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Powerful Amino Acid Derived Bifunctional Phosphine Catalysts Bearing a Hydrogen Bond Donor in Asymmetric Synthesis

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This minireview focuses on the recent advances in the synthetic application of amino acid-derived bifunctional phosphine catalysts bearing a hydrogen-bond donor. In the examples illustrated, the amino acid-based phosphines have already been proven to be versatile, catalyzing a wide range of asymmetric reactions, including (aza)-MBH reactions, [3 + 2] cyclizations, [4 + 2] cycloadditions, allylic alkylation, and Michael addition.

Introduction

Nucleophilic catalysis is one of the most actively pursued research areas in organic chemistry, and Lewis bases bearing nonbonding electrons are the common catalysts for such transformations. Compared with similarly substituted amine catalysts, phosphines often display unique catalytic activities because of their weaker basicity and stronger nucleophilicity.[1,2] A common feature of phosphine organocatalysts developed in the past is their strong and superior nucleophilicity in the construction of densely functionalized cyclic compounds from simple and activated olefins. For synthetic chemists, another very important and privileged topic is to explore catalytic enantioselective processes, especially enantioselective syntheses of complex molecules with high catalytic performance. Therefore, phosphine-promoted catalytic processes, particularly asymmetric reactions that are catalyzed by chiral phosphines have attracted enormous attention from the synthetic community in recent years.[2]

The development of novel chiral phosphine catalysts is one of the most interesting aspects in organocatalysis. The chirality of a chiral catalyst has to be rendered from a chiral source, and it is certainly very attractive and practical if such chirality can be derived from a chiral pool. Natural amino acids are arguably the most common, abundant, and economical chiral building blocks available to chemists, thus amino acid based chiral catalysts undoubtedly belong to a type of catalysts of great interest.[3] However, the design of amino acid based phosphine catalysts that are capable of inducing high asymmetry remains a key challenge. Although the introduction of diphenylphosphinylalanine into a peptide ligand in palladium catalysis by Gilbertson marked a great advance in asymmetric metal catalysis,[4] the use of the amino acid derived phosphine as an organocatalyst was not reported in that work. Notably, the incorporation of hydrogen bonding functionality to chiral phosphines has been proved to be an efficient protocol in tuning the catalytic activity of chiral 1,1′-bi-2-naphthol (BINOL)-derived phosphine.[5] In this context, the group led by Shi has reported that multifunctional chiral phosphines containing Lewis basic and Brønsted acid sites within one molecule could promote the asymmetric Morita–Baylis–Hillman reaction[2e] and related reactions[2h,5] in good to excellent stereoselectivities.

Thus, from the standpoint of asymmetric phosphine catalysis, the use of amino acid derived phosphines bearing a hydrogen donor seems to be practical and compatible for different reactions. In this Minireview, we document the privileged catalytic activity of amino acid derived phosphines and the related progress of catalytic enantioselective transformations, including [3+2] and [4+2] cycloadditions, allylic alkylations, Morita–Baylis–Hillman reactions, and Michael addition reactions.

[3+2] Cycloadditions

In 1995, Lu and coworkers[6a] reported firstly the phosphine-catalyzed [3+2] annulation of electron-deficient olefins and allenes that proceeded through an important intermediate "1,3-dipolar synthon".[6] This novel [3+2] approach involves cycloaddition of activated olefins with simple 2,3-butadienoates as the three-carbon source. Concerning asymmetric phosphine-catalyzed [3+2] cycloadditions, Zhang et al.[7] developed a chiral phosphine with a unique fused bicyclic[2.2.1] ring structure that promoted the [3+2] cycloaddition of 2,3-butadienoates and electron-deficient olefins with excellent regioselectivities (94:6 to ≈100:0) and moderate to excellent enantioselectivities (36–93% *ee*).

In 2007, during the development of an asymmetric version of Lu's [3+2] cycloaddition of allenoate esters and enones,[6]

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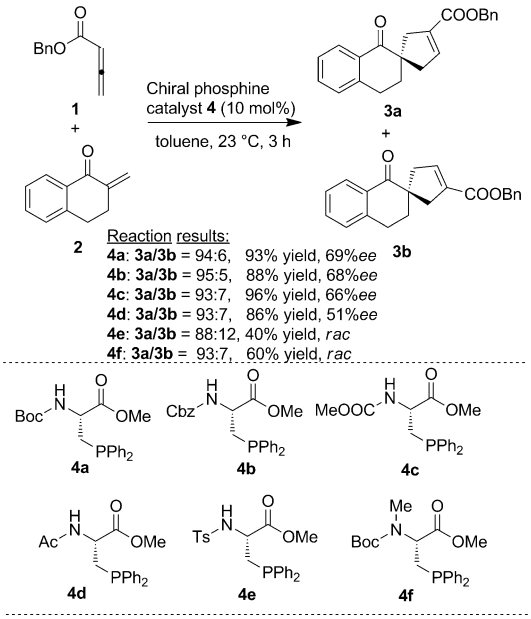
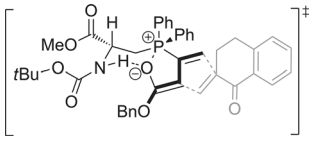
Miller and Cowen further advanced this multifunctional phosphine catalyst and made a seminal contribution by developing a protected, multifunctional phosphine-containing α-amino acid catalyst.[8] As illustrated in Scheme 1, catalyst **4**, which incorporated a phosphine to an α-amino acid side chain, was

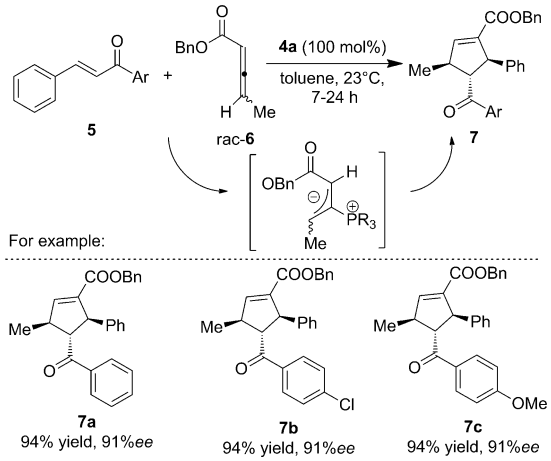


Scheme 1. Protected phosphine-containing α-amino acid catalysts. Bn = benzyl.

found to be an efficient catalysts for promoting enantioselective [3+2] cycloadditions. It is noteworthy that the subtle hydrogen bonding interaction provided by the carbamate N–H was believed to be crucial for the stereochemical control. For example, with catalyst **4a** containing a hydrogen-bond donor, allenoate **1** and tetralone **2** undergo [3+2] cycloadditions to form cycloadducts **3a** and **3b** in a combined yield of 93% with 94:6 regioisomeric ratio, and the major adduct **3a** was obtained in 69% *ee*. Instead of the *tert*-butoxycarbonyl (Boc) group on this amino acid derived phosphine, other protective groups, such as benzyloxycarbonyl (Cbz) or COOMe, led to similar stereoselectivities (66–68% *ee*). However, **4e** and **4f** with a tosyl group and no N–H moiety, respectively, led to racemic products, suggesting that subtle hydrogen bonding effects may be important in the transition state (Scheme 2). In addition, Miller et al. found that chalcone **5** was also a suitable substrate in this [3+2] cycloaddition, in which a unique "deracemization" reaction occurred upon cycloaddition with racemic γ-substituted allenes (Scheme 3).

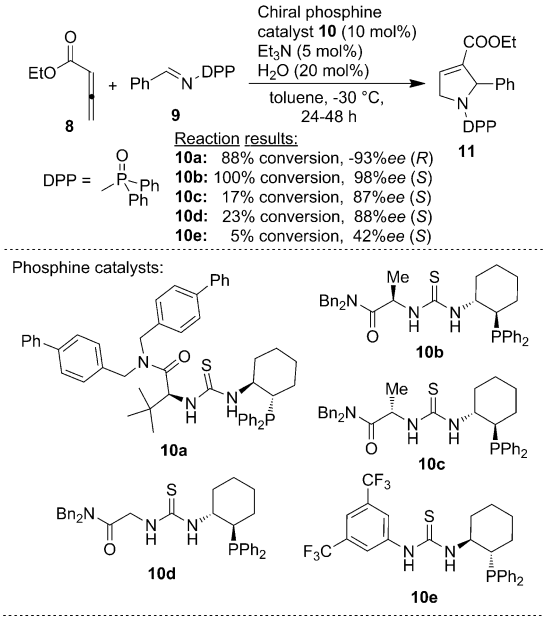


Scheme 2. One of several possible transition state structures (**4a+1+2**): Tetralone approaches from the bottom.



Scheme 3. Chiral phosphine-catalyzed [3+2] cycloadditions of γ-substituted allenic ester and chalcones.

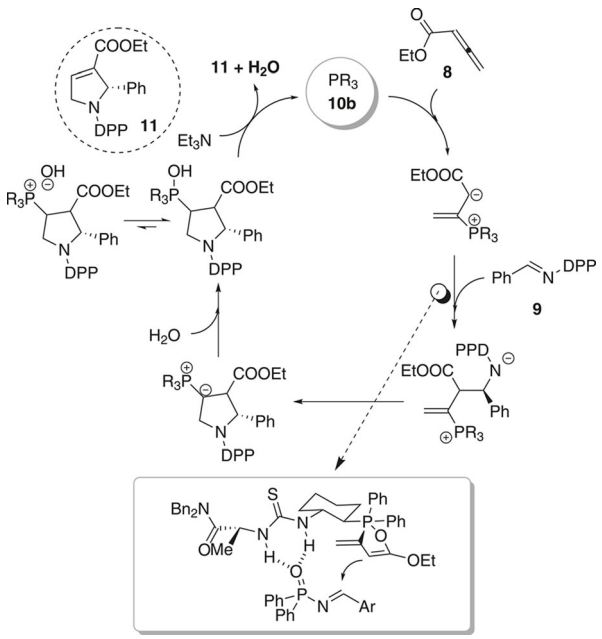
Subsequently, Jacobsen et al. described the development of a new class of chiral amino acid derived bifunctional thiourea–phosphine catalysts for enantioselective imine–allene [3+2] cycloadditions.[9] The authors observed that variation of the α-amino acid as the functional moiety in thiourea phosphines led to the establishment of the best enantioselectivity (98% *ee*) as well as conversion (100%) in the presence of the chiral phosphine catalyst **10b** (Scheme 4). Interestingly, use of the diastereomeric Ala-derived chiral phosphine catalyst **10c** or Gly-derived **10d** resulted in significantly poorer reactivity (17–23%) and slightly diminished *ee* values (87–88% *ee*). The poorer catalytic activity of phosphine catalyst **10e** in this reaction suggested that the amino amide plays a secondary role relative to the chiral aminophosphine center with respect to enantioinduction. Notably, under optimized reaction conditions and in the presence of chiral phosphine catalyst **10b**, the



Scheme 4. Chiral-phosphine-catalyzed imine–allene [3+2] cycloaddition.

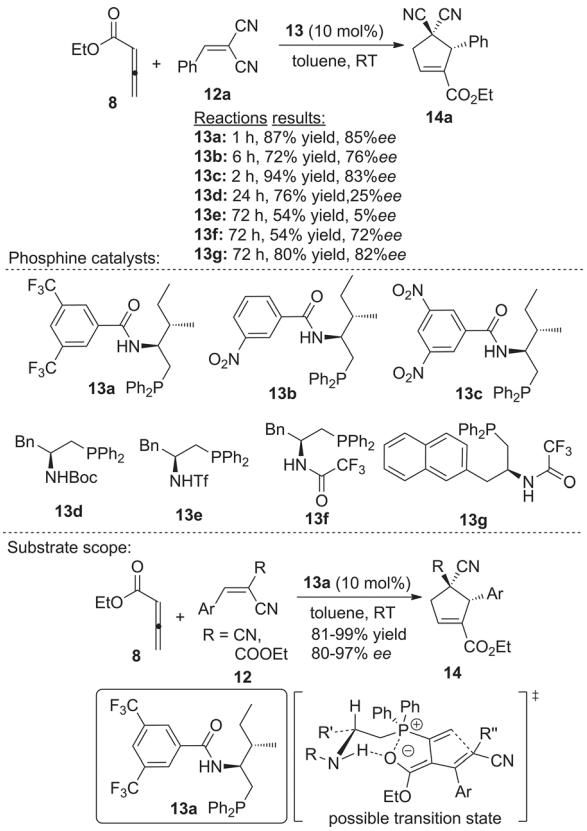
imine–allene [3+2] cycloadditions displayed a broad scope (13 examples). Excellent enantioselectivities and yields were obtained for a variety of substituted aryl and heteroaryl imines.

On the basis of experimental results, Jacobsen et al. proposed that the thiourea could bind and activate the imine by association to the oxygen atom of the phosphinoyl group (Scheme 5),[9] and secondary noncovalent interactions, such as π–π stacking between the amide portion of the phosphine catalyst and the diphenyl portion of the imine, might also be beneficial to the preferential attack at the imine *Re* face with **10b** because of the additional selective stabilization of the lower energy transition state.



Scheme 5. Reaction mechanism proposed by Jacobsen et al.[9]

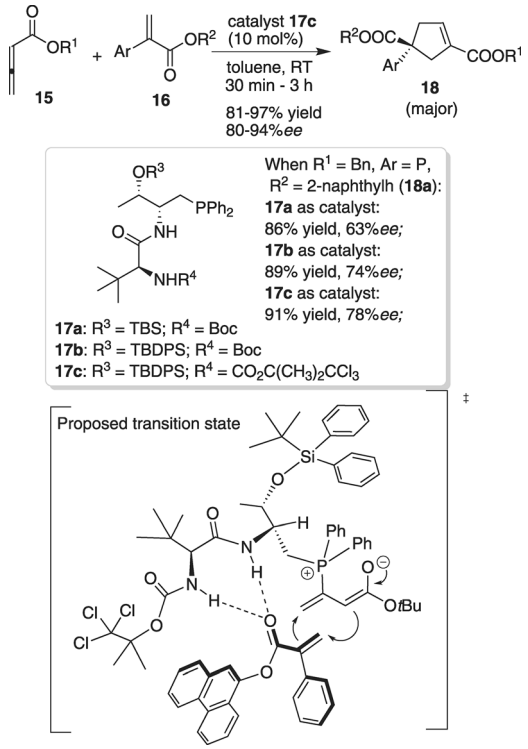
In 2010, Zhao and co-workers reported an asymmetric [3+2] cycloaddition of allenoates and activated olefins catalyzed by bifunctional N-acyl aminophosphine catalysts derived from amino acids (Scheme 6).[10] This work also suggested the importance of the hydrogen-bond-donating amide group of the bifunctional catalysts **13** for the asymmetric induction. For example, with a similar structure, chiral phosphine catalyst **13e** with the most acidic NH function led to an almost racemic product after long reaction time. The phosphine catalyst **13f** or **13g** with a trifluoroacetyl group exhibited good enantioselectivity (72 or 82% *ee*, respectively), although a long reaction time (at least 72 h) was generally needed to give moderate yield. A screening of various phosphine catalysts for the asymmetric [3+2] cycloaddition of ethyl 2,3-butadienoate (**8**) and phenylidenemalononitrile (**12a**) were performed to find a good phosphine catalyst **13a** that gave the desired adduct with 87% yield and 85% *ee* in only 1 h. The chiral phosphine-catalyzed [3+2] cycloaddition is tolerant of a broad of range of activated olefins derived from aromatic aldehydes, providing various chiral cyclopentenes in high yields and good to excellent enantioselectivities (80–97% *ee*). The possible transition state revealed that the amino acid derived phosphine could assemble the allenoate by a synergistic action of its two different functional groups to form a chiral zwitterion (Scheme 6).



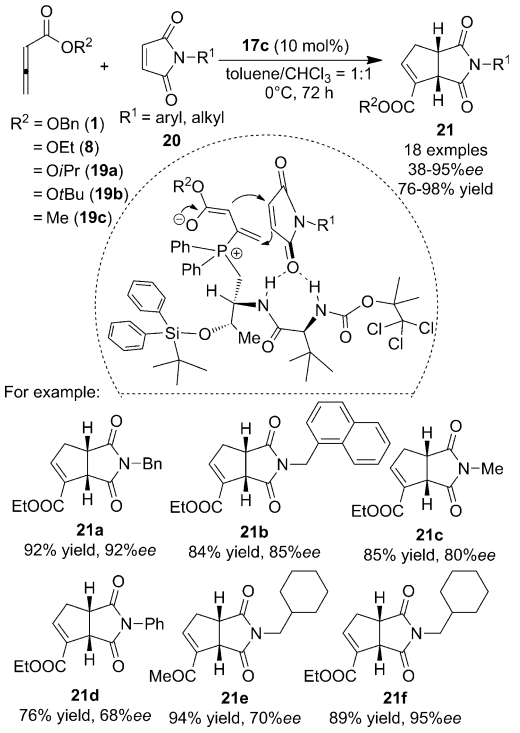
Scheme 6. Asymmetric [3+2] cycloaddition promoted by bifunctional N-acyl aminophosphines. Tf = trifluoromethyl.

Recently, Lu and co-workers developed a new family of dipeptide-based and silane-containing chiral phosphines that are highly efficient for enantioselective [3+2] cycloadditions of allenes to acrylates.[11] Screening of different amino acid or dipeptide-derived chiral phosphines revealed that the D-Thr-L-*tert*-Leu dipeptide backbone was the best, and the effect of the siloxyl groups were also palpable. In enamine or iminium catalysis, introduction of silicon-based bulky groups to amino catalysts has proved to be an effective strategy, which could enhance the catalytic efficiency and selectivity of the reaction.[12] However, inclusion of silyl groups in phosphines was not explored earlier on. In the preliminary mechanistic suggestion made by Lu et al., hydrogen bonding interaction between the bifunctional phosphine and the acrylate is believed to be the key to the stereochemical control (Scheme 7). It is noteworthy that dipeptide-based phosphines could be easily tuned by simply employing different amino acid residues, varying hydrogen bonding moieties, and utilizing different silicon-based bulky groups.

Such dipeptide phosphine catalysts have also been shown to be powerful in a number of asymmetric [3+2] cycloadditions by the groups of Lu and Shi, including cyclizations between allenes and arylamides, maleimides, and imines.[13] For



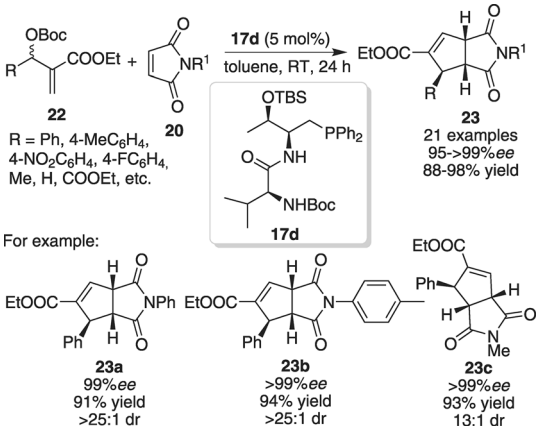
Scheme 7. Dipeptide-based chiral-phosphine-catalyzed [3+2] cycloadditions of allenes to acrylates. TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.



Scheme 8. Dipeptide-based chiral-phosphine-catalyzed [3+2] cycloaddition of maleimides with allenes.

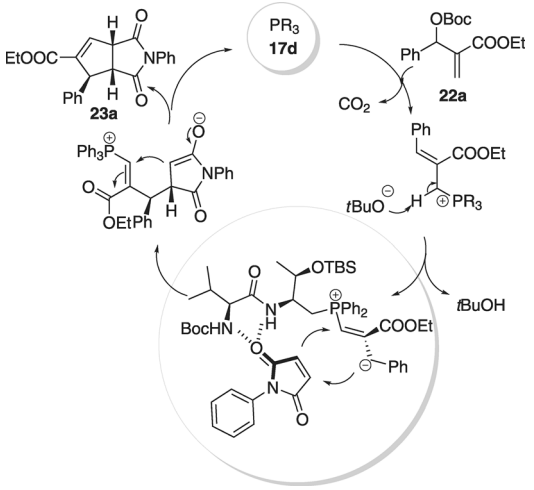
example, the both groups have found that D-threonine-L-*tert*-leucine-derived bifunctional phosphine (**17c**) was an effective organocatalyst in the enantioselective [3+2] cycloaddition of maleimide with allenes (Scheme 8),[13b] allowing an efficient synthesis of optically active functionalized bicyclic cyclopentenes containing two stereogenic centers in good to high yields (76–98%) along with good to excellent enantioselectivities (up to 95% *ee*).

Similarly to allenes, it is well known that Morita–Baylis–Hillman (MBH) carbonates could also afford the 1,3-dipolar synthon in the presence of phosphines.[14] Compared to allenes and alkynes, these MBH carbonates are more readily available and versatile to be expected to have wide applications in asymmetric synthesis.[15] However, there is little in the literature regarding the asymmetric [3+2] annulations of MBH carbonates.[16] Recently in 2012, Lu and coworkers reported a highly enantioselective [3+2] annulation of MBH carbonates and maleimides catalyzed by dipeptide-based phosphine **17d** (Scheme 9). The [3+2] cycloaddition was applicable to MBH carbonates bearing different aromatic groups, regardless of their substitution pattern and electronic nature. The plausible reaction mechanism was suggested on the basis of excellent enantioselectivities (up to >99% *ee* for most of the cases). As shown in Scheme 10, hydrogen bonding interactions between the maleimide and the phosphonium intermediate not only lock the steric position of the maleimide, but also make the preferred γ-attack from the reactive site on the phosphonium enolate more favorable because of the activation of an oxygen atom of the imide.

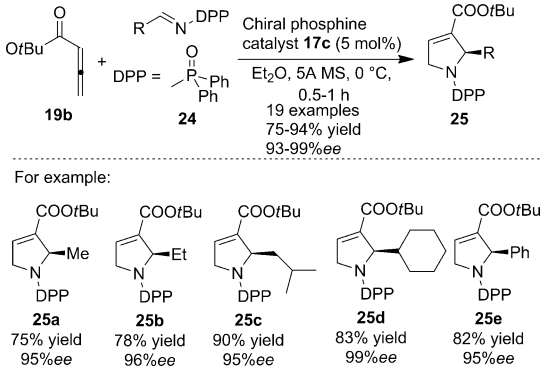


Scheme 9. Dipeptide-based chiral-phosphine-catalyzed [3+2] cycloaddition of MBH carbonates with maleimides.

With the dipeptide phosphine catalysts **17**, Lu and co-workers investigated the enantioselective imine–allene [3+2] cycloaddition.[13d] Although this reaction with similar allenes has been reported by Jacobsen in 2008, the *O*-TBDPS-D-Thr-L-*tert*-Leu-based (TBDPS = *tert*-butyldiphenylsilyl) phosphine catalyst **17c** was the better organocatalyst in this reaction. The broad applicability of catalyst **17c**-catalyzed [3+2] cycloaddition to various imines shifts its synthetic value to a higher level (Scheme 11, up to 99% *ee*), in which the authors used the asymmetric imine–allene [3+2] cycloaddition as a key step in the concise formal synthesis of (+)-trachelanthamidine. It



Scheme 10. Proposed mechanism of the dipeptide-based chiral-phosphine-catalyzed [3+2] cycloaddition of MBH carbonates with maleimides.

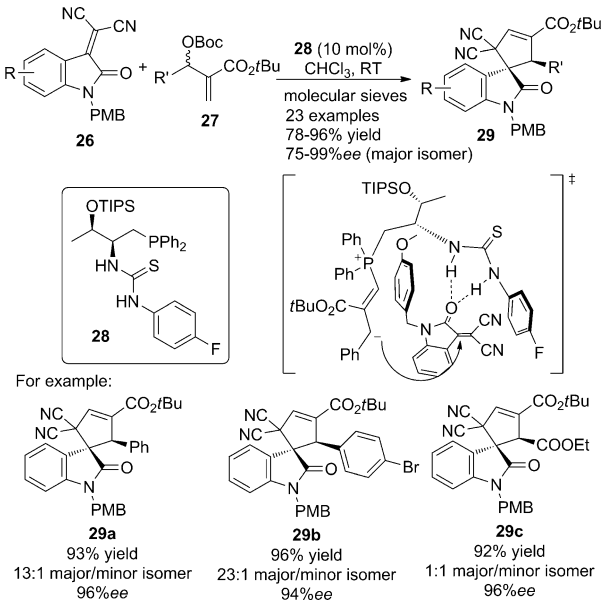


Scheme 11. Dipeptide-based chiral-phosphine-catalyzed imine–allene [3+2] cycloaddition.

should be noted that alkyl imines could be applied in this reaction for the first time.

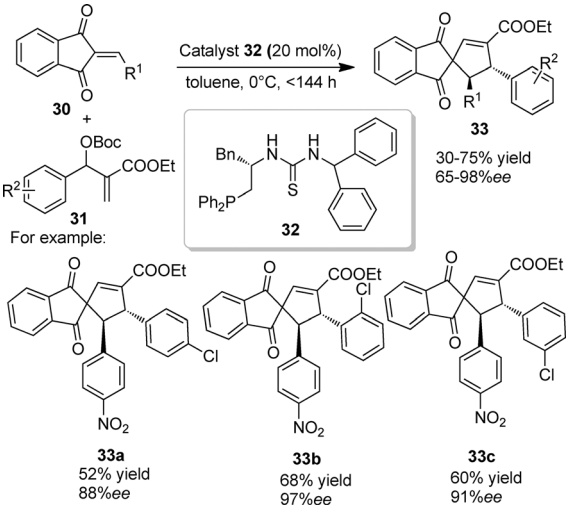
By employing threonine-derived phosphine **28**, Lu and coworkers reported that the [3+2] cycloaddition of MBH adducts to activated alkenes[5e] proceeded smoothly, affording chiral oxindoles **29** containing two contiguous quaternary centers in good to excellent enantioselectivities and yields (Scheme 12).[17] Notably, common sterically hindered bulky siloxyl groups all proved to be effective, and the phosphine catalyst **28** having a triisopropylsilyl (TIPS) group gave slightly better results. And replacement of the thiourea moiety in the organocatalyst with a urea resulted in slightly decreased enantioselectivity. Interestingly, the catalytic activity and enantioselectivity of phosphine catalysts containing 3,5-di-trifluorophenyl thiourea was not better than that of 4-fluorophenyl-derived catalyst **28**.

Very recently, Shi's group has demonstrated that the natural amino acid derived multifunctional phosphine **32** could be applied as an effective catalyst in asymmetric [3+2] annulation of MBH carbonates with various activated alkenes.[18] For example, [3+2] annulation reactions of MBH carbonates with 2-arylideneindane-1,3-diones proceeded smoothly in the pres-

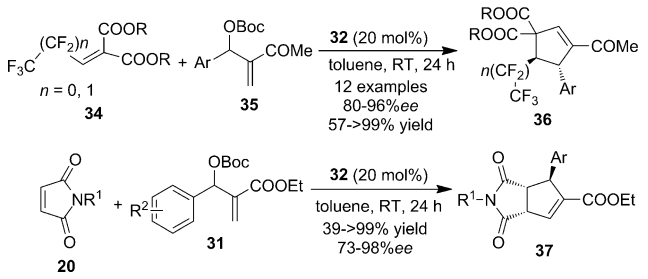


Scheme 12. [3+2] cycloaddition of MBH adducts and allenes catalyzed by an L-threonine-based bifunctional phosphine. PMB = *p*-methoxybenzyl; TIPS = triisopropylsilyl.

ence of catalyst **32** to produce the corresponding quaternary carbon-centered spirocyclic cyclopentenes **33** in moderate yields (up to 75%) but with high diastereoselectivities and enantioselectivities (up to 98% *ee*, Scheme 13).[18a] Under similar conditions, a bifunctional phosphine catalyst derived from an axially chiral binaphthyl scaffold bearing a hydrogen donor[5] led to poor conversion and enantioselectivity. The group also reported asymmetric catalyst **32** catalyzed [3+2] annulations of MBH carbonates with trifluoroethylidenemalonates[18b] and maleimides,[18c] respectively (Scheme 14). Both transformations afforded the corresponding highly functionalized molecules **36** or **37** in good yields and excellent enantioselectivities.



Scheme 13. Amino acid derived phosphine catalyzed [3+2] annulations of MBH carbonates with 2-arylideneindane-1,3-diones.

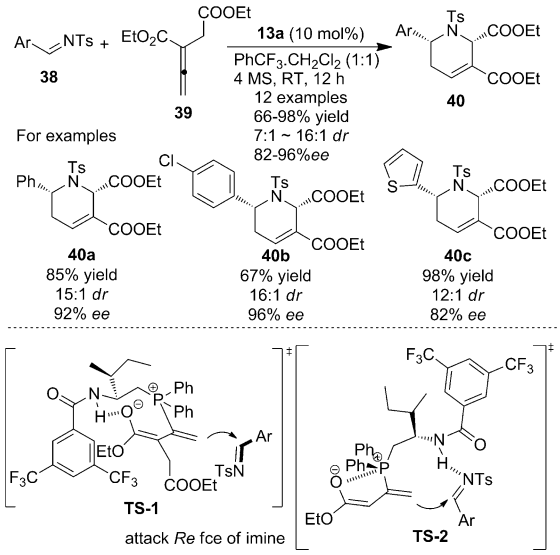


Scheme 14. Amino acid derived phosphine **32** catalyzed [3+2] annulation of MBH carbonates.

On the other hand, also as important and mutually complementary progress in this context, Fu,[19] Marinetti,[20] and other researches[21] have recently reported asymmetric phosphine-catalyzed intermolecular or intramolecular [3+2] annulations of allenoates to the corresponding cyclopentene derivatives in good yields with good to excellent enantioselectivities. These works demonstrated that chiral phosphines have become popular choices as nucleophilic catalysts in novel asymmetric [3+2] cycloadditions and related reactions with various allenoates and activated alkenes.

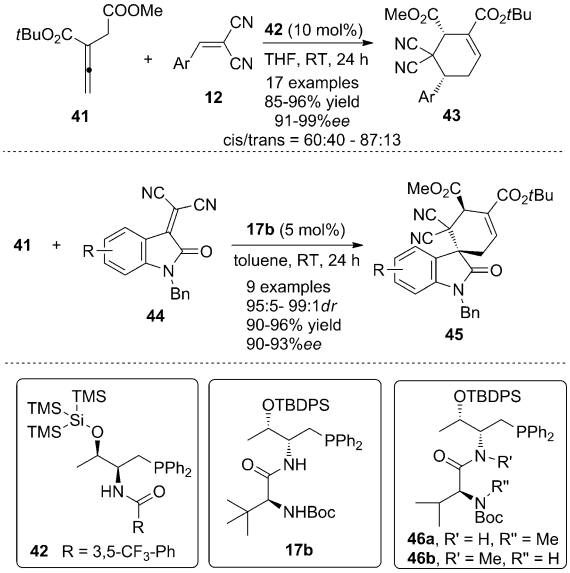
[4+2] Cycloadditions

Phosphine-catalyzed [4+2] annulations of α-alkylallenonates with activated alkenes allow the efficient synthesis of functionalized cyclohexenes or heterocycles.[22] In 2011, Zhao et al. successfully extended the applications of their previous developed amino acid derived bifunctional N-acyl aminophosphine catalyst **13a**[10] to an enantioselective [4+2] cycloaddition of tosylaldimines **38** and α-substituted allenoate **39**, which provided an efficient asymmetric access to optically active tetrahydropyridines (Scheme 15, up to 96% *ee*).[23] Similarly to previously proposed acting models,[8] **TS-1** involves formation of a zwitterion between the chiral phosphine and the allenoate **39**, which is possibly assisted by a hydrogen bonding interaction and a P–O interaction,[24] and the dienolate might approach the *Re* face of the imine to minimize the steric repulsion between the phosphonium intermediate generated from the allenoate and the tosyl (Ts) groups of the imine.



Scheme 15. Asymmetric [4+2] cycloadditions of allenoate with *N*-tosyl aldimines.

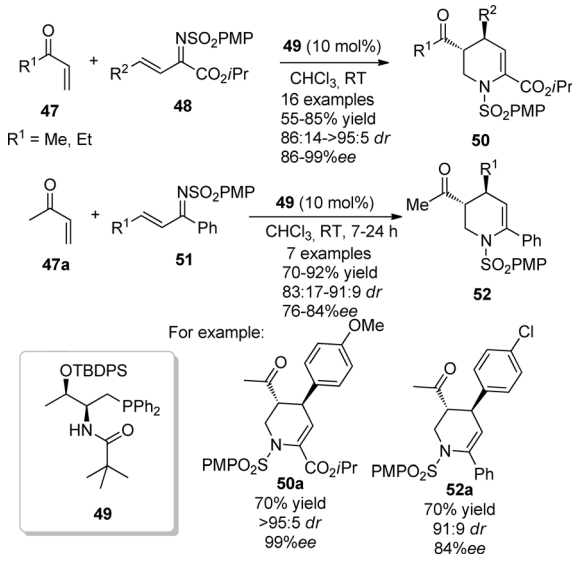
Subsequently in 2012, Lu's group reported their findings in the chiral phosphine-catalyzed [4+2] annulations of activated alkenes with α-substituted allenoates.[25] By employing threonine-derived phosphine **42** containing a highly sterically hindered siloxyl group or utilizing dipeptide-based phosphine **17b**, [4+2] annulations between allenoate **41** with activated alkenes **12** or isatin-derived alkenes **44** proceeded in a highly enantioselective manner (Scheme 16). It is interesting to note



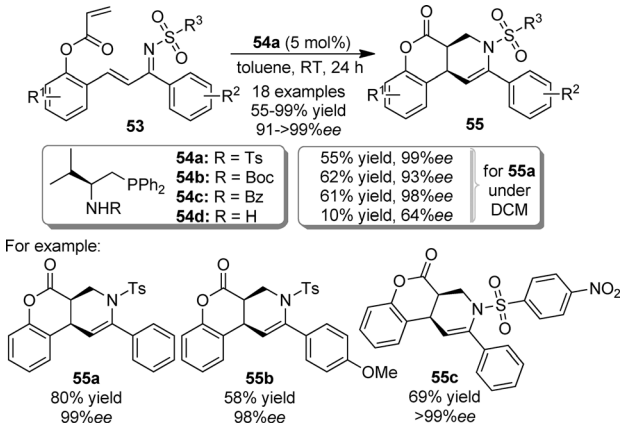
Scheme 16. Asymmetric [4+2] cyclizations catalyzed by L-threonine or threonine-containing dipeptidic phosphines.

that searching of suitable phosphine catalysts and optimizing reaction conditions were readily done by varying the hydrogen bonding units (amide or carbamate), incorporating different sterically hindered siloxy groups, and employing different amino acids. The importance of the hydrogen bond donors on this catalyst has been determined on the basis of several controlled experiments such as the catalytic effects of a series of dipeptide-based phosphines on the [4+2] annulations. For example, one amide on the multifunctional phosphine protected by a methyl group led to poor enantioselectivity as well as low catalytic activity (for **46a**: 12 h, 84% yield, 95:5 *dr*, 70% *ee*; or **46b**: 24 h, 75% yield, 55:45 *dr*, 29% *ee*).

Very recently, Loh and Zhong also disclosed an asymmetric [4+2] cycloaddition between vinyl ketones **47** and substituted *N*-4-methoxy-benzenesulfonyl-1-aza-1,3-diene **45** or chalcone-derived *N*-sulfonyl-1-aza-1,3-dienes **51**, catalyzed by L-threonine-based phosphine **49** (Scheme 17).[26] This protocol provides a new entry to the facile synthesis of a broad spectrum of densely functionalized tetrahydropyridines **50** or **52** with



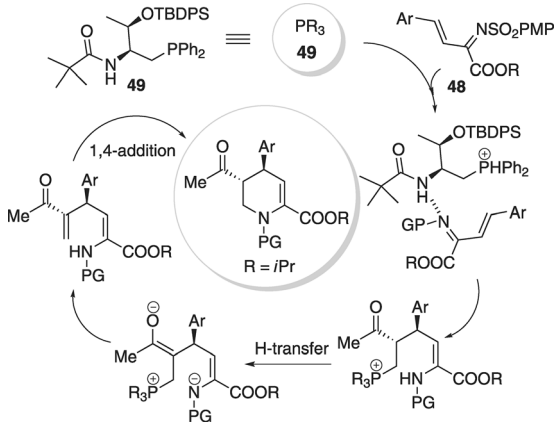
Scheme 17. Asymmetric aza-Rauhut-Currier reaction initiated [4+2] annulation.



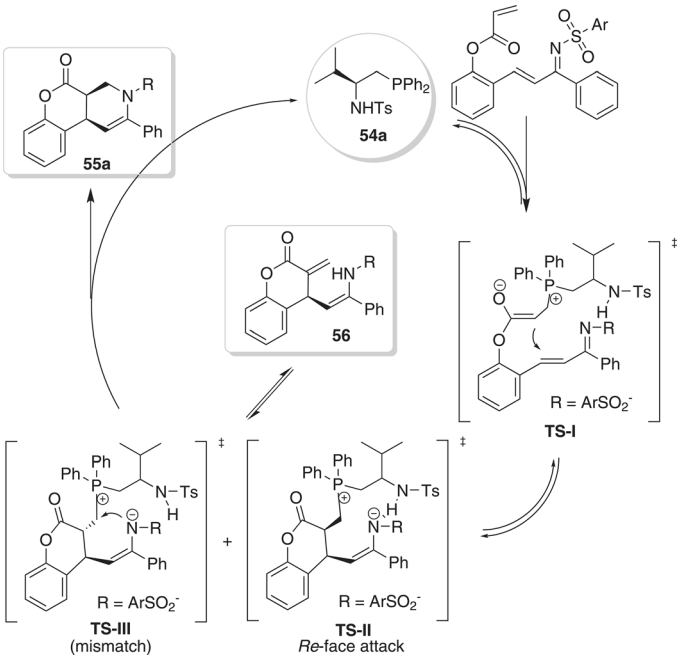
Scheme 19. Enantioselective intramolecular formal [4+2] annulation.

two stereogenic centers in good to excellent yields and good to high enantioselectivities. It should be noted the importance of hydrogen bonding donating units in chiral induction all have been illustrated or supported in the above [4+2] annulations. Although the detailed mechanism was not supported by enough evidences, the authors suggested that the hydrogen bonding between the pivaloyl amide of catalyst **49** and the 1,3-azadiene could direct the alkene side chain outwards to a sterically less-demanding position and away from the bulky pivaloyl group, which is beneficial to the subsequent intramolecular proton transfer of the chiral enolate intermediate generated from chiral phosphine catalyst (Scheme 18).

In 2012, Chi and co-workers reported a chiral phosphine **54a**-catalyzed activation of electron-deficient alkenes for intramolecular formal [4+2] annulations that led to functionalized bicylic N,O-containing compounds with excellent enantioselectivities (91–>99% *ee*, Scheme 19).[27] Notably, replacing the amide moiety of the catalyst **54a** with an amino (primary amine, **54d**) led to a significant drop in yield and enantioselectivity (for **55a**, 10% yield, 64% *ee*). Under optimized conditions, variations on the aryl unit of the substrates were well-tolerated to give nitrogen-containing heterocyclic products as essentially single diastereomer. The chiral phosphine-catalyzed intramolecular [4+2] cycloaddition is postulated to proceed through a tandem Rauhut–Currier/S_N2-nucleophilic substitution sequence. As shown in Scheme 20, the high diastereoselectivity likely resulted from a favorable S_N2-nucleophilic addition of the intermediate **TS-II** and a reversible interconversion between intermediate **TS-II** (or **TS-III**) and the Rauhut–Currier adduct **56**. The byproduct **56** could be isolated in approximately 20% yield if triphenylphosphine was used as a catalyst.



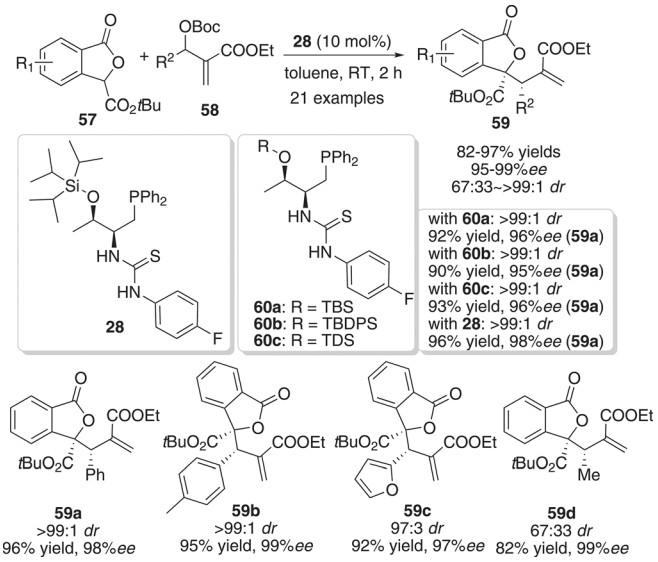
Scheme 18. Plausible transition state and reaction pathway in the asymmetric aza-Rauhut–Currier reaction initiated [4+2] annulation.



Scheme 20. Postulated mechanism of enantioselective intramolecular formal [4+2] annulation.

Allylic Alkylations

Organocatalytic allylic alkylation have recently emerged as an supplementary and powerful method for the construction of allylation products.[28] The power of amino acid derived chiral phosphines has been further demonstrated in this reaction by Lu and co-workers very recently (Scheme 21). In this work,

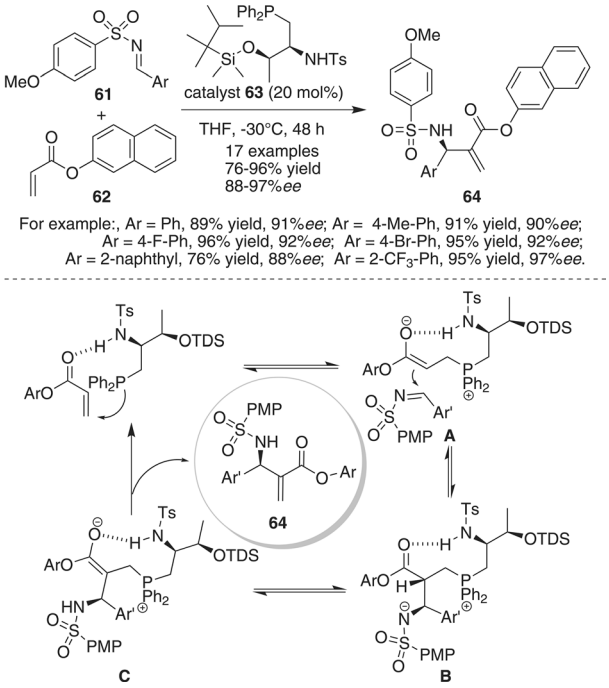


Scheme 21. Chiral-phosphine catalyzed allylic alkylation reaction of phthalides.

L-threonine-derived phosphine–thiourea catalyst **28** was shown to promote allylic alkylations of MBH carbonates with phthalides in a very high enantioselective manner.[29] In addition, consistent with their previous findings,[11] the hydrogen bonding interactions between the Brønsted acid moiety of the catalyst and the ester group of phthalide are crucial for the observed stereoselectivity. The threonine-derived phosphine catalysts containing bulky silicon-based group and thiourea motif proved to be privileged, in which the sterically hindered silyloxy groups were generally effective and triisopropylsilyl-protected phosphine catalyst **28** led to the best results.

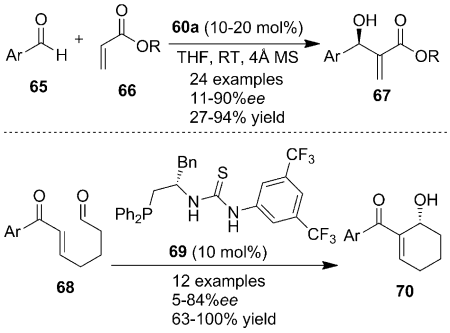
Morita–Baylis–Hillman Reactions

The MBH reaction is one of the most fundamental and important carbon–carbon bond-forming reactions, which provides easy access to heavily functionalized and synthetically useful MBH adducts from simple and available activated olefins and aldehydes.[5a,30] To further expand amino acid based phosphine catalysts in asymmetric catalysis, Lu and co-workers designed and prepared a series of novel bifunctional phosphine–sulfonamide organocatalysts from natural amino acids. And the phosphine catalyst **63** was found to be the effective catalyst in the aza-BMH reaction of *N*-(*p*-methoxybenzenesulfonyl)imine and 2-naphthyl acrylate, which led to the formation of various aza-MBH adducts in good to excellent yields and excellent enantioselectivities in most cases (Scheme 22).[31] In this reaction, hydrogen bonding and the bulky silicon-based group (*O*-tris(2,6-diphenylbenzyl)silyl, OTDS) favor the formation of the structurally well-defined phosphonium enolate intermediate **A**. Consistent with experimental observations, if the OTDS group is replaced by a less hindered *O*-trimethylsilyl (OTMS) group, the less rigid intermediate **A** would be anticipated to provide less stereocontrol (91% *ee* versus 64% *ee*).



Scheme 22. Chiral-phosphine catalyzed aza-MBH reactions. PMP = *p*-methoxyphenyl.

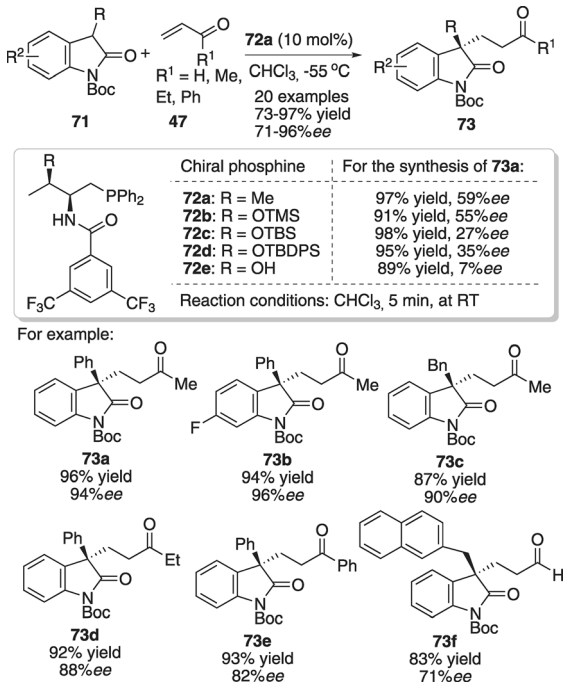
L-Threonine-derived chiral bifunctional phosphine catalyst **60a** was also found to be a good organocatalyst in the asymmetric MBH reaction of acrylates with aromatic aldehydes (up to 90% *ee* and 92% yield).[32] Wu and co-workers also reported an example of chiral amino acid derived phosphine/thiourea catalyst promoted intramolecular MBH reaction.[33] Although the enantioselectivities were only moderate to good (up to 84% *ee*), this process provides a facile method to the construction of chiral cyclic hydroxyl enones in good to excellent yields (Scheme 23).



Scheme 23. Chiral phosphine catalyzed intermolecular or intramolecular MBH reactions.

Michael Addition Reactions

Michael addition or conjugate addition of stabilized nucleophiles to α,β-unsaturated carbonyl compounds is one of the most important and fundamental carbon–carbon bond-forming processes.[34] Trialkyl or triaryl phosphine has been shown to catalyze Michael reactions or conjugate-addition-initiated domino reactions with versatile nucleophiles.[35] However, almost no attention was paid to the design and development of chiral multifunctional phosphine mediated Michael reactions. Very recently, Lu's group described the first chiral amino acid based phosphine-initiated asymmetric Michael addition of oxindoles with good to excellent enantioselectivities (Scheme 24).[36] On the basis of a successful evaluation of the catalytic activity of Me_2PPh_2 in the Michael addition of 3-substituted oxindoles to α,β-unsaturated carbonyl compounds, a set of bifunctional phosphines derived from amino acids were selected as catalysts to promote the enantioselective Michael addition. The chiral bifunctional phosphine **72a** bearing a 3,5-bistrifluoromethylbenzoyl group turned to the best catalyst among these phosphine catalysts. In particular, introduction of a sterically more hindered threonine core into the catalyst structure with bulky silicon-based groups (**72b**, **72c**, and **72d**) did not lead to further improvement. The free hydroxyl group-containing phosphine catalyst **72e** turned out to be ineffective because of low enantioselectivity (7% *ee* of **73a**). In addition, on the basis of experimental results, Lu and co-workers proposed that the hydrogen donor of the phosphine catalyst and the presence of a 3,5-substituted phenyl ring on the catalyst block the favorable stereoselective attack of nucleophile to activated alkane.



Scheme 24. L-Threonine derived phosphine catalyzed Michael addition reactions of various oxindoles to α,β-unsaturated carbonyl compounds.

Summary and Outlook

The chiral phosphines highlighted herein are either derived from a single amino acid or a dipeptide, they are thus readily available at low cost. In view of their remarkable stability in the air,[2] in combination with their economical nature, such catalysts are anticipated to have great practical values in industrial applications. The amino acid based phosphines have already been proven to be versatile, catalyzing a wide range of asymmetric reactions, including (aza)-MBH reactions, various [3+2] cyclizations, [4+2] cycloadditions, allylic alkylations, and Michael additions. In the examples illustrated, the threonine core has been shown to be "privileged" in catalyst structures, which hints that a judicious selection of proper amino acid residues in the catalyst structure is crucial for the design of highly efficient chiral catalysts. The amide or carbamate moieties in the phosphines described all seem to be engaged in hydrogen bonding interactions with the substrates and contribute significantly to the observed stereoselectivities. Such bifunctional phosphines are highly promising in asymmetric catalysis, as cooperative effects between the phosphorus atom and hydrogen bond donors are highly desirable in stereochemical control. The sterically hindered siloxy groups are present in many phosphine catalysts, although their roles in asymmetric induction are not entirely clear; such groups probably provide facial differentiation and induce conformational constraint. Applications of amino acid based phosphines to an even broader array of reactions are certainly very exciting and worth anticipating.

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Keywords: amino acids · asymmetric catalysis · hydrogen bonds · organocatalysis · phosphanes

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