nitroethane addition to *N*-Boc imines. The chiral sulfinyl group serves to both activate the urea part and add an element of stereocontrol.[213] As such, aliphatic imines could be used (>9:1 dr, 96% ee). Recently asymmetric aza-Henry reactions catalyzed by functionalized thioureas have also been reported independently by Wang,[214] Zhou,[215] and Chang.[216]

A related system, **222**, introduced by Jacobsen, involving a chiral pyrrole unit, was identified as the catalyst of choice for an organocatalytic asymmetric acyl Pictet−Spengler reaction (Scheme 83).[217] Under influence of between 5 and 10 mol % of the catalyst, simple precursors of type **223** underwent smooth conversion to the tricyclic diamines **224** in good to high yield and high enantioselectivity. This method, which preceded that of List (vide supra),[191] is an elegant alternative to the methods for synthesis of this class of compounds, which normally involved asymmetric reduction of intermediate Bischler−Napieralski adducts.

Chen et al. have screened a wide range of bifunctional catalysts for the organocatalytic direct vinylogous Mannich reaction and identified cyclohexyl thiourea **225**[207b] as being the best-performing promoter. Exposure of a variety of α,α-dicyano olefins **226** to

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

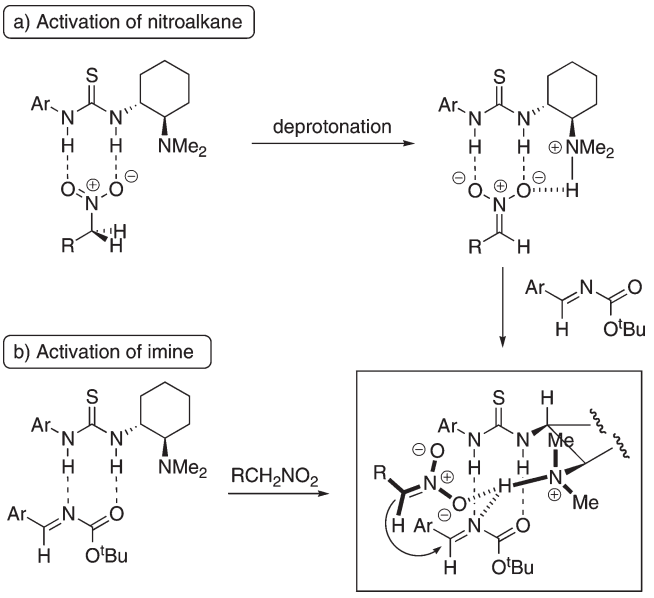
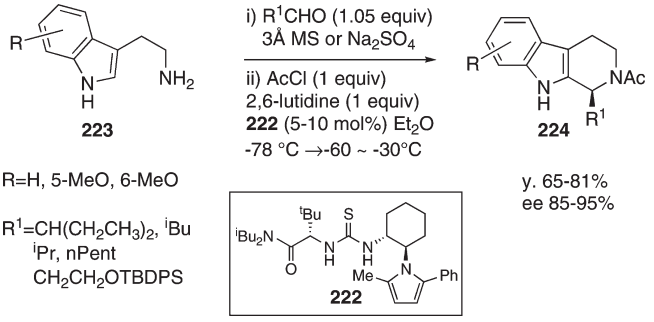


Figure 19. Proposed transition state of thiourea-catalyzed aza-Henry reaction.

Scheme 83. Thiourea-Catalyzed Asymmetric Pictet–Spengler Reaction



N-Boc aldimines in the presence of as little as 0.1 mol % of the catalyst gave the desired addition products **227** in essentially quantitative yield with almost perfect stereoselection and complete diastereocontrol (Scheme 84).[218] Elaboration of one of the adducts **227a** to fused tricyclic heterocycle **234** was achieved quickly and extremely efficiently by Hantzsch ester reduction to give **235**, which was subjected to a hydrolysis/cyclization sequence. Chen et al. also reported chiral thiourea-catalyzed asymmetric Mannich-type or Mannich reactions using other nucleophiles such as phosphorus ylides[219] or 3-substituted oxindoles.[220]

As nucleophiles for chiral thiourea-catalyzed asymmetric Mannich-type or Mannich reactions, unmodified ketones[221] and aldehydes[222] were also utilized in combination with hydrazonoesters or iminoesters as electrophiles.

A subgroup of this class of catalysts is one in which the thiourea fragment is conjugated with a cinchona alkaloid derivative, a number of which species have been introduced as Brønsted acid-type organocatalysts for Mannich and aza-Mannich-type reactions (Figure 20).

Deng and co-workers have utilized catalysts **239**, **241**, and **243** for the addition of malonates and β-keto esters to *N*-Boc imines

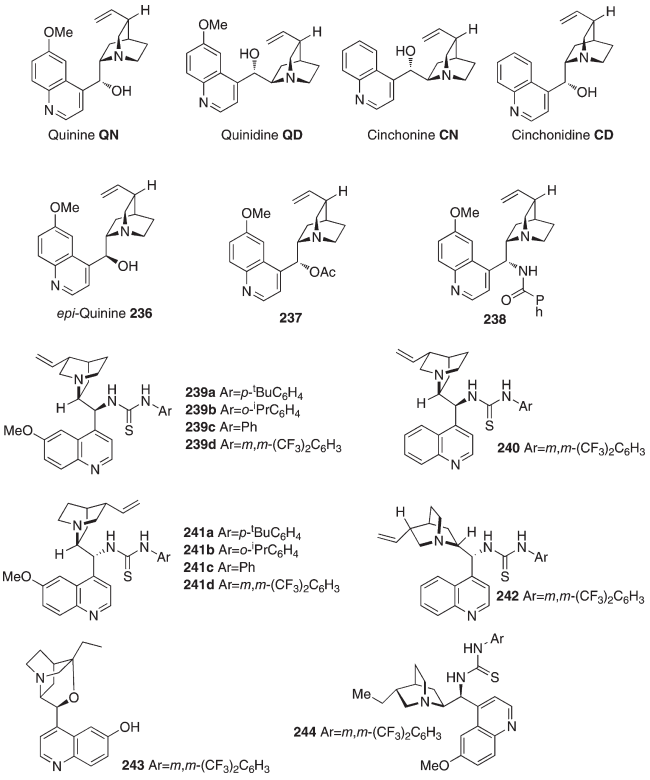
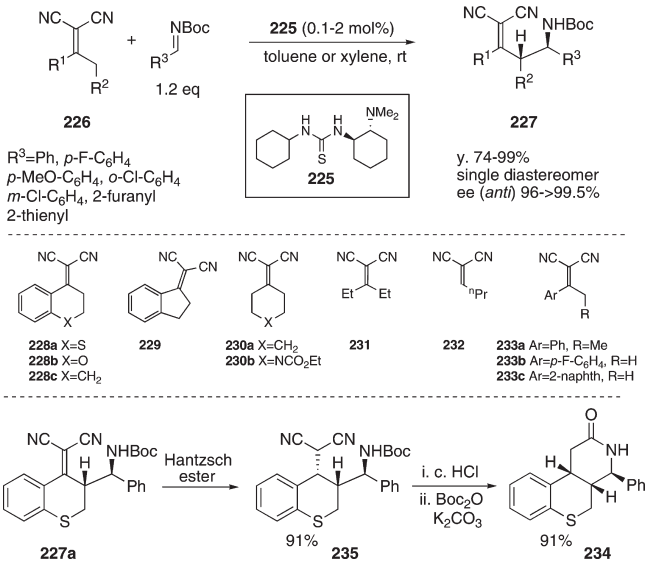


Figure 20. Cinchona alkaloids and their thiourea-conjugated organocatalysts.

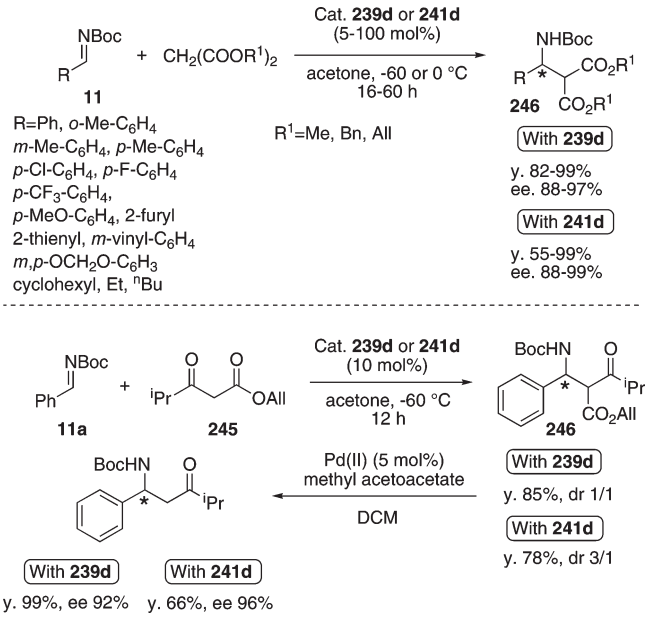
Scheme 84. Thiourea Promoters in the Organocatalytic Direct Vinylogous Mannich Reaction



giving versatile access to a range of β-amino acid precursors.[223] They found *m*,*m*-bis(trifluoromethyl)phenyl-substituted catalysts **239d** and **241d** to give best results in both reactions, affording the corresponding products in excellent yield and enantioselectivities. Addition products arising from the reaction between **245** and *N*-Boc phenylimine were characterized after palladium-catalyzed decarbonylation (Scheme 85).

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 85. Addition of Malonates and β-Keto Esters to *N*-Boc Imines Catalyzed by Cinchona Alkaloid−Thiourea Conjugate Organocatalysts



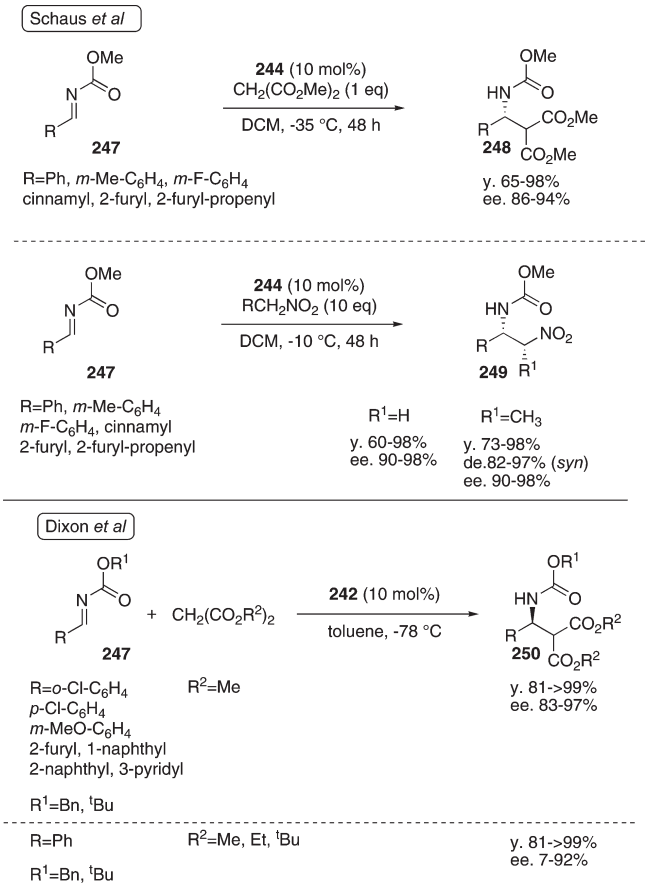
In their search for a general organocatalyst for the addition of stabilized anions to electrophiles, Schaus and co-workers[224] reported a similar procedure for the addition of malonates to carbamoyl-protected imines using hydroquinine-derived thiourea conjugate **244**.[225] Using *N*-methoxycarbonyl protected nonenolizable aldimines, they realized catalytic asymmetric Mannich and nitro-Mannich reactions in high yield and with excellent diastereo- and enantioselectivities (Scheme 86). A related protocol for the addition of malonate nucleophiles was also reported by Dixon et al.[226] In their case, they used thiourea **242**[227] to effect the addition of a range of β-diesters to *N*-carbamoyl imines in good yield and high selectivity. It is important to note that in this case, the products were obtained with the opposite absolute stereochemistry but comparable enantioselectivity to those delivered by the Schaus catalyst (Scheme 86).

In the same paper,[226] the group of Dixon also demonstrated the efficacy of their catalyst system for the addition of β-diketones and β-ketoesters to *N*-carbamoyl imines. Again, yields and both enantio- and diastereoselectivities were good to excellent, and the corresponding addition products were obtained with the same sense of absolute chiral induction as the analogous reaction using malonates (Scheme 87).

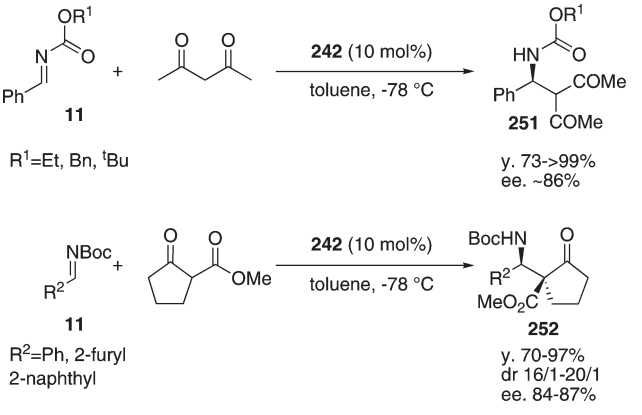
The cinchona−thiourea conjugative species have also been used for the organocatalytic enantioselective aza-Henry reaction. The group of Ricci examined simple cinchona alkaloids **QN-CD** as well as *epi*-quinine **236** and quinine derivatives **237**, **238**, and **243** as potential catalysts before settling on **239d** (Figure 20) as the promoter of choice. Addition of nitromethane to a range of *N*-Boc and *N*-Cbz aromatic aldimines proceeded smoothly in toluene at −24 °C to give the adducts in moderate to good yield (50−95%) and moderate to very high enantioselectivity (44−94%).[228]

3.3.4. Cinchona Alkaloids as Chiral Bases. Schaus and coworkers introduced a subtly different protocol for the organocatalytic Mannich reaction of β-ketoesters in which they take advantage of the basicity of unconjugated members of the cinchona family

Scheme 86. Use of Thiourea Conjugated Organocatalyst for the Mannich Reaction of Malonates



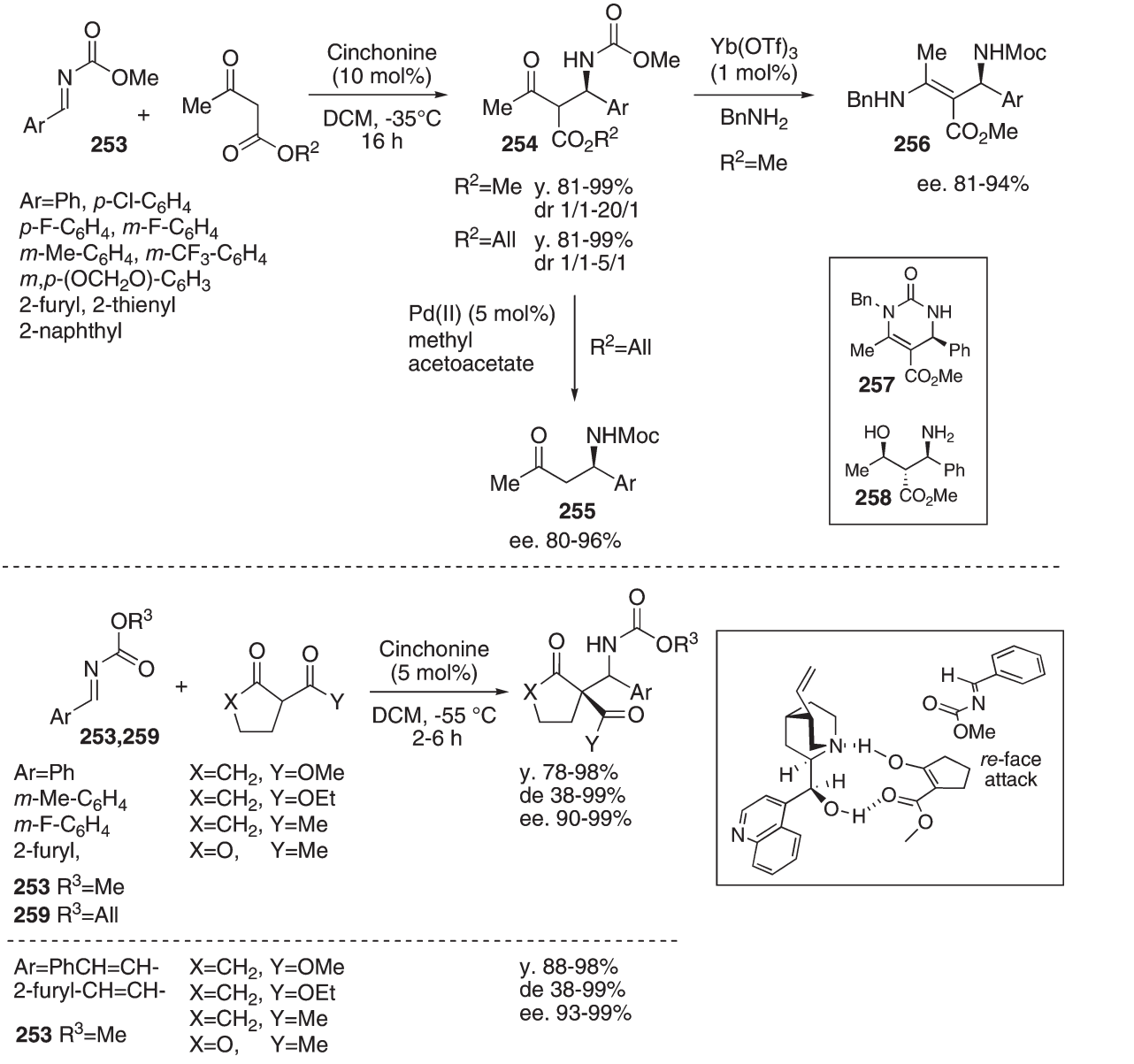
Scheme 87. Addition of β-Diketones and β-Ketoesters to *N*-Carbamoyl Imines Using Catalyst 242



rather than the Brønsted acidity of an appended thiourea side chain (Scheme 88).[229] Cinchonine **CN** was found to be the most effective catalyst for the addition of linear and cyclic β-keto esters in the direct Mannich-type reaction with *N*-methoxycarbonyl imines. While yields and enantioselectivities were high to very high in all cases, for the reactions in which allyl acetoacetate was used as the nucleophile diastereoselectivity was low. In contrast, use of methyl acetoacetate gave better diastereomeric ratios (up to 20/1, major

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 88. Cinchona Alkaloids in the Organocatalytic Direct Mannich-type Reaction



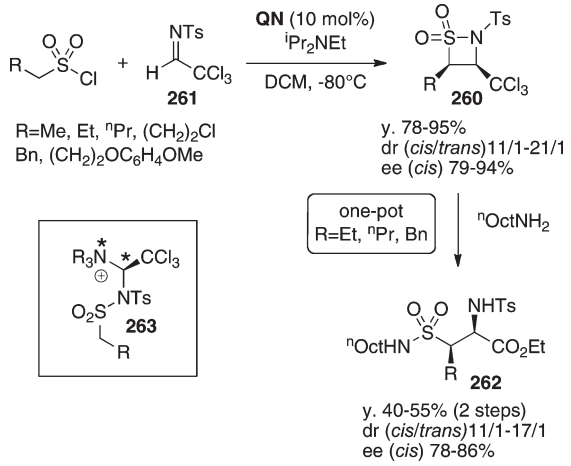
isomer 1*R*,2*S*), as well as high enantioselectivites. In the linear series, enantiomeric excesses were determined on a suitable derivative of the initial addition product: either by Pd(II)-catalyzed decarboxylation to give **255** (in the case of allyl ester adducts) or $Yb(OTf)_3$-catalyzed benzylenamine formation to give products **256** (in the case of methyl ester adducts). Further synthetic manipulation of selected addition products gave rapid access to useful synthetic intermediates such as dihydropyrimidone **257** and β-amino alcohol **258** in good yield and with no loss of stereochemical integrity. The authors also expanded the scope of the reaction to include cyclic α-substituted β-keto esters and β-diketones. The reaction provides a catalytic route toward the construction of α-quaternary carbon centers with high diastereo- and enantioselectivity. The authors proposed a catalytically active complex with the bifunctional nature of the catalyst as a hydrogen bond donor and acceptor (Scheme 88). In their further studies, they applied this methodology to the synthesis of chiral dihydropyrimidones[230] and enantioselective synthesis of SNAP-7941.[231]

The synthesis of β-sultams **260** via a quinine-catalyzed addition of sulfonyl chlorides to *N*-tosyl α-trichloroimines **261** was disclosed by Zajac and Peters. The desired products could be generated under mild conditions and in good yields and high selectivities with a preference for the *cis* form (Scheme 89).[232] Treatment with a primary amine led to opening of the four-membered ring to give β-sulfonyl amines **262**. In certain cases, these two reactions could be carried out sequentially in one pot. The reaction is believed to proceed by the intermediacy of chiral amine salt **263**, which undergoes deprotonation with $^{i}Pr_2NEt$ and collapses to give the sultam by a stereoselective intramolecular S_N2-type reaction.

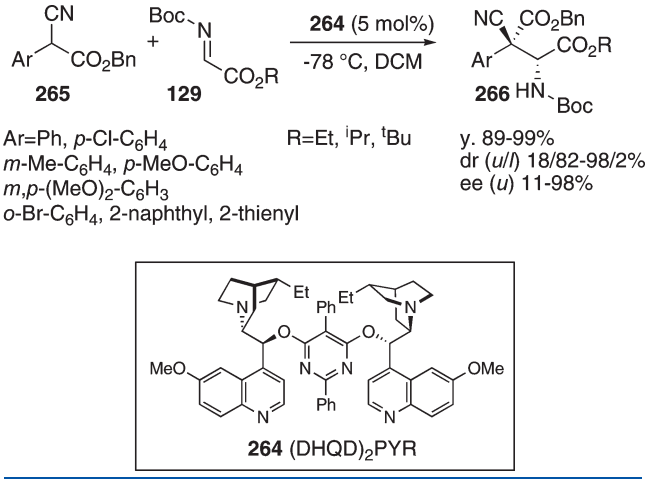
Using $(DHQD)_2PYR$ **264** as a catalyst, Jørgensen and coworkers described a novel DMTR of active methine cyanoacetates **265** with *N*-Boc imines. A notable feature of this reaction is the low catalyst loading (5 mol %), which stands out against its contemporise where 30−50 mol % of catalyst is often employed. The authors managed to obtain excellent yields of the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 89. Catalytic Enantioselective Synthesis of Sultams



Scheme 90. Catalytic Enantioselective Mannich Reaction with Cyanoacetates



corresponding Mannich adducts at low temperature (−78 °C) with extremely high levels of both enantio- and diastereoselectivity (Scheme 90).[233]

Xu showed how a formally [4 + 2] cycloaddition, catalyzed by a cinchona alkaloid could furnish masked Mannich-type adducts of *in situ* generated, enolizable imines.[234]

3.3.5. Catalytic Asymmetric DMTR Mediated by Phase-Transfer Catalysts. Asymmetric phase transfer catalysis is an important and growing field in organic synthesis.[235] Although the technique has witnessed development in a number of areas, its application in the asymmetric catalytic Mannich reaction has been somewhat limited. Maruoka et al., following up on their earlier work on phase transfer catalyzed asymmetric aldol reactions,[236] described a protocol for the direct addition of glycine ester benzylidines **267** to activated imine **49** using heavily hindered chiral ammonium salts **268a**−**c** (Scheme 91).[237] Best results were obtained at −20 °C because at higher temperatures imine decomposition was found to be problematic. The product of the reaction, 3-aminoaspartate, a differentially protected nitrogen analogue of tartrate diester **269** was obtained preferentially as the *syn* diastereomer in moderate to good yield and with moderate to good enantio- and diastereoselectivity. The product was subsequently elaborated into a precursor of streptolidine lactam, a core subunit of the streptothricine family of antibiotics. Ooi and co-workers further investigated onium catalysts and developed ammonium betaines[238] and tetraaminophosphonium carboxylate[239] as chiral catalysts for asymmetric Mannich reactions.

In a related example, Shibasaki and co-workers have used chiral bisammonium salts (*S,S*)-TaDiAS **270**[240] to catalyze the direct addition of the same imino glycine ester to a range of *N*-protected aryl imines (Scheme 92).[241] Among the *N*-protecting groups investigated (Dpp, $CHPh_2$, Bn, Boc, Ts), *tert*-butoxycarbonyl was found to be give best yields and stereoselectivity, and *p*-F-C_6H_4 (*S,S*)-TaDiAS **270g** was determined to be the most efficacious catalyst using fluorobenzene. A broad range of *N*-Boc imines derived from nonenolizable aldehydes were effective in the reaction giving the (*R,R*)-*syn* diamine product **271** in excellent yield and dr but with moderate to good enantioselectivity.

It was shown that the rate-determining step is the deprotonation of the Schiff base by Cs_2CO_3 and does not involve the phase transfer catalyst. Based on these findings, the authors proposed a mechanism in which deprotonation of the Schiff base followed by cation exchange between Cs^+ and TaDiAS to generate a chiral ion pair provides an asymmetric manifold in which the addition to the imine can take place (Figure 21).

Jørgensen reported the catalytic asymmetric vinylogous DMTR of 1,1-dicyanoalkylidene nucleophile **272a** with imines generated *in situ* from α-amido sulfones of nonenolizable aldehydes promoted by a range of chiral PT catalysts (Scheme 93).[242] Although those PT catalysts derived from cinchona alkaloids **274a**−**c** delivered the desired *anti* products **273**, only low to good enantioselectivity was achieved. However, a range of biphenyl catalysts **275**−**277** developed by Lygo[243] gave much higher ee's but of the opposite enantiomer. Screening of solvent, concentration, and base revealed that the combination of toluene and K_3PO_4 at low concentration (0.04 M) was most effective. Application of these conditions to a range of 1,1-dicyanoalkylidene nucleophiles **272b**−**i** and α-amido sulfones gave good to excellent yields of the addition products **273b**−**i** with good to excellent enantioselectivity as essentially a single diastereomer in almost all cases.

In a closely related reaction Herrera and co-workers used commercially available *N*-benzyl quininium chloride **272d** to promote the direct catalytic aza-Henry reaction between nitromethane and *in situ*-generated *N*-carbamoyl imines derived from both aromatic and aliphatic aldimines giving the *R* adducts in good to excellent yield and ee (Scheme 94).[244] Barbas applied the conditions to the organocatalytic Mannich reaction of a trifluoroethyl thioester[245] and Bernardi and Ricci reported asymmetric Mannich reactions of *N*-Boc and *N*-Cbz protected α-amido sulfones with malonates and β-ketoesters using similar cinchona alkaloid-derived phase-transfer catalysts.[246] Shibata and Toru developed catalytic enantioselective monofluoromethylation of in situ generated imines in a similar phase-transfer system,[247] whereas Palomo performed an experimental and theoretical study for catalytic asymmetric aza-Henry reactions under phase-transfer conditions.[248]

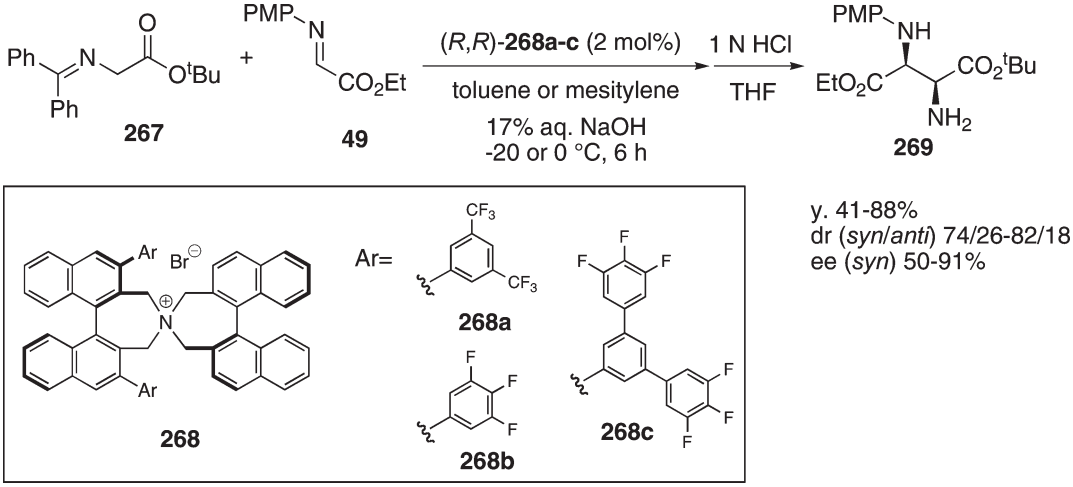
4. AZA-FRIEDEL−CRAFTS REACTIONS

4.1. Aza-Friedel−Crafts Reactions Mediated by Transition Metal Catalysts

The Friedel−Crafts reaction is of great importance in synthesis both in academic and industrial settings.[249] The asymmetric version of this reaction provides rapid access to an array of synthetically important products in enantioenriched form.[250]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 91. Asymmetric Catalytic DMTR Mediated by Chiral PT Catalysts



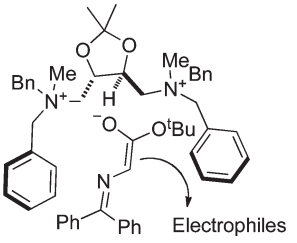
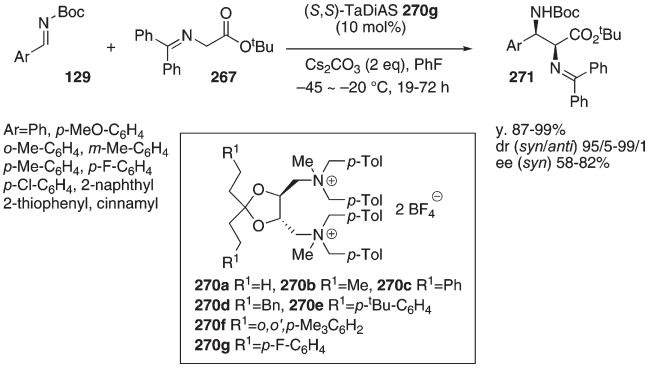


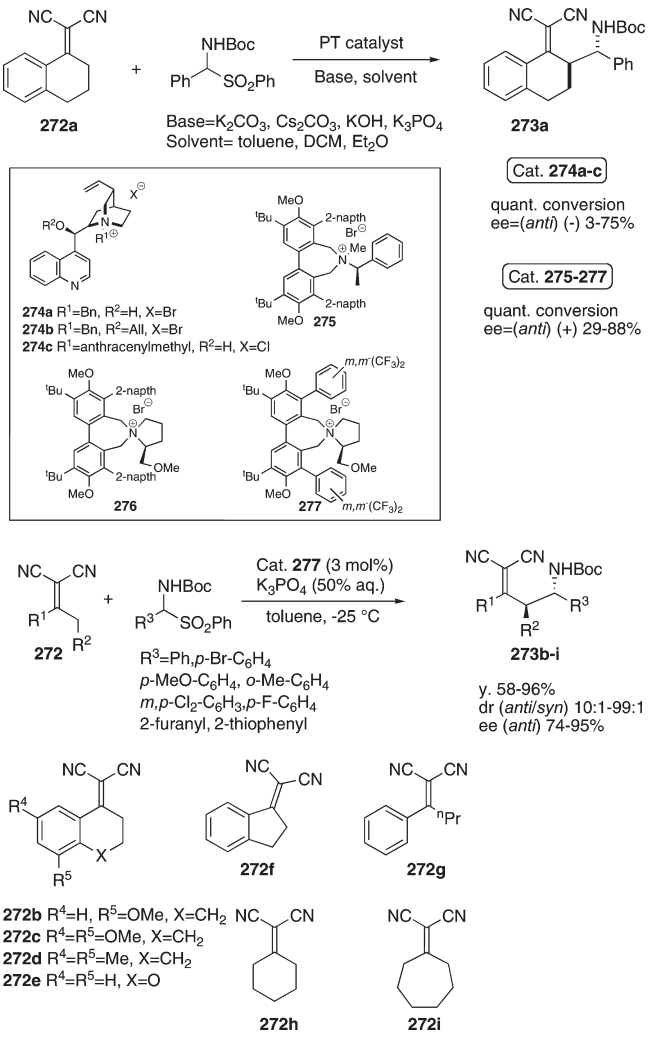
Figure 21. Proposed transition state.

Scheme 92. Catalytic Asymmetric DTMR Promoted by TaDiAS



The analogous catalytic asymmetric aza-Friedel−Crafts reaction where an aromatic system adds to imine electrophiles has been demonstrated by Johannsen.[251] In a seminal publication he demonstrated the addition of 5-substituted indoles to highly activated *N*-tosyl imino ester **41** promoted by relatively low loadings of a simple Cu(I)-phosphine catalyst under mild conditions. Yields and enantioselectivities were high to very high, although only a limited range of substrates were examined. Electron-donating groups at the 5-position of the indole gave best results, those bearing electron-withdrawing groups requiring more elevated temperatures (Scheme 95). In the same paper, an analogous reaction using pyrroles was described. In the case of

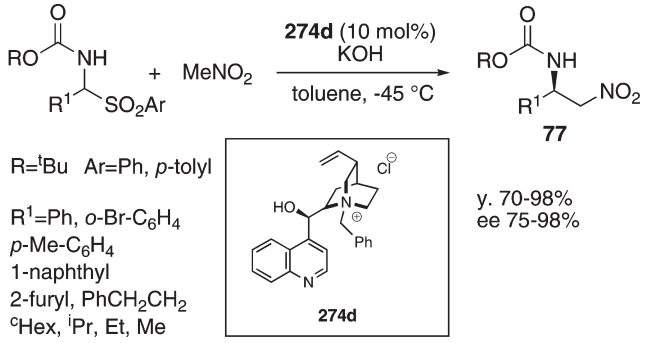
Scheme 93. Catalytic Asymmetric Vinylogous DMTR with PT Catalysts



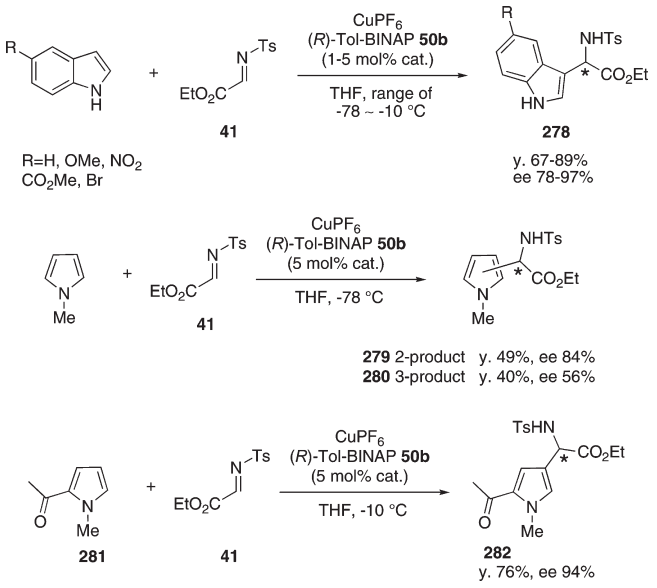
N-methylated pyrrole, regioselectivity was poor in the reaction with the parent heterocycle, although the addition product was

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 94. PTC-Mediated Aza-Henry Reaction Catalyzed by *N*-Benzyl Quininium Chloride



Scheme 95. $CuPF_6$-Tol-BINAP Catalyzed Asymmetric Aza-Friedel−Crafts Reaction of Indoles and Pyrroles with Activated Imines

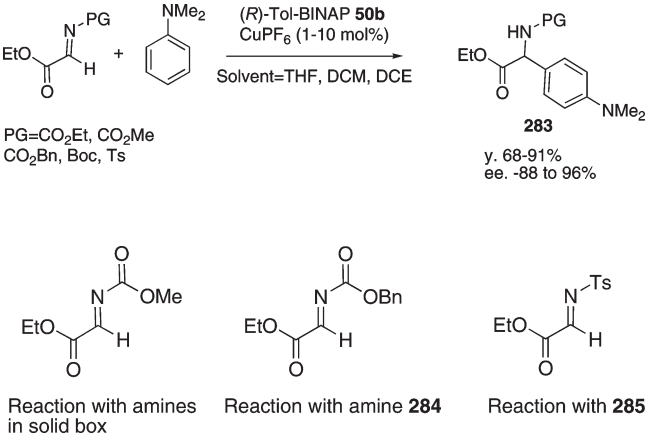


obtained in good overall yield and in respectable enantiomeric excess. In contrast, 2-acetyl pyrrole gave exclusively the 4-substitution product with excellent enantioselectivity.

Shortly after this report, Jørgensen and co-workers described a similar procedure for reactions using *N*-carbamoyl protected imines as substrates and a range of heteroaromatic nucleophiles (Scheme 96).[252] Intriguingly, the absolute stereochemistry of the product was found to depend strongly on the nature of the nitrogen protecting group, with methyl, ethyl, and benzyl carbamates giving the *R* isomer (with *R*-Tol-BINAP) and the Boc and *N*-tosyl derivatives giving the *S* enantiomer of the product.

Furthermore, when *N*-Boc imines were used as substrates, switching the solvent and reaction temperature from DCE at room temperature to THF at −50 °C led to a change in enantioselectivity

Scheme 96. Cu/TolBINAP-Catalyzed Asymmetric Aza-Friedel−Crafts Reaction



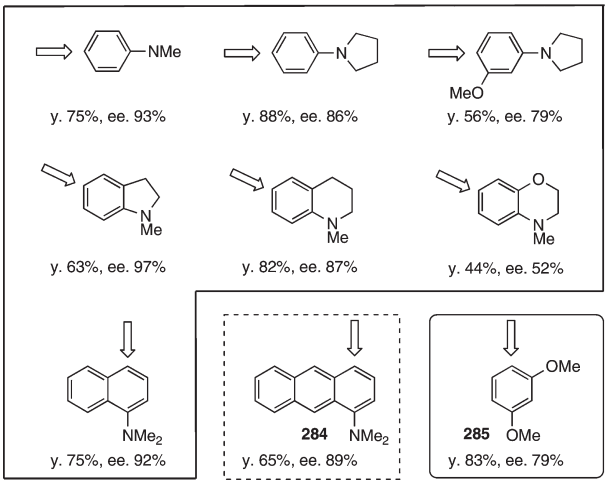
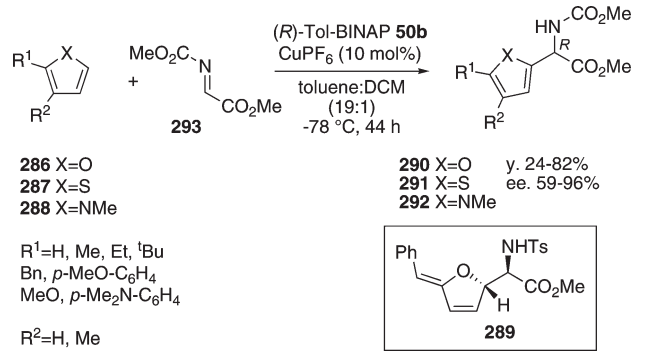


Figure 22. Substrate scope of the Cu/Tol-BINAP catalyzed asymmetric aza-Friedel−Crafts reaction (position of reaction shown by arrow).

Scheme 97. Catalytic Asymmetric Aza-Friedel−Crafts Reactions of Furans, Thiophenes, and Pyrroles



from 64% (*S*) → 14% (*R*). This data indicates a mode of coordination of the imine that is inordinately sensitive to solvation factors. The reaction was found to operate effectively for a number of aromatic tertiary amines (Figure 22). It was subsequently demonstrated that the reaction also tolerated furans, thiophenes, and pyrroles **286**−**288** as substrates (Scheme 97). Here again the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

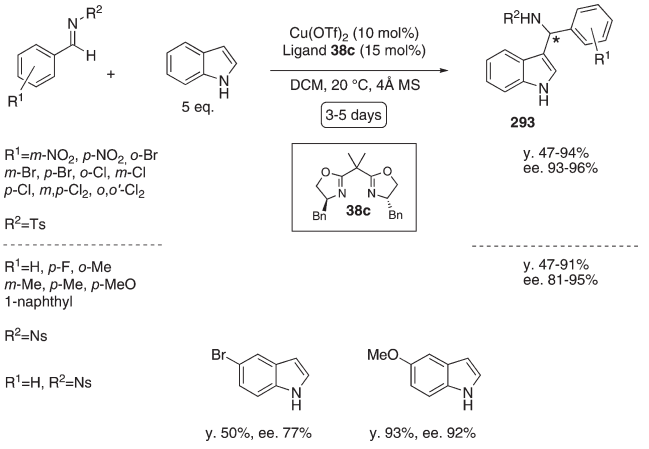
issue of absolute stereochemistry was found to be a complex one, although the authors were able to rationalize the experimental observations, with help of DFT calculations, as arising from a transition state involving five-membered coordination of the imine. A byproduct, **289**, formed in the reaction of **286a** (X = O, R^1 = Bn, R^2 = H) was instrumental in the investigation of the stereochemical outcome of the reaction.[253]

The transition metal-catalyzed asymmetric aza-Friedel−Crafts reaction of indoles has been expanded by the addition of a procedure permitting the use of *N*-sulfonyl imines derived from aromatic aldehydes.[254] After screening a range of combination of Box-type ligands and metal triflates, the group of Zhou utilized a combination of benzyl Box ligand **38c** with $Cu(OTf)_2$ in a 3:2 ratio to effect the addition of indole to a range of *N*-sulfonyl imines in good to excellent yield and enantioselectivity. Conveniently, while electron-poor *N*-tosyl imines were found to be the most reactive toward indole under the conditions, a simple change of the nitrogen protecting group to nosyl permitted the use of electron-rich imines giving the corresponding *N*-Ns imino indoles in similarly good yield and enantioselectivity (Scheme 98). The absolute stereochemistry was determined as being *S* by X-ray crystallographic analysis on a representative product (R^1 = *p*-Br, R^2 = Ts). To explain this stereoselectivity, the authors proposed an unusual 1,3-coordinated transition state with approach of the indole from the *Re* face. They also noted that use of *N*-(4-nitrobenzylidene)aniline (which cannot coordinate to the catalyst by a 1,3-interaction) gave racemic products in the addition reaction, whereas the corresponding *N*-tosyl analogue underwent the analogous transformation within 95% ee (Figure 23).

4.2. Aza-Friedel−Crafts Reactions Mediated by Organocatalysts

The asymmetric catalytic Friedel−Crafts reaction is not limited to promotion by transition metal catalysts but also proceeds under the influence of organocatalysts. Although most of the organocatalytic methods reported to date have been concerned with additions to C=C[255] or C=O, a number of protocols for the analogous aza-Friedel−Crafts reaction have been reported. In an early example, Terada et al. demonstrated

Scheme 98. *N*-Sulfonyl Aromatic Imines in the Catalytic Asymmetric Friedel−Crafts Reaction



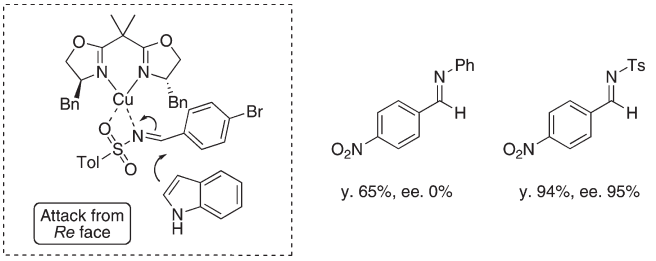
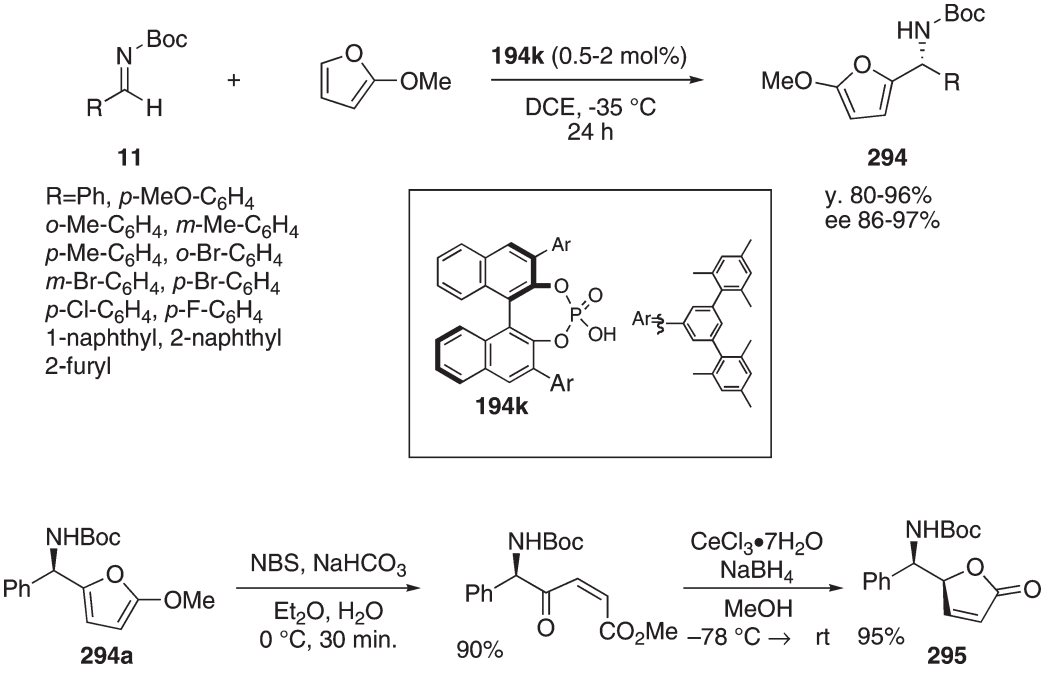


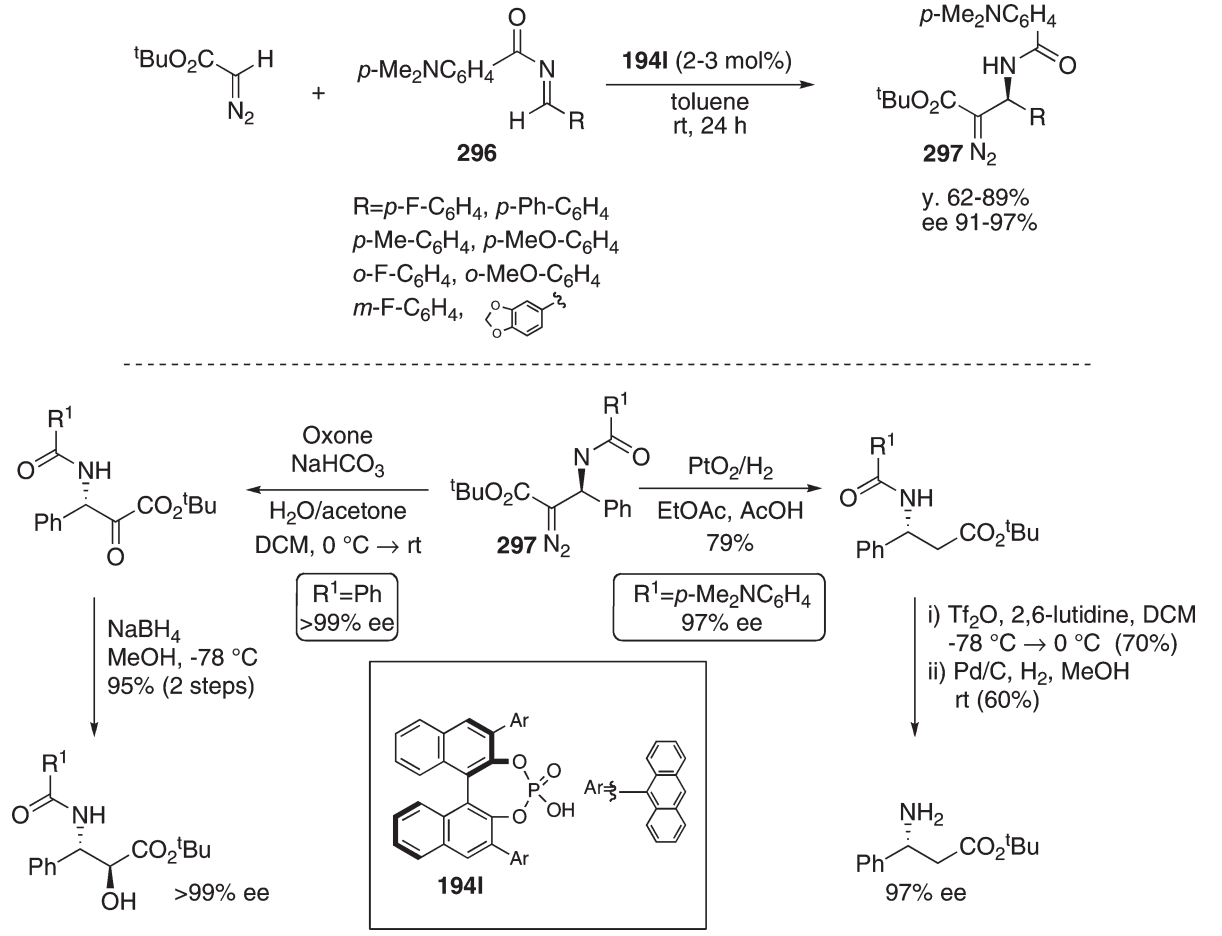
Figure 23. Proposed 1,3-coordinated transition state.

Scheme 99. Organocatalytic Asymmetric Aza-Friedel−Crafts Alkylation of Furan Ethers



dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 100. The Aza-Friedel−Crafts Reaction of Diazoacetates Catalyzed by Chiral Brønsted Acid



the efficacy of their phosphoric acid methodology by using **194k** to catalyze the addition of 2-methoxyfuran to a range of *N*-Boc imines giving the corresponding (*R*)-furan-2-ylamines **294** in good to excellent yield and very high ee (up to 97%) (Scheme 99).[256] Although the reaction was tolerant of most common solvents, halogenated solvents, in particular, 1,2-dichloroethane, were found to give best results. The addition products obtained were converted smoothly via an aza-Achmatowicz reaction into γ-butenolide **295** in good yield and with no loss of stereochemical integrity.

In a subsequent paper, the same authors reported the addition of α-diazoesters to *N*-acylimines promoted by a highly hindered chiral phosphoric acid **194l**.[257] Screening of a large number of protecting groups for the imine nitrogen revealed *p*-$Me_2NC_6H_4$-CO to be the most efficacious. Accordingly the scope was examined with a range of *N*-*p*-(*N*,*N*-dimethylamino)benzoate imines **296** and *tert*-butyl diazoacetate leading to the generation of the corresponding β-amino-α-diazoesters **297** in moderate to high yield and preferentially as the *S* enantiomer in excellent enantioselectivity irrespective of the nature of the imine R group (Scheme 100). The diazomethane addition products could be converted, with no loss of ee, into β-amino esters or α-oxo-β-amino esters using standard methodology. The authors envisaged a reaction pathway involving a dual Brønsted acid/Lewis base role for the phosphoric acid (Figure 24). The corresponding aziridine arising from a Darzen's closure of intermediate **298** was not observed, possibly due to the electrowithdrawing substituent on the imine nitrogen, which rendered it too unreactive to displace the diazo functionality.

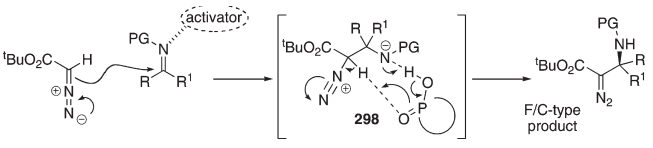


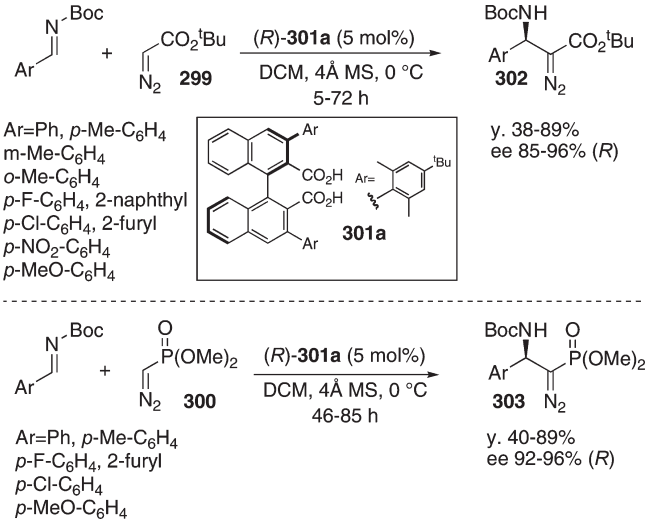
Figure 24. Proposed reaction pathway for the Friedel−Crafts reaction of diazoesters.

Maruoka and Hashimoto reported that bulky 2,2′-binaphthyl carboxylic acids themselves are sufficiently acidic to promote the Friedel−Crafts-type reaction of *N*-Boc imines and diazoesters **299** and diazophosphonates **300**.[258] The highly hindered 3,3′-bis(*o*,*o*-dimethyl-*p*-*tert*-butylphenyl)-BINOL carboxylic acid **301a** delivered the best overall results with DCM as solvent and 4 Å MS with yields of **302** on average to the higher end of the range 38−89% and very high selectivity (Scheme 101). A particularly valuable aspect of this protocol is that it can be used to promote the previously unreported addition of dimethyl diazophosphonate to *N*-Boc imines giving **303** in very high enantiomeric excess although in this case extended reaction times (up to 85 h) were necessary for the realization of good yields.

Indoles have also been successfully exploited as nucleophiles in the organocatalytic asymmetric aza-Friedel−Crafts reaction.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 101. Aza-Friedel−Crafts Reaction of Diazo Esters and Phosphonates Catalyzed by BINOL Carboxylic Acids



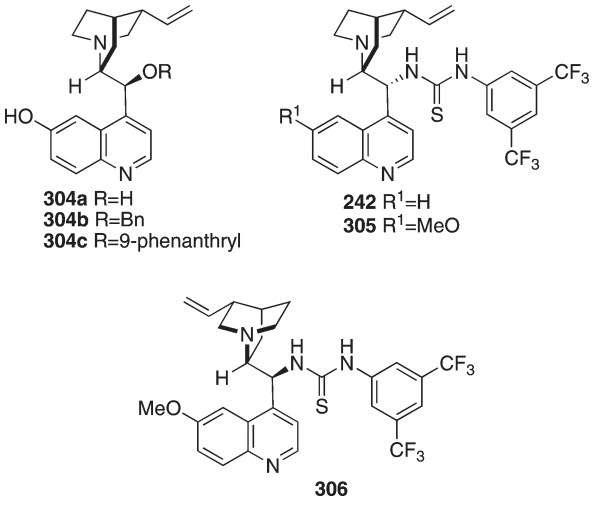
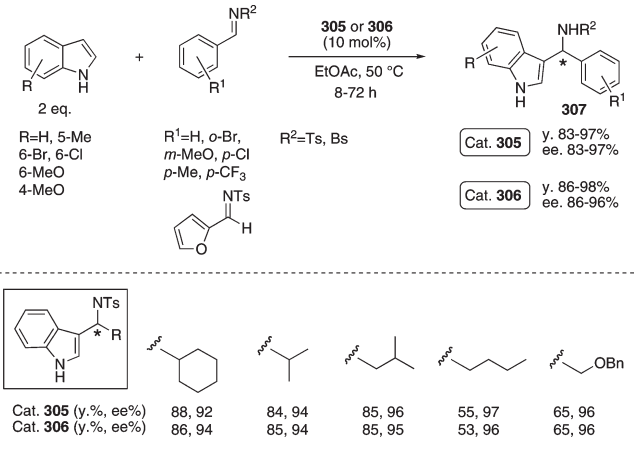


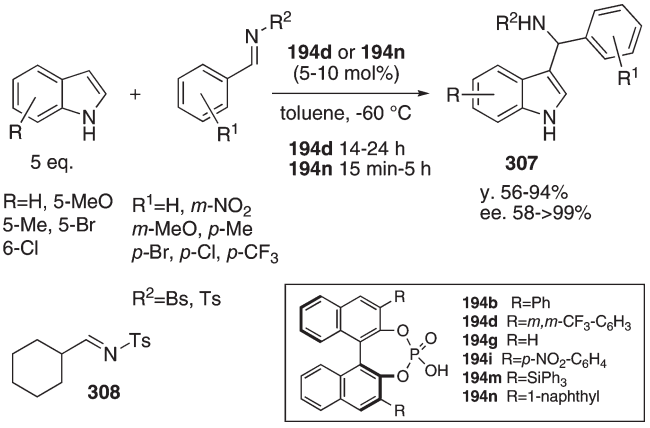
Figure 25. Cinchona alkaloid organocatalysts for the asymmetric catalytic Friedel−Crafts reaction.

In 2006, Deng et al. reported the first example of this transformation where they employed a range of catalysts based on *O*-protected cinchona alkaloids **304a**−**c** and thioureas derivatives **242**, **305**, and **306** (Figure 25).[259] Optimum results were obtained using the thiourea catalysts **305** and **306** (10 mol %) in ethyl acetate at 50 °C. Remarkably, the reaction was not sensitive to the electronic nature of the substituents on the indole ring, electron-donating and -withdrawing substituents giving similar results (Scheme 102). Analysis of a representative example of the product (**307**, R = H, R^1 = *p*-CF_3, R^2 = Ts) obtained using catalyst **H** revealed the absolute stereochemistry to be *S*. The reaction could also be applied to a range of aliphatic imines giving the required adducts in excellent yield and stereoselectivity for both enantiomers (catalyst **305** → *R*, **306** → *S*). Removal of the *N*-Ts group of the product could be accomplished in excellent yield without compromising the stereochemical integrity of the stereogenic center. Subsequently the group of You described the addition

Scheme 102. Asymmetric Catalytic Aza-Friedel−Crafts Reactions of Indoles



Scheme 103. Catalytic Enantioselective Aza-Friedel−Crafts Reactions of *N*-Tosyl Imines Catalyzed by Chiral Phosphoric Acids



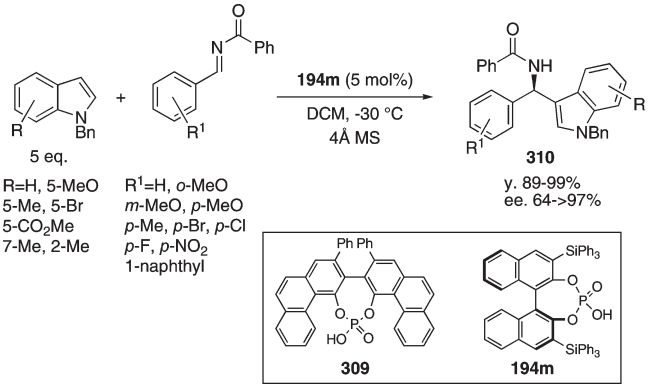
of a range of substituted indoles to *N*-Ts and *N*-Bs aromatic imines using chiral phosphoric acids **194b,d,g,i,m,n**.[260]

Both yields and enantioselectivities were generally very good to excellent; in order to achieve optimum results it was necessary to use an excess (5 equiv) of the indole and 5−10 mol % of the catalysts (Scheme 103). The 1-naphthyl-substituted catalyst **194n** was significantly more potent in the reaction, taking only between 15 min and 5 h to go to completion at −60 °C. On the other hand, reactions using the *m,m*-$(CF_3)_2C_6H_3$ substituted phosphoric acid **194d** required longer reaction times (14−24 h). The reaction gave predominantly the *R* enantiomer and was general for indoles bearing both electron-donating and electron-withdrawing groups, which is in marked contrast to the analogous copper-catalyzed transformation.[254] Use of aliphatic imine **308** gave the respective product in much lower yield and enantioselectivity.

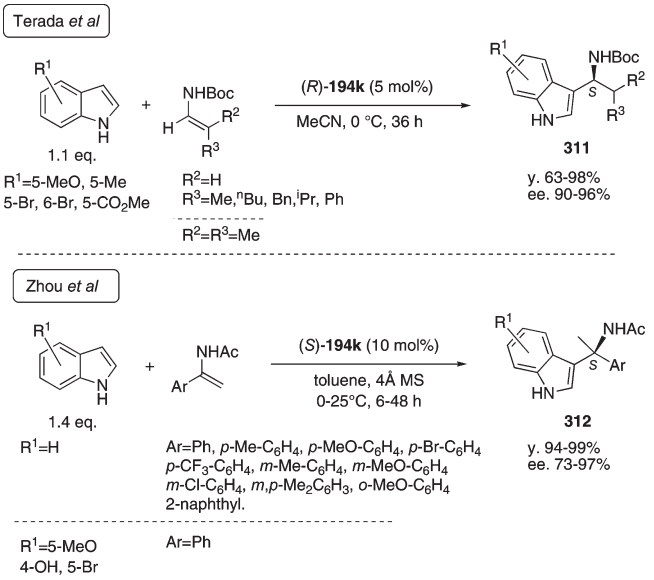
After this Antilla et al. disclosed a related procedure for the Friedel−Crafts-type addition of *N*-benzyl indoles to *N*-acyl imines, using chiral phosphoric acid **309**, derived from the VAPOL ligand, or acid **194m** (R = $SiPh_3$).[261] Ultimately, **194m** was chosen as the catalyst for further substrate scope studies. It was found to be necessary to protect the indole nitrogen to attain high enantioselectivities, with benzyl being

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 104. Catalytic Enantioselective Aza-Friedel−Crafts Reactions of *N*-Acyl Imines and Indoles



Scheme 105. Enamides or Encarbamates As Imine Surrogates in the Organocatalytic Aza-Friedel−Crafts Reaction



the protecting group of choice. In the addition reaction, various aromatic imine substrates were found to give the corresponding products with indoles bearing a range of functionalities in very high to excellent yield and generally very high enantioselectivity (Scheme 104). The absolute stereochemistry of a representative example (**310** R = H, R^1 = *p*-Cl) was determined as being *R* by X-ray crystallographic analysis.

As a variant to this reaction, the groups of Terada,[262] and Zhou[263] reported, in quick succession, the use of enamides or encarbamates as masked imines in the organocatalytic aza-Friedel−Crafts reaction with indole. Both groups employed the highly hindered chiral Brønsted acid **194k** (Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$) to promote the reaction of indole to unsubstituted and aromatic enamides (Scheme 105). Terada employed the *R*-form of the catalyst with α-unsubstituted *N*-Boc enecarbamates giving a range of the corresponding secondary (*S*)-*N*-Boc amine products **311** in very good yield and excellent ee. On the other hand, Zhou opted to use the *S*-form of the catalyst with α-aryl *N*-

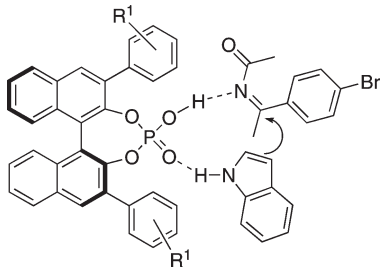


Figure 26. Proposed transition state for the aza-Friedel−Crafts reaction of enamides (Zhou).

Ac enamides leading to the formation of the amide **312** incorporating a quaternary stereogenic carbon center, in almost quantitative yield with high ee. The absolute stereochemistry of this product was also determined as being *S*. In both procedures, the choice of solvent was found to be critical for the attainment of high ee. Terada noticed that the (*Z*) imine isomer showed higher reactivity than (*E*) although the sense and level of enantioselectivity was the same regardless of which isomer was used. Both groups proposed a similar transition state for the reaction in which the enamide or the encarbamate is converted *in situ* to the imine and the indole reacts through an H-bonded arrangement adjacent to the imine (Figure 26). Weight was given to this postulate by Zhou et al., who also noted that use of *N*-methyl indole led to no reaction, presumably due to its inability to hydrogen bond to the catalyst.

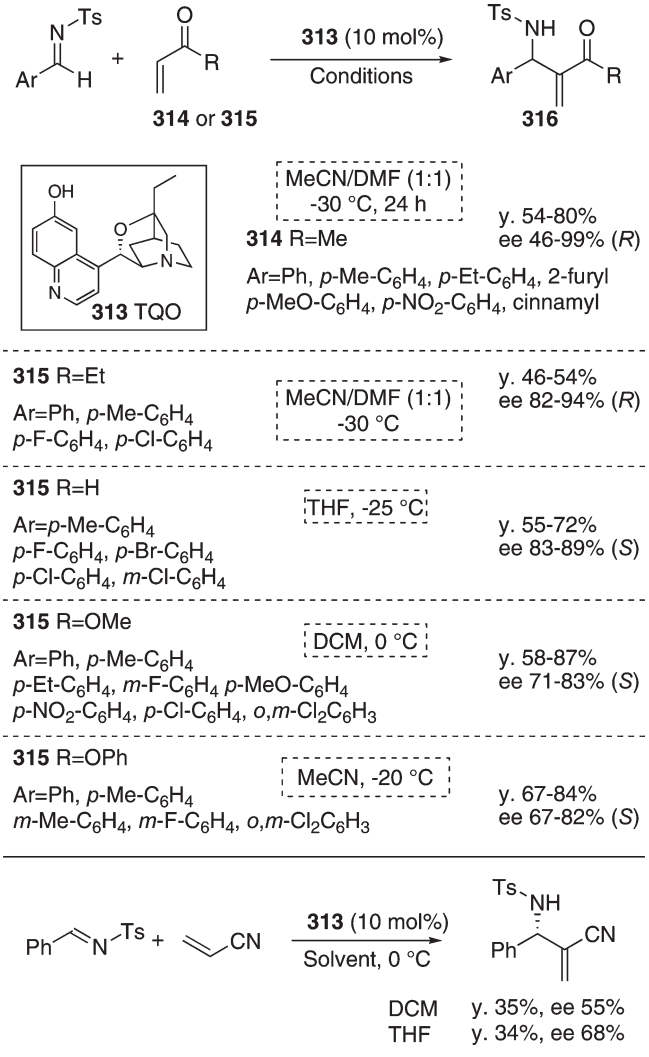
5. AZA-MORITA−BAYLIS−HILLMAN (AMBH) REACTIONS

The Morita−Baylis−Hillman reaction, reported initially by the group of Morita[264] and re-reported later by Baylis and Hillman,[265] is an extremely powerful reaction for the formation of compounds of high functional density.[266] The AMBH reaction between methyl acrylate and imines was first reported in 1984; however, until some years later, the only asymmetric versions of the reaction required stoichiometric quantities of the chirality transfer agent.[267] A number of important advances in this direction have been made since then.[268]

Much of the running in the field has been made by Shi and co-workers. They introduced a protocol for the AMBH reaction of simple acceptors using 4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,0^{3,8}] dec-5-yl)quinolin-6-ol (TQO **313**).[269] Solvent effects were found to be extremely important in the reaction, and extensive optimization studies, which allowed the development of conditions that facilitated the addition of MVK and EVK to a range of *N*-tosyl imines in good yield with a high preference for the *R*-isomer (Scheme 106), were conducted.[270] Significantly, neither (+)-quinidine, (−)-quinine, nor O-methylated TQO were effective in the reaction, indicating that the OH group on the quinoline core is important for effective catalysis. The difference in enantioselection was ascribed by the authors to the relative difference in sizes between the methyl or ethyl group in MVK and EVK compared with OMe or OPh in the acrylates (Figure 27). The reactions of other *N*-sulfonyl imines (Ms, Ns, SES) with MVK and methyl acrylate were also reported (yield 58−72%, ee 77−89%) as was the corresponding reaction with acrylonitrile, which proceeded in low yield and moderate ee in both DCM and THF. The use of phenyl vinyl ketone (PVK) in the reaction with DABCO as base gave the double AMBH product as the sole product, although the corresponding chiral version of the reaction promoted by TQO

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 106. Catalytic Asymmetric AMBH Reaction vsPromoted by TQO



afforded the double addition product with very low stereoinduction (Scheme 107).[271]

In a related report, Hatakeyama[272] and co-workers used TQO **313** as well as Me-TQO **317** and **QN** to catalyze the addition of highly fluorinated acrylic ester 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA **318**) to a range of differentially N-functionalized imines derived from aromatic aldehydes giving products **319** (Scheme 108). It was found that the reaction proceeded to some extent with imines having a wide variety of different N-substituents including *N*-benzoyl, *N*-sulfonyl, and *N*-phosphonyl. The *S*-isomer of the respective additions was obtained regardless of the nature of the substitutent on the imine nitrogen. *N*-DPP imines were found to be the best electrophiles, undergoing addition with up to 97% yield and 73% ee. Treatment with dilute mineral acid led to removal of the *N*-protecting group and concomitant hydrolysis to give the corresponding α,β-unsaturated β-amino acid that could be cyclized to β-lactam **320**. The TQO system has been applied to the demanding AMBH reaction of 3,4-diene-2-ones.[273] Unfortunately only moderate yields and low selectivities were obtained when 10 mol % of the catalyst was used in the reaction with *N*-naphthylsulfonyl imines in DMSO (Scheme 109).

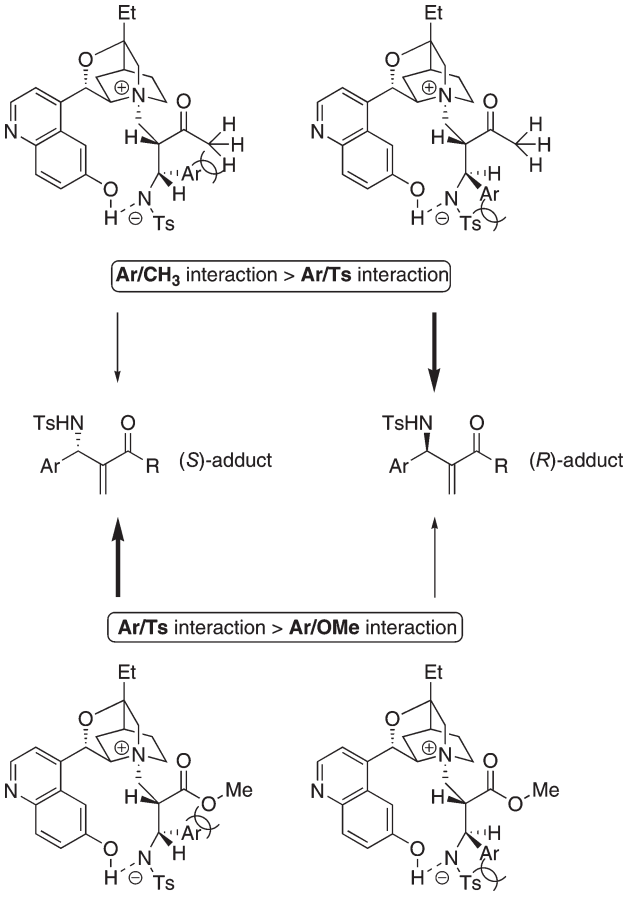
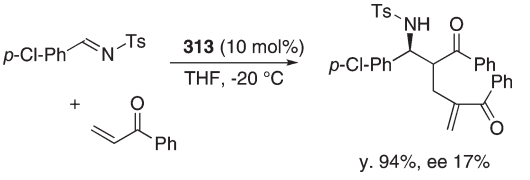


Figure 27. Rationalization of stereochemical outcome of the AMBH reaction catalyzed by TQO.

Scheme 107. Double AMBH Reaction Catalyzed by TQO

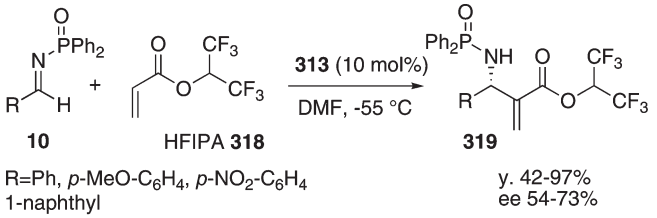


A three-component system for the condensation of aryl aldehydes, tosylamide, and methyl- or *tert*-butyl acrylate using TQO as the chiral source (15 mol %) and $Ti(O^iPr)_4$ (2 mol %) as cocatalyst giving the addition products in high yield and moderate enantioselectivity (yield up to 95%, ee up to 74%) has also been reported.[274] One example of the addition to acrylonitrile, using benzaldehyde and tosylamide, was also described (yield 45%, ee 53%).

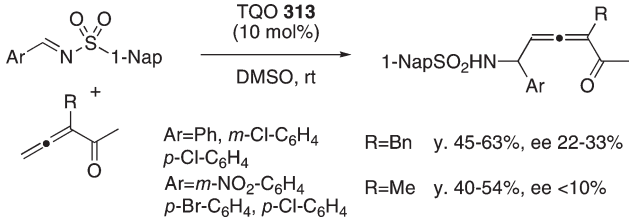
A mixed chiral phosphine/naphthol Lewis base catalyst system has also been developed for the reaction. Shi and co-workers used **321** to catalyze the addition of MVK, acrolein, and phenyl acrylate to *N*-sulfonyl imines providing moderate to high yields of the addition product in high stereoselectivity as the *S*-isomer regardless of the substrate (Scheme 110).[275] As is often the case with multiequilibrium step reactions, pronounced solvent and temperature effects were evident. For example, when phenyl acrylate was employed as the nucleophile precursor, reaction

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 108. Catalytic Asymmetric Aza-MBH Reaction of HFIPA and *N*-DPP Imines



Scheme 109. Catalytic Asymmetric AMBH Reaction of Allenyl Ketone Acceptors

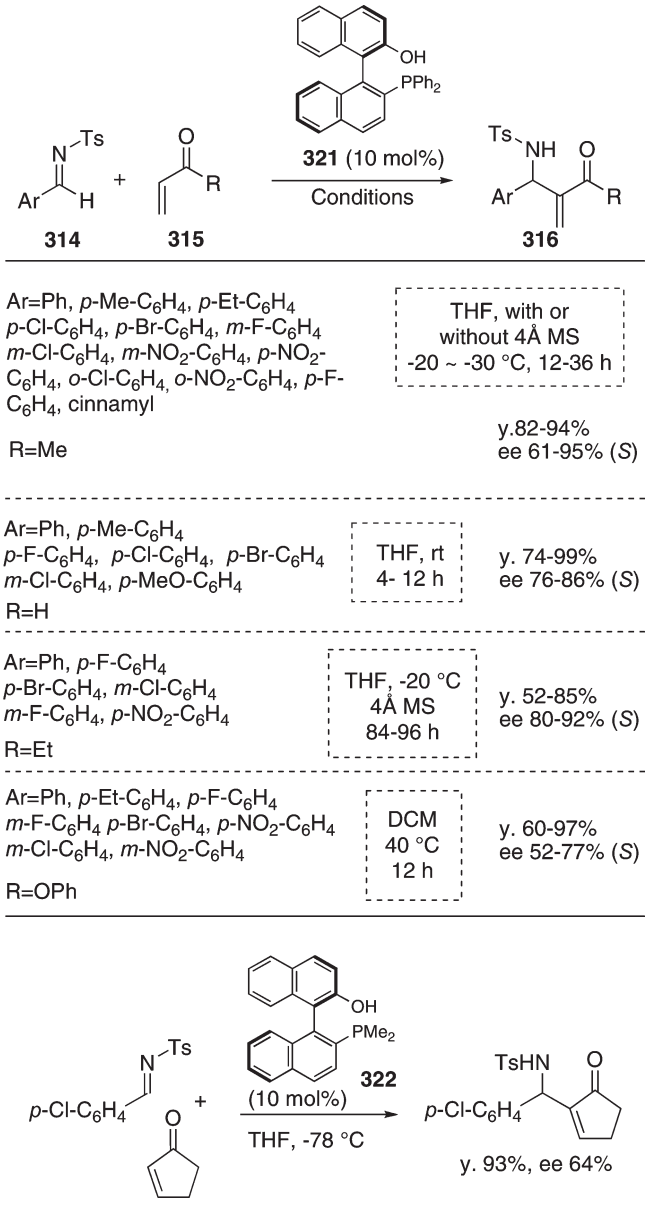


temperatures above ambient were required for efficient reaction, whereas in the case of acrolein, the optimum temperature was room temperature with lower temperatures actually affording the desired products with *lower* enantioselectivities. In the same paper, the authors also reported that *N*-sulfonyl groups other than tosyl could function in the reaction with *p*-Cl-C_6H_4 imine (*N*-Ms, yield 94%, ee 82%; *N*-*p*-$ClC_6H_4SO_2$, yield 94%, ee 89%; *N*-SES, yield 53%, ee 89%). However, both 1- and 2-naphthyl acrylates gave only low yields and selectivities in the reaction with *N*-Ts phenyl imine (1-naphthyl, yield 49%, ee 58%; 2-naphthyl, yield 57%, ee 53%). A closely related monophosphine/BINOL catalyst **322** has been found to promote the closely related AMBH reaction of *N*-tosyl aromatic imines with cyclic enones giving the corresponding adducts in good yield but moderate enantioselectivity (with cyclopentenone, yield 70−93%, ee 30−64%; with cyclohexenone, yield 66−90%, ee 14−23%),[276] a slight modification of the substituent on phosphorus from phenyl to alkyl was found to improve the reaction rate.[277]

In these reactions, the hydroxyl group on the naphthyl ring of the catalyst was found to be essential; the use of structural analogues either having no hydrogen bond donor group (**323**−**325**) or one with a different pK_a (**326**) either did not promote the reaction or gave low yields and ee of the *R* enantiomer. Further modification of binapthyl monophosphines having aromatic hydroxyl groups yielded alternative catalysts **327**−**330** that delivered similar or even slightly superior performance to the parent system (Scheme 111). The authors rationalized the selectivity using the transition state models shown in Figure 28.

Shi and co-workers also reported the use of linked-type phosphine/BINOLs **332**−**334** and dihydroxylated monophosphine/naphthol **335**. They demonstrated that in the reaction between MVK and *p*-chloroimine **35a** all the catalysts delivered

Scheme 110. AMBH Reaction Catalyzed by Chiral Phosphorous Lewis Bases 321 and 322

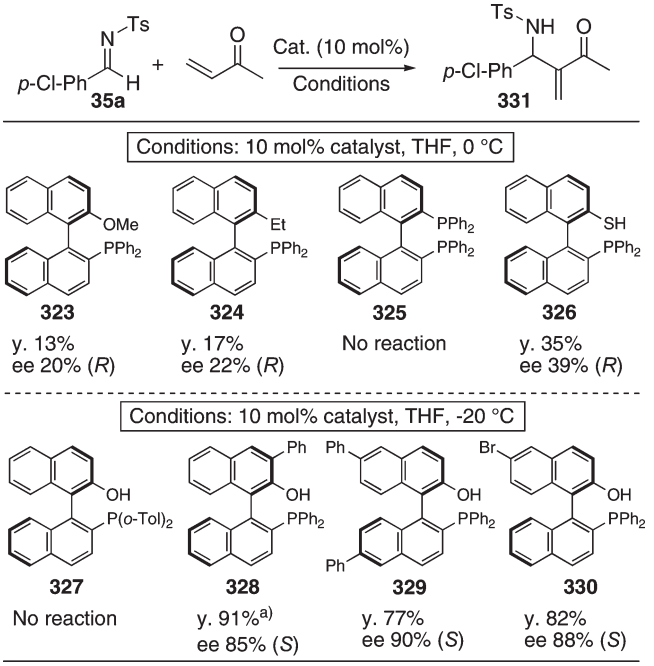


the desired adducts in impressive yield and selectivity (Scheme 112).[278] Catalyst **332** also showed excellent activity in the corresponding reaction with EVK and acrolein. The group of Ito have also introduced tridentate catalyst **336** as a related highly active catalyst for the reaction. Impressively, this system delivers the AMBH adducts in almost quantitative yield and up to 96% ee with as little as 1 mol % loading.[279]

In related work, Shi et al. introduced a range of catalysts **337** and **338** bearing highly fluorinated "ponytails". These systems displayed a similar level of activity as the linked-type monophosphine/BINOL catalysts, delivering the desired AMBH adducts in high to excellent yields and selectivities.[280] Shi also synthesized a dendritic chiral phosphine catalyst and applied it to the same AMBH reaction.[281] Other bifunctional chiral organocatalysts such as thiourea−phosphine and phosphine−amide for the asymmetric AMBH reactions were reported by the same group.[282,283]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 111. Other Phosphorous-Based Catalysts for the Catalytic Aza MBH Reaction



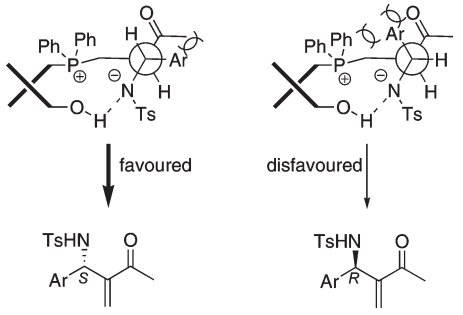
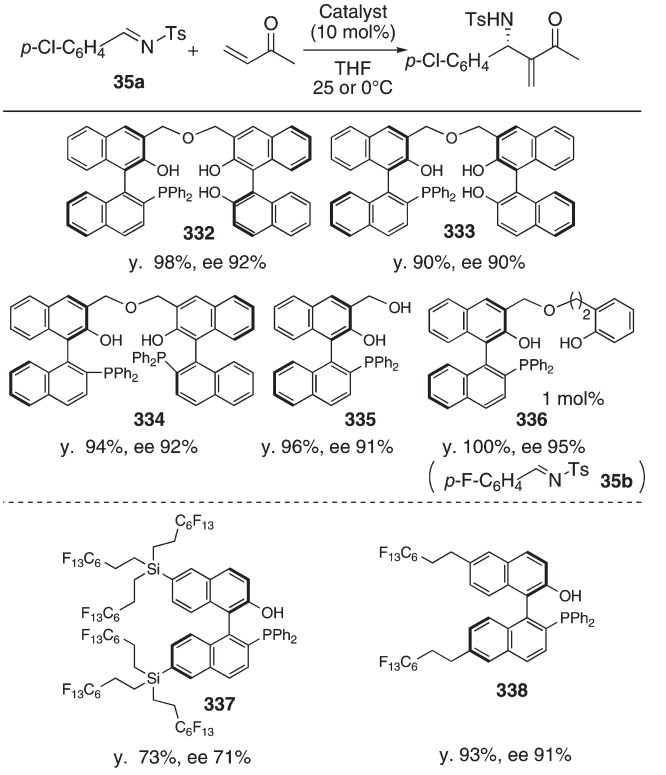


Figure 28. Transition state models for the phosphorus Lewis base-catalyzed AMBH reaction.

Sasai et al. have extended the scope of the reaction by introducing a number of novel nitrogen-[284] and phosphorus-centered[285] hybrid Lewis base−Brønsted acid catalysts **339a** and **340a** for the AMBH reaction. Both catalyst types displayed high activity in the rather exotic solvent system of toluene/cyclopentyl methyl ether or the more usual *tert*-butyl methyl ether with a wide variety of nonenolizable imines (Scheme 113). The authors postulated a bifunctional mode of action for the catalyst in which the heteroatom in the side chain acts first as a Lewis base in attacking the α,β-unsaturated carbonyl component to form an anionic intermediate, which is stabilized by hydrogen bonding to the Brønsted acidic naphthol hydroxyl group and which subsequently goes on to attack the imine partner in a Mannich-type interaction. Evidence for this mechanism was found in the observation that analogous catalysts **339b−d**, **340b−d**, and **341a−c**, which have structural features that would impede this process, either did not promote the reaction or afforded lower yields of products in lower selectivities.

A novel dual activation Lewis base−Brønsted acid protocol consisting of a symbiotic combination of DABCO and thiourea

Scheme 112. AMBH with Linked-type and Fluorinated Monophosphine Catalysts



216c has been introduced for the reaction between *N*-nosyl imines **342** and methyl acrylate by Jacobsen and co-workers.[286] Although yields of **343** were only low to moderate, enantioselectivities were extremely high. It should be noted that modest yields are a characteristic of most other competing protocols that make use of *N*-nosyl imines due to the rapid decomposition in solution of the imine component (Scheme 114).

The authors described the results of detailed kinetic studies, which suggested the existence of two competing pathways between **344a** formed in high ee and more hindered **344b** formed in low ee, having different ultimate fates in the reaction. The latter species was found either to precipitate from the reaction or to undergo retro-Michael addition to give **345**, which could then be funnelled down the route of **344a** thereby raising the ee of the reaction but decreasing yield. On the other hand, **344a** is soluble in the reaction medium and undergoes rate-limiting internal deprotonation/elimination to give the AMBH adduct. In contrast to the conventional Morita−Baylis−Hillman reaction, the imine had no influence on the internal elimination step (Figure 29).

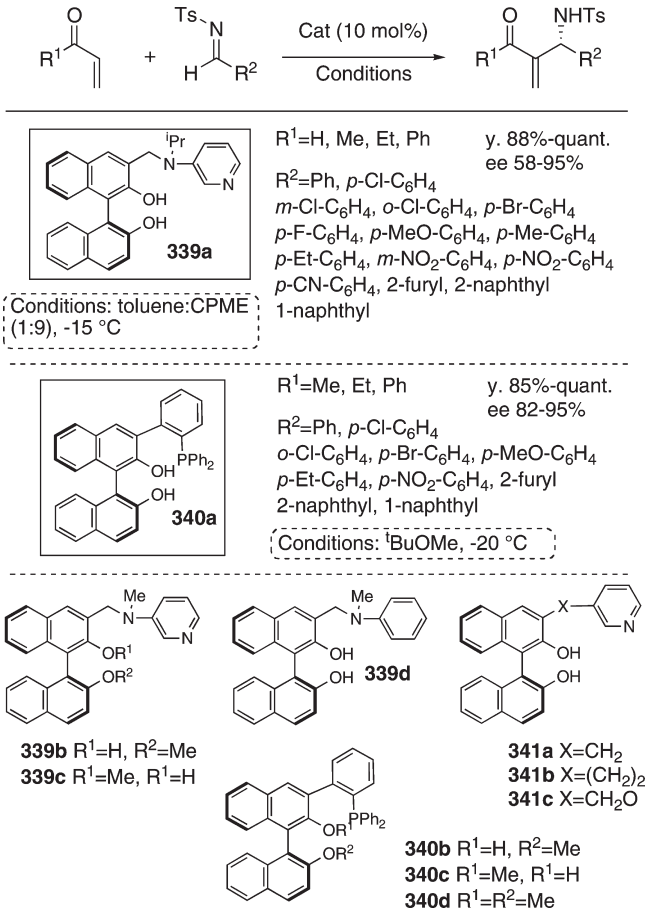
Córdova and co-workers reported that combination of proline and DABCO was effective for asymmetric aza-Morita−Baylis−Hillman-type reaction between *N*-Boc imines and unmodified α,β-unsaturated aldehydes.[287]

6. ASYMMETRIC CATALYTIC ADDITION OF NONSTABILIZED ORGANOMETALLIC NUCLEOPHILES

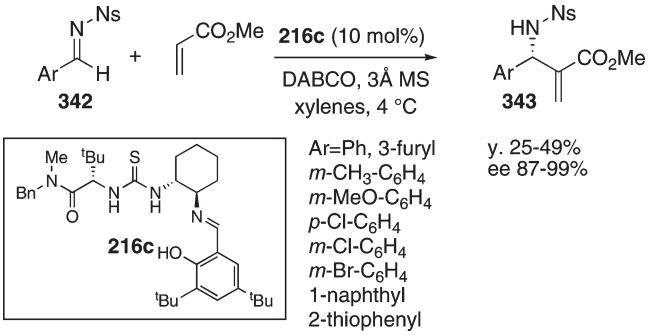
The addition of organometallic reagents to C=N represents an important and attractive area of organic synthesis because it permits rapid entry to a range of chiral building blocks useful for the synthesis of pharmaceutical compounds. Since the publication of

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 113. Sasai's Bifunctional Catalysts for the Asymmetric AMBH Reaction



Scheme 114. Jacobsen's DABCO/Thiourea-Catalyzed AMBH Reaction



our original article a good deal of progress has been made in this area, which for the purposes of the current review will be subdivided into arylation of imines using aryl metal nucleophiles, additions of alkali and alkali-earth organometallics, and additions of alkyl zinc reagents and alkynyl metal reagents, and allylation reactions.

6.1. Transition Metal-Catalyzed Arylation of Imines with Aryl Metal Nucleophiles

Although noncatalytic methods for the asymmetric addition of aryl metal nucleophiles to imines or their surrogates were

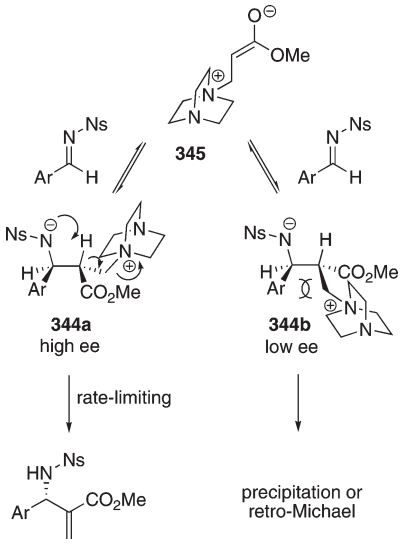


Figure 29. Proposed reaction intermediates in the DABCO/thiourea-catalyzed AMBH reaction.

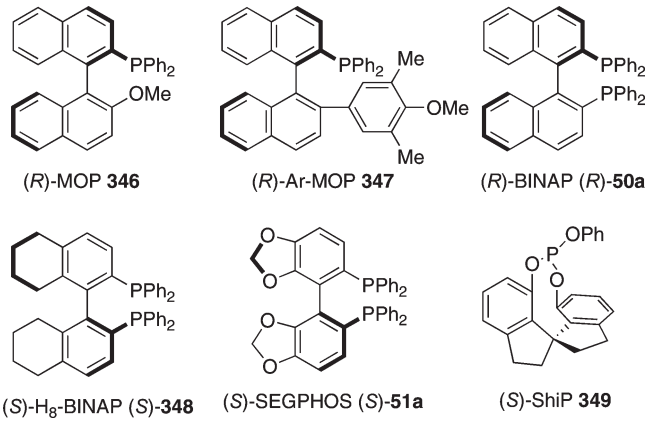


Figure 30. Ligands used in the arylation of imines with aryl metals.

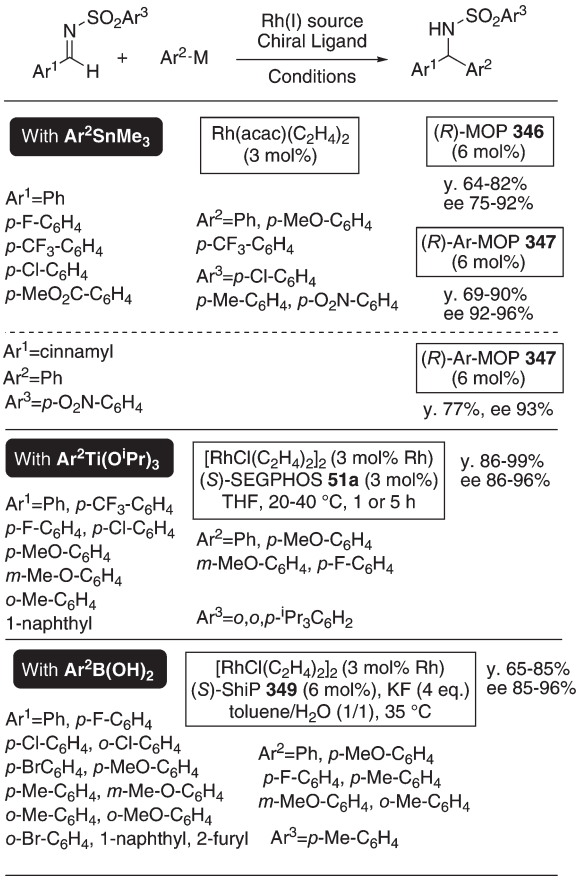
established some time ago,[288] it is only comparatively recently that progress on the catalytic asymmetric addition of aryl metals to imines mediated by transition metals and a wide range of ligands (Figure 30) has been made. The most common catalysts in this area are based on Rh(I) complexes; however a rather wider variety of aryl metal nucleophiles has been studied. The substrates of choice for these reactions are *N*-sulfonyl imine, and they have been smoothly condensed with aryl stannanes[289] using $Rh(acac)(C_2H_4)_2$ with (*R*)-MOP **346**, (*R*)-Ar-MOP **347**, or less successfully with BINAP **50a**, with aryl titanium isopropoxides[290] using $[RhCl(C_2H_4)_2]_2$ and (*S*)-SEGPHOS **51a**, and with aryl boronic acids[291] catalyzed by a combination of Rh(acac) $(CH_2Cl_2)_2$ and (*S*)-ShiP **349** (Scheme 115). In all cases, chemical yields were good to very good, and enantioselectivities were excellent. Judicious choice of the imine and aryl metal allowed the synthesis of the both enantiomers of selected diaryl amines.

6.2. Addition of Alkali and Alkali-Earth Metal Nucleophiles to Imines

The condensation of alkali and alkali-earth metal organometallics with C=N is an established protocol that has been the subject of detailed reviews.[292] Following on from the first reports

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 115. Addition of Aryl Metal Reagents to *N*-Sulfonyl Imines Promoted by Rh(I)



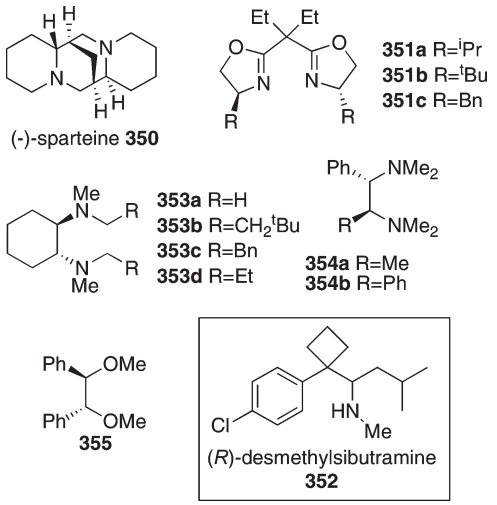
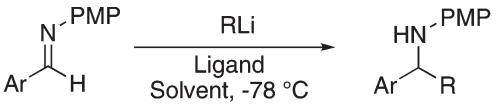


Figure 31. Ligands used in the asymmetric catalytic addition of organolithiums to imines.

by Tomioka,[293] a spate of activity in the field saw and continues to see rapid advances. The most common nucleophiles used in the reaction are allyl and aryl lithiums, and a number of chiral amine ligand systems have been developed as chiral mediators for the catalytic asymmetric addition (Figure 31). Among these, (−)-sparteine **350** has been widely exploited from the very beginning. Generally speaking, while chemical yields in the reaction are

Scheme 116. Asymmetric Addition of Organolithium Reagents to *N*-*p*-Methoxyphenyl Imines



Entry	Ar	R	Solvent	Ligand (mol%)	y. (%)	ee (%)
1	Ph	Me	Et_2O	**350** (50)	97	11 (*R*)
2	Ph	^{n}Bu	Et_2O	**350** (60)	99	25 (*R*)
3	3-thienyl	Ph	toluene	**353a** (20)	95	60(+)
4	3-thienyl	Ph	toluene	**353b** (20)	68	3
5	3-thienyl	Ph	toluene	**353c** (20)	62	12 (–)
6	3-thienyl	Ph	toluene	**353d** (20)	59	7 (–)
7	3-thienyl	Ph	toluene	**354a** (20)	82	61 (–)
8	3-thienyl	Ph	toluene	**354b** (20)	87	59 (–)
9	3-thienyl	Ph	toluene	**350** (20)	79	0
10	*p*-Me-C_6H_4	Ph	toluene	**353a** (20)	42	63 (–)
11	*p*-CF_3-C_6H_4	Ph	toluene	**353a** (20)	72	60 (+)
12	*p*-MeO-C_6H_4	Ph	toluene	**353a** (20)	14	68 (–)
13	1-Naphth	Ph	toluene	**353a** (20)	61	55 (+)
14	2-Naphth	Ph	toluene	**353a** (20)	74	61 (+)
15		Ph	toluene	**353a** (20)	44	64 (–)

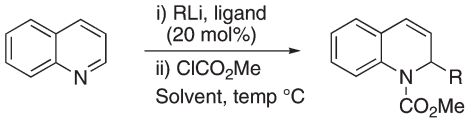
good to excellent, synthetically meaningful levels of enantioselectivity are only achieved with stoichiometric or superstoichiometric quantities of the ligand. In a typical example, Lete and co-workers could only obtain ee's of 11−25% in the addition of MeLi and ^{n}BuLi to simple *N*-PMP imines (Scheme 116, entries 1 and 2) with 50−60 mol % of sparteine.[294]

Box-ligand **351b** and related species **38a** and **38b** were among those examined as chiral promoters of the key addition step in the first asymmetric synthesis of (*R*)-desmethylsibutramine **352**.[295] A combination of ^{i}BuLi and chiral ligand (20 mol %) gave the product in 95% yield but only 40% ee. Better results were obtained by the group of Alexakis who used a range of chiral 1,2-diamines **353a**−**d** and **354a**,**b** to mediate the addition of phenyl lithium to 2-thienyl-*N*-PMP imine (Scheme 116, entries 3−9).[296] They identified **353a** as the ligand of choice and demonstrated the addition of phenyllithium to a range of aromatic *N*-PMP imines obtaining the diaryl amines in 14−74% yield and 55−68% ee. The same group also investigated the addition of alkyl and aryllithiums to quinoline[297] and isoquinoline.[298] In the former case, the group focused on the use of chiral DME ligand **355** and Box-type ligands **351a**−**c** as well as (−)-sparteine **350** and successfully added MeLi, ^{n}BuLi, PhLi, and NaphthLi to the parent quinoline, trapping the N−Li intermediate with methyl chloroformate. While the chemical yields of these reaction were good to excellent, once more enantioselectivities were low to moderate (Scheme 117). A clear influence of temperature and solvent were noted, and only diethyl ether or toluene gave any chiral induction. The same paper also discussed the addition of Grignard, $AlMe_3$, and Me_2Zn reagents to the same substrate.

In the addition of organolithium reagents to isoquinoline, the reaction was complicated by competing mono- and diaddition of

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

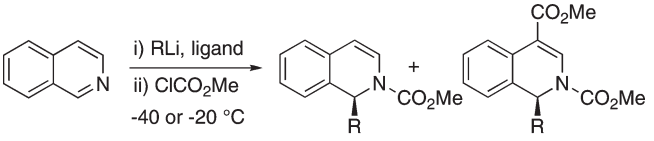
Scheme 117. Addition of Alkyl and Aryllithiums to Quinoline in the Presence of Chiral Ligands



356a R=^{n}Bu, **356b** R=Ph
356c R=Naphth, **356d** R=Me

Entry	R	Solvent	temp (°C)	Ligand (mol%)	y. (%)	ee (%)
1	^{n}Bu	Et_2O	-60	**355**	86	4 (*R*)
2	Ph	toluene	-60	**355**	74	<2 (*S*)
3	Naphth	toluene	-50	**355**	45	5 (*S*)
4	^{n}Bu	toluene	-40	**350**	67	15 (*S*)
5	^{n}Bu	Et_2O	-40	**350**	100	13 (*S*)
6	Ph	toluene	-78	**350**	38	7 (*R*)
7	Ph	Et_2O	-78	**350**	60	24 (*R*)
8	Naphth	toluene	-50	**350**	66	6 (*R*)
8	Naphth	Et_2O	-50	**350**	64	12 (*R*)
10	Me	toluene	-40	**351a**	30	62 (*S*)
11	Me	Et_2O	-60	**351a**	31	31 (*S*)
12	^{n}Bu	toluene	-80	**351a**	55	67 (*S*)
13	^{n}Bu	Et_2O	-70	**351a**	79	45 (*S*)

Scheme 118. Addition of Alkyl and Aryllithiums to Isoquinoline in the Presence of Chiral Ligands



357a R=Me
357b R=Ph

358a R=Me
358b R=Ph

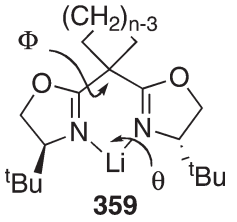
Entry	R	Solvent	Ligand (mol%)	y. (%)	ratio **357**/**358**	ee **357**/**358** (%)
1	Me	toluene	**355** (50)	-	-	13/-
2	Me	toluene	**350** (25)	89	70/30	36/38
3	Me	Et_2O	**350** (20)	76	70/30	23/30
4	Ph	toluene	**350** (20)	79	61/39	37/30
5	Ph	Et_2O	**350** (20)	76	67/33	20/30

methyl chloroformate of the N−Li intermediate giving compounds **357** and **358**, respectively, in ratios between 61/39 and 70/30. High ligand loadings were typically required (up to 50 mol %), and enantioselectivities were again low to moderate (Scheme 118).

Denmark and co-workers have conducted a systematic investigation into the effect of bite angle in tethered BOX-type ligands **359** (Figure 32) on the enantioselectivity of addition of MeLi to *N*-PMP imines derived from benzaldehyde, cinnamaldehyde, and 3-phenylpropanal.[299] High yields and enantioselectivities (up to 91% ee) were realized, although a stoichiometric amount of the chiral ligand was required in every case.

6.3. Addition of Alkyl and Aryl Zinc Reagents to Imines Promoted by Transition Metals

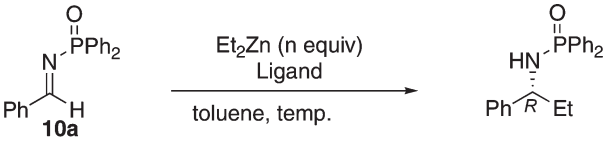
The catalytic asymmetric addition of organozinc reagents to carbonyl compounds is a well-established process in synthesis



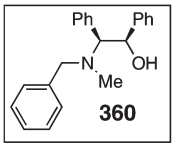
359

Figure 32. Tethered BOX-type ligand.

Scheme 119. Asymmetric Catalytic Addition of Et_2Zn to *N*-DDP Imines with Cinchonidine



Chan *et al*

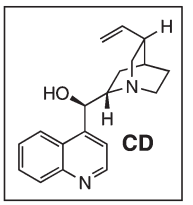


360

Et_2Zn (4 equiv.)
Ligand **360** (50 mol%)
rt, 72 h

y. 67%
ee 90%

Beresford



CD

Et_2Zn (12 equiv.), ligand **CD** (x mol%)

Entry	x mol%	temp (°C)	y. (%)	ee (%)
1	50	rt	77	87
2	20	rt	52	80
3	5	rt	50	69
4	20	4	37	75
5	20	60	50	41
6[a)]	20	rt	70	93

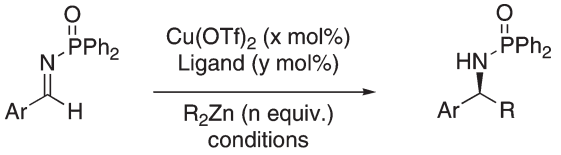
a) MeOH (200 mol%) added

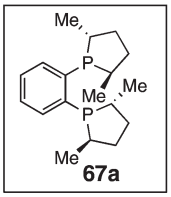
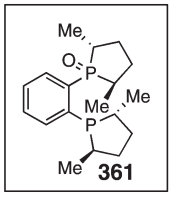
and a large number of protocols for the same have been reported.[300] In contrast, the analogous reaction with C=N compounds has been less extensively explored. While methods for the asymmetric organozincation of imines have been established, they generally require the use of stoichiometric chiral agents and are limited in their scope because commonly used nonactivated imines (*N*-aryl, *N*-benzyl, *N*-silyl, etc.) are not reactive toward addition. Pioneering work by Soai and co-workers[301] introduced *N*-diphenylphosphinoyl (*N*-DPP) imines as viable substrates, and these, along with *N*-sulfonyl and *N*-acyl imines, are the substrates of choice in the reaction.

Following on from this early work, while a number of groups have introduced catalyst systems for the asymmetric addition of alkyl zinc reagents to *N*-DPP imines using stoichiometric quantities of the chiral source,[302] the corresponding version of the reaction using substoichiometric amounts is less well-represented. Chan has reported an isolated example of the addition of diethyl zinc to simple *N*-DPP imine **10a** using chiral ethanolamine **360** in moderate yield and high ee.[303] While the level of asymmetric induction was impressive, it should be noted that 50 mol % of the chiral entity was required. Beresford[304] has conducted a more systematic investigation of the same reaction with cinchona alkaloids as the chiral source, in which he found

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 120. $Cu(OTf)_2$ Catalysts for the Catalytic Asymmetric Addition of Et_2Zn to *N*-DPP Imines



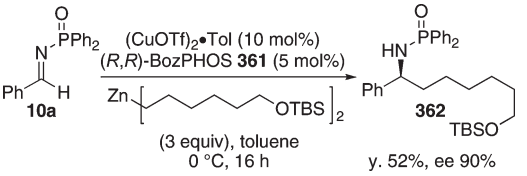
Conditions:	$Cu(OTf)_2$ (10 mol%) (*R*, *R*)-Me-DUPHOS **67a** (5 mol%) toluene, 0 °C, 48 h
 **67a**	**Et_2Zn** (2 equiv.) y. 74-98%, ee 85-96% Ar=Ph, *p*-Cl-C_6H_4 *p*-Br-C_6H_4, *p*-MeO-C_6H_4 *p*-Me-C_6H_4, *m*-Me-C_6H_4 1-naphth, 2-naphth, 2-furyl, cyclopropyl 
	Me_2Zn (2 equiv.) y. 51%, ee 90% **$^nBu_2Zn$** (2 equiv.) y. 71%, ee 91% Ar=Ph
Conditions:	$Cu(OTf)_2$ (6 mol%) (*R*, *R*)-BozPHOS **361** (3 mol%) toluene, 0 °C, 16-20 h
 **361**	**Et_2Zn** (2 equiv.) y. 91-98%, ee 92-99% Ar=Ph, *p*-Cl-C_6H_4 *o*-Cl-C_6H_4, *p*-Br-C_6H_4 *p*-MeO-C_6H_4, *o*-MeO-C_6H_4 *p*-Me-C_6H_4, *m*-Me-C_6H_4 *o*-Me-C_6H_4,  1-naphth 2-naphth, 2-furyl, cyclopropyl
	Me_2Zn (2 equiv.) y. 80-90%, ee 89-97% Ar=Ph, *m*-Me-C_6H_4, 2-furyl
	$^nBu_2Zn$ (2 equiv.), Ar=Ph y. 92%, ee 96% **$^iPr_2Zn$** (2 equiv.), Ar=Ph y. 84%, ee 95%

that moderate to good yields of the desired product could be obtained with 20 mol % cinchonidine **CD** at room temperature (Scheme 119, entry 2). Interestingly higher or lower temperatures delivered inferior results (entries 4,5).

The efficiency of the reaction was found to be strongly dependent on the effect of additives, with the addition of 2 equiv of methanol to the system giving the same levels of yield and enantioselectivity at 20 mol % catalyst loading as had been observed for the reaction in the presence of a stoichiometric amount of the promoter.

More success for the addition to *N*-DPP imines has been realized by the use of catalytic copper-based catalyst systems.[8,305] The group of Charette used a simple combination of $Cu(OTf)_2$ (10 mol %) and phosphine ligand (*R*,*R*)-Me-DUPHOS **67a** to add Et_2Zn to a wide range of *N*-DPP imines derived from aromatic aldehydes in good yield and with moderate to high enantioselectivity (Scheme 120).[306] The protocol could be extended to the addition of dimethyl zinc and dibutyl zinc giving the corresponding amines in moderate yield but high enantiomeric excess as the *S* -isomer. Optimization experiments showed that

Scheme 121. Synthesis of Long-Chain Compound 362



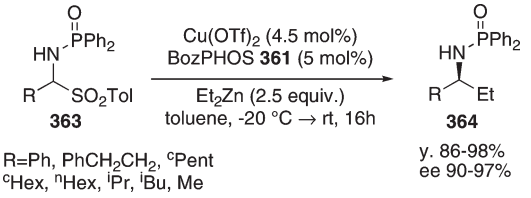
an excess of the Lewis acid relative to the chiral ligand was important for the realization of high yields and enantioselectivities because near equimolar complexes of the copper source and chiral ligand at lower ligand loadings (5 mol % Cu/5.5 mol % ligand) gave inferior results, although this could be ameliorated by the addition of 5 mol % $Zn(OTf)_2$ as a cocatalyst. Shortly after this, the same group introduced the hemilabile bidentate system BozPHOS **361** as a ligand for the copper-catalyzed addition.[307] Their choice was based on the observation that monodentate phosphines as well as bidentate phosphines function as efficient ligands for the reaction and that use of >2 equiv of Me-DUPHOS completely inhibited the reaction. The new system permitted the use of even lower catalyst loadings (down to 6 mol % Cu/3 mol % ligand) and slightly shorter reaction times under the same mild conditions. The substrate scope in the reaction of *N*-DPP imines was expanded, and diethyl, dimethyl, bi-*n*-butyl, and di-isopropyl zinc reagents were used as nucleophiles giving the corresponding *S* amines in excellent yield and enantioselectivity. The addition of long chain functionalized organozinc reagents was also effectively mediated by the BozPHOS system in the presence of Cu(I) as demonstrated by the synthesis of **362** (Scheme 121).

Furthermore, it was found that the BozPHOS/Cu system permitted the generation of the imine *in situ* from the corresponding *N*-phosphinoylamine precursor **363**. This opened the door to the use of imines derived from aliphatic aldehydes whose limited stability normally precludes their use as electrophiles. Application of the BozPHOS/$Cu(OTf)_2$ system with a number of aliphatic *N*-DPP imines gave the desired addition products in excellent yields and enantioselectivities (Scheme 122).[308]

The authors noted that in contrast to the Me-DUPHOS system, the BozPHOS system was not sensitive to the order of addition of reagents. It is known that in the case of Me-DUPHOS, yields and selectivities of the addition reaction are dramatically dependent on the order of mixing of the reagents. Premixing of the copper source and ligand followed by addition of the zinc reagent and substrates gives the addition product in high yields and enantioselectivities; whereas changing the order of addition such that the copper and organozinc species are brought together prior to the addition of the ligand leads to sharply reduced yields and almost no stereoselection. Investigation of this phenomenon led the authors to conclude that in effect the Cu/Me-DUPHOS is only a precatalyst and the actual active species in these catalyst systems in fact consists of a bisphosphine monoxide species. In the case of BozPHOS, this moiety is inherent in the ligand, but with the analogous Me-DUPHOS system, the oxidation occurs during catalyst preparation, a process which is suppressed if the copper catalyst and zinc reagent are premixed before the addition of the ligand.[309]

The group of Shi have introduced an alternative catalyst system for the addition of diethyl zinc based on complexes of copper salts and binaphthylthiophosphoramides.[310] An attractive feature of this system is that it may be applied to a wide range of

Scheme 122. Catalytic Asymmetric Addition of Et_2Zn to Aliphatic *N*-DPP Imines

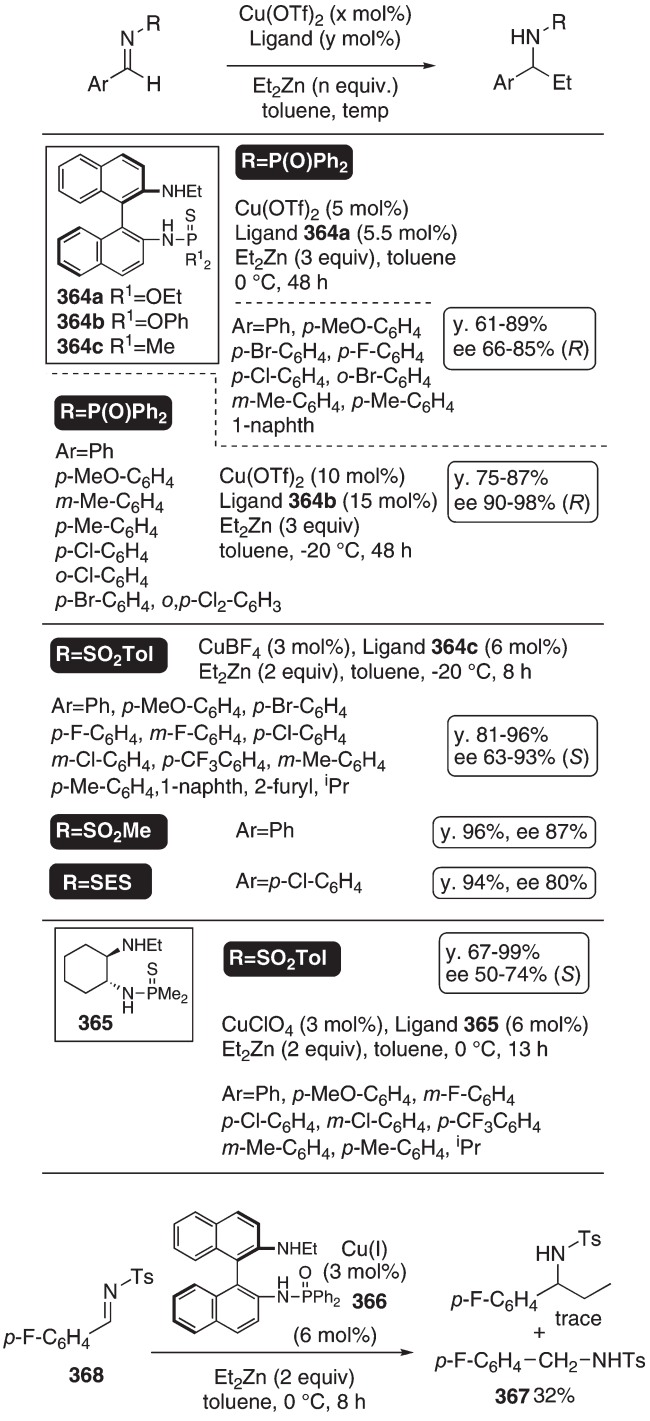


both *N*-DPP imines and *N*-sulfonyl imines (Scheme 123). Screening of a large number of ligand structural analogues and Cu(I) sources identified complexes of the chiral binaphthylthiophosphoramides **364a**[311] or **364b**[312] with $Cu(OTf)_2$ as the best catalyst systems for the addition of Et_2Zn to *N*-DDP imines. Both combinations delivered the expected *R* ethylamine products in moderate to good yield although the use of more bulky aryl phosphoramide ligand **364b** gave superior enantioselectivites. In the *N*-sulfonylimine series, the dimethyl phosphoramide **364c**[313] and $CuBF_4$ was found to be the most efficacious combination for the addition to *N*-Ts, *N*-Ms, and *N*-SES imines, delivering the required products in very high yield and good to excellent ee as predominantly the *S* isomer. One example of addition to an imine derived from an aliphatic aldehyde (isovaleraldehyde) was reported. The closely related aliphatic C_1-symmetric ligand **365** was also identified via a ligand screen and used as its $CuClO_4$ complex to catalyze the same reaction with a similar range of *N*-Ts imine substrates to give the *S* product.[314] While yields were still very good to excellent, selectivities were modest in this case. It was found in all cases that the presence in the ligand of the P═S linkage was essential for high catalyst activity. When the analogous P═O containing ligands **366** were used, little or none of the desired products were obtained; instead low yields of the primary amine **367** arising from direct reduction of the starting material was observed.

Another copper-catalyzed system that can be used for the addition of organozincs to both *N*-DPP and *N*-sulfonyl imines has been reported by Wang et al. They used a ferrocenyl-based ligand **369**[315] and $Cu(OTf)_2$ as the catalyst system for the reaction between *N*-DPP imines[316] or *N*-tosyl imines[317] and diethylzinc, and although in their case slightly higher catalyst loadings were necessary than those reported by Charette, their systems gave comparably high yields and enantioselectivities (Scheme 124). Again an excess of the metal with respect to the ligand was important for the realization of high yields and stereoselectivities. Liao has also reported asimilar copper/*N*-DPP imines system using chiral *tert*-butanesulfinylphosphine ligand.[318]

Prior to these disclosures by Wang et al., a similar amidophosphine ligand system for the addition of organozinc reagents to *N*-sulfonyl imines was introduced by the group of Tomioka. They demonstrated that proline-derived P,N ligands[319] bearing bulky geminal side groups could form highly active and selective catalysts with a range of both Cu(I) and Cu(II) salts. Optimization studies[320] identified *gem*-dibenzyl amidophosphine **370** and *gem*-di(mesitylenemethyl) amidophosphine **371** as the best ligands in the reaction. $Cu(OTf)_2$ was selected as the copper source of choice because it afforded the products in all-round best yields and selectivities; although CuOTf·PhMe gave a more active catalyst in terms of shortened reaction times [0.5 h versus 5 h using $Cu(OTf)_2$], selectivities and yields were inferior.

Scheme 123. Chiral Binaphthylthiophosphoramide Cu(I)-Catalyzed Addition of Et_2Zn to Imines

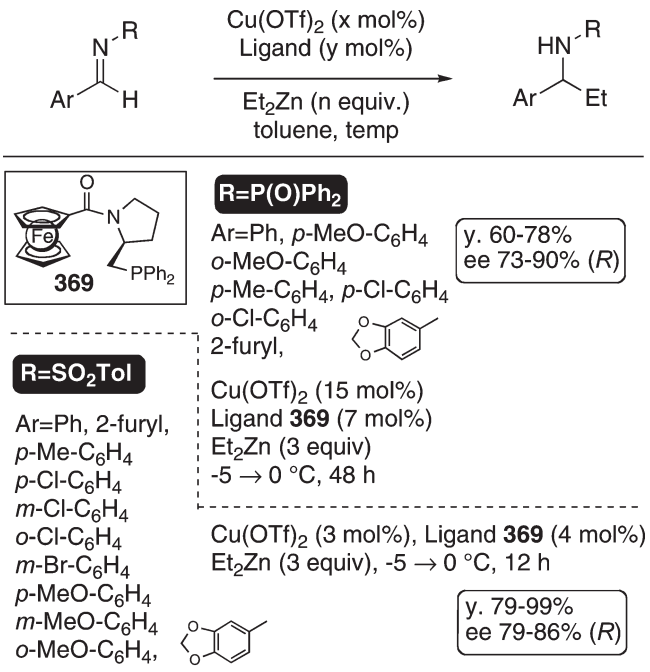


The $Cu(OTf)_2$−**370** system promoted the addition of diethylzinc to *N*-Ts, *N*-Ms, and *N*-SES imines in good to excellent yields and high stereoselectivities.[321] Importantly, the use of the *gem*-di(mesitylenemethyl)-substituted ligand **371** permitted the use of *N*-tosyl imines derived from aliphatic imines **372** in the reaction with diethyl zinc, opening a route to valuable *N*-tosyl aliphatic imines **373** in high yield and selectivity (Scheme 125).[322]

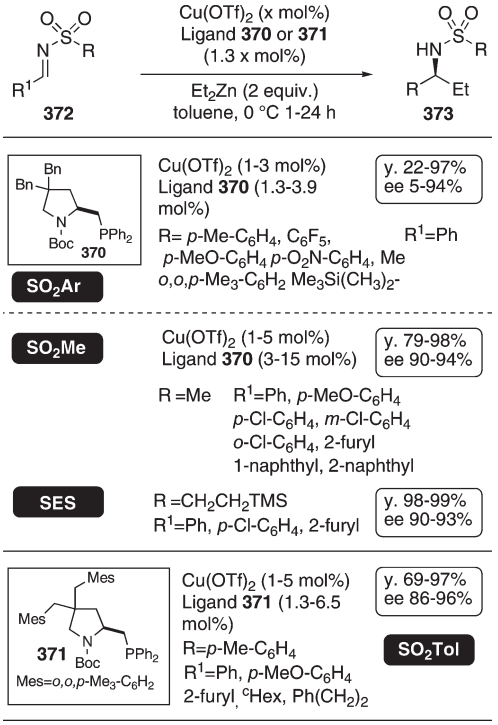
The group of Gong and Mi investigated chiral oxazolines **38** and **374**−**377** as ligands in the Cu(II)-catalyzed reaction

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 124. Catalytic Asymmetric Addition of Et_2Zn to *N*-DPP and *N*-Tosyl Imines Mediated by Cu(II)/369

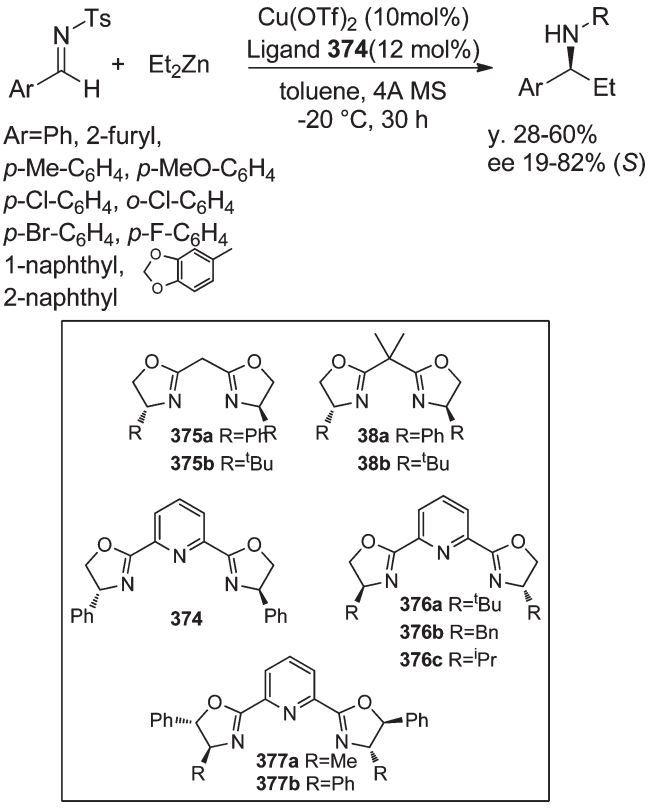


Scheme 125. Tomioka's Chiral Amidophosphine−Cu Catalyzed Ethylzincation of *N*-Sulfonyl Imines



(Scheme 126).[323] A survey of a large number of candidates identified pyBOX-type ligand **374** as optimum ligand with Cu(OTf)$_2$ as the copper source. However, even with this combination, yields of the addition products were low to moderate and enantioselectivities struggled to exceed 80%.

Scheme 126. Addition of Diethylzinc to *N*-Tosylimines Promoted by Cu(II)−Oxazoline Catalysts

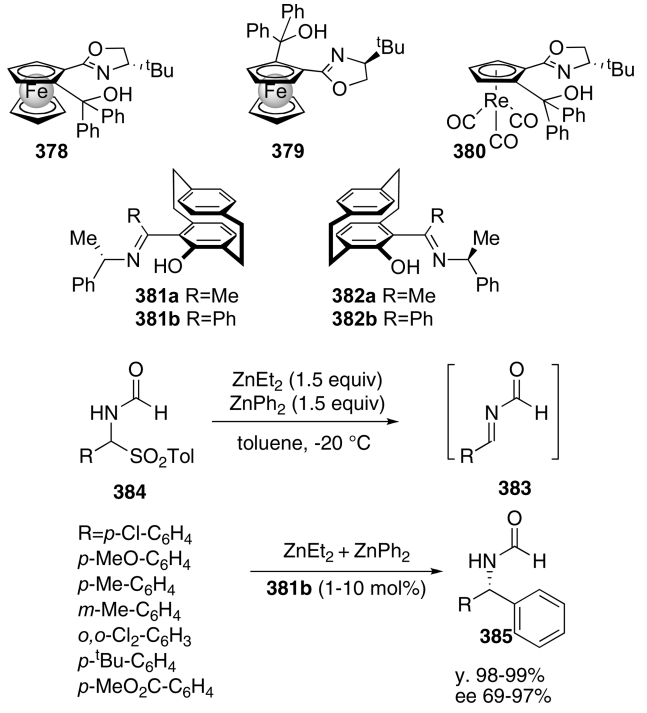


The activating group on the nitrogen of the imine in the reaction is not limited to phosphinoyl or sulfonyl groups. Bräse et al.[324] have reported that a combination of $ZnPh_2$ and $ZnEt_2$ with either ferrocenyl ligands **378** and **379**, disubstituted η^5-cyclopentadienyl rhenium tricarbonyl complex **380** or *S* paracyclophane ligands **381a,b** and **382a,b** permits the addition of Ph_2Zn to *N*-formylimines **383** generated *in situ* from the toluenesulfonyl precursor **384** giving adducts **385** (Scheme 127). Initial screening established paracyclophane **381b** as the ligand of choice. Using between 1 and 10 mol % of the chiral source, the reaction was found to proceed under exceptionally mild conditions in uniformly excellent yield and with enantioselectivities ranging from 69% to 97%. Use of diphenyl zinc alone led to lower ee's presumably due to a fast uncatalyzed back reaction under these conditions. It should be noted that although this reaction requires 1.5 equiv of the metal catalyst, the chiral source is used in less than stoichiometric quantities. The same group have extended the methodology to the efficient functionalization of *N*-carbamoyl, *N*-acyl, and *N*-formyl aromatic imines with diethylzinc.[325] Once again they generated the imine substrates by elimination of toluene sulfinic acid from suitable precursors *in situ* and achieved near quantitative yields and very high levels of enantioselection in the addition reaction (Scheme 128).

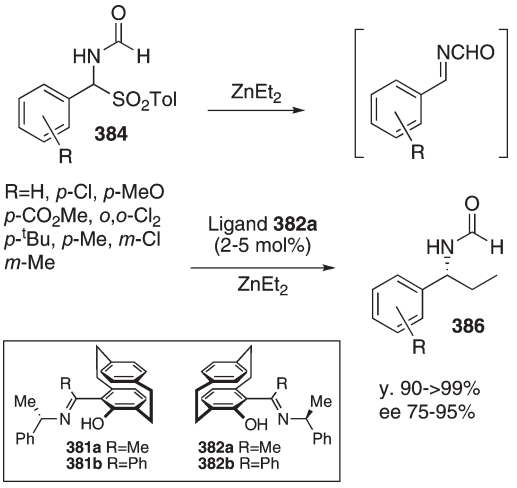
The authors noted that the sense of enantioselection (*R*) was opposite to that observed for the analogous addition of Et_2Zn to aldehydes, which taken in tandem with the higher ee's obtained for the imine addition led them to speculate that in this case the mechanism of the reaction involved the bidentate coordination of the imine to the active zinc species. This methodology, in

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 127. Asymmetric Addition of $ZnPh_2/ZnEt_2$ Reagents with *N*-Formyl Imines



Scheme 128. Bräse's Paracyclophane−$ZnEt_2$ Protocol for the Ethylzincation of *N*-Formyl Imines



contrast to other protocols, it does not involve the use of any metal promoter, other than zinc itself, in the reaction.

An alternative method has been introduced by Gong and co-workers who made used of a double ligand system inspired by the asymmetric activation concept pioneered by Mikami.[326] They screened combinations of homochiral imines and substituted BINOLs as potential catalysts for zincation of imines and showed that a 1:1 mixture of chiral imine **387** and 3,3′-di(3,5-bis-(trifluoromethyl)phenyl)-2,2′-binaphthyl **388a** in the presence of diethyl zinc (Figure 33) formed the optimum catalyst for the addition of diethylzinc to a variety of *N*-formyl imines generated *in situ* (Scheme 129).[327] Although toluene, the conventional

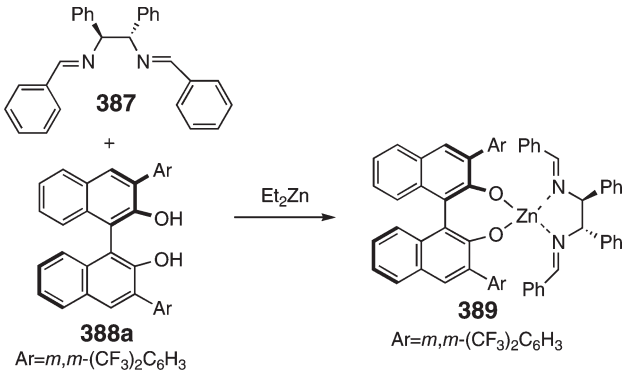
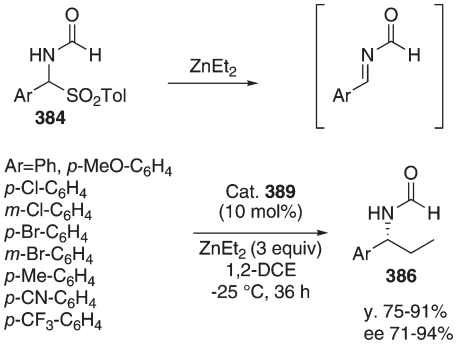


Figure 33. Asymmetric activated chiral catalysts for the addition of Et_2Zn to imines.

Scheme 129. Addition of Et_2Zn to *in situ* Generated Imines Promoted by Catalyst 389



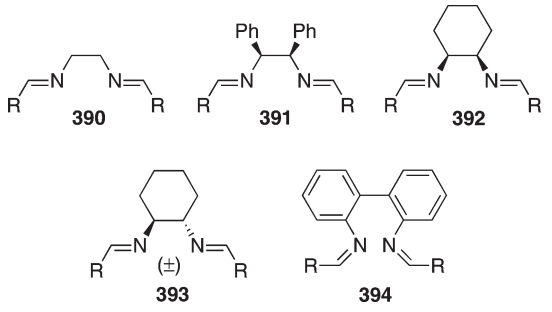


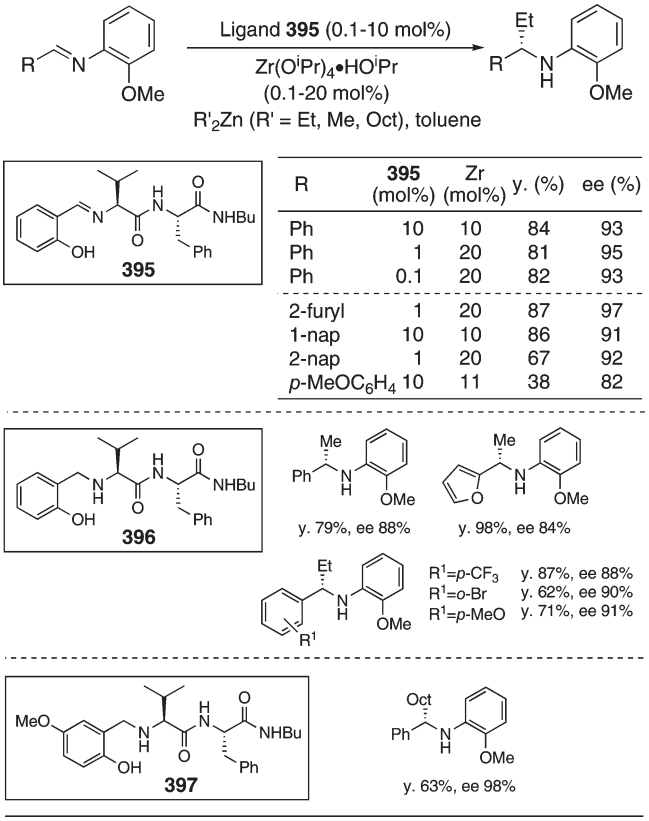
Figure 34. Achiral, racemic, or *meso*-diimino coligands **390**−**394**.

solvent for diethylzinc additions, gave best results at 0 °C and above, lower temperatures (−25 °C) favored DCM or 1,2-DCE, the latter being chosen as the optimum medium for the reaction. Under these conditions, diethylzinc could be added smoothly to a broad range of imines giving the expected products as the *R*-isomer in good to very good yield and up to 94% ee.

The authors later discovered that comparable results could be achieved using achiral, racemic, or *meso*-diimino coligands **390**−**394** (Figure 34) with chiral BINOL as the source of asymmetry. Best results were obtained with a combination of **388a** [Ar = *m*,*m*-$(CF_3)_2C_6H_3$] and racemic auxiliary ligand **393** (R = 2-naphthyl), which catalyzed the addition of Et_3N to a range of *in situ*-generated aromatic *N*-formyl imines in good to excellent yield (71−96%) and very high enantioselectivity (92−97% ee).[328]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 130. Hoveyda's Peptidic/Zr Catalyst System for Addition of Alkyzincs to Imines



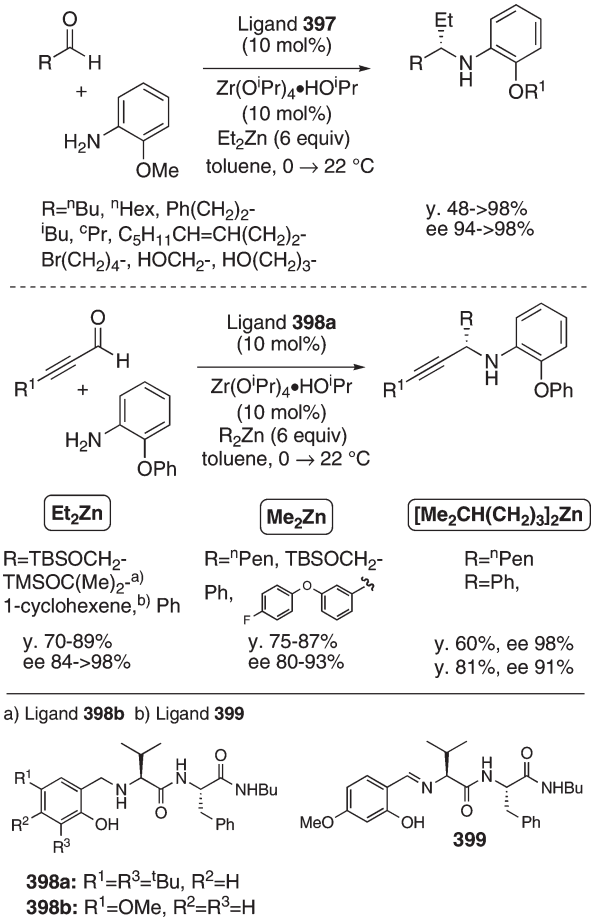
R	395 (mol%)	Zr (mol%)	y. (%)	ee (%)
Ph	10	10	84	93
Ph	1	20	81	95
Ph	0.1	20	82	93
2-furyl	1	20	87	97
1-nap	10	10	86	91
2-nap	1	20	67	92
p-MeOC$_6$H$_4$	10	11	38	82

y. 79%, ee 88%; y. 98%, ee 84%

R^1=*p*-CF_3 y. 87%, ee 88%
R^1=*o*-Br y. 62%, ee 90%
R^1=*p*-MeO y. 71%, ee 91%

y. 63%, ee 98%

Scheme 131. Three-Component Addition of Alkyl Zincs to Alkyl and Alkynyl *N*-Aryl Imines



Less activated imines have also been successfully utilized in the reaction. Hoveyda and Snapper have introduced an elegant method for the transformation using a catalyst formed from a variant of their N,P-oligopeptidic ligand systems (*vide supra*) and zirconium(IV) salts in the addition of organozincs to *N*-*ortho*-methoxyphenyl (OMP) imines. They selected imino peptide **395** as ligand candidate by combinatorial screening and demonstrated its efficacy in the Zr(O^{i}Pr)$_4$ catalyzed addition of Et_2Zn to a range of aromatic imines (Scheme 130). Both yields and enantioselectivities in this procedure were very good to excellent in the presence of as little as 0.1 mol % of the chiral source. Furthermore, the closely related amino ligands **396** and **397** proved very effective in the addition of other organozinc reagents (Me_2Zn and Oct_2Zn) to representative aromatic *N*-OMP imines in similarly high yields and selectivities.[329] The catalyst incorporating ligand **397** also functioned effectively in the three-component ethyl zincation of aliphatic[330] and alkynic[331] imines (Scheme 131). In the case of additions to alkynic imines, the nature of the *ortho* substituent on the imine *N*-aryl group was found to play an important role in obtaining high yields and stereoselectivities; optimization studies determined *ortho*-phenoxy as the substituent of choice. In addition, the oxygen atom in the side group of the imine *N*-aryl ring was found to be essential for smooth reaction.

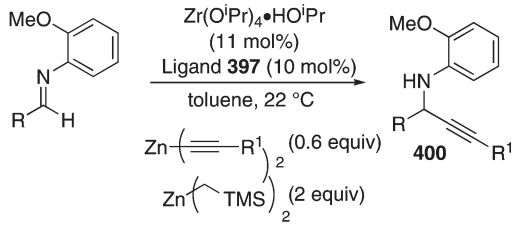
In two cases of the addition reaction of Et_2Zn to alkynyl imines, closely related ligands **397** and **398a** were found to give superior results. The flexibility of the system was nicely illustrated by the discovery that the Zr(O^{i}Pr)$_4$−**397** catalyst can also promote the addition of mixed alkynyl zinc reagents generated from zinc acetylides and bis(trimethylsilyl)methyl zinc[332] to isolated *N*-OMP imines in good yield and reasonable selectivity. Best results were obtained for silyl acetylenes, the analogous alkyl and aryl acetylene reagents giving lower ee's. Facile deprotection of the adducts **400** obtained from the reaction gave an efficient route to homochiral propargylamines **401** (Scheme 132).[333]

It was found that the system can catalyze double organozincations in a novel three-component reaction involving dialdehydes. In this case, **398a** was found to be the ligand of choice, and this combination delivered synthetically C_2-symmetric diamines **402a**−**c** in high yield and almost perfect stereoselectivity (Scheme 133).[334] Furthermore, in the same report the authors disclosed that the corresponding hafnium-based catalyst system formed from **397** and the appropriate metal functions effectively in the three-component addition of diethylzinc to aliphatic imines (Scheme 134). The authors reasoned that the lower Lewis acidity of Hf(O^{i}Pr)$_4$ should lessen the likelihood of adventitious decomposition of the imine *in situ*. Happily this was found generally to be the case because the Hf system delivered superior yields of the addition products with comparable enantioselectivity to that obtained using the parent Zr catalyst.

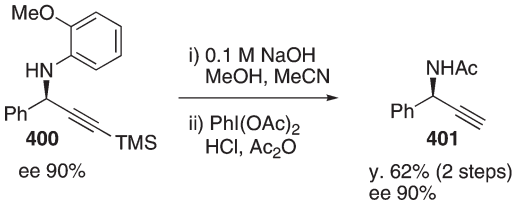
The transition state for addition of the organozinc species to the imine is proposed to involve bidentate coordination of the imine to the catalyst metal center adjacent to the docking position of the zinc reagent, which is believed to be held in the correct orientation by

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

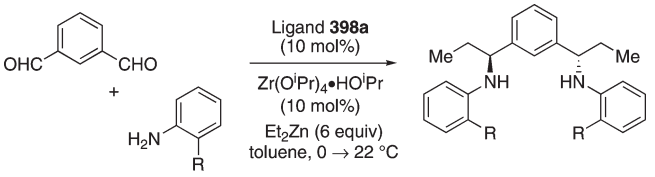
Scheme 132. Addition of Alkynylzinc Regents to *N*-OMP Imines Promoted by $Zr(O^iPr)_4$−397



R	R^1	y. (%)	ee (%)
p-Cl-C_6H_4	TMS	90	81
p-MeO-C_6H_4	TMS	69	86
o-Br-C_6H_4	TMS	84	69
1-naphthyl	TMS	77	86
2-naphthyl	TMS	85	81
2-furyl	TMS	72	82
Ph	^{n}Bu	81	79
Ph	Ph	81	68



Scheme 133. Double Addition of Et_2Zn Giving C_2-Symmetric Diamines



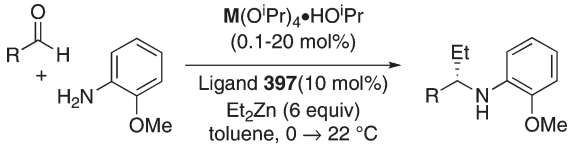
402a R=OMe y. 75%, *anti*/*syn* 6/1, ee 96%
402b R=OPh y. 84%, *anti*/*syn* >20/1, ee >98%
402c R=SMe y. 80%, *anti*/*syn* >20/1, ee >98%

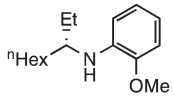
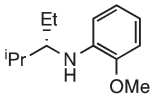
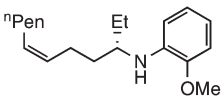
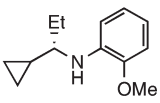
coordination to the oxygen atom of the terminal amide residue (Figure 35a). Alternative binding modes for internal delivery of the ethyl group with opposite enantiofacial selection are sterically disfavored (Figure 35b, left) or lack of proximity between the reacting centers (Figure 35b, right). The use of the ligand incorporating *R*-Phe at the terminal position (Figure 35c) allowed access to one of the alternative binding modes and facilitated delivery of the organozinc reagent to the opposite face of the imine C═N bond leading to reversed enantiofacial selectivity (70% conversion, 80% ee (*R*) compared with >98% conversion, 94% ee (*S*) for the ligand with *S*-Phe in the terminal position).

In their further studies, Snapper and Hoveyda expanded the reaction system to the reaction of ketoimines. Catalytic enantioselective alkylations of aryl-, alkyl-, and trifluoroalkyl-substituted ketoimine esters with dialkylzinc proceeded to afford α-quaternary amino esters with high enantioselectivities.[335]

Recently a number of variations of this type of reaction have Guijarro and Yus reported that β-amino alcohols with the prolinol

Scheme 134. Use of Hf−397 Catalysts in the Addition of Diethylzinc to Aliphatic *N*-OMP Generated Imines



M	Product	y. (%)	ee (%)
Zr		62	97
Hf		91	95
Zr		58	95
Hf		76	91
Zr		60	>98
Hf		83	95
Zr		83	98
Hf		>98	97

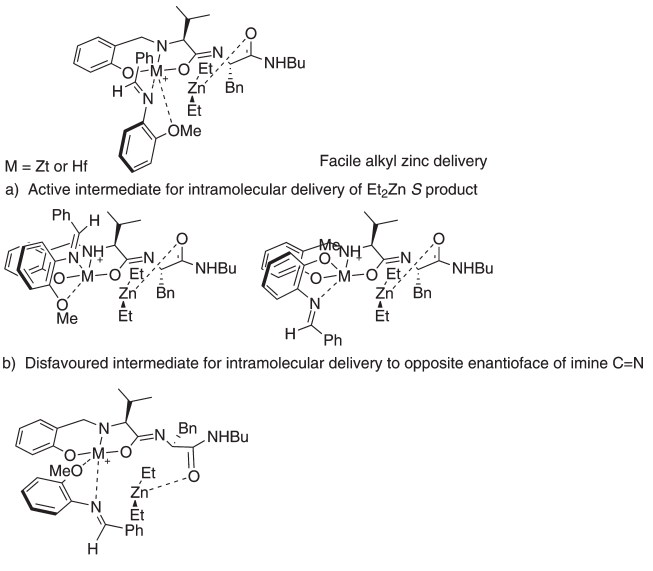


Figure 35. Assumed intermediate configurations for the addition of Et_2Zn to *N*-OMP imines.

skeleton catalyzed enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines.[337] Shortly afterward Minnaard and Feringa reported a copper/chiral phosphoramidite catalyst system for addition of organozinc and organoaluminum reagents to *N*-formylimines,[338] while Alexakis also developed a closely related system independently and applied it to the addition of diethylzinc to Boc-protected imines.[339] Pedro developed enantioselective alkynylation of *N*-sulfonyl aldimines catalyzed by a Zn/BINOL system.[340] Whiting has also applied Zn/BINOL catalyst system to formal aza-Diels−Alder reactions of *N*-arylimines with Danishefsky's diene.[341]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

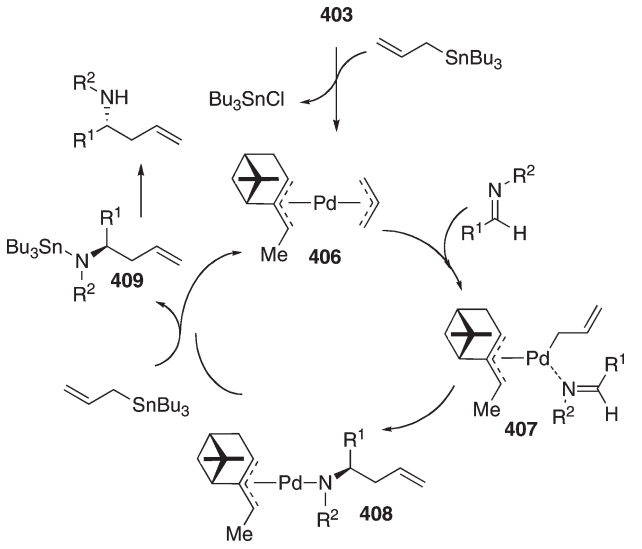


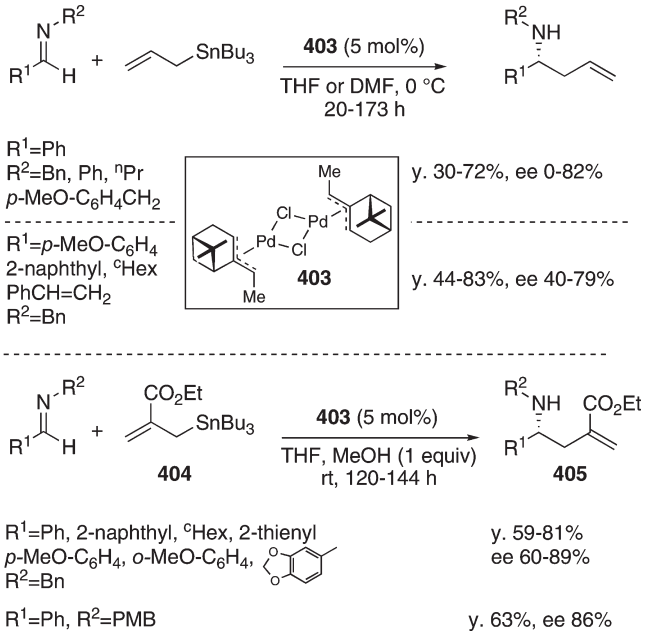
Figure 36. Postulated catalytic cycle for the catalytic asymmetric allylation of imines.

6.4. Catalytic Asymmetric Allylation of Imines and Hydrazones

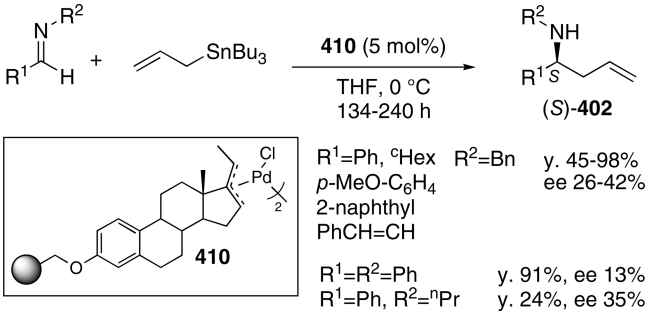
The allylation of imines and hydrazones is a reaction of fundamental importance in organic synthesis.[292b,342] Although a substantial body of work on the racemic and diastereoselective allylation reaction has been presented, it is really only in the past decade that substantial advances in the catalytic asymmetric version of the reaction have been made. The first example of the transformation was reported in 1998 by Yamamoto in which he demonstrated the addition of allyltributyl stannate to a series of unactivated aromatic imines to give the corresponding homoallylic secondary amines catalyzed by 5 mol % of {Pd-η^3-[β-(−)-amino esters **405** in moderate to good yield and with good to high enantioselectivities.[345]

The authors proposed the catalytic cycle shown in Figure 36, in which transmetalation of the stannane to palladium gives the chiral allyl transfer agent **406**, which binds the imine giving intermediate **407**. Allylation via a six-membered cyclic transition state is postulated to occur to give the palladium-bound chiral secondary amine **408**, which subsequently undergoes reaction with another equivalent of the allylstannane to reform the allyl transfer agent with concomitant release of the aminostannane **409**. Hydrolysis of the latter then affords the desired homoallylic amine product. The efficiency of the transmetalation Sn → Pd step proved to be an important factor for reproducibility of the achievement of high yields. The authors noted that addition of 1 equiv of water to the reaction boosted yields and improved reproducibility. This, combined with diligent preparation of the catalyst to afford high regioisomeric purity (*Z*/*E* 400:1), positively affected both yields and ee (28 examples, up to 94% yields, up to 91% ee).[346] Use of other protic additives such as MeOH, PrOH, or AcOH also raised ee's to a certain degree. The role of water is believed to involve formation of a pentacoordinate allylstannane intermediate, thereby accelerating the Sn → Pd transmetalation. The utility of this catalyst system has been further enhanced by the discovery that estrone-derived η^3-allyl Pd complex **410**, immobilized on Merrifield resin promoted the addition of allylstannanes to imines (Scheme 136). Although extended reaction times were required and yields and selectivities were low to moderate, the catalyst could be recovered and reused up to 4 times without loss of yield or selectivity.[347]

Scheme 135. Asymmetric Catalytic Allylstannylation of Imines



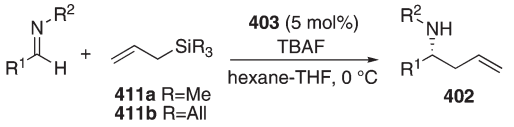
Scheme 136. Catalytic Asymmetric Allylation of Imines Using Immobilized η^3-Allyl Pd Complexes

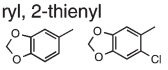


Although the above protocols broke new ground and represent an important addition to the arsenal of synthetic techniques, the toxicity of allylstannanes carries serious implications for safety and green chemistry credentials of the process. In an effort to address these issues, Yamamoto et al. have developed a related procedure utilizing the more environmentally benign allylsilanes as nucleophiles in the reaction (Scheme 137). It is known that these species are considerably less reactive than their tin counterparts, but the authors discovered that the addition reaction proceeded smoothly with 2 equiv of trimethylallyl silane **411a** in the presence of 0.5 equiv of TBAF and 5 mol % of catalyst **403** to give good to very good yields of the desired addition product in up to 84% ee.[348] Furthermore, it was discovered that use of tetraallyl silane **411b** in the presence of 0.25 equiv of TBAF and 1 equiv of MeOH gave the addition products with increased substrate scope in improved yields and with better enantioselectivity.[349] In both reactions, the TBAF is believed to assist the transfer of allyl from

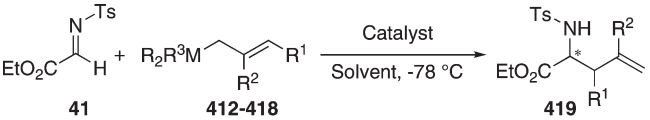
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

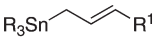
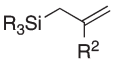
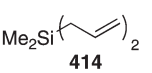
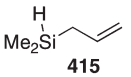
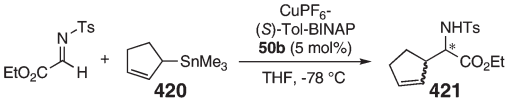
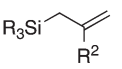
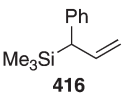
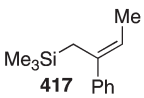
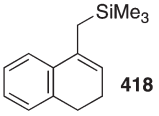
Scheme 137. Asymmetric Catalytic Reaction of Imines and Allylsilanes



R=Me	
R^1=Ph R^2=Bn, Ph, ^{n}Pr, *p*-MeO-C_6H_4, PMB	y. 34-96% ee 3-80%
R^1=*p*-MeO-C_6H_4, 2-naphthyl, PhCH=CH R^2=Bn	y. 60-88% ee 64-84%
R=All (with MeOH)	
R^1=Ph R^2=Bn, *p*-MeO-C_6H_4, *o*-MeO-C_6H_4, All	y. 83-86% ee 84-91%
R^1=*p*-MeO-C_6H_4, *o*-MeO-C_6H_4, 2-naphthyl PhCH=CH, ^{c}Hex, 2-furyl, 2-thienyl 3-pyridyl, *p*-Me-C_6H_4  R^2=Bn	y. 76-98% ee 52-94%
R^1=2-naphthyl, *p*-MeO-C_6H_4  R^2=PMB	y. 78-80% ee 90-92%

Scheme 138. Cu(I)-Catalyzed Asymmetric Allylation on *N*-Tosyl Imino Esters



Jørgensen	$CuPF_6$ -(*S* or *R*)-Tol-BINAP, **50b** (5 or 10 mol%)		
	**412a** R=^{n}Bu, R^1=H **412b** R=allyl, R^1=H **412c** R=^{n}Bu, R^1=Me	THF DCM toluene	y. 87%, ee 80% y. 85%, ee 21% y. 88%, ee 87/89% dr (*syn*/*anti*) 7/1,
	**413a** R=Me, R^2=H **413b** R=Me, R^2=Me	DCM DCM	y. 34%, ee 58% y. 47%, ee 64%
 **414**	DCM, y. 34% ee 57%	 **415**	DCM, y. 40% ee 58%
 **420**	$CuPF_6$-(*S*)-Tol-BINAP **50b** (5 mol%), THF, -78 °C	**421**	y. 95%, dr (*maj*/*min*) 2:1 ee (*maj*/*min*) 71/98%
Lectka	$CuClO_4$-(*S*)-BINAP, **50b** (5 mol%), DCM		
	**415a** R=Me, R^2=H **415b** R=Et, R^2=H **415c** R=^{n}Bu, R^2=H **415d** R=Me, R^2=Ph **415e** R=Me, R^2=2-naphthyl		y. 87%, ee 64% y. 88%, ee 72% y. 89%, ee 51% y. 91%, ee 94% y. 85%, ee 93%
 **416**	y. 85%, ee 75%	 **417**	y. 88%, ee (*anti*) 92% dr (*anti*/*syn*) 20/1
 **418**	y. 88%, ee (*anti*) 87% dr (*anti*/*syn*) 10/1		

Si → Pd by formation of the corresponding ate-complex with the allyl silicon reagent.

The copper-catalyzed allylation of imines with both allylstannanes and allylsilanes has been reported independently by the groups of Jørgensen and Lectka. In the first case, a catalyst formed from $CuPF_6$ and (*S*)-Tol BINAP **50b** was used to effect the addition of a range of different allylating reagents **412**−**418** to the *N*-tosyl imino ester **41** giving the desired adducts **419** in moderate yield and enantioselectivity (Scheme 138).[350] Use of crotyl reagents in toluene or THF gave relatively high yields of the α-amino-*β*-methyl ester with relatively good *syn*/*anti* diastereoselectivity (7:1) and good ee's. The cyclic allylstannane **420** gave an excellent yield of the addition product **421** in modest diastereoselectivity (*syn*/*anti* not assigned) but relatively high enantioselectivities.

Lectka and co-workers used a very similar system to catalyze the addition of trialkylallylsilanes to the same *N*-tosyl imino-ester.[91b,92] They studied a wide selection of silanes achieving comparable yields and slightly improved selectivities to those reported by Jørgensen. Both protocols are assumed to proceed via ene-like open transition state addition of the nucleophile to the imine, which binds to the Cu(I) through both the imine nitrogen and ester oxygen atoms in bidentate fashion.

Prior to this, the two groups reported the simple ene reaction of nonmetallic allylic systems using the same Cu(I)/(*S*)-Tol-BINAP catalyst system almost simultaneously. Lectka's group again opted to use $CuClO_4$ as the copper source to effect the addition of a range of 1,1-disubstituted alkenes to **41** in very high yield and excellent enantiomeric excess (Scheme 139).[351] Jørgensen reported comparable yields and high ee's with low loading (0.1−1 mol %) of a catalyst formed from **50b** and $CuPF_6$.[352,353]

Jørgensen also noted that the analogous reaction of 1,3-butadiene with **41** proceeds preferentially via the aza-Diels−Alder manifold and not the ene route (9:1) although the latter product was obtained in much better ee than the heterocycle (Scheme 140).

An unusual footnote to the Cu-catalyzed ene allylation of imines was provided by Hutchings and Page. They used immobilized catalyst formed from CuH-exchanged zeolite Y modified with bisoxazoline ligands **38a** and **38b** to mediate the addition of α-methyl styrene to imino ester **426** and imine **427** in good yields and ee (Scheme 141).[354]

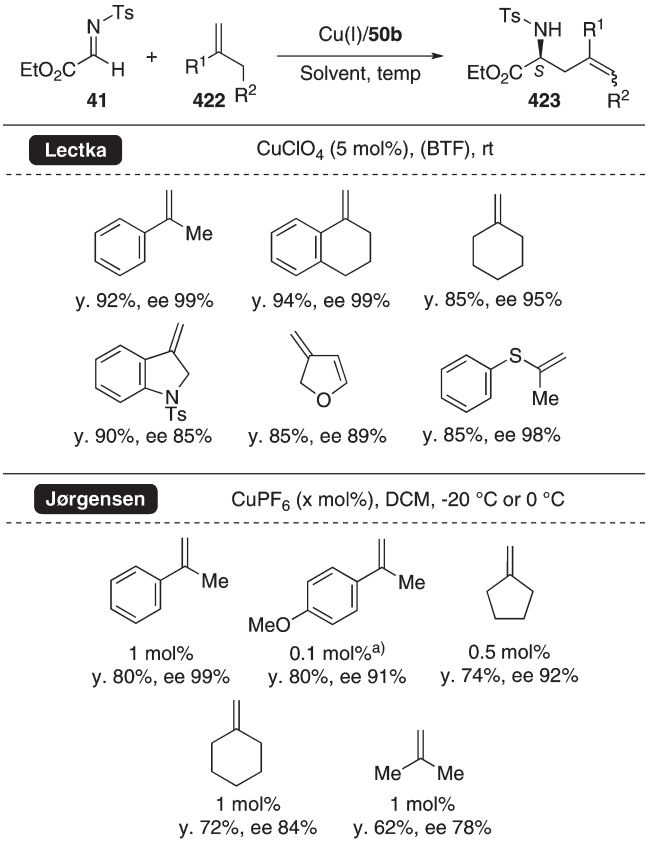
The group of Kobayashi has described a protocol for the crotylation of aromatic *N*-*ortho*-hydroxy imines using complexes generated from 3,3′-halogenated-BINOLs and $Zr(O^tBu)_4$.[355] They found that a combination of either 3,3′-Cl_2-BINOL/$Zr(O^tBu)_4$ **98b** or 3,3′-Br_2-BINOL/$Zr(O^tBu)_4$ **98c** gave best results with oxygenated allylstannanes **428a,b**, affording the product in up to 85% yield and 99% ee (Scheme 142).

The hydroxyl group on the allyl stannane was found to be essential for the realization of high yields and selectivities. When the TBS-protected analogue or the hydrocarbon analogue in which the CH_2OH group was replaced by methyl was used, yields and selectivities were dramatically reduced. This led the authors to suggest a mechanism involving species **430** in which the both the imine and the stannane are bound to the zirconium center.

Kobayashi and co-workers have also reported the asymmetric allylation of benzoyl hydrazones **431** with allyltrimethoxysilanes **432** catalyzed by complexes of ZnF_2 and chiral diamines **122d,e**. The reaction proceeded with a number of different hydrazones and allyltrimethoxysilanes to afford the desired homoallylic

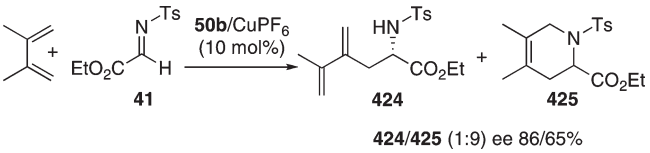
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 139. Cu(I)-Catalyzed Nonmetallic Ene Allylations of *N*-Tosyl Imino Esters



a) $CuClO_4$

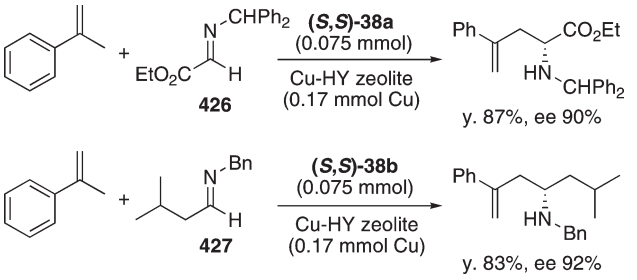
Scheme 140. Ene Reaction with 1,3-Butadiene



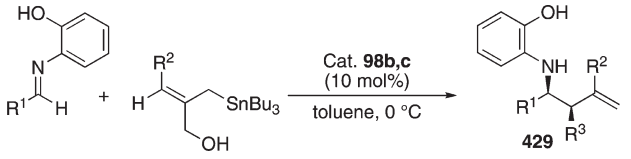
hydrazines in moderate to high yields and with good stereoselectivities (Scheme 143).[356] A number of other diamines were examined in the reaction giving products in 19−99% yield and 31−83% ee. The authors proposed a Lewis acid/Brønsted base double activation pathway for the reaction (Figure 37) in which the allylzinc amide and $(MeO)_3SiF$ are first generated by Si → Zn metathesis from **433**, and the allylation step subsequently occurs to produce the bound homoallylic hydrazine **434**. Hydrolysis of this gives Zn(OH)F species **435**, which interacts with $(MeO)_3$-SiF to reproduce the catalyst, with the concomitant generation of $(MeO)_3SiOH$.

Kobayashi et al. have also described a protocol for the addition of allyltrichlorosilanes to glyoxylate hydrazones **144** using neutral-coordinate organocatalyst (NCO) (*S*)-BINAP oxide **436**. Although an excess (2 equiv) of the NCO was required for high yields and enantioselectivities (up to 96% and 98%, respectively), use of 40 mol % of the catalyst did afford the chiral product **437**, albeit in low yield and only moderate enantioselectivity

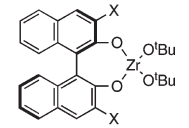
Scheme 141. CuH Zeolite Y/Bisoxazoline Immobilized Catalyzed Asymmetric Ene Addition to Imines

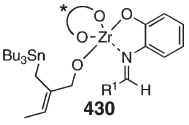


Scheme 142. Catalytic Asymmetric Allylstannylation of Imines Promoted by Zr−BINOL Complexes

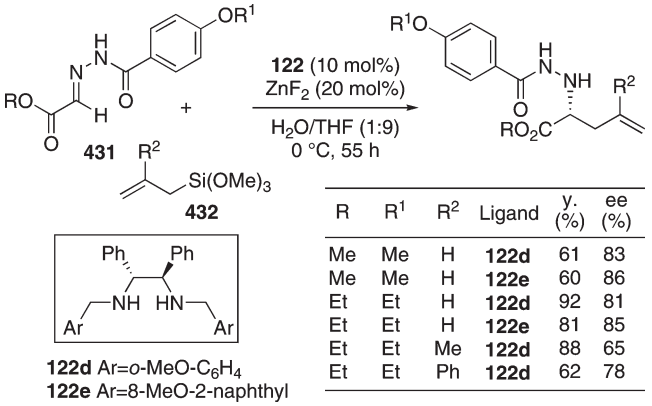


R^1	Stannane	Catalyst	y. (%)	ee (%)
Ph	**428a**	**98c**	84	93
1-Naphthyl	**428a**	**98c**	81	95
3,4-(OCH_2O)-C_6H_3	**428a**	**98c**	72	91
2,3-$(MeO)_2$-C_6H_3	**428a**	**98c**	71	94
2-furyl	**428a**	**98b**	76	92
p-Cl-C_6H_4	**428a**	**98c**	78	87
Ph	**428b**	**98c**	77	96
1-Naphthyl	**428b**	**98b**	85	97
3,4-(OCH_2O)-C_6H_3	**428b**	**98c**	84	99
2,3-$(MeO)_2$-C_6H_3	**428b**	**98c**	80	87
2-furyl	**428b**	**98c**	68	96





Scheme 143. Catalytic Asymmetric Allylation of Hydrazones with Allyltrimethoxylsilanes and ZnF_2



R	R^1	R^2	Ligand	y. (%)	ee (%)
Me	Me	H	**122d**	61	83
Me	Me	H	**122e**	60	86
Et	Et	H	**122d**	92	81
Et	Et	H	**122e**	81	85
Et	Et	Me	**122d**	88	65
Et	Et	Ph	**122d**	62	78

(Scheme 144).[357] C_2-Symmetric disulfoxides as organocatalysts for allylation of benzoylhydrazones were reported by Fernandez and Khiar.[358] Asymmetric allylation of *N*-*ortho*-hydroxyphenylimines using superstoichiometric quantities of NCOs has also been reported.[359]

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

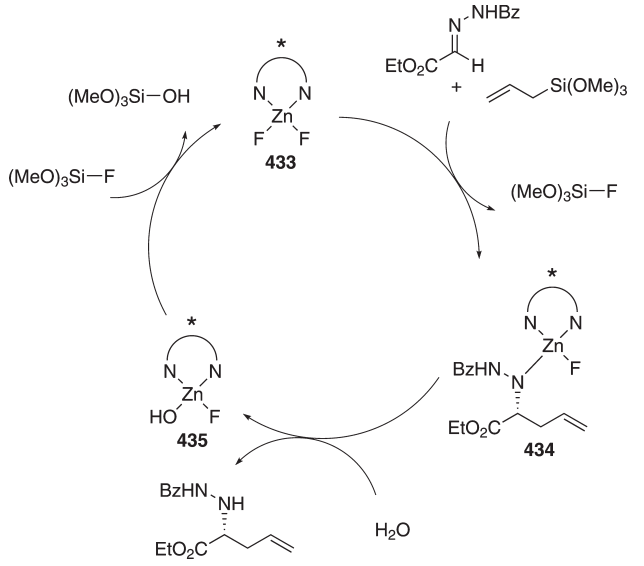
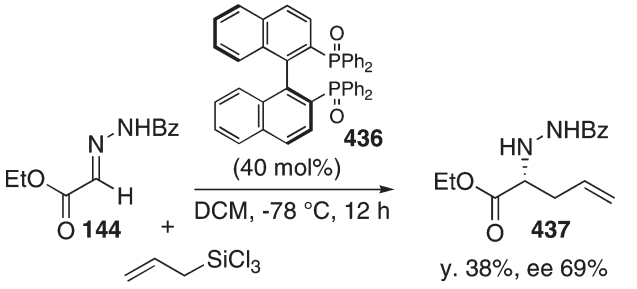


Figure 37. Proposed catalytic cycle for the allylation with allyltrimethoxylsilane.

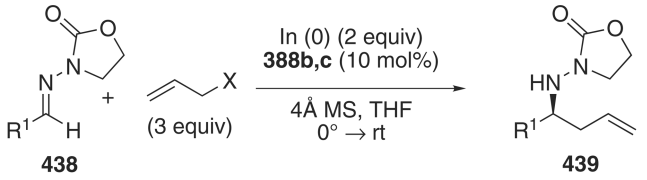
Scheme 144. NCO-Catalyzed Allylation of Hydrazones with Allyltrichlorosilane

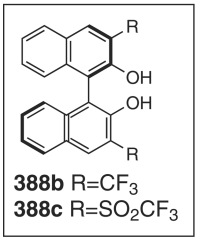


Cook and Lloyd-Jones et al. have introduced an elegant indium metal-based methodology for the allylation of acylhydrazones (Scheme 145). The source of chirality in these reactions is derived from 3,3′-disubstituted BINOL ligands bearing strongly electron-withdrawing groups. The authors developed a modular route to the synthesis of electron-poor BINOLs; after extensive screening, the most effective ligands were identified as **388b** (R = CF_3)[360] and **388c** (R = SO_2CF_3).[361] In both cases, excess quantities of the allylic halide (X = Br, I) and indium metal were required for efficient reaction, and the addition of 4 Å MS was essential for the realization of high selectivities. Overall superior yields and enantioselectivities were realized with ligand **388c** and allyl bromide as the allylic component.

While superficially similar, the protocol differs fundamentally from the related indium-mediated asymmetric allylation methodology introduced by Jacobsen and co-workers. In the latter case, chiral urea organocatalyst **440** is used in conjunction with a standard achiral allylic indium reagent generated *in situ* from allyl bromide and In(0) to afford the homoallylic hydrazines **441** (Scheme 146).[362] In this case, the chirality results from the environment generated by H-bonding of the catalyst to the hydrazone rather than the generation of an asymmetrically ligated indium allyl species. High yields and selectivities were

Scheme 145. Indium−BINOL-Promoted Catalytic Asymmetric Allylation of Hydrazones

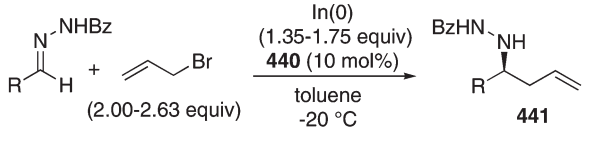


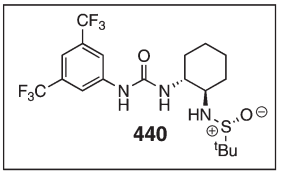


R^1=Ph, *p*-Me-C_6H_4, *p*-MeO-C_6H_4, *p*-Cl-C_6H_4 *o*-Br-C_6H_4, *o*-Cl-C_6H_4, *o*-Me-C_6H_4, $Ph(CH_2)_2$ 1-naphthyl, 2-furyl, cinnamyl, $(CH_2)_2OPh$

Ligand **388b** X=I	Ligand **388c** X=I	Ligand **388c** X=Br
y. 40-79% ee 34-91%	y. 84-98% ee 74-97%	y. 82-99% ee 70-99%

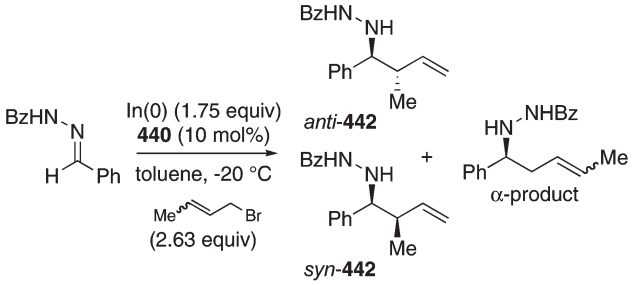
Scheme 146. Catalytic Asymmetric Allylindination of Hydrazones Promoted by a Chiral Urea





R=Ph, *p*-Cl-C_6H_4 *o*-Br-C_6H_4 *o*-Me-C_6H_4 *p*-MeO-C_6H_4 1-naphthyl *p*-(MeO_2C)-C_6H_4 2-furyl, 2-thienyl

y. 78-90% ee 76-95%



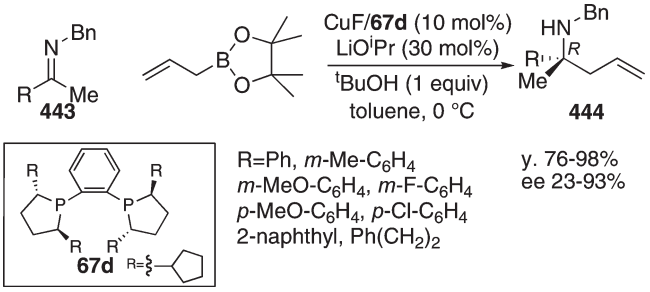
Crotyl reagent	y. (%)	*anti*/*syn*	α-product	ee (*anti*/*syn*)
(*E*)	70	1.10/1	0.40	90/85
(*Z*)	71	1.57/1	0.38	95/86

obtained in the case of *N*-benzoyl hydrazones of aromatic aldehydes, whereas the single example of addition to an aliphatic *N*-benzoyl hydrazone (R = ^{i}Pr) gave inferior results (yield 55%, ee 80%). The corresponding crotylation reaction proceeded in moderate yield with good regioselectivity (γ/α addition) and with good to high enantioselectivities.

Shibasaki et al. have realized an important advance with the discovery of an efficient protocol for the asymmetric catalytic allylation of ketoimines. They employed a catalyst formed from

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 147. Catalytic Asymmetric Allylboration of Ketoimines



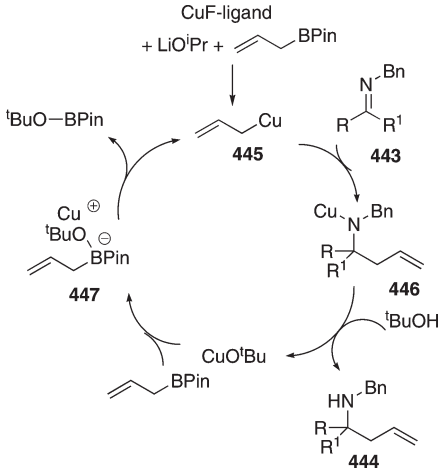


Figure 38. Proposed catalytic cycle for the catalytic asymmetric allylation of ketoimines.

CuF and novel (*R,R*)-biscyclopentyl-DUPHOS **67d** and pinacolallyl borane in toluene at 0 °C to promote the allylation of a range of arylmethyl ketones **443** in good to excellent yield and up to 93% ee (Scheme 147).[363] The copper reagent was actually added as CuF_2 and was then subsequently reduced *in situ* to the Cu(I) salt by 1 equiv of the ligand (2 equiv of ligand with respect to metal source were added).[364] The authors also found that the addition of LiO^{i}Pr and ^{t}BuOH was essential for smooth reaction. NMR spectroscopic studies led them to conclude that the role of the former is to assist in the initial allyltransmetalation from B → Cu to form allyl cuprate **445**, which undergoes reaction with the substrate to form copper amido species **446**. Protonolysis of the Cu−N bond by ^{t}BuOH liberates the product and returns the catalyst, which re-enters the cycle upon reaction with another equivalent of the allylborane to give copper alkoxyborane **447**, which acts as the main allylation reagent (Figure 38). The protocol provides a first solution to the thorny problem of ketoimine reactivity that has limited the application of this transformation in organic synthesis.

6.5. Strecker Reactions

The Strecker addition reaction of cyanide nucleophiles with imines, discovered in 1850 is the oldest and still one of the most efficient methods for the synthesis of α-amino acids.[365] In its most fundamental form, it involves the hydrocyanation of the imine formed by *in situ* condensation of an aldehyde or ketone and a primary amine or ammonia to afford an aza cyanohydrin **448**, which can subsequently be hydrolyzed to the corresponding

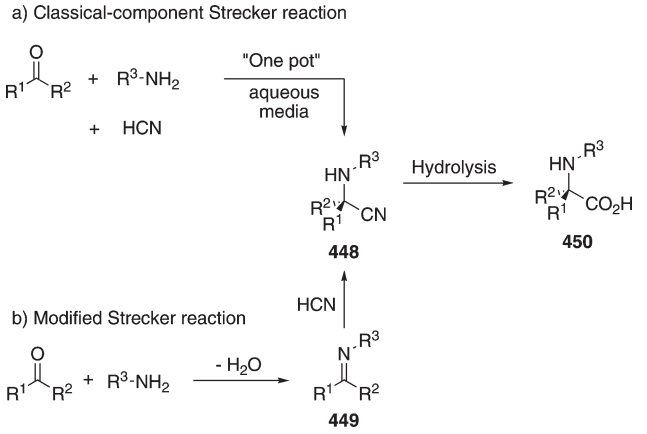


Figure 39. The classic and modified Strecker reactions.

amino acid (Figure 39, path a). A more modern variant involves the use of preformed imines **449**, which can then be made to undergo hydrocyanation and hydrolysis to give the desired α-amino acid product **450** (Figure 39, path b).

In view of the synthetic importance of the reaction, it is not surprising that a great deal of attention has been paid to the development of versatile methods, in particular catalytic asymmetric protocols for its realization.[3,366] As a result, a wide variety of metal-based catalysts[367] and organocatalyst systems[368] have been developed, and research into the field continues unabated.

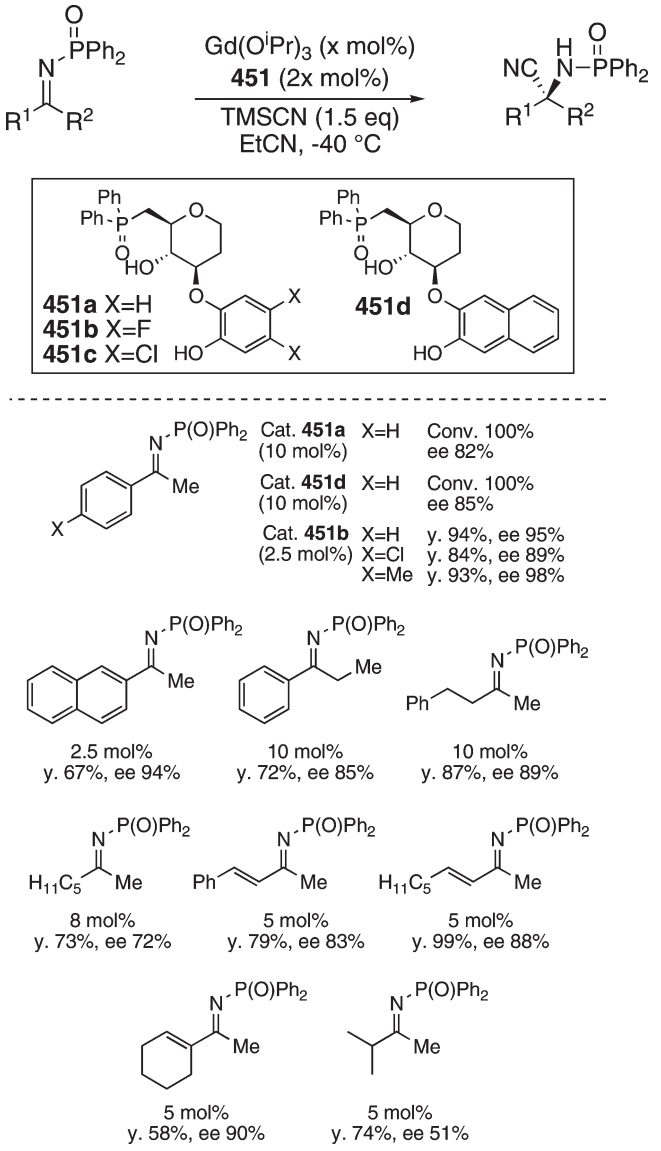
The main development in Strecker methodology involving metal-based systems has been the emergence of efficient catalysts for the hydrocyanation of ketoimines.[203b,c,369,370] In an important series of papers, Shibasaki and co-workers reported highly active catalysts from Gd(O^{i}Pr)$_3$ and glucose-derived chiral ligand **451a,b,d**[371] for the enantioselective addition reaction. Exposure of a range of methyl and ethyl aromatic and aliphatic ketoimines to TMSCN in the presence of between 2.5 and 10 mol % of the catalyst in propionitrile gave moderate to very high yields of the desired amine, although extended reaction times (typically 24−72 h) were generally required. The best yields and selectivities were obtained with the acetophenone derivative but long chain aliphatic methyl ketoimines also gave respectable yields of the addition product in up to 89% ee (Scheme 148). Most notably, under these conditions the previously unreported Strecker reaction of α,β-unsaturated ketoimines proceeded smoothly.

The group subsequently extended the substrate scope of this protocol to include cyclic and heteroaromatic ketoimines. Using a combination of 2−5 mol % of the **451b**-Gd(O^{i}Pr)$_3$ catalyst with 150 mol % TMSCN and 100 mol % 2,6-dimethylphenol (2,6-DMP) as a protic additive, they were able not only to effect the Strecker reaction of a wide range of previously unreactive substrates such as **452**−**457** but to improve the yields and selectivities of previously utilized substrates while dramatically reducing reaction times.[372] Subsequently they were able to show that use of a catalytic amount of TMSCN (2.5−5 mol %) in conjunction with stoichiometric quantities of HCN allowed the catalyst loading to be reduced to as little as 0.1 mol % while maintaining high yields and selectivities (up to yield 99%, ee 93% with 0.1 mol % catalyst) (Scheme 149).[373]

NMR spectroscopic studies of the catalyst species indicated that in the absence of 2,6-DMP the active species is a 3:2 ligand−metal complex **458** of moderate reactivity in equilibrium with the more active catalyst species **459** (Figure 40). It is believed that

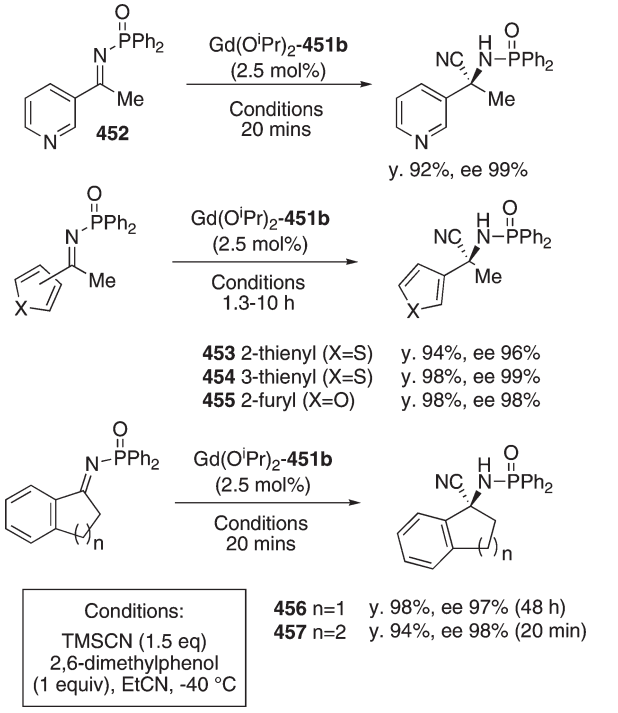
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 148. Gd(O^{i}Pr)$_3$-451 Catalyzed Asymmetric Strecker Reaction of Ketoimines



addition of 2,6-DMP leads to the generation of **459** with the concomitant release of 2 equiv of O-silylated 2,6-DMP and the liberation of 1 equiv of HCN (path a, Figure 40). A similar effect can be realized by the addition of stoichiometric HCN (path b, Figure 40), which strips off the TMS from the phenolic oxygens of the catalyst to generate **459** and recycle the TMSCN. In either case, the presence in the system of large amounts of TMSCN would tend to favor the formation of the less-reactive **458** at the expense of **459**, which explains the large observed difference in efficiency of the stoichiometric TMSCN/2,6-DMP and the much more reactive revised catalytic TMSCN/stoichiometric HCN system. The binuclear catalyst is believed to function in a bifunctional manner with one of the Gd centers acting as a Lewis acid to complex the imine and the other acting to deliver the cyanide. The synthetic utility of this catalyst system was demonstrated in a short synthesis of (*S*)-sorbinil, a therapeutic agent for complications arising from diabetes mellitus (Scheme 150).

Scheme 149. Asymmetric Catalytic Strecker Reaction of Heteroaromatic and Cyclic Ketoimines



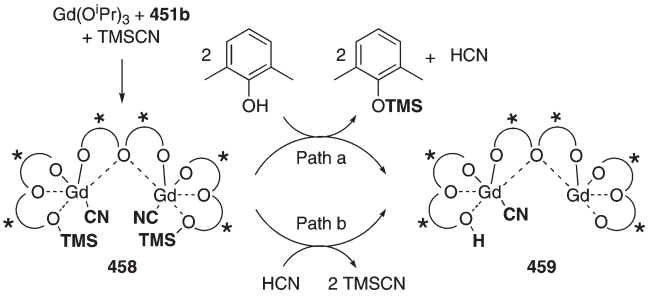
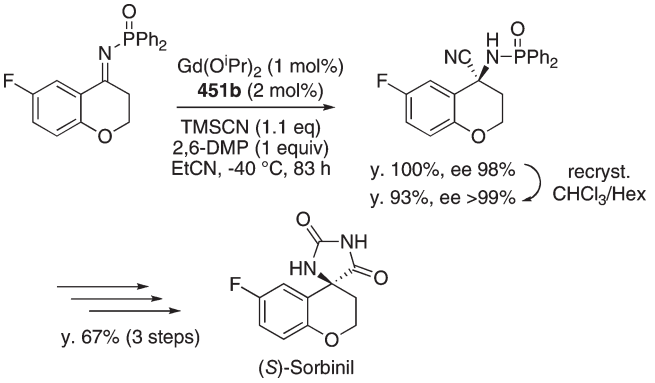


Figure 40. Proposed catalyst structures for the Gd catalyst in the presence of (a) stoichiometric TMSCN/2,6-DMP and (b) catalytic TMSCN/stoichiometric HCN.

In another development, Shibasaki et al. discovered that preparing the complex from Gd(HMDS)$_3$ (HMDS = hexamethyldisilazane) and **451b** resulted in the formation of 2:3 complex, which afforded the Strecker product in even better enantioselectivity and yields.[374] The improved procedure was utilized in as the key transformation in the group's synthesis of lactacystin.[375] The authors discovered that attempted crystallization of the active species from a 2:3 mixture of Gd(O^{i}Pr)$_3$ and ligand **451c** (X = Cl) afforded a 4:5 complex of Gd and **451c** (Figure 41), which persisted in solution. Although approximately 5−50 times less reactive than the *in situ* formed catalyst, the Strecker reaction using the crystallized catalyst proceeded smoothly to afford *the opposite enantiomer* of the adduct with the same or even improved levels of selectivity (Scheme 151).[376] Further investigations of the catalyst structure using the analogous system prepared with La(O^{i}Pr)$_3$ and **451a** led to the isolation of a C_2-symmetric 6:8 La−**451a** complex that persisted in solution. The complex was formed of two domains: a 4:5 La−

Scheme 150. Short Synthesis of (*S*)-Sorbinil



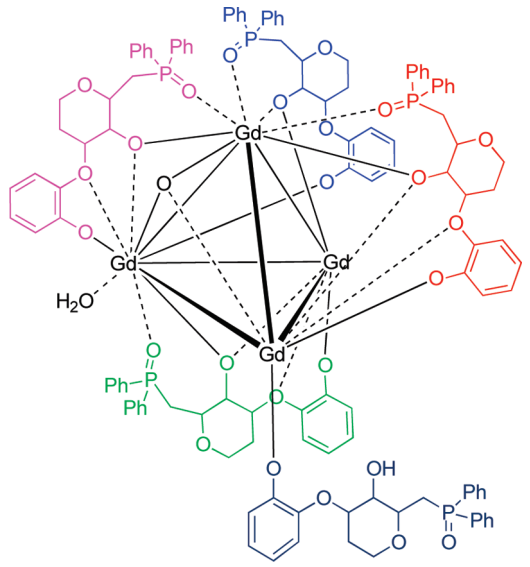


Figure 41. Structural formula of active species Gd(O^{i}Pr)$_3$-**451c**.

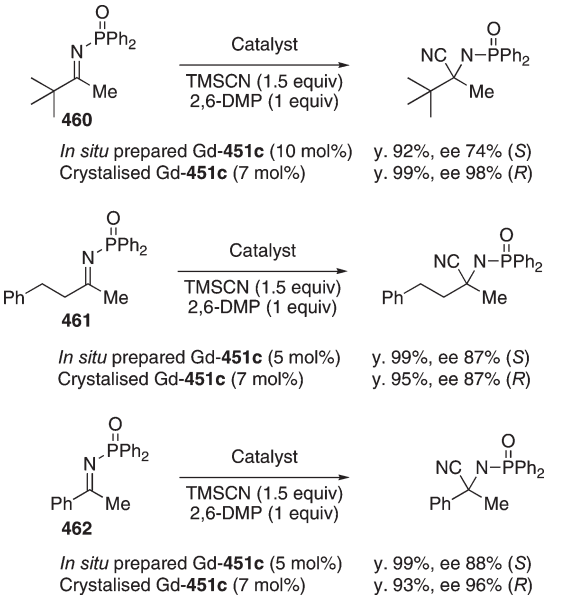
451a domain and a 2:3 La−**451a** domain, the latter part being similar in structure to the postulated active species obtained with the *in situ* formed catalyst.

Use of this second isolated species in the Strecker reaction however gave the product in only 26% ee as the *S* enantiomer. While the variation of function with higher order structural organization is a well-known concept in biological systems,[377] the same effect in artificially assembled catalyst systems is rare.

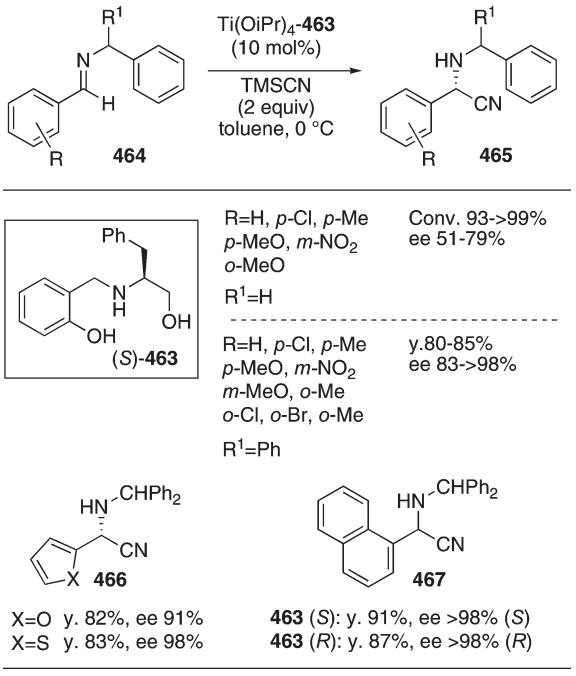
The Lewis acid catalyzed Strecker reaction with aldimines has also been witness to a number of developments. The group of Vilaivan have described a new versatile catalyst system based on Ti(IV)[369,378] complexes of modified amino alcohols. After extensive screening, they alighted on ligand **463** derived from phenyl alaninol and used it to effect the Strecker reaction of TMSCN to a range of aromatic *N*-benzyl and *N*-benzhydryl imines **464** (Scheme 152).[379] In common with many Strecker-type reactions, the addition of a protic additive was found to be important for smooth reaction and high yields and enantioselectivities. The role of the additive is believed to involve generation of HCN from the TMSCN *in situ*, which then acts as the real cyanating agent.

North et al. reported three metal−salen-based catalyst systems for the Strecker reaction of *N*-benzyl imines.[380] Although

Scheme 151. Comparison of Results Obtained with Isolated and *in situ* Prepared Gd(O^{i}Pr)$_3$ Catalysts

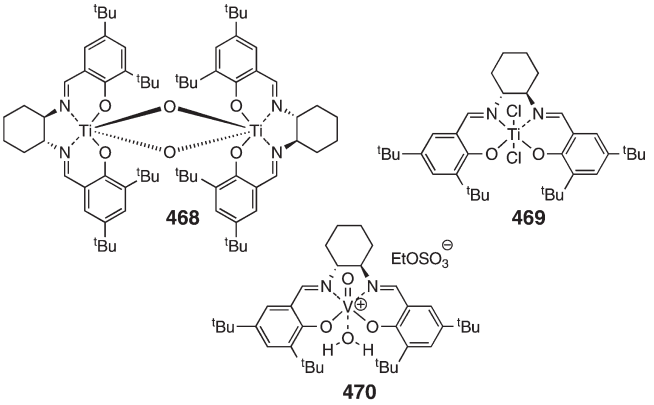


Scheme 152. Ti(IV)-Catalyzed Asymmetric Strecker Reaction



Ti(IV)-centered complexes **468** and **469**[381] were largely ineffective in the reaction, better results were obtained with the V(V) system **470** (Scheme 153). Accordingly, treatment of a range of *N*-benzyl aldimines with TMSCN in toluene with 10 mol % catalyst led to the isolation of the desired adduct in moderate to high yield with up to 75% enantioselectivity. One example each of the reaction of TMSCN with an aliphatic aldimine (Me_3CCH =NBz) and a ketimine [PhC(Me)=NBz] were reported and although in both cases high yields were obtained, enantioselectivities were poor. A key contribution in this area, where a

Scheme 153. Ti(salen)- and V(salen)-Catalyzed Asymmetric Strecker Reaction



Catalyst	R	y. (%)	ee (%)
468	H	90[a]	54
469	H	90[a]	43
470	H, *o*-Me, *m*-Me, *p*-Me *m*-MeO, *p*-MeO *m*-Cl, *p*-Cl, *p*-CF_3	46-88	31-75
470		y. 85%	ee 16%
		y. 92%	ee 43%

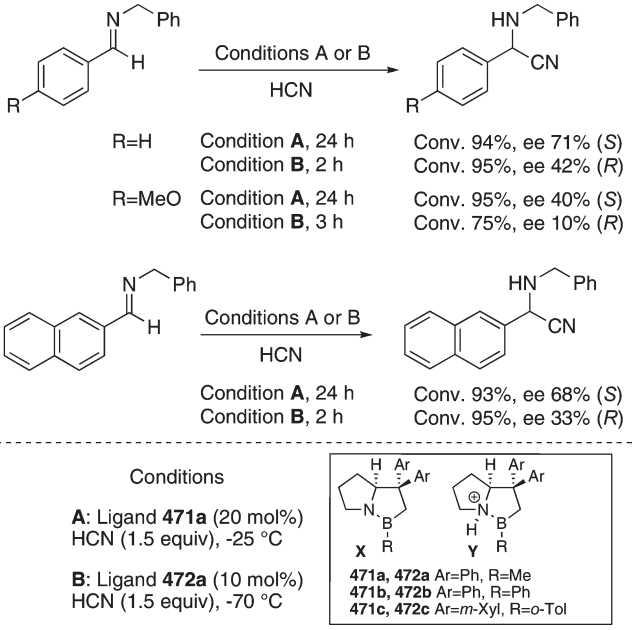
[a]Conversion.

titanium complex delivered an important chiral intermediate in the complex synthesis of chloropeptin I as a result of a highly selective Strecker reaction, exemplifies this reaction strategy as truly useful.[382]

A reversal of enantioselectivity by protonation of chiral oxazaborolidine catalysts in the Strecker reaction has been reported by the group of Berkessel.[383] They applied catalysts **471a**−**c**[384] (20 mol %) to the addition of HCN to *N*-benzylphenylimine obtaining the aza cyanohydrin in 94% yield and 71% ee as the *S* isomer (Scheme 154). It is known that protonation of such oxazaborolidine leads to an increase in reactivity,[385] and thus the authors used the related tosic acid salts **472a**−**c** in an attempt to obtain higher selectivities. While application of the protonated catalyst did not lead to the desired increase in ee, the reaction proceeded at lower temperature in a shorter reaction time with lower catalyst loading (10 mol %). The authors noted that the product was obtained as the opposite, *R*, enantiomer albeit with lower overall selectivity (ee 10−42%).

Although significant advances in the metal-catalyzed asymmetric Strecker reactions have been realized, perhaps the greatest developments have been made in the development of organocatalyzed procedures. List and co-workers used Jacobsen's thiourea catalyst **216b** to perform the catalytic acylcyanation of a range of aromatic and aliphatic imines with acetyl cyanide **473** to afford the N-acetylated aza cyanohydrins **474** in good yield and with

Scheme 154. Reversal of Stereoinduction in the Catalytic Asymmetric Strecker Reaction Using Chiral Oxazaborolidines by Protonation of the Catalyst



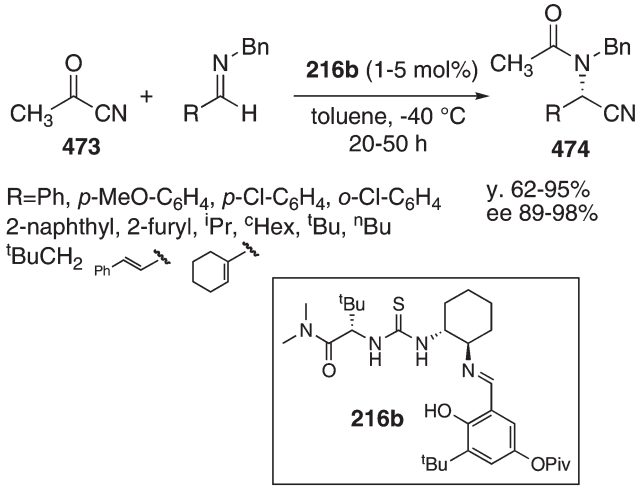
excellent enantioselectivity (Scheme 155).[386] Standard manipulation of the cyanated products gave ready access to non-natural α-amino acids such as **475**. This report represents the first example of the application of acetyl cyanide as a nonvolatile cyanide source in an asymmetric catalytic Strecker reaction although its use in the synthesis of cyanohydrin esters has been documented.[387] Shortly thereafter, the same group reported a three-component variant of the reaction, which affords the products in essentially the same yields and enantioselectivities as the original procedure. They also reported one example of the reaction using hexanylcyanide in place of acetyl cyanide (Scheme 156).[388]

A related urea catalyst **477** derived from glucosamine (Figure 42) has also been used to catalyze the asymmetric Strecker reaction of *N*-allyl imines, this time using TMSCN as the cyanide source.[389] Yields were good to excellent and up to 86% ee was achieved at only 2 mol % loading. Better results were obtained by Corey and Huang for the same reaction with *N*-allyl aldimines using HCN as the cyanide source and TFA salt of cinchona alkaloid derivative alkene dihydroxylation catalyst[390] **478**. Use of 10 mol % of the same gave high yields of the product, which was isolated as the corresponding *N*-trifluoroacetate in up to >99% ee.[391]

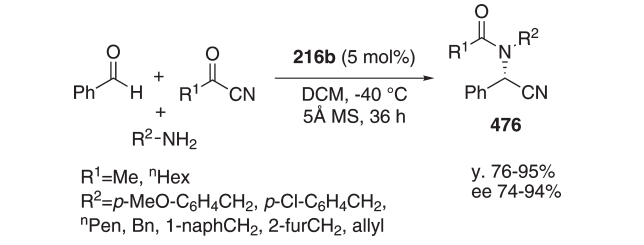
Feng et al. tested a wide range of axially chiral *N*,*N*-isoquinoline dioxides in the Strecker reaction of TMSCN and *N*-benzhydryl aldimines.[392] Best results were obtained using catalyst **479**, which gave the desired products in up 95% ee. The same group reported the use of aliphatic *N*,*N*-dioxide **480** to promote the asymmetric cyanation of *N*-tosyl ketoimines with TMSCN.[393] Almost quantitative yields and moderate to very high enantioselectivity were obtained with 5 mol % of the catalyst and 2,5-di-(1-adamantyl)hydroquinone (DAHQ) as additive (Scheme 157). As we have already seen, the presence of hindered protic additives in the reaction mixture is often required for high yields and selectivities, when TMSCN is used as the cyanide source.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 155. The Catalytic Asymmetric Acylcyanation of Imines



Scheme 156. Three-Component Catalytic Asymmetric Acylcyanation Reaction



The additive is typically thought to play a role in assisting the *in situ* generation of HCN from TMSCN, the former being the real cyanide source in the reaction.

In this case however, the authors found that the *N*-tosyl imines were inert to HCN and postulated a transition state (Figure 43) in which the DAHQ stabilizes the hypervalent silicon/ligand/imine complex by hydrogen bonding, which then undergoes attack at the *Re* face.

Chiral phosphoric acids have not been ignored in the search for ever more active and selective Strecker catalysts. Rueping and co-workers screened a number of highly hindered BINOL-derived chiral phosphoric acids in the reaction, finally selecting **194m** (Ar = 9-phenanthryl) for further studies. Using HCN as the cyanide source in toluene at −40 °C, they were able to realize high yields of the corresponding aza cyanohydrins in up to 99% ee with 10 mol % of the catalyst. One drawback of the system was the extended reaction times: up to 3 days were required in some cases for high yields (Scheme 158).[394] Rueping et al. subsequently applied the same catalyst to the Strecker reaction of ketoimines, and while yields were still reasonable, levels of

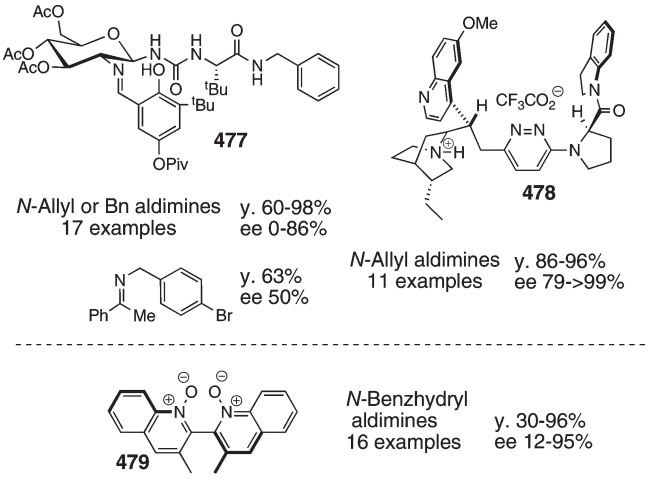
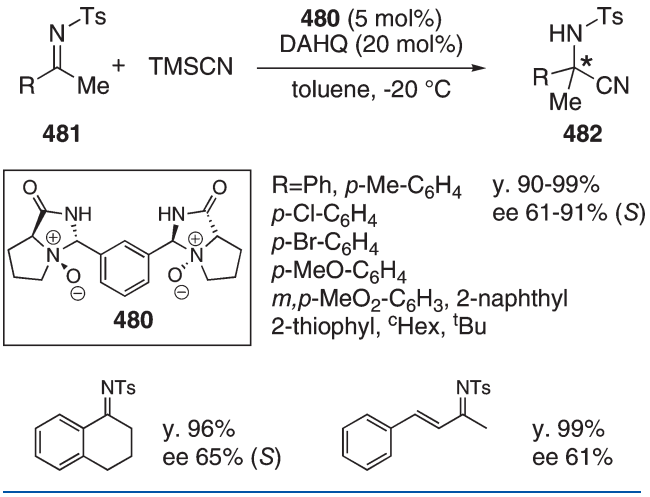


Figure 42. Organocatalysts for the Strecker reaction with aldimines.

Scheme 157. Asymmetric Strecker Addition to *N*-Tosyl Ketoimines Catalyzed by *N,N*-Dioxide 480



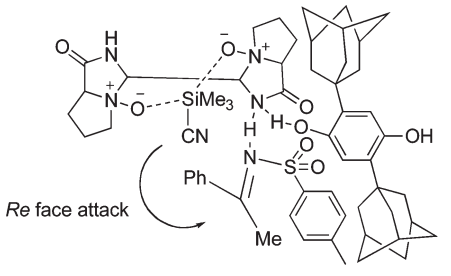
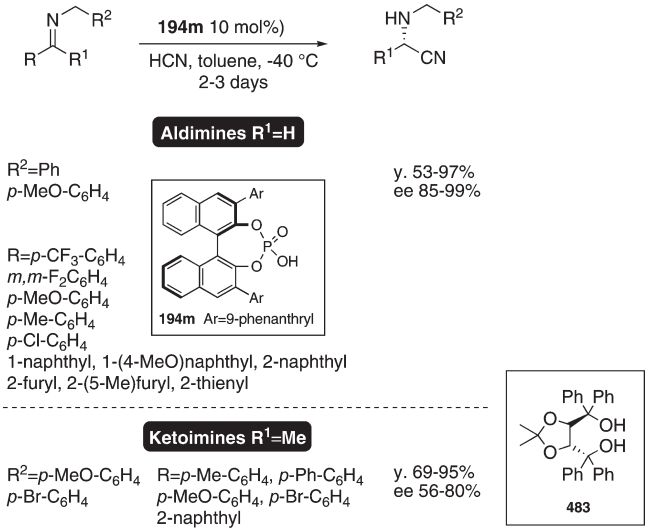


Figure 43. Proposed transition state for the asymmetric Strecker reaction catalyzed by chiral *N,N*-dioxide **480**.

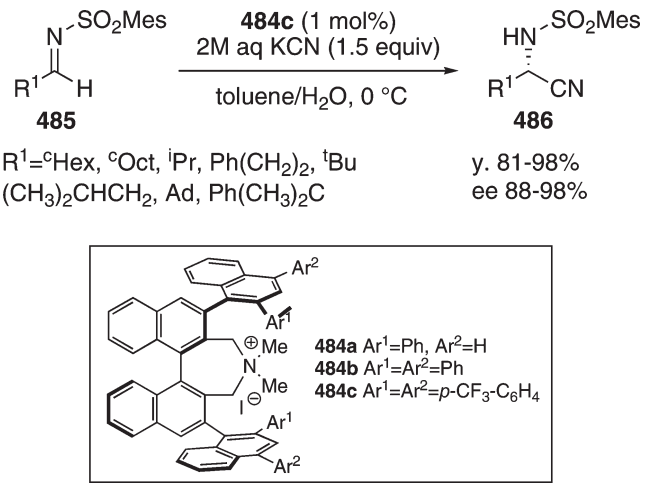
enantioselectivity were much reduced.[395] In the same paper, the authors disclosed the use of TADDOL **483** as an organocatalyst for the Strecker reaction of *N*-benzyl aldimines giving the corresponding adducts in moderate yield and enantioselectivity (10 mol % catalyst, 4 examples, yield 69−93%, ee 22−56%).

The asymmetric catalytic Strecker reaction has also been successfully carried out using solid KCN as the cyanide source under chiral phase transfer conditions. In a very elegant contribution,

Scheme 158. Asymmetric Strecker Reaction Catalyzed by Chiral Phosphoric Acids



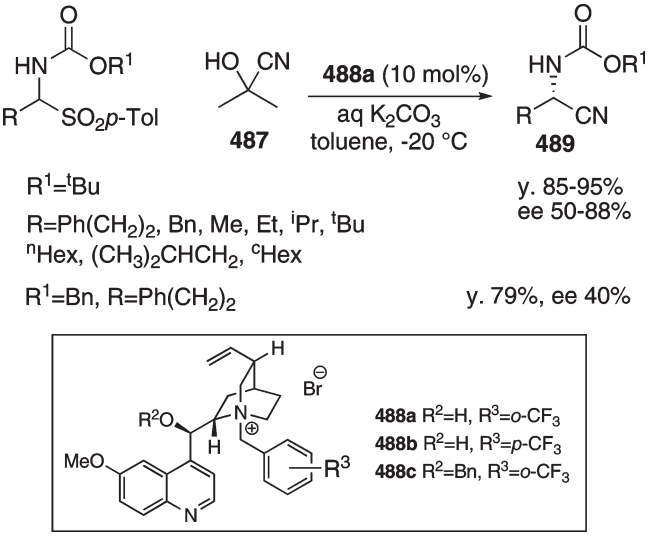
Scheme 159. Asymmetric Catalytic Strecker Reaction Using KCN under Chiral PT Conditions



Maruoka and co-workers used novel catalysts **484a**−**c** derived from their trademark chiral ammonium salts[396] to effect the first efficient Strecker reaction of a range of aliphatic *N*-mesitylsulfonyl imines **485** under PT catalysis. Of the catalysts surveyed, **484c** bearing very electron-withdrawing substituents provided the best results in terms of yield and selectivity, although the other examples also displayed high activity and selectivity (in the reaction of ^{c}HexCH=SO_2Mes, **484a** yield 83%, ee 89%; **484b** yield 90%, ee 90%; cf. **484c** yield 89%, ee 95%) (Scheme 159).[397]

Shortly after this, the related procedure using acetone cyanohydrin **487** as the cyanide source in the reaction with *in situ* generated alkyl *N*-carbamoyl imines under chiral phase transfer conditions was reported.[398] Ricci and co-workers used *N*-(2-trifluoromethyl)benzyl quinine bromide **488a** as the chiral agent in a two-phase system to liberate both the imine and the cyanide source accomplishing the condensation of the two reagents giving

Scheme 160. Asymmetric Strecker Reaction with Acetone Cyanohydrin As the Cyanide Source under Chiral PT Conditions



the *N*-carbamoyl products **489** in high yield and up to 88% ee (Scheme 160).

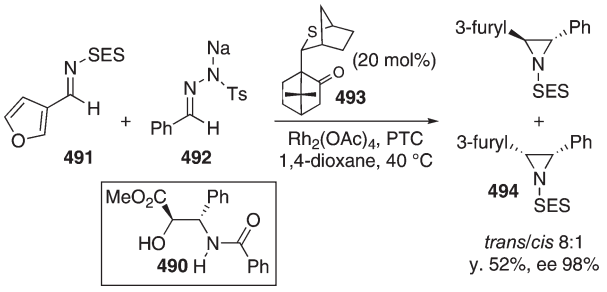
The authors also disclosed the results of trials with other cyanide sources under the same conditions, and while conversions were still very good (>95%), enantioselectivities were highly compromised (KCN, ee 54%; TMSCN, ee 52%).

6.6. Formation of Aziridines

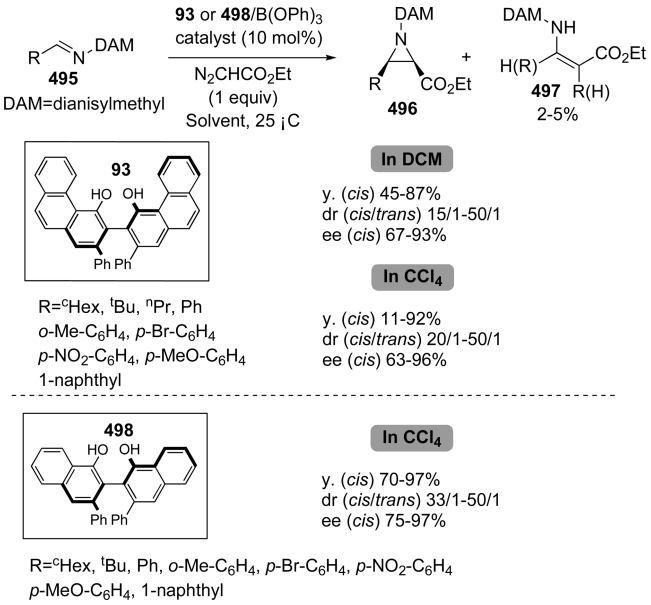
Aziridines are extremely versatile intermediates in organic synthesis due to the ease with which they may be transformed into other compounds by stereoselective and regioselective ring-opening with nucleophiles. Two main methods for the synthesis of these species involve (a) the metal-catalyzed addition of nitrenes to olefins[399] and (b) the addition of carbenes to C=N bonds.[79b,400] In addition to these works, the area was the subject of an excellent review by Müller and Fruit;[401] as a result, only reports appearing in the literature since 2003 will be presented here. While a number of methods for the generation of aziridines via the diastereoselective addition of carbenoid to imines[402] or Darzens-type methods have been reported,[403] few reports of the catalytic asymmetric addition generation of aziridines from imines have appeared in the time period under consideration. Aggarwal and co-workers reported the synthesis of Taxol side chain **490** using their sulfur ylide/Rh carbene catalytic methodology (Scheme 161).[404] Accordingly, treatment of furyl imine **491** with the carbene generated from tosyl hydrazone salt **492**[405] in the presence of dirhodium tetraacetate and 20 mol % of chiral sulfide **493**[406] gave the desired aziridine **494** with excellent enantio- and diastereoselectivity. Manipulation of this product via standard techniques afforded the Taxol side chain in six steps.

Wulff and co-workers have demonstrated the use of their borate−VAPOL/VANOL methodology[79b,c,407] in the catalytic aziridination of *N*-dianisylmethyl (DAM)-protected imine **495** with ethyldiazo acetate (Scheme 162).[408] They noted that both catalysts prepared from borate and either ligand had similar reactivity profiles in the reaction although the effect of solvent was more marked with CCl_4 giving the aziridine

Scheme 161. Catalytic Asymmetric Aziridination of Imines in the Synthesis of the Taxol Side Chain



Scheme 162. VANOL or VAPOL/Borate Catalyzed Asymmetric Aziridination Reactions



product **496** with demonstrably better diastereoselectivities and higher average yields and enantioselectivities. In all cases, the elimination product **497** was isolated as a mixture of regioisomers in 2−5% yield.

Subsequent competition studies suggested that the reaction in the presence of the VANOL-derived catalyst proceeds at about twice the speed of that catalyzed by the VAPOL analogue **93**. The rate of the reaction was also found to be dependent on the nature of the *N*-protecting group. The aziridination of *N*-DAM imines catalyzed by the VAPOL-derived catalyst **93** was found to be 3.8 times faster than that of the analogous *N*-benzhydryl imine, and that with the VANOL catalyst was found to be 3.0 times faster. Although routine investigations were carried out at 10 mol % loading, this could be reduced to as little as 0.5 mol % for the VAPOL catalyst and 0.25 mol % for the VANOL catalyst with no significant erosion of stereoselectivity [R = Ph; VAPOL (10 mol %) yield 91%, ee 96%; (0.5 mol %) yield 82%, ee 95%; VANOL (10 mol %) yield 92%, ee 95%; (0.25 mol %) yield 89%, ee 90%]. Removal of the *N*-DAM protecting group could be effected smoothly and in good yield with 5 equiv of TfOH and the free amine reprotected with a range of *N*-carbamates.

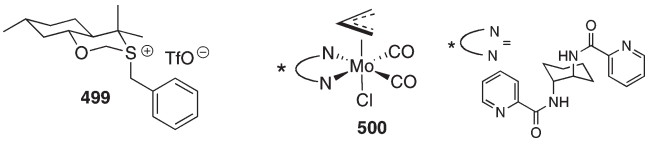


Figure 44

Two other attempted methods for the asymmetric catalytic generation of aziridines have been reported. The first of these involved the asymmetric synthesis of a series of previously unreported heavily hindered *N*-Ts *cis*-phenyl-anthryl, *cis*-phenanthryl-phenyl, *cis*-naphthyl-phenyl, *cis*-*tert*-butyl-phenyl, and *cis*-cyclohexyl-phenyl aziridines using the Eliel oxathane **499** (Figure 44).[409] Although the desired *cis* products were generated in moderate to good yields (60−88%) and very high enantioselectivity (>99% ee), the reaction required stoichiometric quantities of the chiral source. In the second method, η^3-allyl molybdenum complex **500** (Figure 44) was used effectively as a catalyst (1 mol %) for the racemic generation of aziridines from *N*-phenyl benzaldimine and ethyl diazoacetate.[410]

Maruoka has also reported chiral dicarboxylic acid-catalyzed asymmetric aziridination of diazoacetamides and *N*-Boc imines. *trans*-Aziridines were obtained in very high enantioselectivites in the presence of 5 mol % catalyst.[411]

7. CYCLOADDITION REACTIONS OF IMINES AND HYDRAZONES

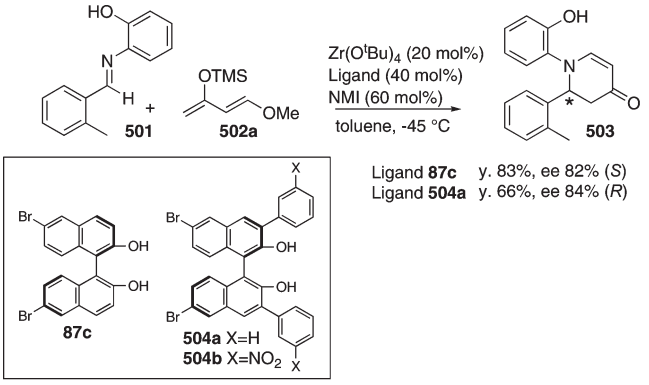
7.1. Diels−Alder Reactions

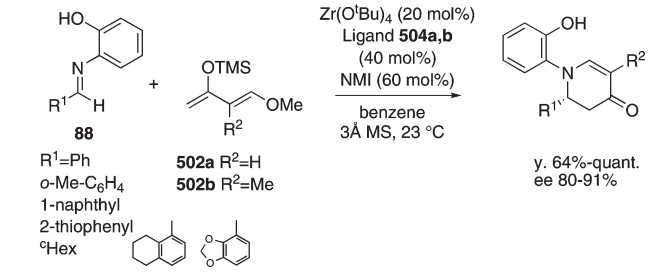
Catalytic asymmetric Diels−Alder reactions utilizing a C═N double bond functionality offer a powerful route to the synthesis of a variety of nitrogen-containing structures of synthetic and biological importance, especially piperidines and tetrahydroquinolones. While the diastereoselective version of the reaction has been known for some time,[412] the development of the catalytic asymmetric version has been much less well explored. A principal reason for this is the tendency for the amine product generated in the reaction (which is more basic than the imine starting material) to coordinate to the catalyst thus retarding catalyst turnover and reducing the efficiency of the reaction. Yamamoto reported an early example of an aza-Diels−Alder reaction promoted by stoichiometric quantities of a chiral boron compound,[413] which was followed by the discovery of a chiral ytterbium[414] Lewis acid catalyst for the reaction of azadienes and zirconium catalysts for the reaction of carbodienes.[415] Kobayashi et al. described the reaction of imine **501** and Danishefsky's diene **502a** in the presence of (*R*)-6,6′-Br_2−BINOL **87c** to give the Diels−Alder product **503** in 83% yield and 82% ee as the *S*-isomer. They later disclosed catalysts formed from Zr(IV), and either (*R*)-3,3′-disubstituted BINOL ligands **504a** or **504b** gave the related Diels−Alder products but as the *R*-isomer (Scheme 163).[416] A range of substrates underwent the reaction giving the desired heterocycles in good yields and ee. Spectroscopic studies suggested structure **505** as being the active catalytic species with NMI occupying the apical positions of an octahedral-like metal geometry, a very similar structure to that established for the 2:1 ligand/metal catalyst **81** (Figure 45).

Subsequently, the same group reported the successful immobilization of this type of catalyst on a polymer support. A 3,3′-diaryl BINOL derivative could be attached to Merrifield resin at the 6-position of one of the naphthol fragments and used to generate catalysts of type **506**, which were used of in the reaction of **501** and **502a** to give the desired product in

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 163. Reversal of Enantioselectivity in the Zr−BINOL Catalyzed Aza-Diels−Alder Reaction





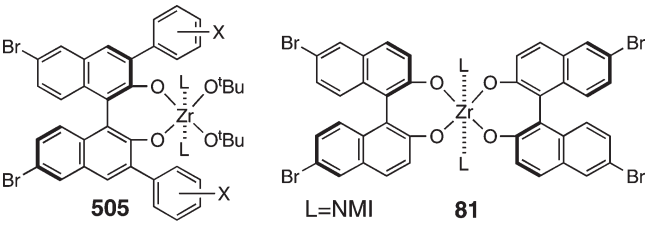


Figure 45. Proposed catalyst structures for the Zr−BINOL catalyzed aza-Diels−Alder reaction.

up to 92% yield and 83% ee.[417] In the same paper, they reported an optimized catalyst species for the solution phase reaction, **507**, which gave good yields and enantioselectivities when used in the reaction of various aldimines and **502a**,**b**. Slow addition of a mixture of both components was found to be advantageous, and the catalyst loading could be reduced to as little as 1 mol % (Figure 46).

The analogous aza-Diels−Alder reaction between *N*-PMP imino ester **49** and Danishefsky's diene **502a** (R^2 = H) has been investigated by the group of Whiting.[418] They examined a very wide variety of metal/ligand complexes for the reaction giving the desired product in moderate yield and good ee. In the case of Et_2Zn/BINOL (Scheme 164, entry 1), ee's of up to 84% were achieved, although use of lower temperatures resulted in lower ee's. This led the authors to suggest the presence of temperature-dependent multiple catalyst species (dimeric or oligomeric) or the existence of an achiral background reaction that persists at lower temperatures. Use of other metals such as MgI_2 or $FeCl_3$ afforded the adduct in >90% yields; however, it should be noted that the reproducibility of these results has been questioned.[419]

Hoveyda and co-workers have applied their *N*,*P*-oligopeptide−Ag(I) catalyst system **107**[94] to the aza-Diels−Alder

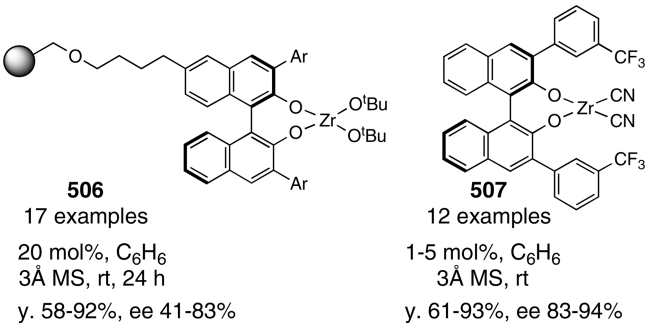
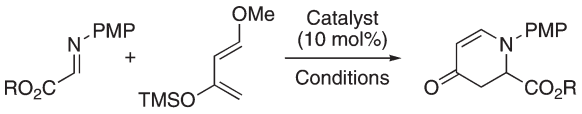
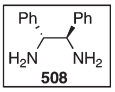


Figure 46. Optimized Zr−BINOL catalysts for solid- and solution-phase aza-Diels−Alder reactions.

Scheme 164. Aza-Diels−Alder Reaction of *N*-PMP Imino Esters and Danishefsky's Diene



Entry	R	Catalyst	Solvent	Additive	y. (%)	ee (%)
1	Et	Et_2Zn/BINOL	toluene	none	52	84
2	Me	MgI_2/**508**	MeCN	2,6-lutidine	64	97
3	Me	$Yb(OTf)_3$/**508**	toluene	2,6-lutidine	60	87
4	Me	$Cu(OTf)_2$/**508**	MeCN	none	58	86
5	Me	$FeCl_3$/**38b**	CH_2Cl_2	4Å MS	67	92

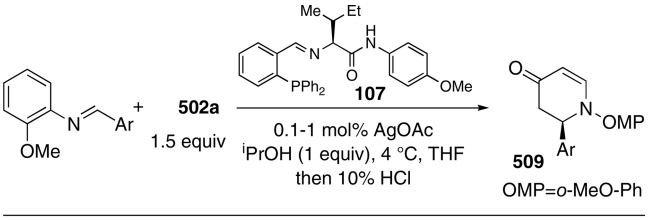


reaction of *N*-*ortho*-methoxyphenyl imines of aromatic aldehydes with Danishefsky's diene **502a**. As little as 1 mol % of the catalyst afforded the adduct **509** in up to >98% yield and 95% ee, but this could be reduced to 0.5 mol % with no significant erosion of yield or selectivity, and 0.1 mol % afforded the adduct in 78% yield and 88% ee (Ar = Ph) (Scheme 165).[420] The authors noted that the presence of the *ortho*-methoxy substituent on the aryl group of the nitrogen substituent was important for selectivity but not yield and that the addition of 1 equiv of ^{i}PrOH was important for smooth and selective reactions. The authors showed that the reaction proceeded efficiently even under an aerobic atmosphere and in undistilled THF (Ar = 2-naphthyl, yield 82%, ee 94% versus yield >98%, ee 95% under anhydrous conditions). They also described a polymer-immobilized version of the catalyst, **510**, that at 5 mol % loading delivered the desired adduct in high yield and selectivity under ambient conditions and could be recycled and reused up to 5 times.

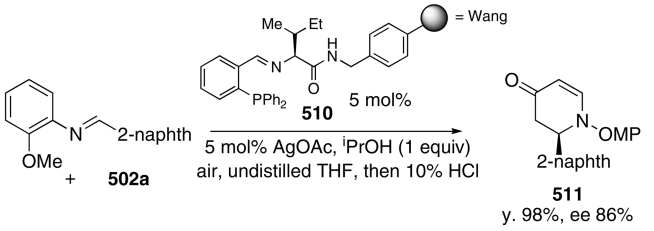
The cycloaddition of highly activated *N*-tosyl imino ester **41** with substituted Danishefsky's dienes has been examined by Jørgensen et al. using a very wide range of metal sources [$CuClO_4$·4MeCN, $CuOTf·{}^1/_2C_6H_6$, $Cu(OTf)_2$, $AgSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, $RuSbF_6$, and $Zn(OTf)_2$] and ligands (Figure 47).[350,421] Of these, $CuClO_4$ was found to produce the best results with the parent diene

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 165. Hoveyda's Ag(I)/Peptide Catalyst in the Aza-Diels–Alder Reaction



Ar=*p*-MeO-C_6H_4, 2-furyl *p*-Cl-C_6H_4, *o*-Br-C_6H_4 *m*-O_2N-C_6H_4, *p*-O_2N-C_6H_4, 1-naphth, 2-naphth	0.5-1.0 mol% catalyst		y. 86->98% ee 89-95%
Ar=Ph	0.1 mol% y. 78% ee 88%	0.5 mol% y. 92% ee 92%	1.0 mol% y. 94% ee 93%



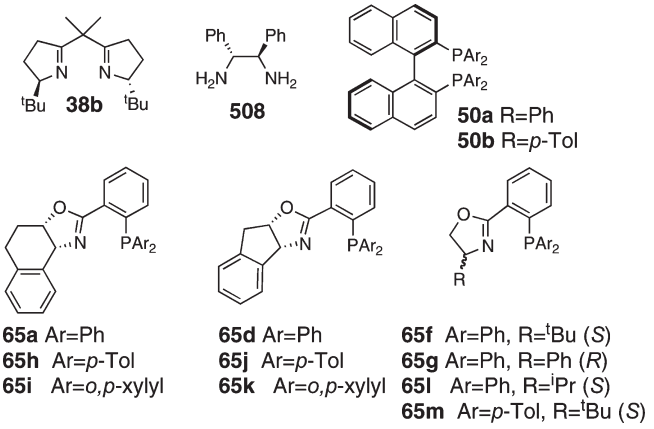
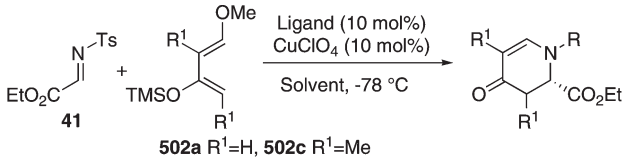


Figure 47. Ligands for the aza-Diels–Alder reaction of *N*-tosyl imino ester **41**.

(affording the adduct in up to 87% ee (ligand **65f** or **65m**) in THF although both average yields and selectivities were better in DCM). In the case of **502c**, the reaction proceeded in a highly diastereoselective manner with the *trans* adduct being significantly favored over *cis*. Yields and enantioselectivities of the *trans* isomer were marginally improved over those obtained with **502a**, whereas the *cis* adduct was generated in low ee (Scheme 166).[45] In the same paper, the authors reported the aza-Diels–Alder of **41** with unactivated cyclic 1,3-dienes such as cyclopentadiene and 1,3-cyclohexadiene (Scheme 167). In both cases, the reaction proceeded in moderate to good yield with high enantio- and diastereoselectivity.

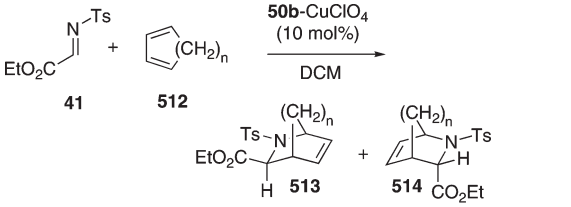
Wulff and co-workers have introduced an updated version of Yamamoto's original borate/BINOL reaction[413] using a mixture of 5–10 mol % (*S*)-VAPOL **93** and 100 mol % of $B(OPh)_3$ with both aryl and aliphatic imines, *N*-benzhydryl imines **464** (R^1 = Ph).[422]

Scheme 166. Aza-Diels–Alder Reaction of *N*-Tosyl Imino Ester 41 with Substituted Danishefsky's Dienes



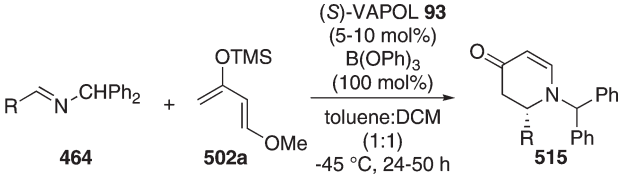
R^1=H	Ligands: **50a,b**; **65a,d,f,g**; **65h-m**	In THF y. 49-97% ee 27-87%	In DCM y. 70-96% ee 10-86%
		trans-isomer	*cis*-isomer
R^1=Me	Ligands: **50b**; **65a,f** (THF)	y. 64-83% ee 66-94%	y. 8-32% ee 0-15%
	Ligand: **65h** (DCM)	y. 48% ee 64%	y. 44% ee 5%

Scheme 167. Catalytic Asymmetric Aza-Diels–Alder Reaction of Unactivated 1,3-Dienes



n=1	y. 85%, ee 83%	y. 7%, ee 83%
n=2	y. 52%, ee 95%	y. 7%, ee 37%

Scheme 168. VAPOL/$B(OPh)_3$ Catalyst in the Aza-Diels–Alder Reaction



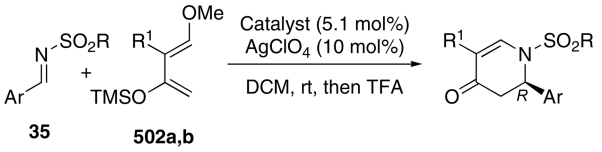
R=Ph, *o*-Me-C_6H_4,
p-Br-C_6H_4, *p*-NO_2-C_6H_4
p-MeO-C_6H_4, *p*-F-*o*-Me-C_6H_3
1-naphthyl, 1-cyclohexenyl
^{c}Hex, ^{i}Pr

y. 45-90%
ee 73-93%

High yields and selectivities were obtained in the reaction producing the *S*-isomer in up to 93% ee (Scheme 168). The result was particularly noteworthy because in the related process stoichiometric quantities of the borate/BINOL catalyst were required for high enantioselectivities, whereas up to 500 mol % of the achiral $B(OPh)_3$ could be used with 10 mol % of the (*S*)-VAPOL with no adverse impact on the enantioselectivity of the reaction. The authors ascribed this behavior to both higher reactivity of the imine with the cyclic VAPOL/$B(OPh)_3$ species versus uncomplexed $B(OPh)_3$ and the excess borate binding to the product more strongly than the catalyst and aiding the recycling of the catalytic species. They estimated the difference in the rates of catalyzed and uncatalyzed reaction to be approximately 100 times.

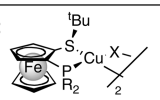
dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 169. Catalytic Asymmetric Aza-Diels−Alder Reaction of *N*-Sulfonyl Aryl Imines



502a R^1=H
35 R=*p*-Tol
Ar=Ph

Catalysts:



516a R=Ph, X=Cl
517a R=Ph, X=Br
516b R=*p*-F-C_6H_4, X=Cl
516c R=2-furyl, X=Cl
516d R=Cy, X=Cl
516e R=*o*-Me-C_6H_4, X=Cl
516f R=1-naphth, X=Cl
517f R=1-naphth, X=Br

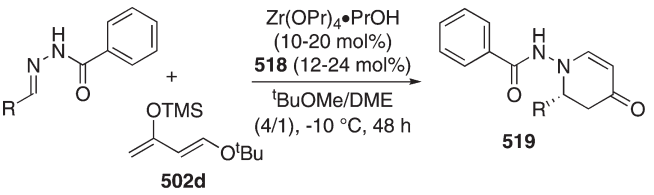
y. 58-96%
ee 55-93%

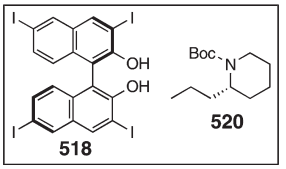
502b R^1=Me
35 R=*p*-Tol, *p*-MeO-Ph
Ar=Ph, *o*-Me-C_6H_4, *p*-F-C_6H_4
p-MeO-C_6H_4, *p*-Me_2N-C_6H_4
2-naphth, cinnamyl, ^{n}Pr

Catalyst **517f**

y. 39-90%
ee 73-94%

Scheme 170. Catalytic Asymmetric Aza-Diels−Alder Reaction of Hydrazones





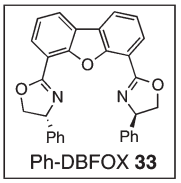
R	y. (%)	ee (%)
$Ph(CH_2)_2$	70	91
^{n}Pr	70	93
^{i}Bu	50	91
^{c}Hex	50	95

Carretero and co-workers have used *P,S*-ferrocenyl-Cu(I) catalysts to promote the asymmetric aza-Diels−Alder of Danishefsky dienes **502a** and **502b** with *N*-sulfonyl aromatic imines.[423] A range of P-substituted catalyst systems were investigated for the benchmark reaction of PhCH═NTs with **502a**, and **517f** was shown to be optimum. The reaction was found not to be concerted because the main product was the intermediate Mannich adduct, which was cyclized upon treatment with TFA. Application of these conditions to reactions of a range of aryl imines gave good yields of the *R*-adducts in up to 94% ee (Scheme 169). The same class of ligand was also exploited in vinylogous indirect Mannich-type reactions by the same group.[424]

The corresponding aza-Diels−Alder reaction using hydrazone as the dienophile has been reported by Kobayashi et al. A catalyst formed from $Zr(OPr)_4$·PrOH and 3,3′,6,6′-I_4-BINOL **518** promoted the cycloaddition of a range of *N*-benzoyl aliphatic hydrazones with Danishefsky dienes **502d** to give the desired heterocyclic products **519** in moderate yield and high enantiomeric excess (Scheme 170).[425] An attractive aspect of this protocol is the robust nature of the reactions with aliphatic hydrazones as opposed to those with the analogous imines. The authors were able to successfully cleave the N−N bond in their adducts and elaborate one of them (**519** R = ^{n}Pr) to *N*-Boc-(*S*)-(+)-coniine **520**.

Scheme 171. Inverse Electron-Demand Aza-Diels−Alder Reaction of 1-Azadienes

R^1=Ph
R^2=Ph, *p*-F-C_6H_4
2-naphthyl, 2-furyl
p-Meo-C_6H_4, ^{t}Bu



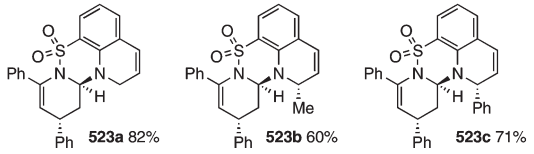
y. 61-75%
exo/*endo* 97:3-98:2
ee 77-92%

R^1=*p*-Cl-C_6H_4, 2-naphthyl
p-CF_3-C_6H_4, cinnamyl
R^2=Ph

y. 67-73%
exo/*endo* 90:10-98:2
ee 6-91%

R^1=*p*-Cl-C_6H_4, *p*-CN-C_6H_4
R^2=cinnamyl

y. 63-70%
exo/*endo* 98:2
ee 92%



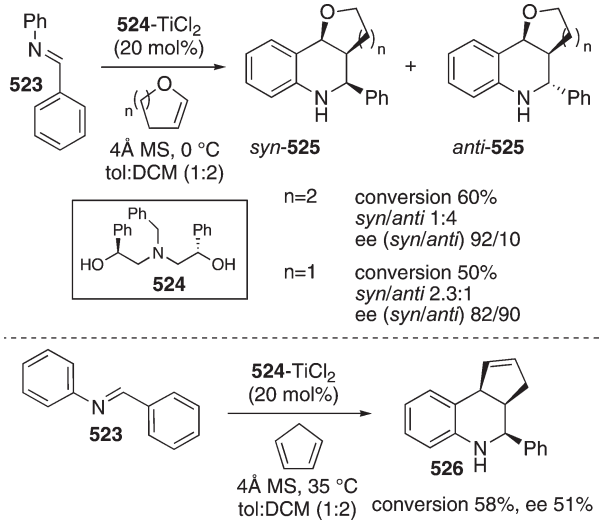
aliphatic hydrazones as opposed to those with the analogous imines. The authors were able to successfully cleave the N−N bond in their adducts and elaborate one of them (**519** R = ^{n}Pr) to *N*-Boc-(*S*)-(+)-coniine **520**.

The low reactivity of 1-azadienes has prevented their widespread use in synthesis,[426] but Carretero et al. have described a catalytic asymmetric reverse electron demand aza-Diels−Alder of *N*-sulfonyl-1-aza-1,3-dienes using a catalyst formed from Ni(II) and DBFOX **33**.[427] Following a screening of metal sources [$Cu(OTf)_2$, $Mg(ClO_4)_2$·$6H_2O$, $Zn(ClO_4)$·$6H_2O$, $Ni(ClO_4)_2$·$6H_2O$] and *N*-sulfonyl groups, they settled on a combination of $Ni(ClO_4)_2$·$6H_2O$ and aza-dienes **521** bearing the highly electron-withdrawing SO_2-(8-quinolyl). Under these conditions, a wide variety of chalcones and related systems underwent the cycloaddition giving the desired adducts **522** with extremely high *endo*/*exo* ratios (up to 98:2) and good to high enantioselectivity (up to 92% ee) (Scheme 171). The *N*-sulfonyl substituents could be used to good effect following completion of the reaction because they could be converted into CNS disorder drug candidate [1,2,4]benzothiadiazine-5,5-dioxide derivatives **523a**−**c** following a BF_3·OEt_2-mediated cyclization followed by reduction or addition of RMgX.

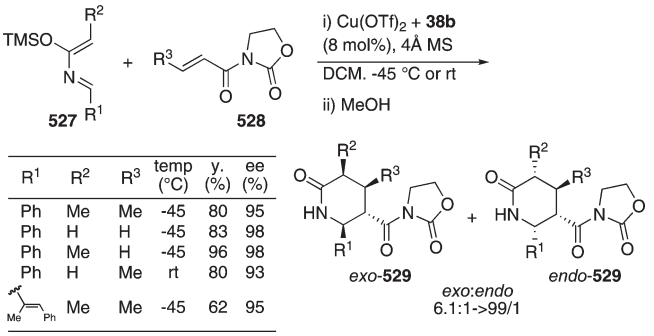
The analogous asymmetric aza-Diels−Alder reaction with 2-azadienes has been described by Sundararajan and co-workers. In their case, they used *N*-benzylideneaniline **523** as the diene component in which one of the C═C of the system is implicit in the aromatic substituent on the nitrogen atom. Activation of this with 20 mol % of a catalyst formed from $TiCl_2$ and chiral diol **524** in the presence of enol ethers or cyclopentadiene gave moderate conversions to the expected tricyclic adducts **525** with moderate diastereoselectivity in the case of DHP and DHF as dienophile and as a single (*syn*) diastereomer when cyclopentadiene was used (Scheme 172).[428] Enantioselectivities were generally good in the case of the *syn* form.

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 172. Ti(II)-Catalyzed Enantioselective Aza-Diels–Alder Reaction



Scheme 173. Asymmetric Aza-Diels–Alder Reaction of 2-Azadienes Promoted by Cu-Box Catalysts



R^1	R^2	R^3	temp (°C)	y. (%)	ee (%)
Ph	Me	Me	-45	80	95
Ph	H	H	-45	83	98
Ph	Me	H	-45	96	98
Ph	H	Me	rt	80	93
	Me	Me	-45	62	95

The aza-Diels–Alder reaction of a true 2-azadiene has been reported by Jnoff and Ghosez.[429] The instability of these dienes in the presence of common Lewis acid systems has limited their applicability in synthesis, but the authors discovered that a simple combination of $Cu(OTf)_2$ and *S,S*-^{t}Bu-Box **38b** promoted the reaction of a range of 2-azadienes **527** with carbamate dieneophiles **528** in good to very good yield and excellent stereoselectivity (*exo*/*endo* > 99:1, up to 98% ee) (Scheme 173). The reaction is believed to proceed via a square planar complex formed by coordination of the metal–ligand complex to the imide group of the dienophile (Figure 48). This binding mode not only creates the required chiral manifold for the reaction but is also thought to limit decomposition of the diene.

In view of the fact that research into reactions promoted by organocatalysts has been a very active field since around 2000, it is perhaps surprising that investigation of the organocatalytic aza-Diels–Alder reaction commenced only in 2005. In the first reported example of the transformation, Córdova and co-workers used (*S*)-proline in DMSO to promote the three-component coupling of cyclic enones **530**, formaldehyde, and a variety of anilines to give the corresponding bicyclic amines **531** (Scheme 174).[430] As expected enantioselectivites were excellent in all cases although yields were only low to moderate,

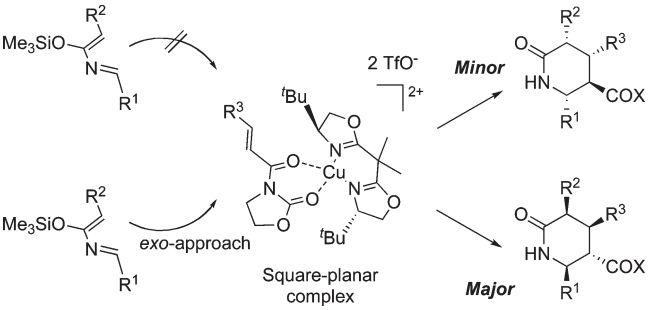
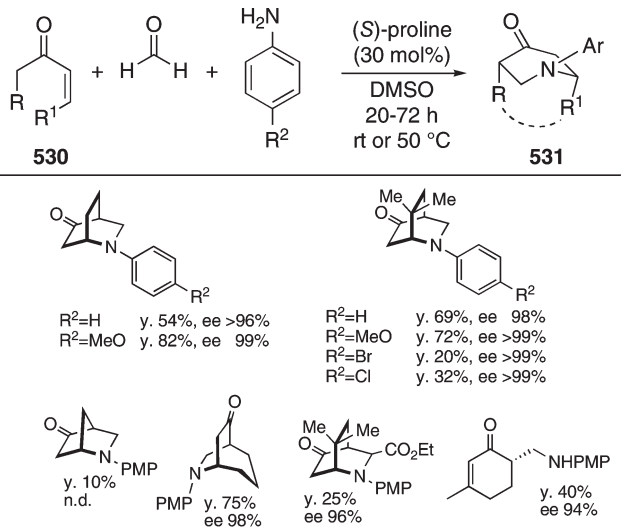


Figure 48. Proposed transition state for the aza-Diels–Alder of 2-azadienes.

Scheme 174. Direct Catalytic Enantioselective Aza-Diels–Alder Reaction Promoted by (*S*)-Proline



particularly in the case of anilines bearing electron-withdrawing substituents. One example of the addition using the *N*-PMP imine derived from ethyl glyoxylate was reported (yield 25%, ee 96%). The authors invoked a reaction mechanism in which the enamine **532** derived from the cyclic enone and proline reacts with the imine **533** formed from formaldehyde and the aniline in a Mannich-type fashion to give iminium ion intermediate **534**, which undergoes intramolecular Michael reaction to give the corresponding bicyclic adduct **535**. Hydrolysis of this liberates the product and returns the catalyst to the system (Figure 49).

Gong et al. disclosed a protocol for the closely related reaction between cyclohexanone and a series of preformed *N*-PMP aldimines, catalyzed by chiral phosphoric acid **536** (Figure 50 and Scheme 175).[431] A wide range of common aromatic aldimines functioned in the reaction giving good yields of the bicyclic adducts with moderate to high enantioselectivity as predominantly the *endo* form at 5 mol % catalyst loading. The authors also reported the corresponding three-component reaction, which gave the desired adducts in almost the same yield and enantioselectivity as the procedure using preformed imines with slightly improved *endo*/*exo* selectivity.

Chiral phosphoric acids have also been used to catalyze the aza-Diels–Alder reaction of imines with electron-rich dienes. In this regard, Akiyama has reported the successful union of

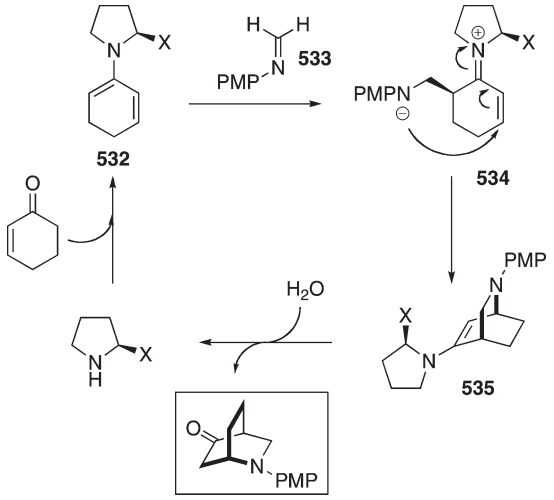


Figure 49. Proposed catalytic cycle for the organocatalytic aza-Diels–Alder reaction.

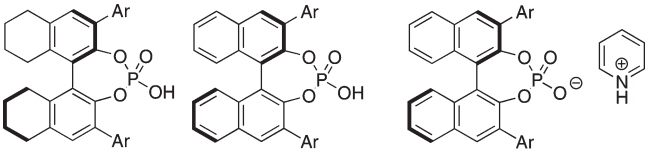
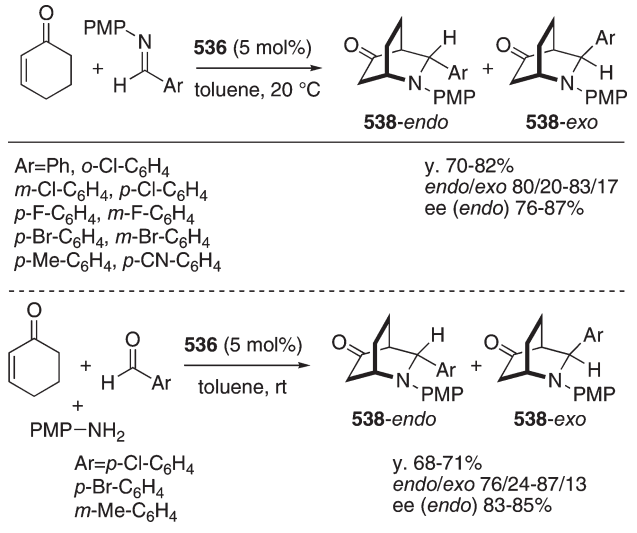


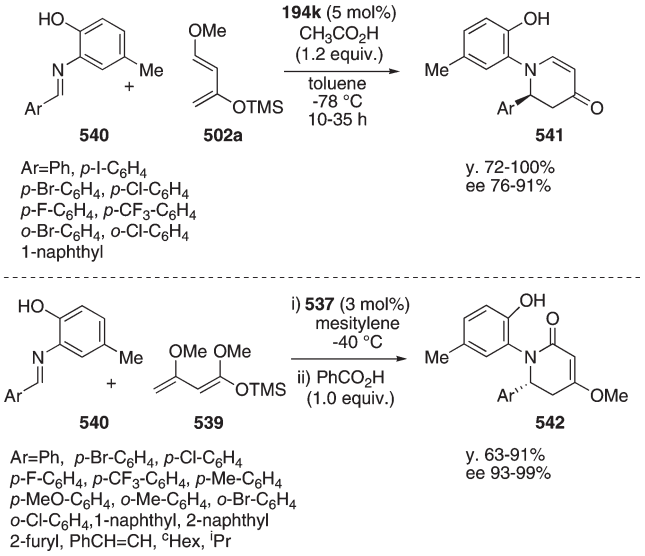
Figure 50. Chiral phosphoric acids and their pyridine salts used in the organocatalytic asymmetric aza-Diels–Alder reaction.

Scheme 175. Asymmetric Catalytic Aza-Diels–Alder Reaction Mediated by Chiral Phosphoric Acids

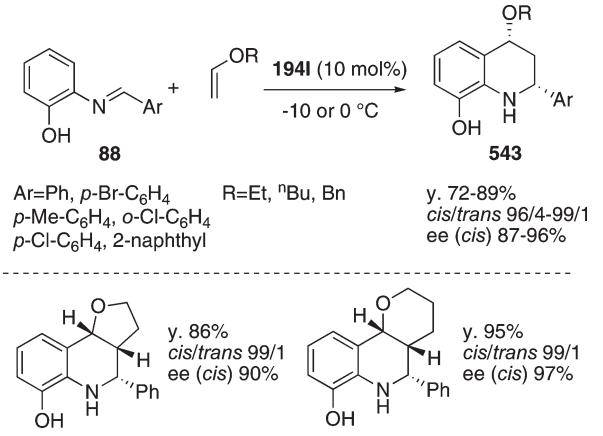


N-ortho-hydroxyphenyl imines **540** with Danishefsky's diene **502a** using the highly hindered phosphoric acid **194k** in up to quantitative yields and high ee (Scheme 176). The stereoselectivity of the reaction was found to be dependent on the nature of additives in the reaction: Addition of a slight excess of an alcohol improved the ee, while carboxylic acids such as benzoic and acetic acid gave even better selectivities. The use of stronger acids such as $PhSO_3H$ led to a dominant achiral

Scheme 176. Organocatalytic Asymmetric Aza-Diels–Alder Reaction with Danishefsky's and Brassard's Dienes



Scheme 177. Catalytic Asymmetric Inverse Electron Demand Aza-Diels–Alder Reaction of Azadienes



background reaction.[432] The more acid-sensitive Brassards diene **539** decomposed in the presence of unattenuated phosphoric acids such as **194k**, so the authors employed the corresponding pyridinium salt **537** in the reaction. Under these conditions, **539** underwent smooth Diels–Alder addition with a series of imines derived from 2-amino-*para*-cresol **540** in good yield and excellent ee in the presence of 1 equiv of benzoic acid.[433] The reaction was successfully scaled up to afford the product on gram scale with no loss of yield or enantioselectivity (Ar = Ph).

The same group have reported a highly efficient catalytic asymmetric inverse electron demand aza-Diels–Alder reaction of *N*-orthohydroxy azadienes **88** with enol ethers catalyzed by chiral phosphoric acid **194l**.[434] Using 10 mol % catalyst, the authors obtained adducts **543** in good yield, excellent enantioselectivity, and near-perfect *cis*/*trans* selectivity (Scheme 177). The *ortho*-hydroxy group on the imine nitrogen substituent was found to be essential for high selectivity, leading the authors to propose a 9-membered transition state in which the imine is bound to the

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 178. Catalytic Asymmetric Aza-Diels−Alder Reactions Promoted by *N*-Heterocyclic Carbenes

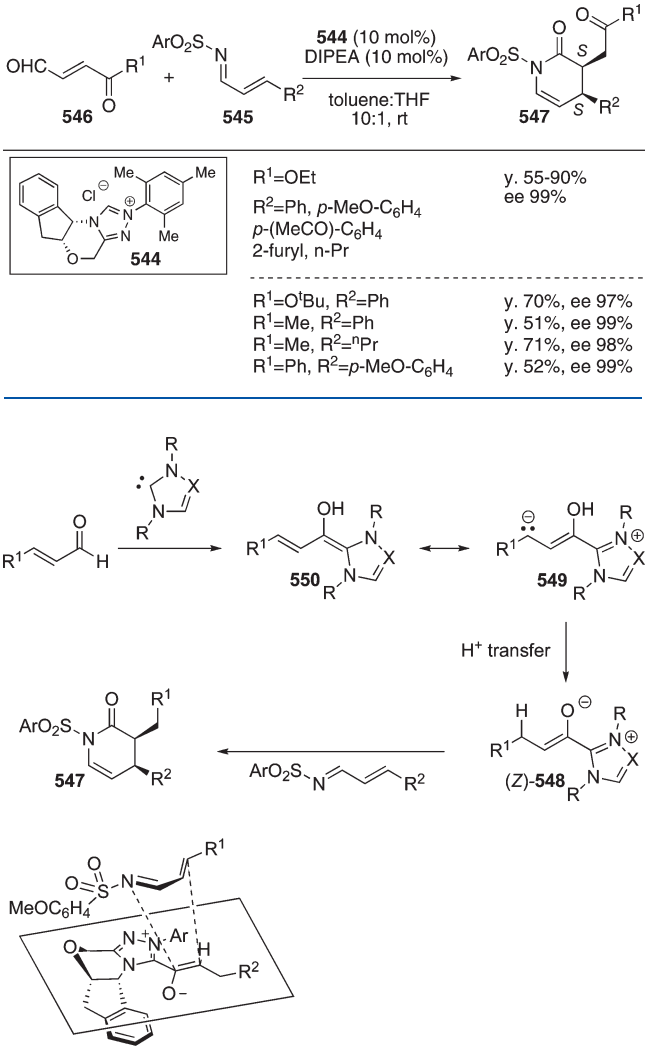
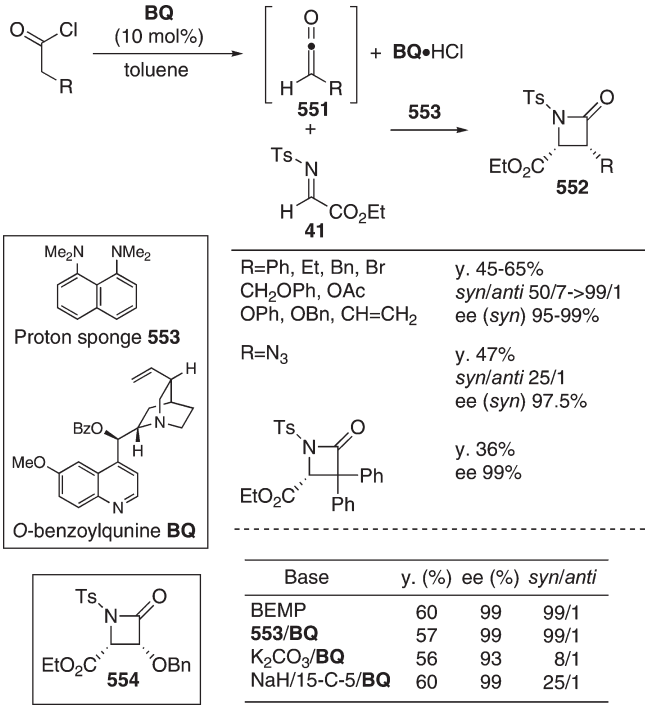


Figure 51. Postulated reaction mechanism and stereochemical rationale for the reaction.

catalyst in bidentate fashion by H-bonds between the phosphate and both the imine nitrogen and *N*-hydroxyl group.

In an early example of an organocatalyzed aza-Diels−Alder reaction of azadienes, Bode described an elegant protocol using chiral *N*-heterocyclic carbene **544** to promote the addition of *N*-sulfonyl azadienes **545** to a range of α,β-unsaturated-δ-dicarbonyl compounds **546** giving the desired unsaturated lactam adducts **547** as preferentially the *syn* diastereomer in moderate to good yield and excellent enantioselectivity (Scheme 178).[435] The reaction is believed to proceed via the interaction of the azadiene and enolate **548**, which arises from proton transfer to the homoenolate resonance form **549** of the Breslow intermediate **550** generated by attack of the nucleophilic carbene on the aldehyde starting material (Figure 51). The high *syn* selectivity of the reaction is determined by the *Z*-geometry of the enolate **548**, and the reaction proceeds under remarkably mild conditions. The reaction showed broad substrate scope with both aromatic and aliphatic azadienes being amenable, and both δ-ester aldehyde and δ-keto aldehyde dieneophiles underwent

Scheme 179. Catalytic Enantioselective Formal [2 + 2] Cycloaddition of Imines and Ketenes



Base	y. (%)	ee (%)	*syn*/*anti*
BEMP	60	99	99/1
553/**BQ**	57	99	99/1
K_2CO_3/**BQ**	56	93	8/1
NaH/15-C-5/**BQ**	60	99	25/1

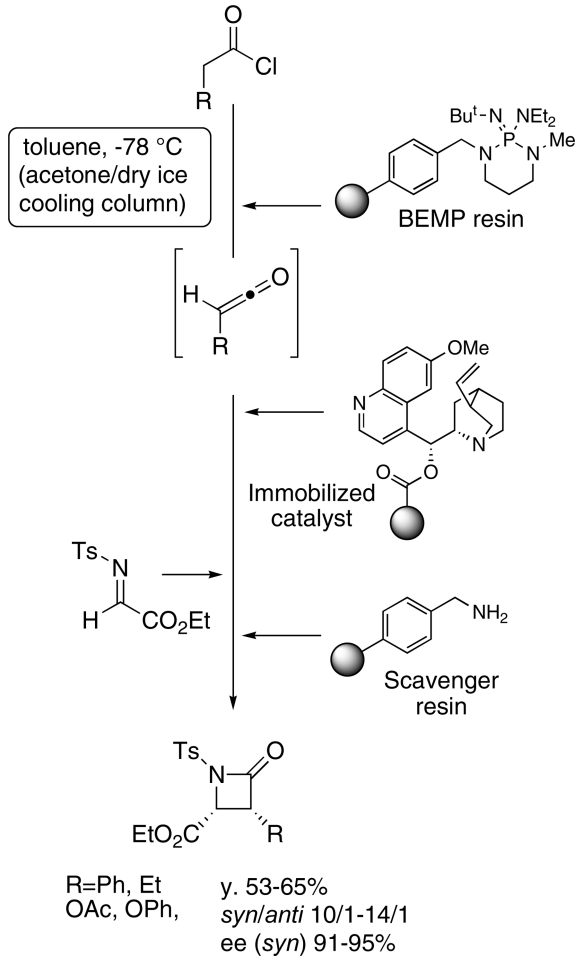
smooth conversion. The requirement for the incorporation of an ester group into the dienophile component is believed to be due purely to the higher reaction of a more electron-poor dienophile, rather than any mechanistic reasons requiring extended conjugate systems such as would be afforded by the enolization of the ester functional group. The aldehyde group however was found to be necessary for efficient reaction because use of fumarates or corresponding structures lacking the aldehyde function were unsuccessful.

7.2. Formal [2 + 2] Aza Cycloaddition Processes

The formal [2 + 2] cycloaddition reaction of imines is a potentially extremely useful procedure, particularly if the cyclization partner is a ketene, because this would afford access to β-lactam derivatives. Most of the methodology for their asymmetric synthesis to date has been reagent-based and relies on the noncatalyzed reaction of an imine with a ketene.[436] Efforts to develop an efficient catalytic asymmetric approach to the reaction have been led by Lectka, and in this context, the benzoyl quinine (**BQ**)-catalyzed formal [2 + 2] addition of highly activated *N*-Ts imino ester **41** with a range of ketenes **551** giving the desired β-lactam products **552** with almost perfect enantioselectivity and as essentially only the *cis* isomer (Scheme 179) was reported.[437,438] The ketene was generated *in situ* by elimination of HCl from the corresponding acyl chloride using a "shuttle-base" technique in which the non-nucleophilic strong base proton sponge **553** is used stoichiometrically in conjunction with the **BQ** which plays a dual role both as base and as nucleophilic catalyst. Dehydrohalogenation of the acyl chloride by the **BQ** affords the ketene and **BQ** hydrochloride, which, if not removed, can catalyze a low ee background reaction. Sequestration of the HCl by proton sponge returns the free **BQ**, which then goes on to

dx.doi.org/10.1021/cr100204f |*Chem. Rev.* 2011, 111, 2626–2704

Scheme 180. Solid-Phase Catalytic Asymmetric Formal [2 + 2] Addition of Imines to Ketenes



catalyze the reaction stereoselectively. Other bases can be used in combination with **BQ** including NaH/15-crown-5,[439] K_2CO_3, and BEMP giving the *cis*-β-lactam **554** in very similar yields and enantioselectivities. Subsequent treatment of the addition products with either methanol or a primary amine gave β-aspartic acid derivatives or α,β-amino acids, respectively.[440]

The practicality of this reaction was increased by the discovery that the sequence can be carried out on solid phase using a sequence of immobilized reagents (Scheme 180).[441] Addition of a solution of the acid chloride over BEMP resin cooled to −78 °C produced a stream of the ketene, which was then exposed to the immobilized chiral catalyst and the imine at −43 °C. Final treatment with a scavenger resin removed unreacted ketene and byproduct to give the desired *cis*-β-lactams in virtually identical yields and enantioselectivities. The high cost of BEMP resin prompted the authors to develop an alternative system in which a mixture of the acid chloride and imine was passed over the supported quinine catalyst at −43 °C to give the product (R = Ph) in 61% yield and 91% ee as a 7:1 *cis*/*trans* mixture.[442] Addition of an inorganic base such as K_2CO_3 impeded reaction and led to lower selectivities. Both protocols could be operated smoothly on a gram scale, and the resins could be recovered and regenerated (up to 60 times). In view of the uncertainty in determining loading of catalyst onto the resin, the effective quantity of catalyst required for the reaction is difficult to estimate. Other factors such as flow rate and possible leaching of the asymmetric catalyst from the resin must be acknowledged as potential drawbacks to the system.

Although this method represented an interesting technical advance and presented a route to biologically important molecules with exceptional selectivity, the relatively low yields (40−65%) of the process limit its synthetic utility. In an attempt to obviate this, Lectka and co-workers have developed a bifunctional catalyst system involving **BQ** and a metallic cocatalyst. After screening a number of metals [Mg(II), Cu(I), Yb(III), La(III), Ag(I), Al(III), Sc(III), Zn(II), and In(III)], they identified an optimum catalyst system consisting of a 1:1 complex of **BQ** and $In(OTf)_3$. Application of this in the reaction of imine **41** with a range of ketenes (**551**, R = Ph, Bn, CH_2OPh, OPh, OAc, or OBn) gave the desired products in greatly improved yields (92−98% versus 45−65% with the simple **BQ** system) and excellent selectivities of 96−98% ee and up to 60/1 *syn*/*anti* diastereoselectivity.[443]

8. CONCLUSION

The addition reactions of C═N systems, particularly imine and hydrazones, remains a field of very great importance in organic synthesis and is still the focus of Herculean efforts on the part of a large number of research groups as they respond to the demand for ever more efficient and selective catalysts.

Although significant advances have been made in Lewis acid based systems, it is the explosive growth of research into organocatalysts in the last 10 years that has made the greatest impact. The almost quantitative yields and very high enantioselectivites, routinely in the realm of >95%, coupled with their robust nature and, certainly in the case of proline-derived catalytic systems, their simplicity, ensures that they will be the focus of intensive research efforts for some time to come. Principal problems that will require attention will surely include reduction of catalyst loading and substrate scope. In these areas, Lewis acid catalysts still display superior performance. The exact nature of the real catalytic species in these systems is still in many cases a mystery, and the subtle effects of additives and solvents on catalyst structure and the consequent implications for enantioselectivity ensure a steady supply of discoveries and elucidations for the foreseeable future.

AUTHOR INFORMATION

Corresponding Author

*E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp.

BIOGRAPHIES

Shū Kobayashi studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as an assistant professor, he was promoted to a lecturer, then an associate professor at the Science University of Tokyo. In 1998, he moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as a full professor. In April 2007, he was appointed to his current position as a professor of organic chemistry in the Department of Chemistry, within the Faculty of Science of The University of Tokyo. Professor Kobayashi was also a director of the ERATO project of the Japan Science Agency (JST). He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), and Philipps-University of Marburg (1997)

Yuichiro Mori received his Ph.D. on the development of catalyst systems in water under the supervision of Professor Shū Kobayashi in 2001, and he became an Assistant Professor at the Graduate School of Pharmaceutical Sciences at the University of Tokyo. He worked as a group leader in the Kobayashi Highly Functionalized Reaction Environments Project in the Japan Science and Technology Agency (JST) from 2003 to 2008. He has been engaged in Green Sustainable Chemical Process Project (NEDO) as a group leader from 2008. His current research interests involve the development of practical catalytic processes and organic reactions in water.

John S. Fossey received his MChem degree from Cardiff University in 2000; he then obtained a Ph.D. from Queen Mary University of London, under the direction of Dr. C. J. Richards, in 2003. He was awarded a Japan Society for the Promotion of Science (JSPS) overseas research fellowship to work with Professor Shū Kobayashi in the Graduate School of Pharmaceutical Sciences, University of Tokyo. He was appointed to a temporary faculty position at the University of Bath in 2005 and became a lecturer at the University of Birmingham in 2008. In 2010, he was an inaugural recipient of a JSPS Re-Invitation Bridge Fellowship; he was visiting associate professor at Tokyo Metropolitan University and visiting professor at East China University of Science and Technology. His current research interests are in catalysis and sensing, and the development of self-reporting synthetic systems.

Matthew M. Salter received his B.Sc. from Imperial College London in 1990 and was awarded a Ph.D. from the same institution where he worked under the direction of Professor S. E. Gibson (née Thomas), in 1993. Upon graduation, his dual love of Chemistry and the Far East led him to study as a JSPS Overseas Research Fellow in the group of Professor Y. Yamamoto at Tohoku University, Japan, until 1995, whereupon he returned to his alma mater as a research assistant in the group of Professor A. G. M. Barrett FRS. Following a brief stint in agrochemical research at Sumitomo Chemical Ltd. in Osaka, Japan, he returned to the U.K. to take up a lectureship in Chemistry at King's College London in 1999. Upon closure of the Chemistry Department at KCL in 2005, he moved to the University of Tokyo as a JSTAsia-PacificERATO Group Leader in the group of Professor Shū Kobayashi. His research interests include indium-mediated synthetic methods and the development of novel chiral Lewis acids for asymmetric synthesis. He then headed up Tokyo Chemical Industries' U.K. operation and before returning to Japan in 2008 where he is currently Editor and Publisher at Macmillan Scientific Communications (Asia-Pacific), the custom publishing arm of Macmillan Publisher Ltd., the publishers of *Nature* and the Nature research journals.

ACKNOWLEDGMENT

We thank Japan Science Technology Agency (JST), a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program, The University of Tokyo, MEXT, and New Energy and Industrial Technology Development Organization (NEDO), METI, Japan. J.S.F. thanks the University of Tokyo, the University of Birmingham, ERDF AWM II, and the JSPS for the award of an Inaugural Bridge Re-Invitation Fellowship (JSPS/FF4/13).

REFERENCES

(1) For salient attention of this area see: (a) Ma, J. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(2) (a) Takao, K. I.; Munakata, R.; Tadano, K. I. *Chem. Rev.* **2005**, *105*, 4779. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Boger, D. A. *Chem. Rev.* **1986**, *86*, 781.

(3) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.

(4) (a) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon: New York, 1991; Vol. 1, Chapter 1.10. (b) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; RademacherP.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (c) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

(5) (a) McCarty, C. G. *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed., Pergamon: New York, 1970; Chapter 9. (b) Biørgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 757.

(6) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(7) For a selection, see: (a) Skucas, E.; Ngai, M.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (b) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912. (c) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315. (d) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley Interscience: New York, 1994. (e) Kobayashi, S.; Sugiura, M.; Schneider, U.; Matsubara, R.; Fossey, J.; Yamashita, Y. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, 2007.

(8) Yamada, K. I.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874.

(9) Mannich, C.; Krosche, W. *Arch. Pharm. (Weinheim, Ger.)* **1912**, *250*, 647.

(10) For reviews of the subject, see: (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; p 923. (b) Arend, M; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(11) For examples see: Silyl enol ethers. (a) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (b) Enders, D.; Oberbörsch, S.; Adam, J. *Synlett* **2000**, 644. Enamines. (c) Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689. (d) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Balalaie, S.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem.* **1998**, 197. Boron enolates.(e) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. Lithium enolates. (f) Palomo, C.; Oiarbide, M.; Gonzalez-Rego, M. C.; Sharma, A. K.; Garcia, J. M.; Gonzalez, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063.

(12) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(13) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M. *Science* **1991**, *254*, 1471.

(14) Pan, C. F.; Wang, Z. Y. *Coord. Chem. Rev.* **2008**, *252*, 736.

(15) Kazmaier, U. *Angew. Chem., Int. Ed.* **2009**, *48*, 5790.

(16) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857.

(17) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871. (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem.—Eur. J.* **1998**, *4*, 1137. (c) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561.

(18) (a) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Ito, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. (b) Takeoka, E.; Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Heterocycles* **1997**, *46*, 157. (c) Sasai, H.; Hiroi, M.; Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 6031.

(19) Arai, T.; Sasai, H.; Aoe, K. I.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104.

(20) For a review of metal/linked BINOL complexes, see: (a) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. Oxygen-linked BINOL in the desymmetrization of meso-epoxides: (b) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252.

(21) (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777.

(22) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(23) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

(24) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

(25) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

(26) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985.

(27) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339.

(28) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365.

(29) Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3146.

(30) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588.

(31) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319.

(32) For a racemic DMTR promoted by a barium catalysts, see: Saito, S.; Tsubogo, T.; Kobayashi, S. *Chem. Commun.* **2007**, 1236.

(33) Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 3387.

(34) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.

(35) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 2359.

(36) (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (b) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211.

(37) For previous applications of this and related catalyst systems, see:(a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Támas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (c) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225. (d) Hamashima, Y.; Sodeoka, M. *Chem. Rec.* **2004**, *4*, 231.

(38) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.

(39) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2007**, *128*, 14010.

(40) Li, Z. P.; MacLeod, P. D.; Li, C. J. *Tetrahedron: Asymmetry* **2006**, *17*, 590.

(41) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859.

(42) Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem.—Asian J.* **2008**, *3*, 1443.

(43) For a review of glycine imino esters in synthesis, see:O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3.

(44) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583.

(45) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2000**, *6*, 2435.

(46) For related work, see:Kobayashi, J.; Yamashita, Y.; Kobayashi, S. *Chem. Lett.* **2005**, *34*, 268.

(47) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533.

(48) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151.

(49) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.

(50) Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.

(51) Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276.

(52) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.

(53) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.
(54) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881.
(55) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117.
(56) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.
(57) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741.
(58) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.
(59) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6847.
(60) Chen, Z. H.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.
(61) Chen, Z.; Yakura, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 3239.
(62) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630.
(63) Tan, C.; Liu, X. H.; Wang, L. W.; Wang, J.; Feng, X. M. *Org. Lett.* **2008**, *10*, 5305.
(64) Zhou, H.; Peng, D.; Qin, B.; Hou, Z. R.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 10302.
(65) Chen, S. K.; Hou, Z. R.; Zhu, Y.; Wang, J.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2009**, *15*, 5884.
(66) Shibasaki, M.; Matsunaga, S.; Kumagai, N. *Synlett* **2008**, 1583.
(67) Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60.
(68) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153.
(69) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180.
(70) Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem.—Eur. J.* **2002**, *8*, 4185.
(71) Kobayashi, S.; Kobayashi, J.; Yazaki, R.; Ueno, M. *Chem.—Asian J.* **2007**, *2*, 135.
(72) Kobayashi, S.; Yazaki, R.; Seki, K.; Ueno, M. *Tetrahedron* **2007**, *63*, 8425.
(73) (a) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476. (b) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395. See also: (c) Kobayashi, S.; Saito, S.; Ueno, M.; Yamashita, Y. *Chem. Commun.* **2003**, 2016.
(74) Saruhashi, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11232.
(75) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949.
(76) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230.
(77) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961.
(78) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.
(79) (a) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271For other reaction promoted by VAPOL see:. (b) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (c) Antilla, J.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518and references therein.
(80) The original paper incorrectly identifies this approach as occurring on the *re*-face.
(81) BBM ligands were developed independently by Shibasaki's group for enantioselective ring-opening of *meso*-epoxides.
(82) (a) Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528. (b) Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161.
(83) Sensitivity of catalyst structure to mixing ratios and the addition of small amounts of protic solvent have been noted in related BINOL-based catalyst for the aldol reaction:Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.
(84) (a) Kobayashi, S.; Arai, K.; Shimizu, H.; Ihori, Y.; Ishitani, H.; Yamashita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 761. See also: (b) Arai, K.; Lucarini, S.; Salter, M. M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103. (c) Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955.
(85) (a) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403. (b) Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861.
(86) Yamashita, Y.; Ueno, M.; Kuriyama, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, *334*, 929.
(87) (a) Jaber, N.; Carrée, F.; Fiaud, J. C.; Collin, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2067. For other examples of chiral catalysis with Sm−BINOL complexes, see: (b) Collin, J.; Carrée, F.; Giuseppone, N.; Santos, I. *J. Mol. Catal. A: Chem.* **2003**, *200*, 185. (c) Jaber, N.; Fiaud, J. C.; Collin, J. *Tetrahedron Lett.* **2001**, *42*, 9157. (d) Collin, J.; Jaber, N.; Lannou, M. *Tetrahedron Lett.* **2001**, *42*, 7405. (e) Giuseppone, N.; Collin, J. *Tetrahedron* **2001**, *57*, 8989.
(88) Izumiseki, A.; Yoshida, K.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 5310.
(89) (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (b) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (c) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 728.
(90) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.
(91) (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (c) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090.
(92) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168.
(93) Fujii, A.; Sodeoka, M. *Tetrahedron Lett.* **1999**, *40*, 8011.
(94) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734.
(95) (a) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *Organometallics* **2005**, *24*, 557. (b) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (c) Mancheño, O. G.; Priego, J.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679.
(96) González, A. S.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 2977.
(97) Gonzalez, A. S.; Arrayas, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335.
(98) Yuan, Z. L.; Jiang, J. J.; Shi, M. *Tetrahedron* **2009**, *65*, 6001.
(99) Deng, H. P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2009**, *351*, 2897.
(100) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500.
(101) Du, Y.; Xu, L. W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146.
(102) (a) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. (b) Oisaki, K.; Zhao, D.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4325. (c) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644.
(103) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.
(104) Yan, X. X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X. L.; Wu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 14362.
(105) Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 6145.
(106) Kobayashi, S.; Kitagawa, H.; Matsubara, R. *J. Comb. Chem.* **2001**, *3*, 401.
(107) (a) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (b) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143.
(108) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481.
(109) (a) Yasuda, S.; Kitagawa, H.; Ueno, M.; Ishitani, H.; Fukusawa, M.; Nishijima, M.; Kobayashi, S.; Hanada, K. *J. Biol. Chem.* **2001**, *276*, 43994. (b) Ueno, M.; Kitagawa, H.; Ishitani, H.; Yasuda, S.;

Nishijima, K.; Hanada, K.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 7863.
(110) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679.
(111) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558.
(112) (a) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem.—Eur. J.* **2006**, *12*, 1205. (b) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640.
(113) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.
(114) (a) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549. (b) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.
(115) For general reviews, see: (a) *Asymmetric Organocatalysis − From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Bekessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. For Special Issues and Highlights on Organocatalysis:(c) *Chimia*, **2007**, *61*, issue 5. (d) *Acc. Chem. Res.* **2004**, *37*, issue 8. (e) List, B. *Chem. Commun.* **2006**, 819. (f) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (g) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. (h) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (i) List, B. *Tetrahedron* **2002**, *58*, 5573. (j) List, B. *Synlett* **2001**, 1675. (k) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797.
(116) Ma, J. J.; Li, N.; Wu, Q. H.; Zhou, X.; Zang, X. H.; Wang, C. *Progr. Chem.* **2008**, *20*, 76.
(117) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757.
(118) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(119) (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
(120) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
(121) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453.
(122) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
(123) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R. *Helv. Chim. Acta* **2007**, *90*, 425.
(124) Parasuk, W.; Parasuk, V. *J. Org. Chem.* **2008**, *73*, 9388.
(125) (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Córdova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Watanabe, S. I.; Córdova, A.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2002**, *4*, 4519. (e) Córdova, A.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 7749. (f) Notz, W.; Tanaka, F.; Watanabe, S. I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, *68*, 9624. (g) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. *J. Am. Chem. Soc.* **2007**, *129*, 288.
(126) List, B. *Acc. Chem. Res.* **2004**, *37*, 548and references therein.
(127) (a) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (b) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928. (c) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058and references therein.
(128) (a) Córdova, A. *Chem.—Eur. J.* **2004**, *10*, 1987. (b) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.—Eur. J.* **2005**, *11*, 7024. (c) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (d) Sunden, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877. (e) Córdova, A. *Synlett* **2003**, 1651.
(129) (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (c) Hayashi, Y.; Urushima, T.; Tsuboi, W.; Shoji, M. *Nat. Protoc.* **2007**, *2*, 113.
(130) (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(131) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P.; Rutjes, F. *Chem. Soc. Rev.* **2008**, *37*, 29.
(132) Buckley, B. R. *Annu. Rep. Prog. Chem., Sect. B* **2009**, *105*, 113.
(133) Xu, L-. W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047.
(134) (a) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417. (b) Zhang, H. L.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H. Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2008**, *130*, 875. (c) Sun, C. X.; Li, H. G.; Wu, H. H.; Liu, Y. M.; Wu, P. *Chin. J. Catal.* **2008**, *29*, 351. (d) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. *Tetrahedron: Asymmetry* **2008**, *19*, 761. (e) Xu, L. W.; Lu, Y. X. *Org. Biomol. Chem.* **2008**, *6*, 2047. (f) Valero, G.; Balaguer, A. N.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2008**, *49*, 6559. (g) Teo, Y. C.; Lau, J. J.; Wu, M. C. *Tetrahedron: Asymmetry* **2008**, *19*, 186. (h) Kim, S. G.; Park, T. H. *Tetrahedron: Asymmetry* **2008**, *19*, 1626. (i) Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* **2008**, *64*, 1197. (j) Hahn, B. T.; Frohlich, R.; Harms, K.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 9985. (k) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053. (l) Fu, A. P.; Li, H. L.; Si, H. Z.; Yuan, S. P.; Duan, Y. B. *Tetrahedron: Asymmetry* **2008**, *19*, 2285. (m) Das, S.; Singh, R. K. *Asian J. Chem.* **2008**, *20*, 5203. (n) Han, R. G.; Wang, Y.; Li, Y. Y.; Xu, P. F. *Adv. Synth. Catal.* **2008**, *350*, 1474. (o) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21. (p) Gu, Q.; Gong, J. J.; Feng, J.; Wu, X. Y.; Zhou, Q. L. *Chin. J. Chem.* **2008**, *26*, 1902. (q) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.
(135) (a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (b) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem.—Eur. J.* **2009**, *15*, 6678.
(136) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 1040.
(137) Karlsson, S.; Högberg, H. E. *Eur. J. Org. Chem.* **2003**, 2782.
(138) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055.
(139) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838.
(140) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 9630.
(141) Enders, D.; Vrettou, M. *Synthesis* **2006**, *2006*, 2155.
(142) Yang, J.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.
(143) Vesely, J.; Rios, R.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 421.
(144) Dziedzic, P.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 6631.
(145) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077.
(146) (a) Suri, J. T.; Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1383. (b) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F. *J. Org. Chem.* **2006**, *71*, 3822.
(147) (a) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363. (b) Córdova, A.; Zou, W. B.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W. W. *Chem. Commun.* **2005**, 3586.
(148) (a) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329. (b) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210. (c) Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655.
(149) Liao, W.-W.; Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 674.
(150) (a) Notz, W.; Watanabe, S. I.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III *Adv. Synth. Catal.* **2004**, *346*, 1131. (b) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III *Synlett* **2003**, 1906.
(151) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

(152) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.
(153) (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (b) For a summary of applications of 5-pyrrolidin-2-yl-1H-tetrazoles, see:Longbottom, D. A.; Franckevicius, V.; Ley, S. V. *Chimia* **2007**, *61*, 247.
(154) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2006**, *8*, 2839.
(155) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357.
(156) Mauksch, M.; Tsogoeva, S. B.; Wei, S. W.; Martynova, I. M. *Chirality* **2007**, *19*, 816.
(157) Amedjkouh, M.; Brandberg, M. *Chem. Commun.* **2008**, 3043.
(158) Chi, Y. G.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.
(159) Ibrahem, I.; Zhao, G. L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 683.
(160) (a) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *Tetrahedron Lett.* **2004**, *45*, 4353. (b) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 8683.
(161) Hayashi, Y.; Urushima, T.; Shin, M.; Shoji, M. *Tetrahedron* **2005**, *61*, 11393.
(162) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.—Eur. J.* **2005**, *11*, 7024.
(163) Dziedzic, P.; Córdova, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1033.
(164) Cheng, L. L.; Wu, X. Y.; Lu, Y. I. *Org. Biomol. Chem.* **2007**, *5*, 1018.
(165) Cheng, L. L.; Han, X.; Huang, H. M.; Wong, M. W.; Lu, Y. X. *Chem. Commun.* **2007**, 4143.
(166) (a) Allemann, C.; Gordillo, R.; Clememte, F. R.; Cheong, P. H. Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (b) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912and references therein.
(167) For related applications of bisphenylprolinol-based catalysts, see: (a) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (d) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
(168) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
(169) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760.
(170) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476.
(171) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8700.
(172) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2507.
(173) Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, 1928.
(174) Jiang, B.; Dong, J. J.; Si, Y. G.; Zhao, X. L.; Huang, Z. G.; Xu, M. *Adv. Synth. Catal.* **2008**, *350*, 1360.
(175) Liu, B. Y.; Xu, D. Q.; Dong, J. F.; Yang, H. L.; Zhao, D. S.; Luo, S. P.; Xu, Z. Y. *Synth. Commun.* **2007**, *37*, 3003.
(176) Liu, B. Y.; Zhao, D. S.; Xu, D. Q.; Xu, Z. Y. *Chem. Res. Chin. Univ.* **2007**, *23*, 163.
(177) (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.
(178) For a review of Brønsted acid catalysis including addition to C═N reactions, see:Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
(179) (a) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.
(180) Guo, Q. X.; Liu, H.; Guo, C.; Luo, S. W.; Gu, Y.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790.
(181) Uraguchi, M.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
(182) Gridnev, I. D.; Kouchi, M.; Sorimachi, K.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 497.
(183) Terada, M.; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, 133.
(184) (a) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (b) Kiyohara, H.; Matsubara, R.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 5333.
(185) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254.
(186) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336.
(187) Matsubara, M.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814.
(188) Terada, M.; Tanaka, H.; Sorimachi, K. *Synlett* **2008**, 1661.
(189) Tillman, A. L.; Dixon, D. J. *Org. Biomol. Chem.* **2007**, *5*, 606.
(190) Dixon, D. J.; Tillman, A. L. *Synlett* **2005**, 2635.
(191) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.
(192) (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2008**, 1319.
(193) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.
(194) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631.
(195) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259.
(196) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, 1441.
(197) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.
(198) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175.
(199) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147.
(200) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397.
(201) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.
(202) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.
(203) (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
(204) For a review of H-bonding catalysis including C═N activation examples, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Yu, X. H.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516.
(205) (a) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
(206) Xie, J. W.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, *49*, 6910.
(207) (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898. (c) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603.
(208) Han, B.; Liu, Q. P.; Li, R.; Tian, X.; Xiong, X. F.; Deng, J. G.; Chen, Y. C. *Chem.—Eur. J.* **2008**, *14*, 8094.
(209) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(210) Yoon, T. P; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466.
(211) (a) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.
(212) Chiral bis-thioureas have been employed as catalysts for the reaction of nitromethane with aromatic aldehyde-derived Boc imines. Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785.
(213) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.
(214) Wang, C. J.; Dong, X. Q.; Zhang, Z. H.; Xue, Z. Y.; Teng, H. L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.
(215) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707.

(216) Chang, Y. W.; Wang, J. J.; Dang, J. N.; Xue, Y. X. *Synlett* **2007**, 2283.
(217) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
(218) Liu, T. Y.; Cui, H. L.; Long, J.; Li, B. J.; Wu, Y.; Ding, L. S.; Chen, Y. C. *J. Am. Chem. Soc.* **2007**, *129*, 1878.
(219) Zhang, Y.; Liu, Y. K.; Kang, T. R.; Hu, Z. K.; Chen, Y. C. *J. Am. Chem. Soc.* **2008**, *130*, 2456.
(220) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y. C. *Org. Lett.* **2008**, *10*, 3583.
(221) Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624.
(222) Zhang, H.; Chuan, Y. M.; Li, Z. Y.; Peng, Y. G. *Adv. Synth. Catal.* **2009**, *351*, 2288.
(223) (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603.
(224) Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499.
(225) (a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (b) Vakulya, B.; Varga, S.; Csampal, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.
(226) Tillman, A. L.; Ye, J. X.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.
(227) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.
(228) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375.
(229) (a) Goss, J. M.; Schaus, S. E. *J. Org. Chem.* **2008**, *73*, 7651. (b) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998. (c) Tian, S. K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (e) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003.
(230) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998.
(231) Goss, J. M.; Schaus, S. E. *J. Org. Chem.* **2008**, *73*, 7651.
(232) Zajac, M.; Peters, R. *Org. Lett.* **2007**, *9*, 2007.
(233) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896.
(234) Xu, X. A.; Wang, K.; Nelson, S. G. *J. Am. Chem. Soc.* **2007**, *129*, 11690.
(235) See for a review:Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013and references therein.
(236) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *44*, 4542.
(237) (a) Ooi, T.; Kameda, M.; Fujii, J. I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (b) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679.
(238) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878.
(239) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088.
(240) For application of this catalyst to other catalytic asymmetric reactions, see:(a) Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino., T.; Shibasaki, M. *Proc. Natl. Acad. Sci. U. S.A.* **2004**, *101*, 5433. (b) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743. (c) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206. (d) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539.
(241) (a) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem.—Asian J.* **2007**, *2*, 794. (b) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564.
(242) Niess, B.; Jørgensen, K. A. *Chem, Commun.* **2007**, 1620.
(243) (a) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461. (b) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629.
(244) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975.
(245) Utsumi, N.; Kitagaki, S.; Barbas, C. F. *Org. Lett.* **2008**, *10*, 3405.
(246) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem.—Eur. J.* **2007**, *13*, 8338.
(247) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394.
(248) Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.
(249) For an introduction, see:Olah, G. A.; Khrisnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol 3, p 293.
(250) For reviews of catalytic asymmetric Friedel−Crafts reaction, see:(a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Jørgensen, K. A. *Synthesis* **2003**, 1117.
(251) Johannsen, M. *Chem. Commun.* **1999**, 2233.
(252) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114.
(253) Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352.
(254) Jia, Y. X.; Xie, J. H.; Duan, H. F.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1621.
(255) (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
(256) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
(257) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.
(258) (a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (b) Hashimoto, T.; Maruoka, K. *Synthesis* **2008**, 3703.
(259) Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.
(260) Kang, Q.; Zhao, Z. A.; You, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.
(261) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609.
(262) Terada, M.; Sorimachi, K. *J. Am. Chem .Soc.* **2007**, *129*, 292.
(263) Jia, Y. X.; Zhong, J.; Zhu, S. F.; Zhang, C. M.; Zhou, Q. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565.
(264) Morita, K. I.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
(265) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
(266) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201.
(267) (a) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577. (b) Kündig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413. (c) Kündig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.
(268) The aza-Baylis−Hillman reaction is the subject of an extensive review where catalytic asymmetric examples are discussed:Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1.
(269) von Riesen, C.; Hoffman, H. M. R. *Chem.—Eur. J.* **1996**, *2*, 680.
(270) (a) Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem.—Eur. J.* **2005**, *11*, 1794. (b) Shi, M.; Xu, Y. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507.
(271) Shi, M.; Xu, Y. M. *J. Org. Chem.* **2003**, *68*, 4784.
(272) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103. Note that in this paper the authors refer to TQO as β-isocupreidine, which is an alternative name for the same compound (see references therein).
(273) (a) Shi, M.; Guo, Y. W.; Li, H. B. *Chin. J. Chem.* **2007**, *25*, 828. (b) Zhao, G. L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686.
(274) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521.
(275) (a) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (b) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310.
(276) Shi, M.; Li, C. Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385.
(277) Lei, Z. Y.; Ma, G. N.; Shi, M. *Eur. J. Org. Chem.* **2008**, 3817.

(278) Liu, Y. H.; Chen, L. H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973.
(279) Ito, K.; Nishida, K.; Gotanda, T. *Tetrahedron Lett.* **2007**, *48*, 6147.
(280) Shi, M.; Chen, L. H.; Teng, W. D. *Adv. Synth. Catal.* **2005**, *347*, 1781.
(281) Liu, Y. H.; Shi, M. *Adv. Synth. Catal.* **2008**, *350*, 122.
(282) Shi, Y. L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129.
(283) (a) Qi, M. J.; Ai, T.; Shi, M.; Li, G. G. *Tetrahedron* **2008**, *64*, 1181. (b) Guan, X. Y.; Jiang, Y. Q.; Shi, M. *Eur. J. Org. Chem.* **2008**, 2150.
(284) (a) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578. (b) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.
(285) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.
(286) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.
(287) Vesely, J.; Dziedzic, P.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6900.
(288) For early methods using stoichiometric or superstoichiometric quantities of the chiral source, see:(a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837. (b) Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron: Asymmetry* **1998**, *9*, 3963. (c) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237.
(289) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.
(290) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.
(291) Duan, H. F.; Jia, Y. X.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 2567.
(292) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Denmark, S. E.; Nicaise, O. J. C. *Chem. Commun.* **1996**, 999.
(293) (a) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527. (b) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429. (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603. (d) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095. (e) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681.
(294) Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron: Asymmetry* **2001**, *12*, 2077.
(295) Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 2331.
(296) Cabello, N.; Kizirian, J. C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639.
(297) Amiot, F.; Cointeaux, L.; Silve, E. J.; Alexakis, A. *Tetrahedron* **2004**, *60*, 8221.
(298) Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117.
(299) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875.
(300) For leading references into organozinc chemistry, see: (a) *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2006; Vols 1−2. (b) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325.(c) *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; University Press: Oxford, U.K., 1999.
(301) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097.
(302) (a) Zhang, H. L.; Jiang, F.; Zhang, X. M.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *Chem.—Eur. J.* **2004**, *10*, 1481. (b) Zhang, X. M.; Zhang, H. L.; Lin, W. Q.; Gong, L. Z.; Mi, A. Q.; Cui, X.; Jiang, Y. Z.; Yu, K. B. *J. Org. Chem.* **2003**, *68*, 4322. (c) Zhang, H. L.; Zhang, X. M.; Gong, L. Z.; Mi, A. Q.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399. (d) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1535. (e) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157.
(303) Zhang, X.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 6369.
(304) (a) Beresford, K. J. M. *Tetrahedron Lett.* **2004**, *45*, 6041. (b) Beresford, K. J. M. *Tetrahedron Lett.* **2002**, *43*, 7175.
(305) For review of copper-catalyzed addition to C═N, see:Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.
(306) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692.
(307) (a) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (b) Further studies of hemilabile ligands: Bonnaventure, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6330.
(308) (a) Desrosiers, J. N.; Côté, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186. (b) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405.
(309) Côté, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6525.
(310) For other applications of this class of ligand, see:(a) Shi, M.; Sui, W.-S. *Chirality* **2000**, *12*, 574. (b) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 773. (c) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 835. (d) Shi, M.; Sui, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319.
(311) Shi, M.; Wang, C.-J. *Adv. Synth. Catal.* **2003**, *345*, 971.
(312) Shi, M.; Lei, Z.-Y.; Xu, Q. *Adv. Synth. Catal.* **2006**, *348*, 2237.
(313) Wang, C. J.; Shi, M. *J. Org. Chem.* **2003**, *68*, 6229.
(314) Shi, M.; Zhang, W. *Tetrahedron: Asymmetry* **2003**, *14*, 3407.
(315) For other applications of this class of ligand, see:(a) Wang, M. C.; Wang, D. K.; Zhu, Y.; Liu, L. T.; Guo, Y. F. *Tetrahedron: Asymmetry* **2004**, *15*, 1289. (b) Wang, M. C.; Liu, L. T.; Zhang, J. S.; Shi, Y. Y.; Wang, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3853. (c) Wang, M. C.; Wang, D. K.; Lou, J. P.; Hua, Y. Z. *Chin. J. Chem.* **2004**, *22*, 512.
(316) Wang, M. C.; Xu, C. L.; Cheng, F.; Ding, X. *Tetrahedron* **2006**, *62*, 12220.
(317) Wang, M. C.; Xu, C. L.; Zou, Y. X.; Liu, H. M.; Wang, D. K. *Tetrahedron Lett.* **2005**, *46*, 5413.
(318) Chen, J. M.; Li, D.; Ma, H. F.; Cun, L. F.; Zhu, J.; Deng, J. G.; Liao, J. *Tetrahedron Lett.* **2008**, *49*, 6921.
(319) Nakagawa, Y.; Kanai, M.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **1998**, *54*, 10295.
(320) Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K. I.; Tomioka, K. *Chem. Lett.* **2002**, 8.
(321) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055.
(322) Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723.
(323) Li, X.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3829.
(324) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692.
(325) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940.
(326) (a) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613. (b) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem.—Eur. J.* **2004**, *10*, 2872.
(327) Zhang, H. L.; Liu, H.; Cui, X.; Mi, A. Q.; Jiang, Y.-Z.; Gong, L. Z. *Synlett* **2005**, 615.
(328) Liu, H.; Zhang, H. L.; Wang, S. J.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2005**, *16*, 2901.
(329) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984.
(330) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409.
(331) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244.
(332) (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed.* **1997**, *36*, 1496. (b) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.
(333) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273.
(334) Akullian, L. C.; Porter, J. C.; Traverse, J. F.; Snapper, M. L.; Hoveyda, A. H. *Adv. Synth. Catal.* **2005**, *347*, 417.
(335) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530.

(336) Liu, J. T.; Liu, B.; Jia, M.; Li, X. S.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396.
(337) (a) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 896. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2828. (c) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1376.
(338) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940.
(339) Perron, Q.; Alexakis, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1871.
(340) Blay, G.; Cardona, L.; Climent, E.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5593.
(341) Di Bari, L.; Guillarme, S.; Hanan, J.; Henderson, A. P.; Howard, J. A. K.; Pescitelli, G.; Probert, M. R.; Salvadori, P.; Whiting, A. *Eur. J. Org. Chem.* **2007**, 5771.
(342) For representative reviews on the subject, see: (a) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595.(b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(343) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
(344) For previous achiral reactions using this concept, see:(a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *Chem. Commun.* **1996**, 1459. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. (c) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1273.
(345) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3562.
(346) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.
(347) Bao, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 131.
(348) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614.
(349) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735.
(350) Fang, X. M.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.
(351) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006.
(352) Yao, S.; Fang, X. M.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547.
(353) For discussion concerning alternative reaction modes of such imino esters with organometallics reagents, see:Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev.* **2008**, *37*, 1166.
(354) Caplan, N. A.; Hancock, F. E.; Page, P. C. B.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1685.
(355) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896.
(356) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927.
(357) (a) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491. (b) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610.
(358) Fernandez, I.; Valdivia, V.; Leal, M. P.; Khiar, N. *Org. Lett.* **2007**, *9*, 2215.
(359) Jagtap, S. B.; Tsogoeva, S. B. *Chem. Commun.* **2006**, 4747.
(360) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767.
(361) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846.
(362) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315.
(363) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(364) Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153.
(365) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(366) (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (c) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764. (d) Yet, L. *Angew Chem. Int. Ed.* **2001**, *40*, 875. (e) Gröger, H. *Chem.—Eur. J.* **2001**, *7*, 5264.
(367) For a selection, see:(a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186. (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (c) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650. (f) Kobayashi, S.; Ishitani, H. *Chirality* **2000**, *12*, 540. (g) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 279. (h) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594.
(368) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (c) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. *Synlett* **2001**, 1551.
(369) For an earlier example of the catalytic enantioselective Strecker reaction of ketoimines, see:Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147.
(370) For a review of TMS-nucleophile addition to electrophiles including C═N, see:Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227.
(371) (a) Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027. (b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.
(372) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147.
(373) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153.
(374) Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 2527.
(375) (a) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem.—Asian J.* **2007**, *2*, 20. (b) Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220.
(376) Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768.
(377) Li, K.; He, T.; Li, C.; Feng, X. W.; Wang, N.; Yu, X. Q. *Green Chem.* **2009**, *11*, 777.
(378) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Vallée, Y. *Tetrahedron Lett.* **2000**, *41*, 873.
(379) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2004**, *60*, 10559.
(380) Blacker, J.; Clutterbuck, L. A.; Crampton, M. R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1449.
(381) (a) Achard, T. R. J.; Clutterbuck, L. A.; North, M. *Synlett* **2005**, 1828. (b) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771. (c) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147.
(382) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032.
(383) Berkessel, A.; Mukherjee, S.; Lex, J. *Synlett* **2006**, 41.
(384) For the use of these ligands in the related hydrocyanation of aldehydes and ketones, see:(a) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384.
(385) (a) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (b) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (c) Ryu, D.; Lee., T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (d) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979.
(386) (a) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (b) Pan, S. C.; List, B. *Chem.—Asian J.* **2008**, *3*, 430.
(387) (a) Belokon, Y. N.; Ishibashi, E.; Nomura, H.; North, M. *Chem. Commun.* **2006**, 1775. (b) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592. (c) Belokon, Y. N.;

Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505and references therein.
(388) Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149.
(389) Becker, C.; Hoben, C.; Kunz, H. *Adv. Synth. Catal.* **2007**, *349*, 417.
(390) Huang, J.; Corey, E. J. *Org. Lett.* **2003**, *4*, 3455.
(391) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027.
(392) Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2003**, 3818.
(393) Huang, X.; Huang, J.; Wen, Y.; Feng, X. *Adv. Synth. Catal.* **2006**, *348*, 2579.
(394) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617.
(395) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759.
(396) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.
(397) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.
(398) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869.
(399) For leading references, see:(a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.
(400) For leading references, see:(a) Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705. (b) Mayer, M. F.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 6839. (c) Xie, W.-H.; Fang, J.-W.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929. (d) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.
(401) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
(402) (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (c) Huang, D.; Yan, M.; Shen, O *Chin. J. Org. Chem.* **2004**, *24*, 1200.
(403) (a) Sweeney, J. B.; Cantrill, A. A.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3681. (b) Sweeney, J. B.; Cantrill, A. A.; Drew, M. G. B.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3694.
(404) Aggarwal, V. K.; Vasse, J. L. *Org. Lett.* **2003**, *5*, 3987.
(405) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.
(406) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926.
(407) (a) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675. (b) Patwardhan, A. P.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169.
(408) Lu, Z. J.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185.
(409) Solladié-Cavallo, A.; Roje, M.; Welter, R.; Sunjic, V. *J. Org. Chem.* **2004**, *69*, 1409.
(410) Morales, D.; Pérez, J.; Riera, L.; Riera, V.; Corzo-Suárez, R.; García-Granda, S.; Miguel, D. *Organometallics* **2002**, *21*, 1540.
(411) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380.
(412) (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.(b) Kobayashi, S. In *Cycloaddition Reaction in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley VCH; Weinheim, Germany, 2002; p 187. (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
(413) (a) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749. (c) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264.
(414) (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357. (b) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (c) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (d) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (e) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535.
(415) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979.
(416) Kobayashi, S.; Kusakabe, K. I.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220.
(417) Kobayashi, S.; Kusakabe, K. I.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225.
(418) (a) Guillarme, S.; Whiting, A. *Synlett* **2004**, 711. (b) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905.
(419) Bundu, A.; Guillarme, S.; Hannan, J.; Wan, H.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7849.
(420) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018.
(421) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121.
(422) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A. V.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216.
(423) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456.
(424) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 2343.
(425) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803.
(426) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259.
(427) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480.
(428) Sundararajan, G.; Prabgaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.
(429) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617.
(430) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877.
(431) Liu, H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 6023.
(432) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.
(433) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796.
(434) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.
(435) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.
(436) (a) France, S.; Weatherwax, A.; Taggi, A. G.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.
(437) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
(438) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655.
(439) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627.
(440) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387.
(441) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963.
(442) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853.
(443) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603.