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Catalytic asymmetric synthesis using P-chiral diaminophosphine oxide preligands: DIAPHOXs

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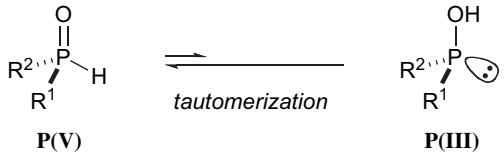
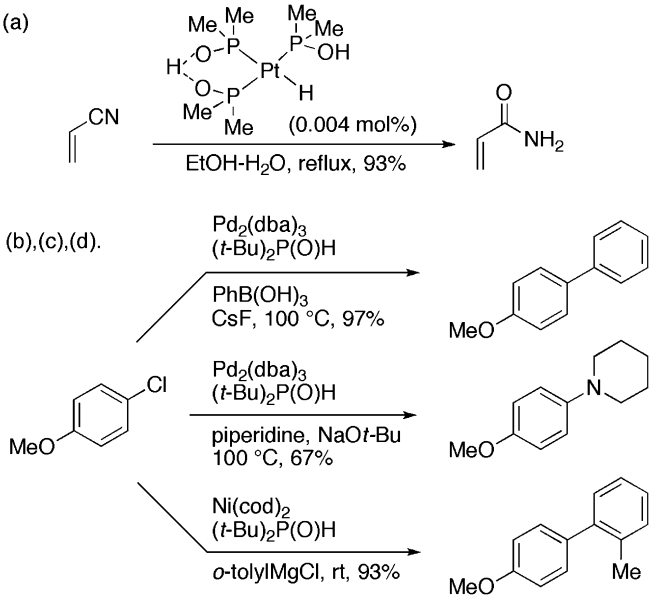
1. Introduction

Since the early 1970s, a variety of chiral ligands for transition metal-mediated asymmetric reactions have been developed.[1] From a functional point of view, enantiomeric excess is the simplest index for evaluating the ability of chiral ligands. On the other hand, from a practical point of view, air-stable, inexpensive, and easily accessible ligands are highly desirable. Secondary phosphine oxides and phosphonic acid derivatives are air- and moisture-stable pentavalent phosphorus compounds and exist in equilibrium between pentavalent forms [RR′P(O)H] and trivalent tautomeric forms (RR′POH) (Scheme 1).[2] This property allows for the use of these compounds as air- and moisture-stable preligands in transition metal catalysis.[3–7]



Scheme 1.

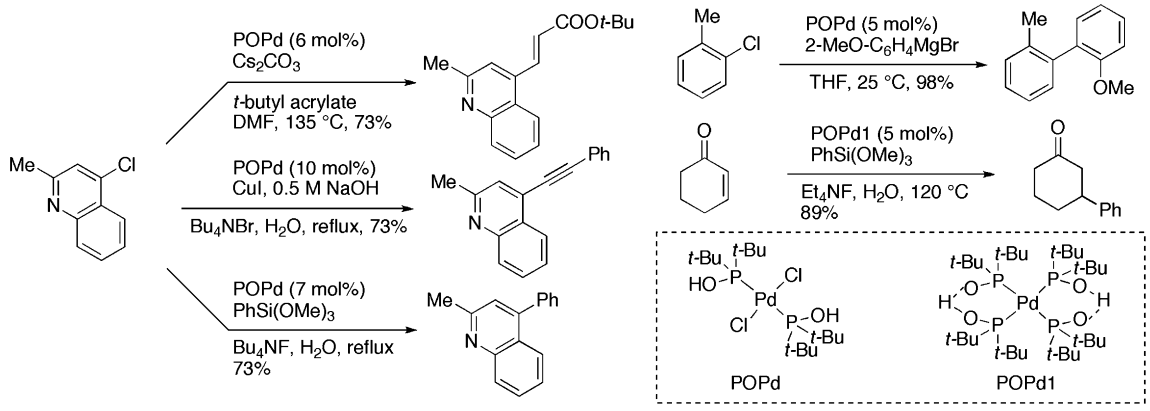
In 1986, van Leeuwen et al. reported the potential of secondary phosphine oxides as preligands in Pt-catalyzed hydroformylation.[8,9] Catalytic hydrolysis of nitriles using a similar platinum–phosphinous acid complex was also reported later by Parkins and Ghaffar and by de Vries et al. [Scheme 2(a)].[10–12] In 2001, Li et al. first demonstrated that air-stable secondary phosphine oxides are ideal ligand precursors for transition metal catalysis. Pd- and Ni-catalyzed cross-coupling reactions with aryl chlorides proceeded using di-*tert*-butylphosphine oxide as the preligand, providing the corresponding products in good-to-excellent yield [Scheme 2(b–d)].[13,14] Palladium–phosphinous acid complexes such as $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (abbreviated as POPd) and $[[(t\text{-Bu})_2PO\cdot H\cdot OP(t\text{-Bu})_2]PdCl]_2$ (abbreviated as POPd1), which can be prepared from $Pd(II)Cl_2$ and di-*tert*-butylphosphine oxide,[15] have been also utilized as air-stable catalysts. Wolf and his co-workers have most actively investigated catalytic transformations using these palladium complexes. Heck reaction,[16] Stille coupling,[17] Sonogashira coupling,[18] Hiyama coupling,[19,20] Kumada coupling,[21] Negishi coupling,[22] Suzuki–Miyaura coupling,[23–27] cross coupling of acyl chlorides with boronic acids[28] or organostannanes,[29] direct C-3 arylation of indoles,[30] conjugate addition of arylsiloxanes,[31] and oxidative esterification of aldehydes[32] have been all reported to date (Scheme 3). In addition, [2+1] cycloadditions of terminal alkynes to bicyclic alkenes using palladium- and platinum-phosphinous acid complexes have been reported by Giordano and Buono et al.[33–35]



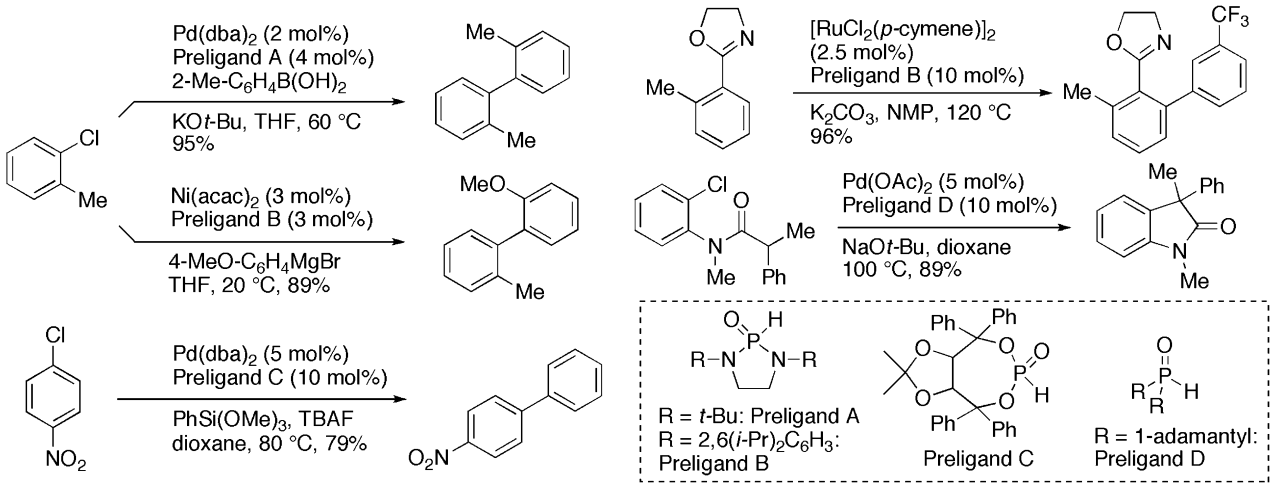
Scheme 2.

Another highlight in this field was the application of diaminophosphine oxides and related secondary phosphine oxides to several transition metal-catalyzed reactions by Ackermann et al. (Scheme 4). In addition to Pd- or Ni-catalyzed cross-coupling reactions,[36–41] this class of preligands have been successfully applied to Ru-catalyzed arylation reactions via C–H bond activation[42–44] and Pd-catalyzed intramolecular α-arylation.[45]

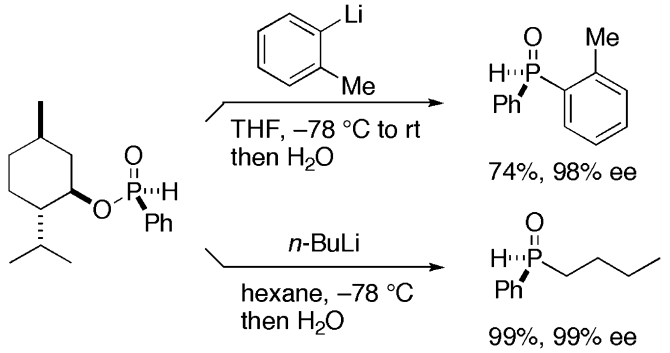
During the P(V)–P(III) equilibrium, stereochemical arrangement around the phosphorus center is retained. This interesting property has inspired the creation of a new research field: asymmetric catalysis with P-chiral secondary phosphine oxides. Simple P-chiral secondary phosphine oxides, such as *tert*-butylphenylphosphine oxide, were conventionally prepared by optical resolution[46–49] or separation of chiral chromatography.[50] Very recently, Buono et al. and Han et al. independently reported a stereospecific nucleophilic substitution of optically pure (R_P)-(−)-menthyl phenylphosphinate with organometallic reagents, which made various P-chiral secondary phosphine oxides accessible with high enantiomeric purity (Scheme 5).[51,52] In 2003, the first application of P-chiral secondary phosphine oxides to Ir-catalyzed asymmetric hydrogenation was reported by Minnaard, Feringa, and de Vries et al. [Scheme 6(a)].[50,53] Toffano and Fiaud et al. also reported Rh-catalyzed asymmetric hydrogenation of an *N*-acetyl dehydrophenylalanine using a cyclic chiral secondary phosphine oxide [Scheme 6(b)].[54] In



Scheme 3.



Scheme 4.



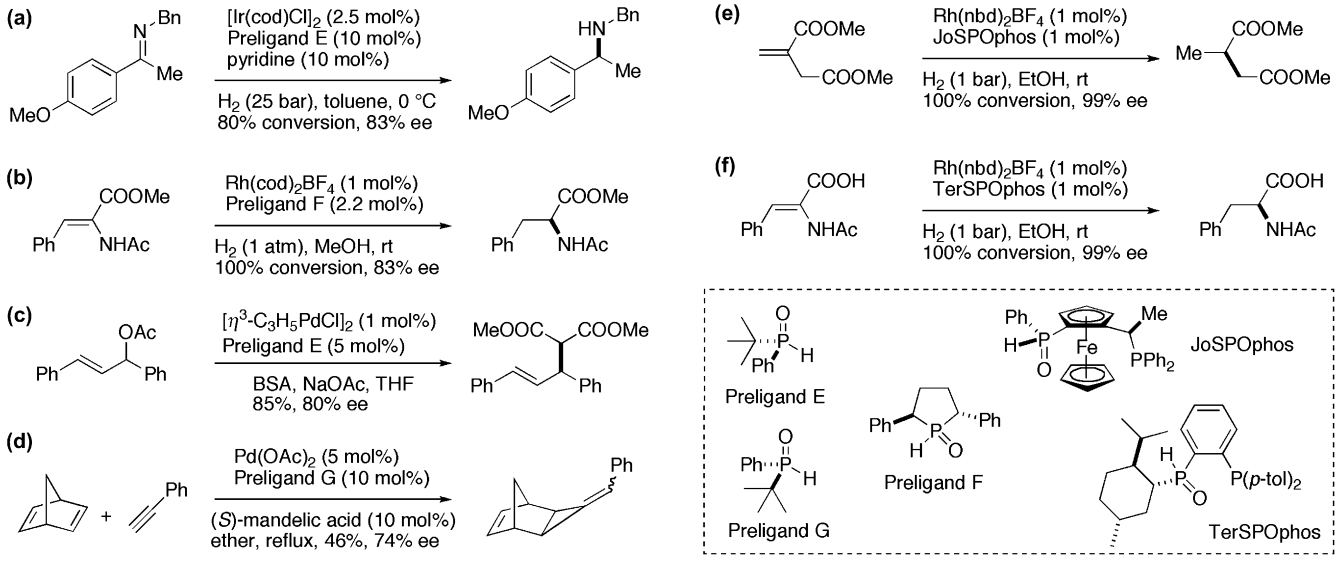
Scheme 5.

these results clearly indicate the synthetic utility of chiral secondary phosphine oxide preligands, the scope of applications has been mainly limited to asymmetric hydrogenation. To develop more practical chiral preligands applicable to asymmetric carbon–carbon and carbon–heteroatom bond formations, it was necessary to establish a new strategy to synthesize various P-chiral secondary phosphine oxides or their equivalents in an optically pure form. We envisaged that this task could be accomplished by designing new ligands based on a chiral diamine framework, and finally succeeded in developing a new class of chiral phosphorus ligands. This review presents our recent research on transition metal-catalyzed asymmetric allylic substitution reactions[58,59] using amino acid-derived P-chiral diaminophosphine oxides: DIAPHOXs.[6,7]

addition, Pd-catalyzed asymmetric allylic alkylation and asymmetric benzylidencyclopropanation were reported by Dai et al. and by Giordano and Buono et al., respectively [Scheme 6(c,d)].[55,56] Very recently, Pugin and Pfaltz et al. developed novel bidentate-type chiral secondary phosphine oxide preligands: JoSPOphos and TerSPOphos, which were successfully applied to Rh-catalyzed asymmetric hydrogenations of olefins [Scheme 6(e,f)].[57] Although

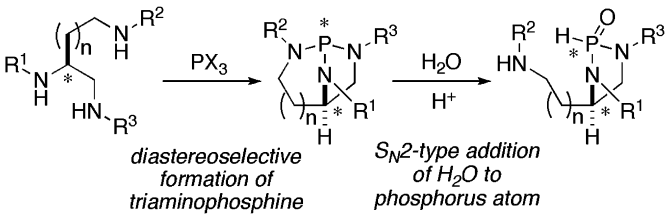
2. Design and synthesis of P-chiral diaminophosphine oxides: DIAPHOXs[60]

Cyclic diaminophosphine oxides with a stereogenic center on the phosphorus atom can be prepared from chiral (or achiral) asymmetric diamines. Separation of the diastereomeric (or enantiomeric) mixture, however, is necessary to obtain the optically



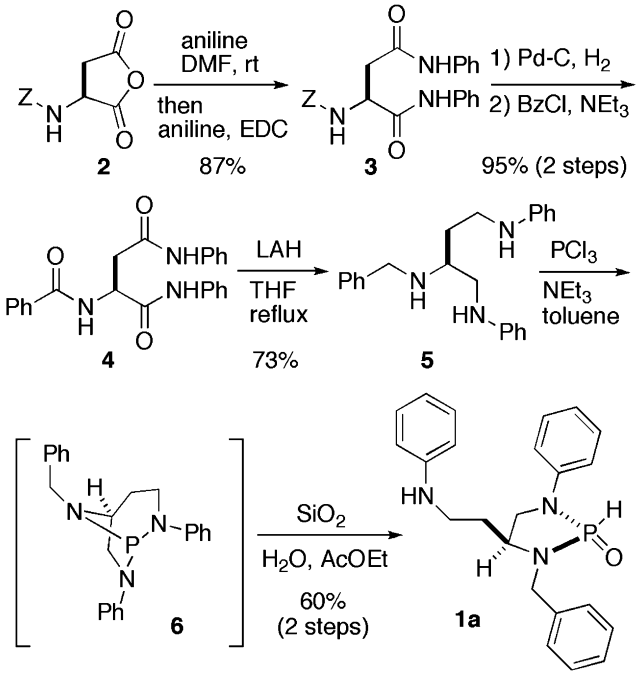
Scheme 6.

pure P-chiral diaminophosphine oxide. Our strategy to synthesize P-chiral diaminophosphine oxides is based on the observation that triaminophosphines are reactive to water under acidic conditions via an S_N2-type process, affording the corresponding diaminophosphine oxides through P(III) to P(V) tautomerization. Therefore, we expected that diastereoselective formation of P-chiral triaminophosphines starting from optically active branched triamines, followed by the introduction of an oxygen functionality on the phosphorus atom, would be an efficient synthetic route (Scheme 7).



Scheme 7.

The synthetic route for (*S*,R_P)-DIAPHOX **1a** is shown in Scheme 8. Our synthesis started with the commercially available acid anhydride **2**, which can be easily prepared from (*S*)-aspartic acid. Nucleophilic opening of **2**, followed by condensation with aniline in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), yielded the corresponding dianilide **3**. Removal of a carbobenzyloxy (Z) group, followed by amide formation with benzoyl chloride, afforded the triamide **4**. After reduction of all of the amide groups, the obtained triamine **5** was reacted with phosphorus trichloride to afford the corresponding triaminophosphine **6**, which was converted into (*S*,R_P)-DIAPHOX **1a** by treatment with silica in wet ethyl acetate. Direct purification of the crude triaminophosphine residue with silica gel column chromatography could be utilized as a more convenient alternative method. Similarly, structurally modified aspartic acid-derived (*S*,R_P)-DIAPHOXs **1b**–**j** could be prepared using the corresponding aromatic amines and acid chlorides (Fig. 1).



Scheme 8.

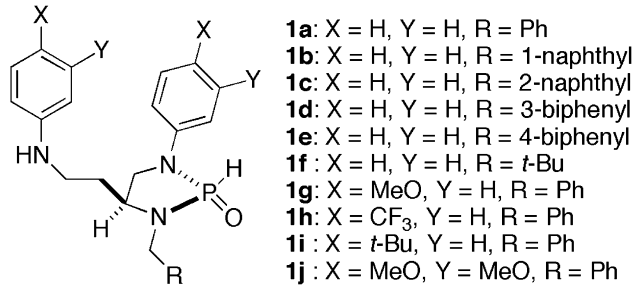
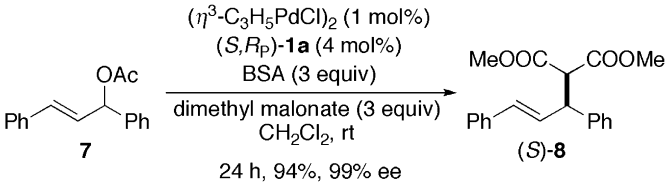


Fig. 1. Structure of aspartic acid-derived (*S*,R_P)-DIAPHOX.

3. Pd-catalyzed asymmetric allylic substitution reactions using carbon nucleophiles

3.1. Asymmetric allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate and determination of the actual ligand structure[61]

With the optically pure DIAPHOXs in hand, we attempted to use them as chiral ligands. We first examined Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acetate **7** with dimethyl malonate, because this reaction is recognized as the benchmark system to evaluate the ability of newly developed chiral ligands. The examinations were performed using 1 mol % of (η^3-$C_3H_5PdCl)_2$ and 4 mol % of (*S*,R_P)-**1a** in CH_2Cl_2. No reaction occurred when a variety of bases, such as NaH, lithium diisopropylamide, 1,1,3,3-tetramethyguanidine, and diisopropylethylamine, were used. In contrast to other bases, *N*,*O*-bis(trimethysilyl)acetamide (BSA)[62] promoted the reaction very efficiently to afford the corresponding product (*S*)-**8** in 94% yield and in 99% ee (Scheme 9).



Scheme 9.

Very interestingly, typical bases other than BSA did not promote the reaction. ^{31}P NMR studies revealed that pentavalent **1a** [δ 12.5 ppm ($CDCl_3$)] first reacts with BSA to provide a trivalent phosphorus compound [δ 110.0 ppm ($CDCl_3$)]. To clarify the structure of the observed trivalent species, several mechanistic experiments were performed. Preliminary experiments using diaminophosphine oxide **9** indicated that a trivalent phosphorus compound **10** is formed in the presence of BSA (Fig. 2). This result was very informative for determining the structure of the diamidophosphite moiety of the trivalent species derived from **1a**. To obtain experimental information on the structure of the nitrogen moiety on the sidearm of **1a**, we performed a fast atom bombardment–mass spectrometry (FAB-MS) analysis (Fig. 2). FAB-MS analysis of the residue obtained from a CH_2Cl_2 solution of **1a** and BSA (30 equiv to **1a**) exhibited a peak at 464 *m*/*z*. The detected peak corresponded to the molecular weight of **11**. In addition, FAB-MS analysis of the residue obtained from a CH_2Cl_2 solution of (η^3-$C_3H_5PdCl)_2$, **1a**, and BSA in a ratio of 1:2:60 exhibited a peak at 610 *m*/*z*. The detected peak corresponded to the molecular weight of the cationic complex **12**. In addition, the observation that no trimethylsilylation of *N*-methylaniline occurred in the presence of BSA suggested that the nitrogen atom on the sidearm in **1a** is not silylated. On the basis of these results, we concluded that DIAPHOX **1a**, the preligand, reacts with BSA

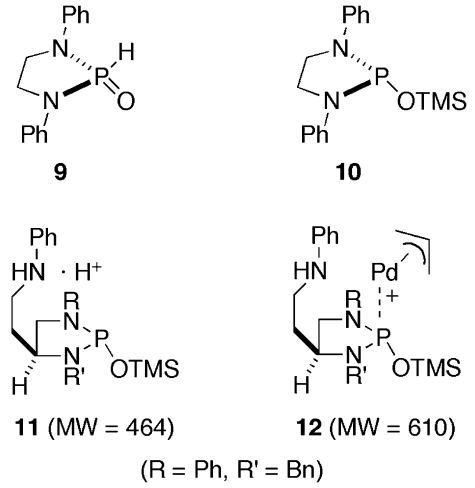
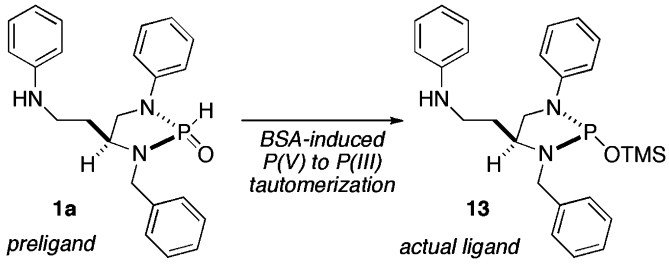


Fig. 2. Observed species in the preliminary experiments and the FABMS analysis.

in the reaction mixture, affording the trivalent phosphorus compound **13**, which is proposed to be the actual ligand structure (Scheme 10) (for more detailed discussions, see Ref. 61).



Scheme 10.

3.2. Enantioselective construction of all-carbon quaternary stereocenter using a Pd-DIAPHOX catalyst system[60,61]

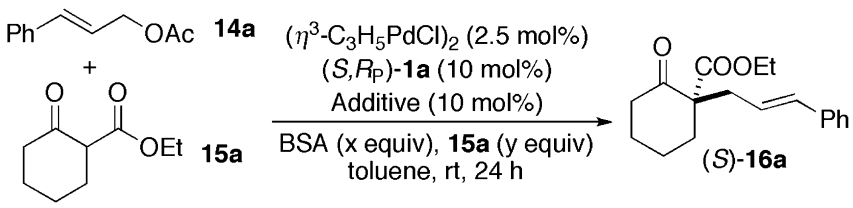
Catalytic enantioselective construction of a quaternary carbon center is a formidable challenge in organic synthesis.[63–66] Pd-catalyzed asymmetric allylic substitution using prochiral nucleophiles is one of the most straightforward approaches toward this end. Few successful reactions of this type have been reported since the 1980s.[67–79] There were, however, several unsolved difficulties in substrate generality in each catalytic process, indicating that there is still room for developing a novel catalytic asymmetric process. These background studies led us to attempt this type of reaction using the Pd-DIAPHOX catalyst system. We first examined asymmetric allylic substitution of cinnamyl acetate **14a** with ethyl 2-oxocyclohexanecarboxylate **15a** (Table 1). When the reaction was performed using 2.5 mol % of $(\eta^3\text{-}C_3H_5PdCl)_2$, 10 mol % of (S,R_P)-**1a**, and BSA as the base, (*S*)-**16a** was obtained in 53% ee, even though the yield was only 10%. Encouraged by this result, we investigated the effect of the addition of an acetate salt. Detailed screening revealed that $Zn(OAc)_2$ was the best additive for asymmetric induction. After several studies to determine the optimal amount of BSA and **15a**, 4 equiv of BSA and 1.5 equiv of **15a**–**14a** gave the best reactivity (entry 8).

Having developed efficient conditions, we examined the scope and limitations of different substrates (Table 2). When 0.5–5 mol % of the catalyst was employed, asymmetric allylic substitution of **14a** using prochiral nucleophiles with five-, six-, seven-, and eight-membered rings **15a**–**f** proceeded smoothly at room temperature to provide the corresponding products **16a**–**f** in good yield with modest to high enantioselectivity (72–94% ee) (entries 1–7). In addition to γ-Aryl substituted-allyl acetates **14b** and **14c**, γ-alkyl substituted-allyl acetates **14d** and **14e** reacted with β-keto ester **15g** to afford the corresponding products **16g**–**j** in good yield with good-to-high enantioselectivity (80–92% ee) (entries 8–11). Reaction using simple allyl acetate **14f**, however, gave a less satisfactory result (entry 12). It is noteworthy that γ-acetoxy α,β-unsaturated carbonyl compounds **14g** and **14h** are compatible with this reaction system.[80] With the use of 2 mol % of Pd catalyst and 4 mol % of (S,R_P)-**1c**, characteristic reaction adducts **16l** and **16m** with three different carbonyl groups were obtained in excellent yield with high enantiomeric excess (up to 95% ee) (entries 13 and 14).

3.3. Mechanistic studies: source of enantioselection in construction of quaternary stereocenters[61]

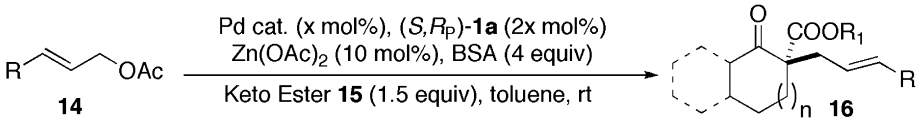
The sources of enantioselection are quite different between the two types of reactions examined: attack at enantiotopic termini of the *meso*-π-allyl complex (Scheme 9) and differentiation of the prochiral nucleophile face (Table 2). Despite the mechanistic difference, a high level of enantioselection was realized in both cases. Enantioselective nucleophilic attack of a stabilized prochiral anion to π-allylpalladium is not easy to control by the chiral ligand on the palladium atom, because the incoming nucleophile resides at the side opposite to the stereogenic center in the transition state. Interestingly, this difficult process proceeded with high enantioselectivity in the presence of $Zn(OAc)_2$. To clarify the role of Zn

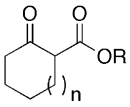
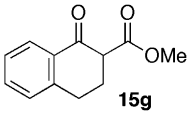
Table 1
Optimization of the reaction conditions



Entry	Additive	*x*	*y*	Yield (%)	ee (%)
1	—	3	1.25	10	53
2	LiOAc	3	1.25	53	8
3	$Mg(OAc)_2{\cdot}4H_2O$	3	1.25	99	66
4	$In(OAc)_3$	3	1.25	17	73
5	$Zn(OAc)_2{\cdot}H_2O$	3	1.25	81	89
6	$Zn(OAc)_2$	3	1.25	80	91
7	$Zn(OAc)_2$	3	1.5	86	91
8	$Zn(OAc)_2$	4	1.5	99	92

Table 2
Scope and limitations



Entry	Acetate	Keto ester		x	Product	Time (h)	Yield (%)	ee (%)
1	**14a**: R=Ph	**15a**: n=1, R^1=Et		2	**16a**	16	99	93(*S*)
2	**14a**: R=Ph	**15a**: n=1, R^1=Et		0.5	**16a**	32	85	93(*S*)
3	**14a**: R=Ph	**15b**: n=1, R^1=Me		2	**16b**	20	93	94
4	**14a**: R=Ph	**15c**: n=1, R^1=Bn		2	**16c**	15	99	91(*S*)
5	**14a**: R=Ph	**15d**: n=0, R^1=Me		5	**16d**	24	75	85(*S*)
6	**14a**: R=Ph	**15e**: n=2, R^1=Me		2	**16e**	24	85	78
7	**14a**: R=Ph	**15f**: n=3, R^1=Me		2	**16f**	20	97	72
8	**14b**: R=4-Me-C_6H_5	**15g**		2	**16g**	10	98	92
9	**14c**: R=4-Cl-C_6H_5	**15g**		2	**16h**	7	99	91
10	**14d**: R=CH_2CH_2Ph	**15g**		5	**16i**	24	74	82
11	**14e**: R=cHex	**15g**		5	**16j**	20	83	80
12	**14f**: R=H	**15g**		5	**16k**	48	24	63(*S*)
13[a]	**14g**: R=COO*t*-Bu	**15a**: n=1, R^1=Et		2	**16l**	24	99	95(*S*)
14[a]	**14h**: R=COPh	**15a**: n=1, R^1=Et		2	**16m**	20	97	90(*S*)

[a] (*S*,R_P)-**1c** was used as the ligand.

$(OAc)_2$ in the formation of quaternary stereocenters, we performed detailed mechanistic studies.

Considering the structure of **13**, it is possible that **13** chelates to the Pd metal in a bidentate manner through both the phosphorus atom and the nitrogen atom. This led us to question whether this Pd-ligand ratio (Pd/**1a**=1:2) was optimal. To resolve this issue, we first investigated the Pd-ligand ratio using two representative reactions: **7** to **8** and **14a** to **16a**. The obtained results were in marked contrast to those obtained using the optimal conditions. No reaction occurred in both cases using the catalyst prepared from the Pd source and **1a** in a ratio of 1:1. In addition, there were positive nonlinear effects in both types of reactions. These results led us to hypothesize that the Pd–**13** (1:2) complex exists in the reaction mixture, and might function as the catalytically active species. To elucidate the detailed reaction profiles, we performed kinetic experiments. The reaction rate of allylic alkylation of **7** with dimethyl malonate (reaction type A) had first-order dependency on the Pd catalyst, zero-order dependency on **7**, and first-order dependency on dimethyl malonate. Similarly, the reaction rate of allylic substitution of **14a** with **15a** (reaction type B) had first-order dependency on the Pd catalyst, zero-order dependency on **14a**, first-order dependency on **15a**, and first-order dependency on $Zn(OAc)_2$. The rate dependency on the Pd catalyst supports our expectation that two molecules of **13** chelate to the Pd metal and result in a positive nonlinear effect. Consequently, the Pd(0) complex **17** (Pd/**13**=1:2) is proposed to be the common active species (Fig. 3) (for more detailed discussions, see Ref. 61).

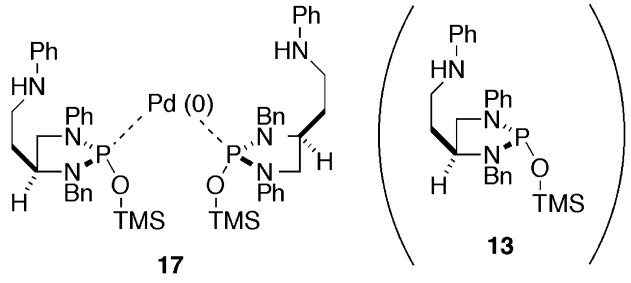
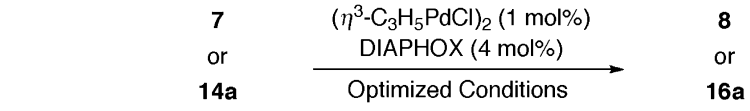


Fig. 3. Proposed structure of the catalytically active species.

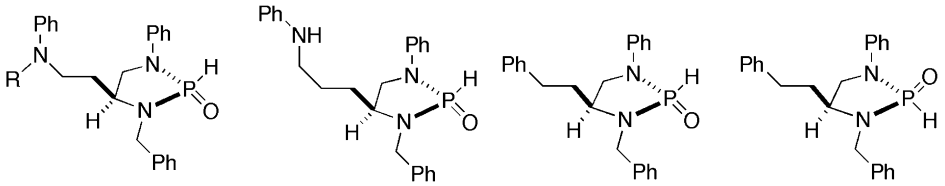
Kinetic experiments also indicate that, in the case of reaction type B, the rate-determining nucleophilic attack of the enol silyl ether, derived from **15a** and BSA, on a cationic π-allylpalladium complex is achieved in cooperation with a single molecule of Zn $(OAc)_2$. This suggestion led us to hypothesize that a nitrogen atom on the sidearm in **13** could fix the prochiral nucleophile in the appropriate position through a secondary ligand substrate interaction[81,82] mediated by Zn metal. To examine this possibility, we investigated the effect of ligand modifications (Table 3). When structurally modified diaminophosphine oxides (*S*,R_P)-**18**–**21** were used as the ligand, there were no significant changes in the stereoselectivity in the case of reaction type A (entries 1–5). In contrast, however, remarkable changes were observed in the case of reaction type B. Electronic and steric changes on the nitrogen atom (entries 8 and 9), as well as changes in the sidearm length (entry 10), influenced the catalytic activity, resulting in decreased reactivity and selectivity. It is particularly noteworthy that there was a significant decrease in the enantioselectivity when (*S*,R_P)-**21**, a ligand without a nitrogen atom on the sidearm, was used (entry 11). In addition, with the use of (*S*,S_P)-**22**, opposite stereoselection was observed in reaction type A (entry 6). Moreover, no reaction occurred when (*S*,S_P)-**22** was used in reaction type B (entry 12). These results clearly indicate that the ligand structure with a sidearm possessing a nitrogen atom is very important to achieve the present asymmetric catalysis. These findings led us to conclude that the secondary ligand substrate interaction mediated by N–Zn coordination has a crucial role on the enantiofacial recognition of prochiral nucleophiles in reaction type B.

To obtain more detailed structural information on the sources of enantioselection, we tried crystallizing the catalyst species. Unfortunately, a crystal suitable for X-ray analysis could not be obtained. Although the complete transition state is not clear, the enantioselection in reaction type B would be explained by the working model shown in Fig. 4. The observed absolute configurations of **16a** and

Table 3
Effect of ligand structure



Entry	Substrate	DIAPHOX	Time (h)	Yield (%)	ee (%)
1	**7**	**1a**	0.5	84	99(*S*)
2	**7**	**18**	0.5	98	98(*S*)
3	**7**	**19**	0.5	82	94(*S*)
4	**7**	**20**	0.5	50	97(*S*)
5	**7**	**21**	0.5	85	97(*S*)
6	**7**	**22**	0.5	96	80(*R*)
7	**14a**	**1a**	2	89	93(*S*)
8	**14a**	**18**	2	37	79(*S*)
9	**14a**	**19**	2	55	64(*S*)
10	**14a**	**20**	2	90	84(*S*)
11	**14a**	**21**	2	29	63(*S*)
12	**14a**	**22**	2	No reaction	



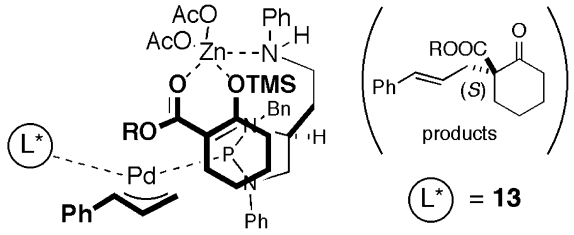
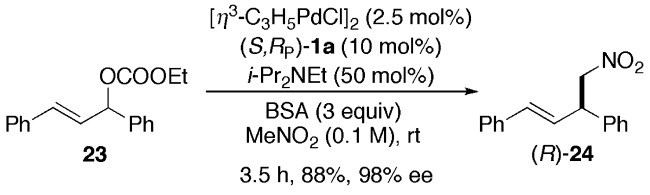


Fig. 4. Working model.

other products indicate that the C–C bond formation occurs on the *Si*-face of the enolate nucleophile. The observation that nucleophiles with a smaller methyl ester gave higher enantioselectivities suggests that the ester moiety of the nucleophiles is located inside the chiral pocket. This spatial arrangement is stabilized through the Zn-mediated secondary ligand substrate interaction. Effective fixation of the three reactants results in not only an increase in the enantiofacial discrimination of nucleophiles, but also an enhancement of the reactivity.

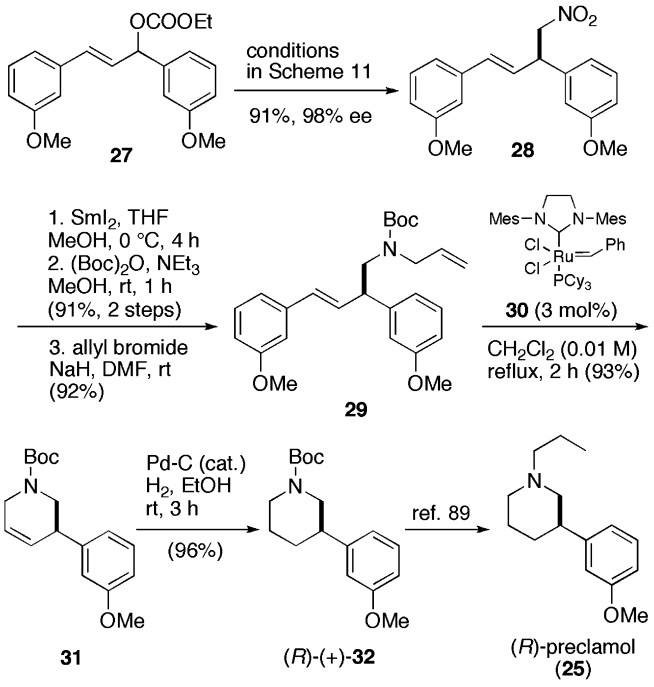
3.4. Asymmetric allylic alkylation using nitromethane as the nucleophile[83]

Various stabilized carbon nucleophiles are applicable to Pd-catalyzed asymmetric allylic alkylation. There are, however, only a few reports of Pd-catalyzed asymmetric allylic alkylation using nitronate nucleophiles, perhaps due to multiple alkylations and the formation of side products.[84–88] In our experiments, catalytic asymmetric allylic alkylation of 1,3-diphenylallyl ethyl carbonate **23** with nitromethane was performed using similar conditions to those for asymmetric allylic alkylation with dimethyl malonate (reaction conditions in Scheme 9), giving the desired product **24** in only 5% yield and 66% ee, accompanied by the formation of some other side products. Although the chemical yield was low, there was a significant improvement in the enantioselectivity when nitromethane was used as the solvent (4 h, 26% yield, 96% ee). This result encouraged us to optimize the reaction in nitromethane. Silyl nitronates are efficiently generated from nitroalkanes in the presence of BSA and amine. Therefore, the addition of amine to the reaction was examined in detail. We were pleased to find that catalytic amounts of *N*,*N*-diisopropylethylamine improved the chemical yield dramatically (88% yield) and provided a slight increase in the enantiomeric excess (98% ee) (Scheme 11).



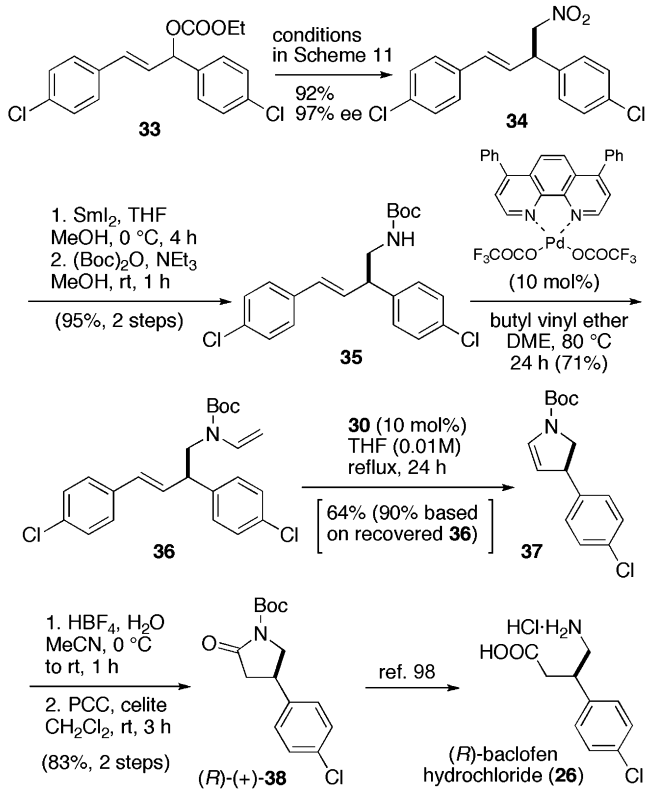
Scheme 11.

The present reaction system was successfully applied to the catalytic asymmetric synthesis of (*R*)-preclamol [(+)-3-PPP] (**25**), a selective dopamine D_2 autoreceptor agonist, and (*R*)-baclofen hydrochloride (**26**), a $GABA_B$ receptor agonist. The synthetic route for the enantioselective synthesis of (*R*)-preclamol is outlined in Scheme 12. Pd-catalyzed asymmetric allylic substitution of **27** with nitromethane proceeded under the optimized conditions to afford **28** in 91% yield with 98% ee. Reduction of the nitro group with SmI_2, followed by protection of the resulting amine with a Boc group and allylation, gave **29**. Subsequently, **29** was treated with 3 mol % of the Grubbs catalyst (**30**) to afford the corresponding cyclic product **31**, which was successfully transformed into a chiral piperidine intermediate (*R*)-(+)-**32**. The known intermediate **32** can be converted into (*R*)-preclamol (**25**) using the reported procedure.[89,90]



Scheme 12.

The synthetic route for the enantioselective synthesis of (*R*)-baclofen hydrochloride (**26**) is outlined in Scheme 13.[91–96] Pd-catalyzed asymmetric allylic substitution of **33** with nitromethane proceeded under the optimized conditions to afford compound **34** in 92% yield with 97% ee. Compound **34** was transformed into **35** using the same method as that for **28**. After formation of the enamide **36** using a Pd-catalyzed vinyl transfer reaction,[97] a ring-closing metathesis was performed in the presence of **30**, affording the cyclic compound **37**. Introduction of a hydroxyl group followed by oxidation of the resulting crude lactamol with PCC gave the known lactam (*R*)-(+)-**38**. The obtained lactam could be transformed into (*R*)-baclofen hydrochloride (**26**) using the reported procedure.[98]



Scheme 13.

3.5. Asymmetric allylic alkylation of 2-phenyl cycloalkenyl carbonates[99]

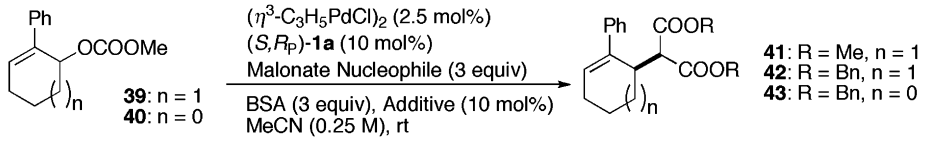
There are many reports of asymmetric allylic substitution using simple cycloalkenyl alcohol derivatives as substrates. Only limited success of asymmetric allylic substitution of 2-substituted cycloalkenyl alcohol derivatives, however, has been reported so far.[100–108] The success of the asymmetric allylic alkylation of 1,3-diphenylallyl acetate led us to examine the asymmetric allylic alkylation of 2-substituted cycloalkenyl alcohol derivatives using the Pd-DIAPHOX catalyst system. We first optimized the reaction conditions using asymmetric allylic alkylation of 2-phenylcyclohexenyl carbonate **39** with malonate nucleophiles (Table 4). Using 2.5 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$ and 10 mol % of (*S*,*R*$_P$)-**1a** in MeCN, the reaction proceeded slowly at room temperature to afford the product **41** in 43% yield and 68% ee. To improve the reactivity and enantioselectivity, we investigated the effect of the additive in detail. Both the reactivity and the enantioselectivity were remarkably affected by the addition of acetate salts, and LiOAc was the best additive for both reactivity and enantioselectivity (entry 2). Further optimization of the ester substituents of a malonate nucleophile indicated that dibenzyl malonate resulted in the best enantioselectivity (entry 7). When a lithium enolate prepared from dibenzyl malonate and LiH was used as the nucleophile, **42** was obtained in 99% yield with 86% ee. This result indicates that LiOAc is likely to be related to the generation of lithium enolate in situ, resulting in increased enantioselectivity. 2-Phenyl-substituted cyclopentenyl carbonate **40** was also applicable to this reaction, and the corresponding product **43** was obtained in 92% yield with 89% ee (entry 8).

3.6. Pd-catalyzed enantioselective synthesis of quaternary α-amino acid derivatives using chiral diaminophosphine oxides[109]

Pd-catalyzed asymmetric allylic substitution using β-keto esters with a nitrogen functional group at the α-carbon as the prochiral nucleophiles is one of the most straightforward approaches for synthesizing chiral quaternary α-amino acid derivatives.[110–113] Although several types of Pd-catalyzed asymmetric allylic substitutions using prochiral nucleophiles have been investigated since the 1980s, there are only a few reports of asymmetric synthesis of such tetrasubstituted carbons using this strategy.[114–118]

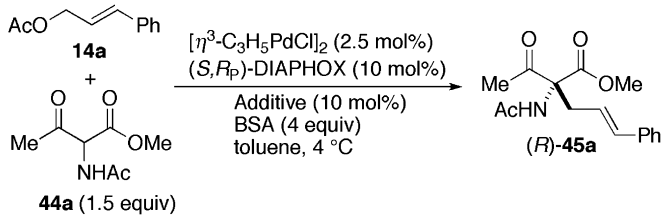
We first examined asymmetric allylic substitution of **14a** with α-acetoamido β-keto ester **44a** based on the reaction conditions using cyclic β-keto ester nucleophiles (Table 5). There was a slight decrease in the enantioselectivity, however, when 10 mol % of Zn $(OAc)_2$ was used as the additive (entry 1 vs entry 2). We then investigated the effect of the structure of DIAPHOX under additive-free conditions. When the reaction was performed using (*S*)-aspartic acid-derived DIAPHOXs, there was no remarkable increase in the enantioselectivity (entries 2–8). Further studies revealed that the enantioselectivity was improved when the reaction was performed using DIAPHOXs **20**, **46**, and **47** prepared from other amino acids. Finally, (*S*,*R*$_P$)-**47**, prepared from (*S*)-phenylalanine, was best for asymmetric induction, affording (*R*)-**45a** in 98% yield with 92% ee (entry 11). Further optimization of the reaction conditions revealed that 10 mol % of KOAc dramatically increased the reactivity (entry 12).

Table 4
Pd-catalyzed asymmetric allylic alkylation of 2-phenyl cycloalkenyl carbonates

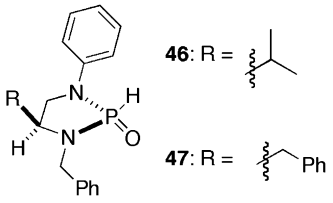


Entry	Substrate	Nucleophile	Additive	Product	Time (h)	Yield (%)	ee (%)
1	**39**	$CH_2(COOMe)_2$	—	**41**	48	43	68
2	**39**	$CH_2(COOMe)_2$	LiOAc	**41**	4	94	80
3	**39**	$CH_2(COOMe)_2$	NaOAc	**41**	4	95	67
4	**39**	$CH_2(COOMe)_2$	KOAc	**41**	4	93	66
5	**39**	$CH_2(COOMe)_2$	$Mg(OAc)_2$	**41**	96	55	80
6	**39**	$CH_2(COOMe)_2$	$Zn(OAc)_2$	**41**	96	40	81
7	**39**	$CH_2(COOBn)_2$	LiOAc	**42**	4	94	86(*R*)
8	**40**	$CH_2(COOBn)_2$	LiOAc	**43**	4	92	89(*R*)

Table 5
Optimization of reaction conditions



Entry	DIAPHOX	Additive	Time (h)	Yield (%)	ee (%)
1	**1a**	$Zn(OAc)_2$	48	96	74
2	**1a**	—	48	90	78
3	**1b**	—	60	23	51
4	**1c**	—	48	94	78
5	**1g**	—	48	90	79
6	**1h**	—	48	36	79
7	**1i**	—	20	99	69
8	**1j**	—	48	49	77
9	**20**	—	48	95	88
10	**46**	—	60	60	78
11	**47**	—	24	98	92
12	**47**	KOAc	12	99	90



The scope and limitations of different substrates were further examined under optimized conditions (Table 6). Asymmetric allylic substitutions using *N*-acyl-protected alkyl ketone-type substrates **44a**–**f** proceeded smoothly in the presence of KOAc, affording the corresponding quaternary α-amino acid derivatives **45a**–**f** in excellent yield with high enantioselectivity (86–92% ee) (entries 1–6). The reaction adducts were highly crystalline compounds and the optical purity was efficiently enriched by a single recrystallization (entry 1). The present reaction conditions were also effective in asymmetric allylic substitution using carbamate-type substrates **44g** and **44h**. The corresponding products **45g** and **45h** were obtained in excellent yield with high enantioselectivity (entries 7 and 8). In contrast, however, no reaction occurred under the same reaction conditions when a phenyl ketone-type substrate **44i** was used as the prochiral nucleophile. This problem could be overcome by the addition of KOAc (10 mol %) and KCl (10 mol %), and the corresponding product **45i** was obtained in 99% yield with 80% ee (entry 9).

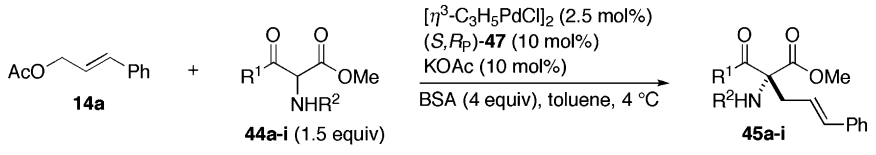
3.7. Enantioselective synthesis of axially chiral allenes[119]

Enantioselective synthesis of axially chiral allenes has gained much attention due to their synthetic utility as chiral synthons,[120] as well as their distribution in various biologically active natural products.[121] In 2000, Hayashi and Ogasawara et al. reported a novel method for synthesizing functionalized allenes based on a formal S_N2' substitution of 2-bromo-1,3-butadienes catalyzed by a palladium complex.[122–124] This method was successfully extended to the asymmetric synthesis of axially chiral allenes using a chiral palladium complex, which was applied to a total synthesis of a natural product, as well as a unique transformation with transfer of axial chirality.[125–129] Murahashi, Imada, and Naota et al.[130–132] and Trost et al.[133] also reported the enantioselective synthesis of allenes through Pd-catalyzed asymmetric allylic substitution using 2,3-allenyl alcohol derivatives as substrates. Although different electrophiles are utilized in each reaction, both reactions proceed via the same α-methylidene π-allylpalladium intermediates, and the enantioselectivity of this type of asymmetric allylic substitution is controlled by a dynamic kinetic asymmetric transformation (DYKAT).[134] These preceding examples led us to extend the Pd-DIAPHOX catalyst system to the asymmetric synthesis of allenes.

We first selected the asymmetric allylic alkylation of allenyl acetate **48a** with dimethyl malonate **49a** as the model reaction. When 5 mol % of $Pd(OAc)_2$ and 10 mol % of (S,R_P)-**1a** were used as the catalyst, the reaction proceeded in MeCN at 4 °C to provide the corresponding mono-alkylated product (−)-**50aa** in 98% yield with 69% ee (Table 7, entry 1). The absolute configuration of the major enantiomer was deduced to be (*R*) by the Lowe–Brewster rule.[135,136] To improve the enantioselectivity, we investigated the effect of adding acetate salts to the reaction. Enantioselectivity was significantly affected by the counter cations of acetate salts, and LiOAc was found to be the best additive for asymmetric induction (83% ee) (entry 2).

We next examined the scope and limitations of different substrates under the optimized conditions (Table 7). When 5 mol % of $Pd(OAc)_2$ and 10 mol % of (S,R_P)-**1a** were used, asymmetric allylic alkylation of **48a** with dimethyl methylmalonate **49b** proceeded smoothly in the presence of LiOAc, affording the chiral allene (−)-**50ab** in 99% yield with much higher enantioselectivity (98% ee) than that obtained using dimethyl malonate (entry 3). Moreover, the enantioselectivity was increased when the reaction was performed at a lower temperature (99% ee) (entry 4). Other α-monosubstituted-dimethyl malonates **49c**–**g** were also applicable to the

Table 6
Scope and limitations

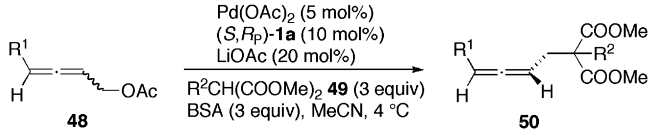


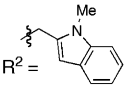
44a, 45a: R^1 = Me, R^2 = Ac
44b, 45b: R^1 = Et, R^2 = Ac
44c, 45c: R^1 = CH_2CH_2Ph, R^2 = Ac
44d, 45d: R^1 = *i*-Pr, R^2 = Ac
44e, 45e: R^1 = cHex, R^2 = Ac
44f, 45f: R^1 = Me, R^2 = Bz
44g, 45g: R^1 = Me, R^2 = methoxycarbonyl
44h, 45h: R^1 = Me, R^2 = benzyloxycarbonyl
44i, 45i: R^1 = Ph, R^2 = Ac

Entry	Nucleophile	Time (h)	Yield (%)	ee (%)
1	**44a**	12	99 (70)[a]	90 (99)[b] (*R*)
2	**44b**	24	98	87
3	**44c**	24	99	89
4	**44d**	48	99	90
5	**44e**	48	99	86
6	**44f**	20	99	92
7	**44g**	60 (24)[c]	73 (99)[c]	89 (90)[c]
8	**44h**	60	99	89
9	**44i**	72 (46)[c]	No reaction (99)[c]	–(80)[c]

[a] Yield of recrystallization from EtOH.
[b] Enantiomeric excess after single recrystallization from EtOH.
[c] KOAc (10 mol %) and 10 mol % of KCl were used as the additive.

Table 7
Enantioselective synthesis of axially chiral allenes



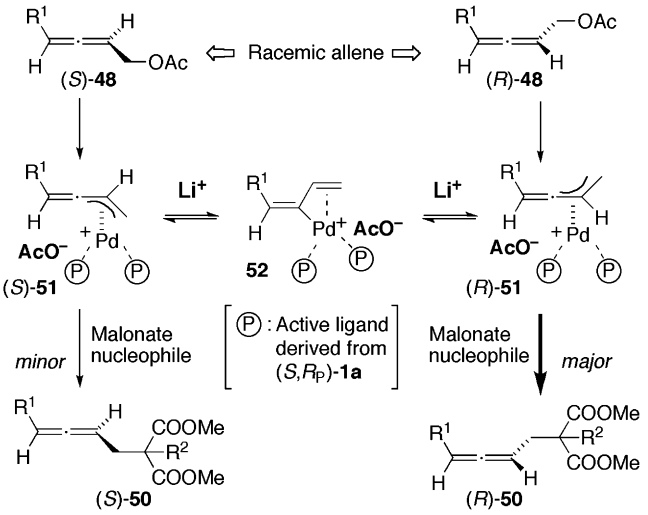
48a: R^1 = *t*-Bu
48b: R^1 = 
48c: R^1 = 
48d: R^1 = cHex
48e: R^1 = CH_2CH_2Ph
49a: R^2 = H **49b**: R^2 = Me **49c**: R^2 = allyl
49d: R^2 = Bn **49e**: R^2 = Ph
49f: R^2 = CH_2CH_2OTBS
49g: R^2 = 

Entry	Allene	Malonate	Product	Time (h)	Yield (%)	ee (%)
1[a]	**48a**	**49a**	**50aa**	24	98	69 (–)-(*R*)
2	**48a**	**49a**	**50aa**	24	93	83 (–)-(*R*)
3[b]	**48a**	**49b**	**50ab**	24	99	98 (–)-(*R*)
4[b,c]	**48a**	**49b**	**50ab**	48	98	99 (–)-(*R*)
5[b,d]	**48a**	**49b**	**50ab**	96	99	97 (–)-(*R*)
6	**48a**	**49c**	**50ac**	24	98	96 (–)-(*R*)
7[d]	**48a**	**49c**	**50ac**	96	88	95 (–)-(*R*)
8	**48a**	**49d**	**50ad**	96	99	97 (–)-(*R*)
9[e]	**48a**	**49e**	**50ae**	16	99	91 (–)-(*R*)
10	**48a**	**49f**	**50af**	48	99	97 (–)-(*R*)
11	**48a**	**49g**	**50ag**	48	99	95 (–)-(*R*)
12	**48b**	**49b**	**50bb**	24	86	91 (–)-(*R*)
13	**48c**	**49b**	**50cb**	24	99	92 (–)-(*R*)
14[d]	**48c**	**49c**	**50cc**	24	96	90 (–)-(*R*)
15	**48d**	**49b**	**50db**	48	99	72 (–)-(*R*)
16	**48e**	**49b**	**50eb**	24	99	66 (–)-(*R*)

[a] In the absence of LiOAc.
[b] LiOAc (30 mol %) was used.
[c] Reaction was performed at –4 °C.
[d] $Pd(OAc)_2$ (1 mol %) and 2 mol % of (*S*,R_P)-**1a** were used. The reaction was performed in a 0.4 M solution.
[e] LiF (30 mol %) was used as the additive. (LiOAc as the additive: 72 h, 18% yield, 77% ee).

present catalysis, providing the corresponding chiral allenes (–)-**50ac**–**ag** in excellent yield and enantiomeric excess (91–97% ee) (entries 6–11). These reactions could be performed using 1 mol % of $Pd(OAc)_2$ and 2 mol % of (*S*,R_P)-**1a**, and the corresponding products were obtained in good yield without a significant decrease in the enantiomeric excess, compared with that obtained using 5 mol % of the catalyst (entries 5 and 7). Racemic allenyl acetates **48b** and **48c**, bearing a *tert*-alkyl substituent on the terminal allenyl carbon, were also effective substrates for this asymmetric catalysis and gave the corresponding products **50bb**, **50cb**, and **50cc** with high enantiomeric excess (90–92% ee) (entries 12–14). Decreasing the size of the allene substituent affected the enantioselectivity (entries 15 and 16). Asymmetric allylic alkylation of secondary- and primary-alkyl substituted-substrates **48d** and **48e** using **49b** gave the corresponding products **50db** and **50eb** with 72% ee and 66% ee, respectively.

Mechanistic studies including (1) effect of the amount of LiOAc (2) effect of the counter anions of the Li salt (3) effect of the Pd



Scheme 14.

source (4) nonlinear effect and (5) kinetic experiments led us to propose a plausible mechanism for this asymmetric catalysis (Scheme 14) (for more detailed discussions, see Ref. 118). First, oxidative addition of racemic allene **48** forms two diastereomeric π-allylpalladium complexes (*S*)-**51** and (*R*)-**51** in an almost 1:1 ratio. The complexes (*S*)-**51** and (*R*)-**51** are in rapid equilibrium via σ-allylpalladium complex **52**. The absolute configuration of the products suggests that nucleophilic addition of a malonate nucleophile to (*R*)-**51** proceeds preferentially to afford (*R*)-**50** with high enantiomeric excess. Kinetic experiments revealed that the reaction rate of asymmetric allylic alkylation of **48a** with **49b** was not affected by the concentration of LiOAc, suggesting that the lithium cations are not related to the rate-determining nucleophilic addition. Based on this information, we speculate that lithium cations would facilitate the dynamic kinetic resolution process by accelerating the equilibrium between (*S*)-**51** and (*R*)-**51**, resulting in increased enantioselectivity.

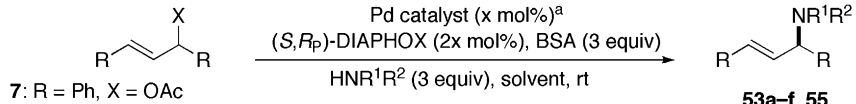
4. Pd-catalyzed asymmetric allylic substitution reactions using nitrogen nucleophiles

Considerable effort has been directed toward the catalytic asymmetric synthesis of α-chiral amines because chiral amine units are ubiquitous in biologically active compounds. A transition metal-catalyzed asymmetric allylic amination is one of the most useful methods for synthesizing chiral allylic amines.[137] The success of the asymmetric allylic substitution reactions with carbon nucleophiles led us to examine asymmetric allylic amination using the Pd-DIAPHOX catalyst system.

4.1. Pd-catalyzed asymmetric allylic amination of linear substrates[138]

We first examined the asymmetric allylic amination of 1,3-diphenylallyl acetate **7** with benzylamine using (*S*,R_P)-**1a**. The reaction was performed under conditions similar to those used for the asymmetric allylic alkylation of **7** with dimethyl malonate, and the corresponding product (*R*)-**53a** was obtained in 91% yield with 98% ee (Table 8, entry 1). Various amine nucleophiles were applied to this type of asymmetric allylic amination. Using 1–2 mol % of Pd catalyst and 2–4 mol % of (*S*,R_P)-**1a**, asymmetric allylic amination of **7** with both primary and secondary amines proceeded at room temperature to give the corresponding products **53b**–**e** in good yield with high stereoselectivity. No reaction, however, occurred to form **53f** when *p*-anisidine was utilized as the nucleophile (entries 6 and 7). This catalyst system was also applied to asymmetric allylic amination of 1,3-dialkyl-substituted allyl carbonate **54**. The reaction was performed using (*S*,R_P)-**1a** in MeCN, affording the corresponding product **55** in moderate yield with low enantiomeric excess. There was a slight improvement in the enantioselectivity when (*S*,R_P)-**1b** was used (entries 8 and 9).

Table 8
Pd-catalyzed asymmetric allylic amination of 1,3-disubstituted allyl alcohol derivatives



7: R = Ph, X = OAc
23: R = Ph, X = OCOOEt
54: R = CH_2CH_2Ph, X = OCOOMe

53a–f, **55**

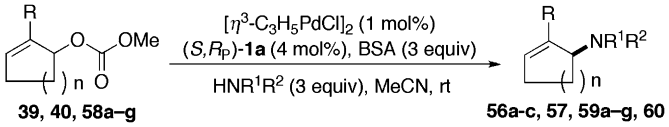
Entry	Substrate	Amine	*x*	Solvent	DIAPHOX	Product	Time (h)	Yield (%)	ee (%)
1	**7**	Benzylamine	2	CH_2Cl_2	**1a**	**53a**	24	91	98 (*R*)
2	**7**	Furfurylamine	2	CH_2Cl_2	**1a**	**53b**	24	92	96
3	**7**	*n*-Butylamine	2	CH_2Cl_2	**1a**	**53c**	60	79	99
4	**7**	Cyclohexylamine	2	CH_2Cl_2	**1a**	**53d**	24	87	98
5	**7**	Morpholine	1	CH_2Cl_2	**1a**	**53e**	12	90	97
6	**7**	*p*-Anisidine	2	CH_2Cl_2	**1a**	**53f**	24	No reaction	
7	**23**	*p*-Anisidine	2	CH_2Cl_2	**1a**	**53f**	24	No reaction	
8	**54**	Benzylamine	5	MeCN	**1a**	**55**	23	63	35
9	**54**	Benzylamine	5	MeCN	**1b**	**55**	23	72	52

[a] $[\eta^3\text{-}C_3H_5PdCl]_2$ was used as the source of Pd catalyst.

4.2. Pd-catalyzed asymmetric allylic amination of cyclic substrates[138]

The satisfactory results in the reaction system using a conventional substrate led us to examine asymmetric allylic amination of cyclic substrates. Asymmetric allylic amination of 2-substituted cycloalkenyl alcohol derivatives affords versatile adducts for the synthesis of nitrogen-containing natural products. Despite its usefulness, the success of this type of reaction is limited.[102–106] Although no reaction occurred when 2-phenylcyclohexenyl acetate was used as the substrate, allylic amination of 2-phenylcyclohexenyl carbonate **39** with benzylamine proceeded in CH_2Cl_2 using 2 mol % of the catalyst, affording the corresponding product **56a** in 75% yield and 93% ee. Examination of the solvent effect revealed that the reaction medium dramatically affected the reactivity rather than the enantioselectivity, and the best results were obtained when MeCN was used as the solvent (Table 9, entry 1). We

Table 9
Pd-catalyzed asymmetric allylic amination of 2-substituted cycloalkenyl carbonates



39, 40, 58a–g **56a-c, 57, 59a–g, 60**

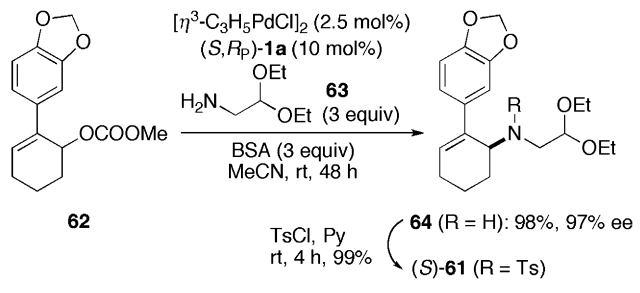
Entry	R	*n*	Substrate	Amine	Product	Time (h)	Yield (%)	ee (%)
1	Ph	2	**39**	Benzylamine	**56a**	17	93	96
2	Ph	2	**39**	$EtOOCCH_2NH_2$	**56b**	48	88	96 (*S*)
3	Ph	2	**39**	Morpholine	**56c**	7	90	97
4	Ph	1	**40**	Benzylamine	**57**	8	99	93
5[a]	Ph	3	**58a**	Benzylamine	**59a**	3	84	83
6	4-F–C_6H_4	2	**58b**	Benzylamine	**59b**	5	95	93
7[a]	3-MeO–C_6H_4	2	**58c**	Benzylamine	**59c**	4	93	93
8	2-F–C_6H_4	2	**58d**	Benzylamine	**59d**	7	83	98
9a	TBSO	2	**58e**	Benzylamine	**59e**	4	95	72
10	Ph	2	**58f**	Benzylamine	**59f**	24	55	94
11	Ph	2	**58g**	Benzylamine	**59g**	24	75	80
12	Ph	2	**39**	*p*-Anisidine	**60**	24	Trace	—

[a] Pd (5 mol %) catalyst and 10 mol % of (*S*,R_P)-**1a** were used.

speculate that coordination of MeCN to palladium metal might prevent catalyst deactivation by competitive coordination of the product, resulting in the higher reactivity compared to the other solvents.

The scope and limitations of different substrates were further examined under optimized conditions (Table 9). As shown in entries 1–3, asymmetric allylic amination of 2-phenylcyclohexenyl carbonate **39** using primary and secondary amines proceeded at room temperature to provide the corresponding products **56a**–**c** in good yield with high enantioselectivity. Other cyclic substrates with a five- or seven-membered ring **40** and **58a** were also applicable to this reaction, affording chiral allylic amines **57** and **59a** with 93% or 83% ee, respectively (entries 4 and 5). Asymmetric allylic amination of cyclohexenyl carbonates with various substituents at the 2-position was also examined using benzylamine as the nucleophile (entries 6–11). Aryl groups with an electron-withdrawing functional group, as well as an electron-donating functional group, were tolerant to this reaction, giving products **59b**–**d** with high enantioselectivity. Furthermore, substrates with alkyl (**58e**), alkenyl (**58f**), or alkynyl (**58g**) substituents were also applicable to this reaction, and the corresponding products **59e**–**g** were obtained in moderate to good enantiomeric excess. Asymmetric allylic amination of **39** with *p*-anisidine as the nucleophile, however, gave unsatisfactory results (entry 12).

We applied this catalyst system to the catalytic asymmetric synthesis of (*S*)-**61**, which is the key intermediate for Mori's total synthesis of crinine-type alkaloids (Scheme 15).[139] Using 5 mol % of Pd catalyst and 10 mol % of (*S*,R_P)-**1a**, asymmetric allylic amination of **62** with amine **63** proceeded at room temperature, affording the chiral allylic amine **64** in 98% yield and 97% ee, which could be converted into the key intermediate (*S*)-**61**.



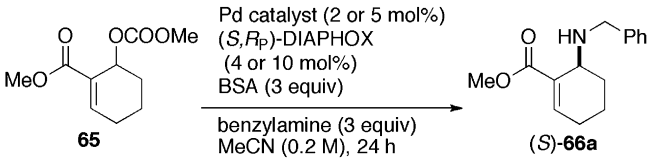
62

Scheme 15.

4.3. Enantioselective synthesis of aza-Morita–Baylis–Hillman reaction products using asymmetric allylic amination[140]

The catalytic enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction provides functionalized chiral allylic amines.[141] To date, several asymmetric catalysts for this reaction have been developed. The scope of these asymmetric catalysts, however, is limited in intermolecular aza-MBH reactions.[142–153] There are no reports of a catalytic asymmetric intramolecular aza-MBH reaction. Pd-catalyzed asymmetric allylic amination of cycloalkenyl carbonates with an electron-withdrawing group at the 2-position is an alternative to the intramolecular aza-MBH reaction via nucleophilic catalysis. Although this type of transformation using oxygen nucleophiles has been investigated in detail by Trost et al.[154–156] there are limited applications of nitrogen nucleophiles.[103,106] This background led us to examine asymmetric allylic amination of a 2-methoxycarbonyl 2-cyclohexenyl alcohol derivative **65** with benzylamine using our catalyst system (Table 10). The effect of the ligand structure revealed that the introduction of electron-

Table 10
Optimization of reaction conditions



65 (*S*)-**66a**

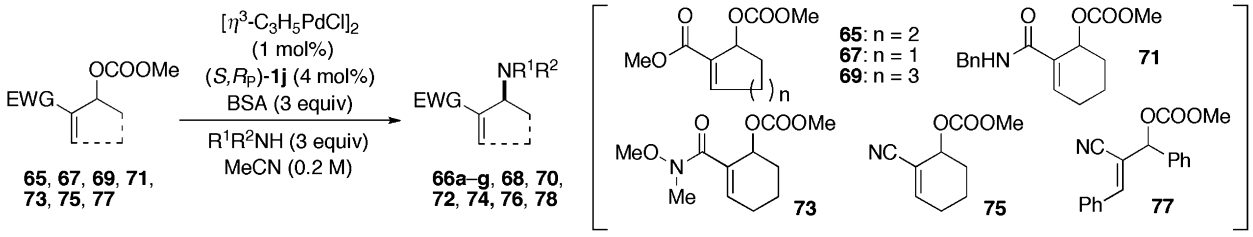
Entry	DIAPHOX	Pd cat. (mol %)	Temp (°C)	Yield (%)	ee (%)
1	**1a**	5	4	91	87
2	**1b**	5	4	92	89
3	**1c**	5	4	97	83
4	**1g**	5	4	96	90
5	**1h**	5	4	99	71
6	**1i**	5	4	99	89
7	**1j**	5	4	99	94
8	**1j**	2	4	99	94
9	**1j**	2	−30	99	99

donating groups onto the aromatic rings attached to the nitrogen atoms increases the enantioselectivity, and the 3,4-dimethoxy-type ligand (*S*,R_P)-**1j** was best for asymmetric induction. Moreover, the enantioselectivity was increased when the reaction was performed at a lower temperature. Using 2 mol % of Pd catalyst and 4 mol % of (*S*,R_P)-**1j**, the cyclic product (*S*)-**66a** was obtained in 99% yield with 99% ee (entry 9).

The scope and limitations of different substrates were examined using the optimized reaction conditions (Table 11). When 2 mol % of Pd catalyst and 4 mol % of (*S*,R_P)-**1j** were used, asymmetric allylic amination of **65** using primary amines (entries 1–5), a secondary amine (entry 6), and an aromatic amine (entry 7) proceeded efficiently to provide the corresponding products **66a**–**g** in excellent yield and enantiomeric excess. Other cyclic substrates with a five- and a seven-membered ring **67** and **69** were also applicable to this reaction, affording the corresponding chiral allylic amines **68** and **70** in 91% ee and 84% ee, respectively (entries 8 and 9). Furthermore, a substrate with a simple secondary amide **71**, as well as the Weinreb amide-type substrate **73**, could be utilized for this reaction system, giving the corresponding products **72** and **74** in excellent yield and enantiomeric excess (entries 10 and 11). Similarly, a reaction using a cyclic substrate with a nitrile group **75** proceeded at −40 °C to provide the corresponding product **76** in high enantiomeric excess (entry 12). In addition, asymmetric allylic amination of 1,3-diphenylallyl carbonate derivative **77** proceeded at 4 °C to provide the corresponding product **78** in 89% ee (entry 13).

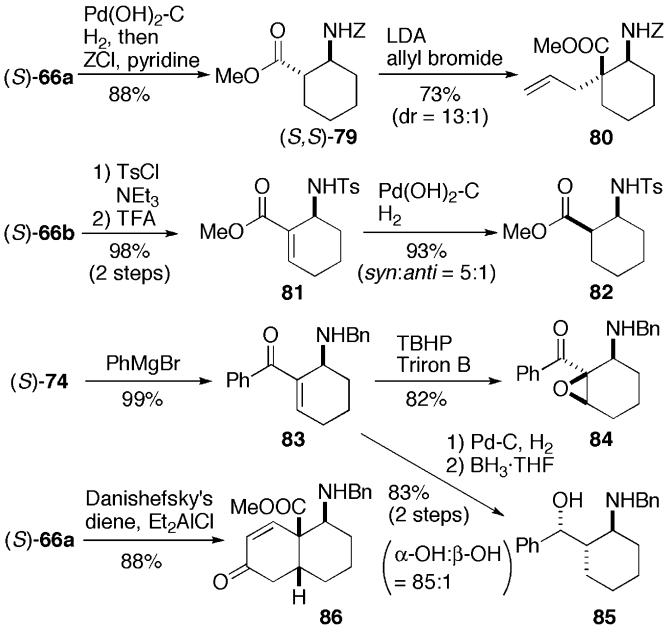
To demonstrate the usefulness of these chiral allylic amines, several diastereoselective modifications were performed (Scheme 16). Chiral cyclic β-amino acids have gained much attention, due to their increasing importance for the synthesis of β-peptides.[157] There are, however, relatively few catalytic asymmetric synthetic methods.[158,159] Our synthesis started with (*S*)-**66a** and (*S*)-**66b**. Both olefin hydrogenation and debenzylation of (*S*)-**66a** using Pd(OH)$_2$–C, followed by protection of the resulting free amine with a carbobenzyloxy (Z) group, afforded the cyclic *anti*-β-amino acid derivative (*S*,*S*)-**79** in 88% yield as a nearly optically pure compound (99% ee). In this hydrogenation, the reaction proceeded with complete diastereoselection, giving the *anti*-product exclusively. On the other hand, protection of (*S*)-**66b** with a tosyl group, followed by treatment with trifluoroacetic acid, gave the α,β-unsaturated ester **81** in 98% yield without any noticeable loss of optical purity (97% ee). This product could be transformed into the cyclic *syn*-β-amino acid derivative **82** with good diastereoselectivity (*syn*/*anti*=5:1). The usefulness of these compounds was further demonstrated. After the formation of the lithium enolate of **79**, diastereoselective alkylation

Table 11
Scope and limitations



Entry	Substrate	R^1R^2NH	Product	Temp (°C)	Time (h)	Yield (%)	Ee (%)
1	**65**	Benzylamine	**66a**	−30	24	99	99 (*S*)
2	**65**	4-Methoxybenzylamine	**66b**	−30	24	99	97 (*S*)
3	**65**	Furfurylamine	**66c**	−30	24	99	98
4	**65**	Allylamine	**66d**	−40	24	99	98
5	**65**	Isopropylamine	**66e**	−30	24	92	99
6	**65**	Morpholine	**66f**	−10	15	98	99
7[a]	**65**	*p*-Anisidine	**66g**	−30	47	99	94 (*S*)
8[a,b]	**67**	Benzylamine	**68**	−40	18	81	91 (*S*)
9[a]	**69**	Benzylamine	**70**	−40	18	99	84
10	**71**	Benzylamine	**72**	−30	48	94	98
11[a]	**73**	Benzylamine	**74**	−30	32	98	99 (*S*)
12[c]	**75**	Benzylamine	**76**	−40	18	99	95
13	**77**	Benzylamine	**78**	4	24	96	89

[a] (*S*,R_P)-**1a** was used.
[b] Dichloroethane was used as the solvent.
[c] (*S*,R_P)-**1g** was used.



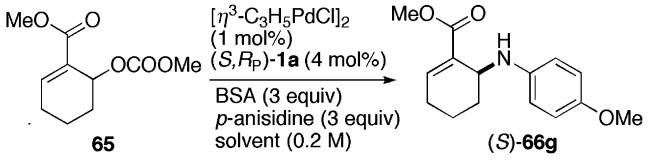
Scheme 16.

was performed using allyl bromide as an electrophile,[160] affording **80** with an all-carbon quaternary stereocenter in 73% yield with high diastereoselectivity (dr=13:1). Weinreb amide-type adduct (*S*)-**74** (99% ee) reacted with a Grignard reagent at −40 °C to provide the corresponding enone **83** in 99% yield (99% ee). This enone could be converted into the α,β-epoxy ketone **84** (82% yield) and 1,3-amino-alcohol **85** (83% yield) in a highly diastereoselective manner. Moreover, Diels–Alder reaction of (*S*)-**66a** with Danishefsky's diene proceeded in the presence of Et_2AlCl, giving the bicyclic product **86** in 88% yield as a single diastereomer.

4.4. Pd-catalyzed asymmetric allylic amination using aromatic amine nucleophiles[161]

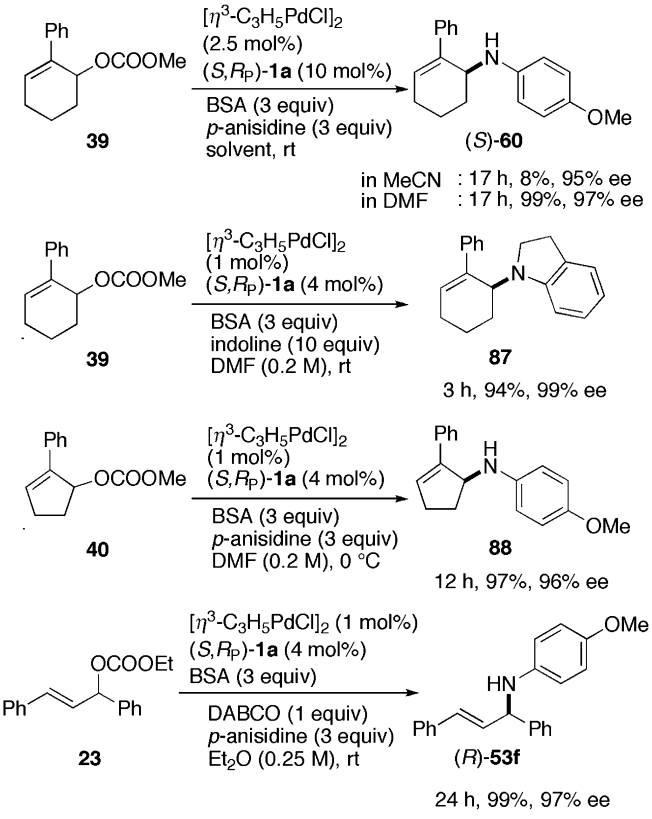
Although various nitrogen nucleophiles are available for Pd-catalyzed asymmetric allylic aminations, aromatic amines are not commonly used in these reactions,[162] probably due to the lower nucleophilicity of aromatic amines, compared with that of aliphatic amines or stabilized anionic nitrogen nucleophiles derived from aromatic amines. Actually, asymmetric allylic amination of **7**, **23**, and **39** using *p*-anisidine did not proceed under the optimized conditions for asymmetric allylic amination with aliphatic amines (Table 8, entries 6 and 7, and Table 9, entry 12). As shown in Table 10, the cyclic substrate **65** exhibited a much higher reactivity toward *p*-anisidine, providing the corresponding product (*S*)-**66g** in 99% yield with 94% ee. Therefore, asymmetric allylic amination of **65** using *p*-anisidine was selected for initial optimization of the reaction conditions (Table 12). Examination of the solvent effect revealed that the reaction medium dramatically affected reactivity, as well as enantioselectivity, and the best reactivity was obtained when DMF was used as the solvent (entry 4). Although the enhanced reactivity in DMF was not observed at a lower temperature, the reaction proceeded in 48 h to afford (*S*)-**66g** in 99% yield with 95% ee (entry 6).

Table 12
Optimization of the reaction conditions



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	MeCN	4	7	99	90
2	EtCN	4	16	99	73
3	CH_2Cl_2	4	24	98	78
4	DMF	4	4	99	90
5	MeCN	−30	47	99	94
6	DMF	−30	48	99	95

Based on these results, we examined asymmetric allylic amination of 2-phenylcyclohexenyl alcohol derivative **39** with *p*-anisidine using DMF as the solvent (Scheme 17). The reaction rate was remarkably enhanced when the reaction was performed in DMF using 5 mol % of Pd catalyst and 10 mol % of (S,R_P)-**1a**, and the corresponding product (*S*)-**60** was obtained in 99% yield with 97% ee. Indoline, a secondary aromatic amine, was also applicable to this reaction, affording the corresponding product **87** with excellent enantioselectivity. In addition, asymmetric allylic amination of 2-phenyl-substituted cyclopentenol-type substrate **40** was examined using DMF as the solvent, providing the corresponding product **88** in 97% yield with 96% ee. On the other hand, asymmetric allylic amination of **23** with *p*-anisidine was sluggish, even with use of DMF as the solvent (5 mol % catalyst, 24 h, 30% yield, 74% ee).



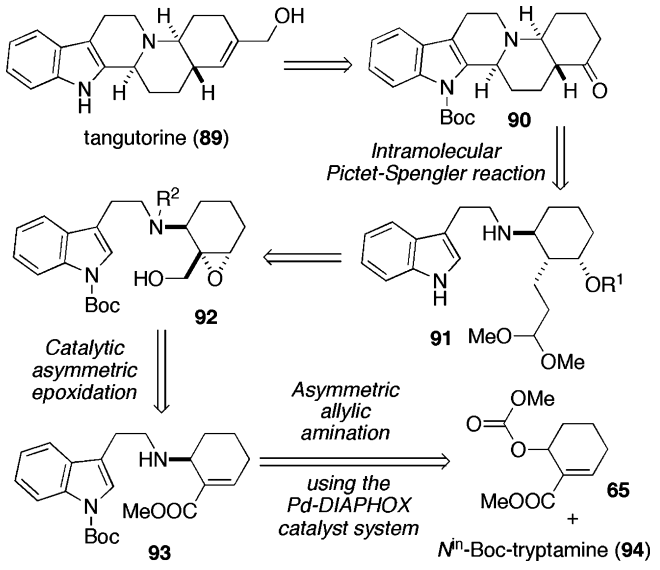
Scheme 17.

Further optimizations of the reaction conditions revealed that there was a remarkable increase in the reactivity by the addition of base, such as DABCO or *N*,*N*-dimethylpiperazine. Finally, the best result was obtained when the reaction was performed in Et_2O using 1 equiv of DABCO as the additive (99% yield, 97% ee).

4.5. Application to catalytic asymmetric total synthesis of tangutorine[163]

Asymmetric allylic amination can be a useful tool in enantioselective total synthesis of nitrogen-containing natural products. Our catalytic asymmetric reaction was successfully applied to the first enantioselective total synthesis of tangutorine (**89**), which exhibits cytotoxic activity against human colon cancer HT-29 cells.[164,165] The plan for the enantioselective synthesis of tangutorine is shown in Scheme 18. Our retrosynthetic disconnection began with compound **90**, which was utilized as the key intermediate in previous racemic syntheses.[166–169] Control of the stereochemical arrangement on the piperidine ring is a challenging task in this synthesis. We envisioned that an intramolecular Pictet–Spengler reaction of amino acetal **91** would be applicable to construct the quinolizidine moiety. Compound **91**, bearing three contiguous chiral centers on the cyclohexane ring, would be prepared from epoxy alcohol **92** using an epoxide-opening reaction with hydride nucleophile, which, in turn, would be obtained by catalytic asymmetric epoxidation. Finally, compound **93**, a reasonable precursor of the chiral epoxy alcohol, would be prepared via asymmetric allylic amination of **65** with N^{in}-Boc-tryptamine (**94**) using the Pd-DIAPHOX catalyst system.

The target asymmetric allylic amination proceeded using 2 mol % of the Pd catalyst at −30 °C, providing the corresponding chiral amine (*S*)-**93** in 99% yield with 95% ee. After converting into the allylic alcohol **95**, Sharpless asymmetric epoxidation[170,171] of enantiomerically enriched **95** (95% ee) was performed in the presence of 10 mol % of Ti(O*i*-Pr)$_4$, 10 mol % of (+)-diisopropyl



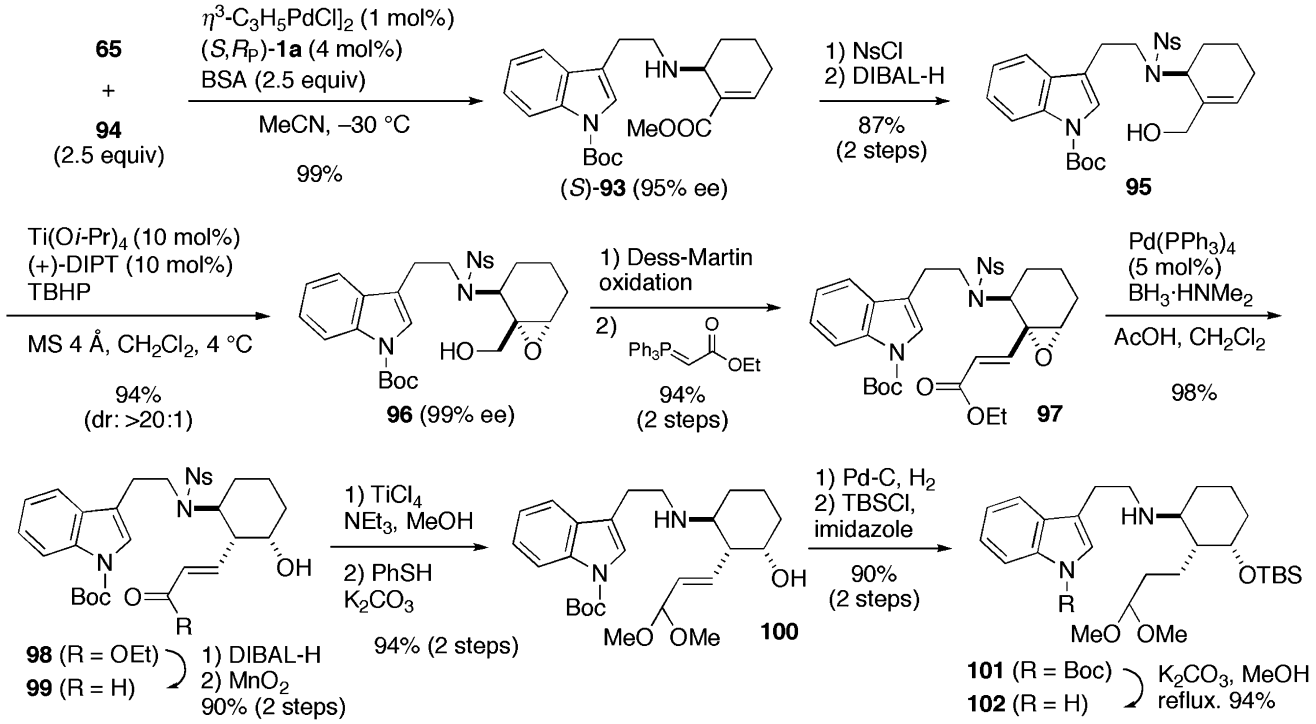
Scheme 18.

tartrate, 2 equiv of *tert*-butyl hydroperoxide, and MS 4 Å at 4 °C, giving the corresponding epoxy alcohol **96** with the α-epoxide in 94% yield with a high diastereomeric ratio. The enantiomeric excess of the major isomer was determined by chiral HPLC analysis (99% ee). Dess–Martin oxidation of **96**, followed by the treatment with a Wittig reagent, afforded α,β-unsaturated ester **97** in 94% yield over two steps. Subsequent reductive epoxide-opening reaction via a π-allylpalladium intermediate proceeded in the presence of 5 mol % of $Pd(PPh_3)_4$, providing alcohol **98** in 98% yield in a highly diastereoselective manner.[172] Conversion of α,β-unsaturated ester **98** into aldehyde **99** was achieved by a two-step process involving DIBAL-H reduction, followed by MnO_2 oxidation (90% yield, two steps). After transformation of the aldehyde moiety into the dimethyl acetal, the Ns group was deprotected with thiophenol to give compound **100** in 94% yield over two steps. The following hydrogenation of an olefin, as well as protection of the secondary alcohol with a TBS group, proceeded smoothly to provide compound **101** in 90% yield over two steps. Finally, deprotection of the Boc group was performed under basic conditions, affording amino acetal **102** in 94% yield (Scheme 19).

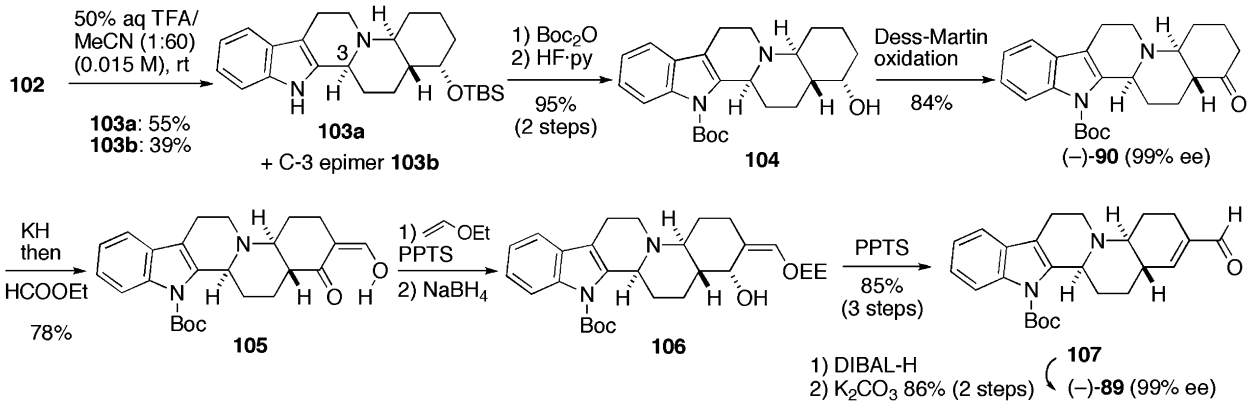
Subsequent intramolecular Pictet–Spengler reaction of **102** proceeded to completion in 48 h using trifluoroacetic acid (TFA) as a promoter in a $MeCN/H_2O$ solvent system (50% aq TFA/MeCN=1/60), affording **103a** and **103b** in 55 and 39% isolated yield, respectively. The undesired isomer **103b** could be converted into **103a** through acid-induced epimerization (for a detailed discussion, see Ref. 162). Protection of the nitrogen on the indole ring of **103a** with a Boc group, followed by deprotection of the TBS group using HF·pyridine complex, afforded compound **104** in 95% yield over two steps. Subsequent oxidation of the resulting hydroxyl group with Dess–Martin reagent gave the known synthetic intermediate (−)-**90** in 84% yield. Transformation of the intermediate (−)-**90** into tangutorine was performed using the mixed enol acetalization protocol.[173,174] Introduction of a C1 unit on the α-position to the ketone was achieved by the formation of an enolate with KH at 0 °C, followed by the addition of ethyl formate. As a result, enal **105** was obtained in 78% yield. After protection of the enal with an ethoxyethyl (EE) group (89% yield, 1:1 inseparable diastereomer mixture), the resulting product was reduced with $NaBH_4$ to give alcohol **106** in a highly stereoselective manner. The obtained crude residue was treated with PPTS without purification, affording the α,β-unsaturated aldehyde **107** in 95% yield over two steps. Finally, reduction of the α,β-unsaturated aldehyde with DIBAL-H, followed by deprotection of the Boc group on the indole, afforded (−)-tangutorine (**89**) in 86% yield over two steps ($[\alpha]_D^{21}$ −99.1 [*c* 0.23, DMF]) (15.8% overall yield in 24 steps from **65**) (Scheme 20).

5. Ir-catalyzed asymmetric allylic substitution reactions

Phosphites and phosphoroamidites are effective ligands in Ir-catalyzed allylic substitution reactions of terminal allylic electrophiles to give branched products.[175–177] As shown in Scheme 10,



Scheme 19.



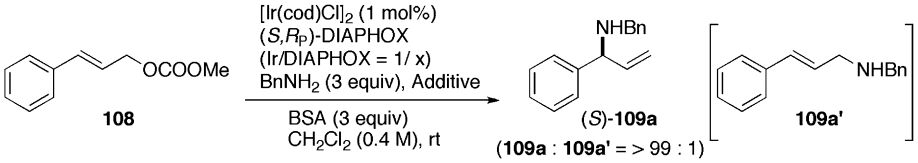
Scheme 20.

DIAPHOX **1a** is activated by *N*,*O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization to afford the trivalent phosphorus compound **13**, which functions as the actual ligand. The diamidophosphite structure of **13** led us to hypothesize that the present ligand system could be extended to Ir-catalyzed asymmetric allylic substitution reactions.[178]

5.1. Ir-catalyzed asymmetric allylic amination[179]

We first examined asymmetric allylic amination of cinnamyl carbonate **108** with benzylamine (Table 13).[180–192] No reaction occurred when 1 mol % of chloro(1,5-cyclooctadiene)iridium(I) dimer ([Ir(cod)Cl]$_2$) and 4 mol % of (S,R_P)-**1a** (Ir/**1a**=1:2) were used in CH_2Cl_2 at room temperature (entry 1). In contrast, when 1 mol % of [Ir(cod)Cl]$_2$ and 2 mol % of (S,R_P)-**1a** (Ir/**1a**=1:1) were used, the branched product **109a** was obtained in 63% ee, even though the yield was only 10% (entry 2). In this reaction, the formation of a linear product **109a′** was not observed in ^{1}H NMR analysis of the crude sample. Encouraged by this result, we investigated the effect of the addition of sodium salts. Both the reactivity and enantioselectivity were dramatically affected by the counter anion of sodium salts, and the best reactivity was obtained when the hexafluorophosphate salt was used. Although there was a slight decrease in the enantiomeric excess (59% ee), the branched product **109a** was obtained in 99% yield using 5 mol % of $NaPF_6$ (entry 6). Although the role of the hexafluorophosphate anion is unknown, we speculate that a cationic iridium complex might be formed by anion exchange between hexafluorophosphate ion and a coordinated species around the Ir metal, resulting in the increased reactivity. We next attempted to improve the enantioselectivity by tuning the structure of DIAPHOX (entries 7–12). Detailed investigations into the ligand structure indicated that the introduction of substituents onto the aromatic rings attached to the nitrogen atoms tended to improve the enantioselectivity. The best result was obtained using the chiral diaminophosphine oxide (S,R_P)-**1i**, which possessed a *t*-Bu substituent on the *para*-position of the aromatic rings, and the enantiomeric excess of **109a** increased to 92% ee when the reaction was performed at −20 °C (entry 12). On the other hand, when the reaction was performed using (S,R_P)-**21**, a diaminophosphine oxide without a nitrogen atom on the sidearm, there was no significant change in the enantioselectivity, compared with that obtained using (S,R_P)-**1a** (entry 6 vs entry 11). This result indicates that this series of diaminophosphine oxides coordinates to the Ir metal in a monodentate manner through the phosphorus atom.

Table 13
Optimization of reaction conditions

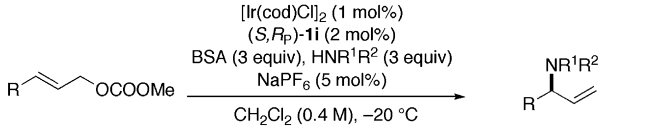


Entry	x	DIAPHOX	Additive (mol %)	Time (h)	Yield (%)	ee (%)
1	2	**1a**	—	22	No reaction	—
2	1	**1a**	—	22	10	63
3	1	**1a**	NaI (10)	22	16	60
4	1	**1a**	$NaBF_4$ (10)	22	70	66
5	1	**1a**	$NaPF_6$ (10)	7	86	58
6	1	**1a**	$NaPF_6$ (5)	7	99	59
7	1	**1g**	$NaPF_6$ (5)	19	51	60
8	1	**1h**	$NaPF_6$ (5)	19	10	73
9	1	**1i**	$NaPF_6$ (5)	19	93	86
10	1	**1j**	$NaPF_6$ (5)	19	25	68
11	1	**22**	$NaPF_6$ (5)	19	99	58
12[a]	1	**1i**	$NaPF_6$ (5)	48	96	92

[a] Reaction performed at −20 °C.

The scope and limitations of different substrates were examined using the optimized conditions (Table 14). When 2 mol % of Ir catalyst, 2 mol % of (S,R_P)-**1i**, and 5 mol % of $NaPF_6$ were used, asymmetric allylic amination of **108** with primary amines and an α-branched primary amine proceeded at −20 °C to provide the corresponding branched (b) allylic amines **109a**–**c** in good yield and in

Table 14
Scope and limitations



108, **110**, **112**, **114**, **116**, **118**, **120**, **122**, **124** → **109**, **111**, **113**, **115**, **117**, **119**, **121**, **123**, **125**

Entry	Substrate	Amine	Product	Time (h)	Yield (%)	Ratio (*b*/*l*)	ee (%)
1	**108**: R=phenyl	Benzylamine	**109a**	48	96	>99/1	92 (*S*)
2	**108**: R=phenyl	Frufurylamine	**109b**	48	95	>99/1	94
3	**108**: R=phenyl	Isopropylamine	**109c**	60	98	>99/1	92
4[a]	**108**: R=phenyl	Morpholine	**109d**	24	96	>99/1	65
5	**110**: R=4-methoxyphenyl	Benzylamine	**111**	24	99	>99/1	91
6	**112**: R=4-chlorophenyl	Benzylamine	**113**	48	99	>99/1	94
7	**114**: R=3-fluorophenyl	Benzylamine	**115**	48	92	>99/1	95
8	**116**: R=2-methoxyphenyl	Benzylamine	**117**	48	97	>99/1	93
9[b]	**118**: R=1-naphthyl	Benzylamine	**119**	60	98	>99/1	87
10[b]	**120**: R=2-naphthyl	Benzylamine	**121**	60	97	>99/1	87
11	**122**: R=2-furanyl	Benzylamine	**123**	36	94	>99/1	88
12	**124**: R=CH_2CH_2Ph	Benzylamine	**125**	60	74	[c]	68

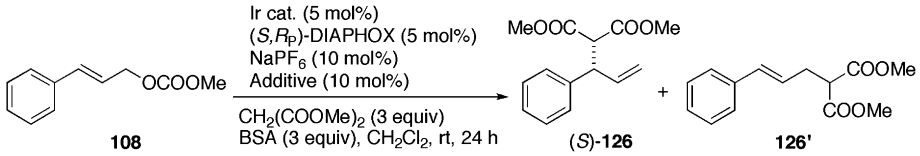
[a] Reaction was performed at room temperature.
[b] Reactions were performed at −5 °C.
[c] Linear–linear product (8%) and 5% of branched-linear product were obtained.

high enantioselectivity (entries 1–3). In contrast, there was a decreased enantioselectivity when morpholine was used as a nucleophile (entry 4). Asymmetric allylic amination of various terminal allylic carbonates was also examined using benzylamine as the nucleophile. Aromatic substituents with electron-donating (**110** and **116**) and -withdrawing functionalities (**112** and **114**) were tolerant to this reaction, giving the products **111**, **113**, **115**, and **117** with good-to-high enantioselectivity (entries 5–8). Terminal allylic carbonates with a naphthyl substituent **118** and **120** (entries 9 and 10) or a heteroaromatic substituent **122** (entry 11) were also applicable to this reaction, affording the corresponding product **119**, **121**, and **123** with good enantioselectivity. In addition, asymmetric allylic amination of **124**, a substrate with an alkyl substituent, was examined using 2 mol % of the catalyst, giving the corresponding product **125** in 74% yield with 68% ee, accompanied by 8% of linear–linear (l–l) product and 5% of branched-linear (b-l) product (entry 12).

5.2. Ir-catalyzed asymmetric allylic alkylation[193]

The success of the asymmetric allylic amination led us to examine asymmetric allylic alkylation using the Ir-DIAPHOX catalyst system.[194–211] Optimizations of reaction conditions were performed using asymmetric allylic alkylation of **108** with dimethyl malonate using (*S*,*R*P)-**1a** (Table 15). Although no reaction occurred when 2.5 mol % of $[Ir(cod)Cl]_2$ and 5 mol % of (*S*,*R*P)-**1a** (Ir/**1a**=1/1) were used, the same reaction proceeded in the presence of 10 mol % of $NaPF_6$, affording the branched product (*S*)-**126** with high regioselectivity (29% yield, **126**/**126**′=97/3, 75% ee) (entry 1). The addition of LiCl remarkably increases both the reactivity and the enantioselectivity in the Ir-catalyzed asymmetric allylic alkylation.[196,197,201] Thus, we investigated the effect of adding a lithium salt. Although the reactivity was significantly improved when LiCl was used as the additive, there was a slight decrease in the enantioselectivity (entry 2). Both the reactivity and the enantioselectivity, on the other hand, were affected by the addition of LiOAc. Further optimization with regard to the reaction concentration resulted in the formation of the branched product (*S*)-**126** in good yield (90% yield, **126**/**126**′=95/5) with 88% ee (entry 5). The increased reactivity under the diluted reaction conditions is likely to be related to the solubility of LiOAc in CH_2Cl_2. We next attempted to improve the regioselectivity and enantioselectivity by tuning the structure of DIAPHOX (entries 6–11). Studies of the effect of substituents on the aromatic rings revealed that (*S*,*R*P)-**1d**, which

Table 15
Optimization of reaction conditions

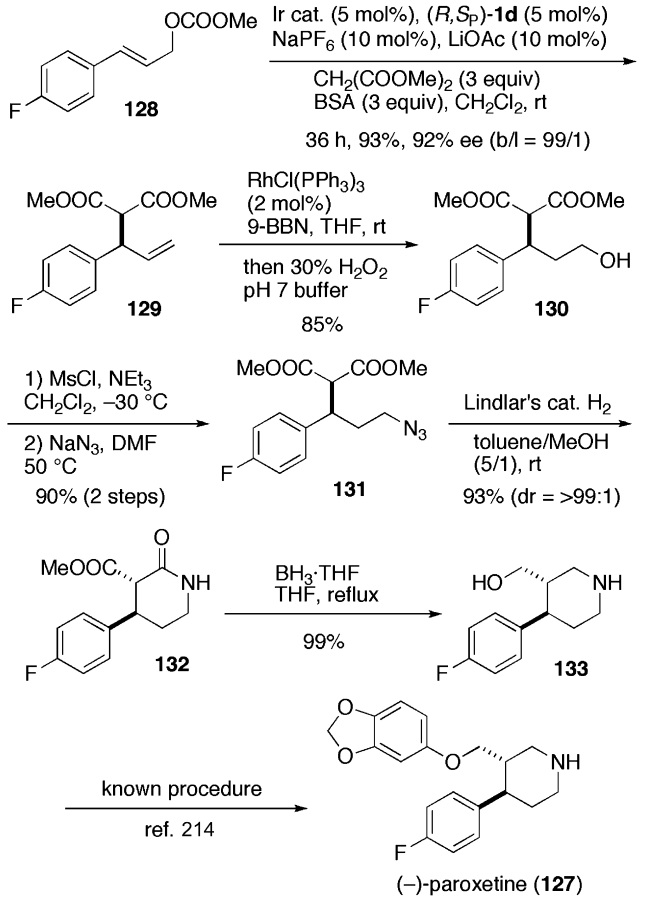


108 → (*S*)-**126** + **126′**

Entry	Additive	DIAPHOX	Concn (M)	Yield (%)	Ratio (**126**/**126**′)	ee (%)
1	—	**1a**	0.4	29	97/3	75
2	LiCl	**1a**	0.4	95	97/3	72
3	LiOAc	**1a**	0.4	71	95/5	90
4	LiOAc	**1a**	0.5	73	96/4	88
5	LiOAc	**1a**	0.25	90	95/5	88
6	LiOAc	**1b**	0.25	54	95/5	57
7	LiOAc	**1c**	0.25	69	96/4	74
8	LiOAc	**1d**	0.25	92	99/1	90
9	LiOAc	**1e**	0.25	92	97/3	82
10	LiOAc	**1f**	0.25	28	95/5	81
11	LiOAc	**1i**	0.25	78	90/10	45

possesses a 3-biphenyl group at the benzylic moiety, was best for asymmetric induction (90% ee), giving the branched product (*S*)-**126** in good yield with excellent regioselectivity (92% yield, **126**/**126′**=99/1) (entry 8).

The developed reaction system was successfully applied to the enantioselective synthesis of (−)-paroxetine **127** (Scheme 21).[212–221] First, Ir-catalyzed asymmetric allylic alkylation of **128** with dimethyl malonate was performed using (R,S_P)-**1d**, affording **129** in 93% yield (b/l=99/1) with 92% ee. Hydroboration of the olefin with 9-BBN in the presence of Wilkinson's catalyst, followed by work up with hydrogen peroxide, gave **130** in 85% yield.[222] After conversion of the hydroxyl group into an azide (90% yield), **131** was treated with Lindlar's catalyst in toluene/MeOH (5/1) under a hydrogen atmosphere to provide the lactam **132** in 93% yield as a single diastereomer (*anti*/*syn*=>99/1). Subsequent reduction of **132** with a BH_3·THF complex gave (3*S*,4*R*)-(−)-**133** in 99% yield. The known intermediate **133** can be converted into **127** using the reported procedure.[214]



Scheme 21.

6. Conclusions

Transition metal-catalyzed reactions using secondary phosphine oxides or their equivalents have attracted attention in the past several years, due to the air and moisture stability of pentavalent phosphine oxides. Application to asymmetric catalysis using chiral phosphine oxides is, however, still limited. We have developed a new class of P-chiral secondary phosphine oxide preligands based on a chiral diamine framework, the P-chiral diaminophosphine oxides (DIAPHOXs). These pentavalent phosphorus compounds, the preligands, reacted with BSA to provide the trivalent diamidophosphite species, which functioned as the actual ligands. Asymmetric allylic alkylation, asymmetric allylic amination, enantioselective construction of quaternary carbons, and enantioselective synthesis of axially chiral allenes controlled by a dynamic kinetic asymmetric transformation were investigated using the Pd- and Ir-DIAPHOX catalyst systems, affording various chiral compounds with good-to-excellent enantioselectivity. Furthermore, the developed reactions were successfully applied to catalytic asymmetric syntheses of biologically active compounds. We believe that DIAPHOX ligands have great potential and will be applied to a variety of transition metal-mediated asymmetric reactions. As that occurs, the development of new conditions for activating DIAPHOXs other than the BSA-induced P(V)-to-P(III) tautomerization will become an important key.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.069.

References and notes

1. For a general review, see: Ojima, I. *Catalytic Asymmetric Synthesis II*; Wiley-VCH: New York, NY, 2000.
2. Barton, D.; Ollis, W. D. In *Comprehensive Organic Chemistry*; Sutherland, I. O., Ed.; Pergammon: Oxford, 1979; Vol. 2, Part 10.
3. For a review, see: Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883.
4. For a review, see: Ackermann, L. *Synthesis* **2006**, 1557.
5. For a review, see: Ackermann, L. *Synlett* **2007**, 507.
6. For a review, see: Nemoto, T.; Hamada, Y. *Chem. Rec.* **2007**, *7*, 150.
7. For a review, see: Nemoto, T. *Chem. Pharm. Bull.* **2008**, *56*, 1213.
8. van Leeuwen, P. W. N. M.; Roobeek, C. F.; Wife, R. L.; Frijns, J. H. G. *J. Chem. Soc., Chem. Commun.* **1986**, 31.
9. van Leeuwen, P. W. N. M.; Roobeek, C. F.; Frijns, J. H. G.; Orpen, A. G. *Organometallics* **1990**, *9*, 1211.
10. Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.
11. Cobley, C. J.; van den Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467.
12. Jiang, X.-b.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327.
13. Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513.
14. Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677.
15. Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.
16. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077.
17. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.
18. Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, *2*, 2161.
19. Wolf, C.; Lerebours, R.; Tanzini, E. H. *Synthesis* **2003**, 2069.
20. Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147.
21. Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162.
22. Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638.
23. Yang, W.; Wang, Y.; Corte, J. R. *Org. Lett.* **2003**, *5*, 3131.
24. Poondra, R. R.; Fischer, P. M.; Turner, N. J. *J. Org. Chem.* **2004**, *69*, 6920.
25. Khanapure, S. P.; Garvey, D. S. *Tetrahedron Lett.* **2004**, *45*, 5283.
26. Cao, P.; Qu, J.; Burton, G.; Rivero, R. A. *J. Org. Chem.* **2008**, *73*, 7204.
27. Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381.
28. Ekoue-Kovi, K.; Xu, H.; Wolf, C. *Tetrahedron Lett.* **2008**, *49*, 5773.
29. Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601.
30. Zhang, Z. .; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415.
31. Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737.
32. Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052.
33. Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753.

34. Bigeault, J.; Giordano, L.; de Riggi, I.; Gimbert, Y.; Buono, G. *Org. Lett.* **2007**, *9*, 3567.
35. Bigeault, J.; de Riggi, I.; Gimbert, Y.; Giordano, L.; Buono, G. *Synlett* **2008**, 1071.
36. Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444.
37. Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216.
38. Gavryushin, A.; Kofink, C.; Manolikakes, G.; Kochel, P. *Org. Lett.* **2005**, *7*, 4871.
39. Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457.
40. Ackermann, L.; Gschrei, C. J.; Althammer, A.; Riederer, M. *Chem. Commun.* **2006**, 1419.
41. Ackermann, L.; Potukuchi, H. K. *Synlett* **2009**, 2852.
42. Ackermann, L. *Org. Lett.* **2005**, *7*, 3123.
43. Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619.
44. Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043.
45. Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274.
46. Drabowicz, J.; Lyzwa, P.; Omelanczuk, J.; Pietrusiewicz, K. M.; Mikolajajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2757.
47. Haynes, R. K.; Au-Yeung, Y.-L.; Chen, W.-K.; Lam, W.-L.; Li, Z.-Y.; Yeung, L.-L.; Chen, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem.* **2000**, 3205.
48. Kolodiazhnyi, O. L.; Gryshkun, E. V.; Andrushko, N. V.; Freytag, M.; Jones, P. G.; Schmutzler, R. *Tetrahedron: Asymmetry* **2003**, *14*, 181.
49. Leyris, A.; Nuel, D.; Giordano, L.; Achard, M.; Buono, G. *Tetrahedron Lett.* **2005**, *46*, 8677.
50. Jiang, X.-b.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Booger, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503.
51. Leyris, A.; Bigeault, J.; Nuel, D.; Giordano, L.; Buono, G. *Tetrahedron Lett.* **2007**, *48*, 5247.
52. Xu, Q.; Zhao, C.-Q.; Han, L.-B. *J. Am. Chem. Soc.* **2008**, *130*, 12648.
53. Jiang, X.-b.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223.
54. Galland, A.; Dobrota, C.; Toffano, M.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2006**, *17*, 2354.
55. Dai, W.-M.; Yeung, K. K. Y.; Leung, W. H.; Haynes, R. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2821.
56. Gatineau, D.; Moraleda, D.; Naubron, J.-V.; Bürgi, T.; Giordano, L.; Buono, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1912.
57. Landert, H.; Spindler, F.; Wyss, A.; Blaser, H.-U.; Pugin, B.; Ribourduoille, Y.; Gschwend, B.; Ramalingamm, B.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 6873.
58. For a review, see: Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
59. For a review, see: Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.
60. Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690.
61. Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172.
62. For a review, see: El Gihani, M. T.; Heaney, H. *Synthesis* **1998**, 357.
63. For a review, see: Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.
64. For a review, see: Shibasaki, M.; Erasmus, V. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.
65. For a review, see: Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.
66. For a review, see: Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027.
67. For a representative example, see: Hayashi, T.; Kanehira, K.; Tsuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162.
68. For a representative example, see: Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586.
69. For a representative example, see: Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309.
70. For a representative example, see: Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879.
71. For a representative example, see: Nakoji, M.; Kaneyama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418.
72. For a representative example, see: Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177.
73. For a representative example, see: Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.
74. For a representative example, see: Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.
75. For a representative example, see: Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109.
76. For a representative example, see: Fukuda, Y.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 3389.
77. For a representative example, see: Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228.
78. For a representative example, see: Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.
79. For a review, see: Mohr, J. T.; Stoltz, B. M. *Chem.—Asian. J.* **2007**, *2*, 1476.
80. Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504.
81. For a review on secondary ligand substrate interaction, see: Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.
82. For a review on secondary ligand substrate interaction, see: Börner, A. *Eur. J. Inorg. Chem.* **2001**, 327.
83. Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 6577.
84. Genet, J. P.; Grisoni, S. *Tetrahedron Lett.* **1988**, *29*, 4543.
85. Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687.
86. Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122.
87. Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644.
88. Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250.
89. For a representative synthesis, see: Wikström, H.; Sanshez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030.
90. For a representative synthesis, see: Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343.
91. For a representative catalytic asymmetric synthesis, see: Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257.
92. For a representative catalytic asymmetric synthesis, see: Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275.
93. For a representative catalytic asymmetric synthesis, see: Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
94. For a representative catalytic asymmetric synthesis, see: Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660.
95. For a representative catalytic asymmetric synthesis, see: Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 4209.
96. For a representative catalytic asymmetric synthesis, see: Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 6022.
97. Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845.
98. Carpes, M. J. S.; Correia, C. R. D. *Tetrahedron Lett.* **2002**, *43*, 741.
99. Jin, L.; Nemoto, T.; Nakamura, H.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1106.
100. For a representative example using carbon nucleophiles, see: Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297.
101. For a representative example using carbon nucleophiles, see Stang, A. Q.; Helmchen, G. *Helv. Chim. Acta* **2005**, *88*, 2738.
102. For a representative example using nitrogen nucleophiles, see Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263.
103. For a representative example using nitrogen nucleophiles, see Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.
104. For a representative example using nitrogen nucleophiles, see: Mori, M.; Nishimata, T.; Nagasawa, Y.; Sato, Y. *Adv. Synth. Catal.* **2001**, *343*, 34.
105. For a representative example using nitrogen nucleophiles, see: Mori, M.; Nakanishi, D.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.
106. For a representative example using nitrogen nucleophiles, see: Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190.
107. For a representative example using oxygen nucleophiles, see: Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.
108. For a representative example using oxygen nucleophiles, see: Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
109. Nemoto, T.; Harada, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 6304.
110. For a review on asymmetric synthesis of quaternary α-amino-acid derivatives, see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
111. For a review on asymmetric synthesis of quaternary α-amino-acid derivatives, see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
112. For a review on asymmetric synthesis of quaternary α-amino-acid derivatives, see: Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629.
113. For a review on asymmetric synthesis of quaternary α-amino-acid derivatives, see: Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.
114. Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236.
115. Ogasawara, M.; Ngo, H.; Sakamoto, T.; Takahashi, T. *Org. Lett.* **2005**, *7*, 2881.
116. α-Acetoamido β-keto phosphonates as the nucleophiles, see: Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837.
117. Azlactones are also useful nucleophiles for providing access to chiral quaternary α-amino acid derivatives, see: Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed.* **1997**, *36*, 2635.
118. Azlactones are also useful nucleophiles for providing access to chiral quaternary α-amino acid derivatives, see: Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256.
119. Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y. *Adv. Synth. Catal.* **2009**, *351*, 1773.
120. Ma, S. *Chem. Rev.* **2005**, *105*, 2829.
121. Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.
122. Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042.
123. Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *Org. Lett.* **2001**, *3*, 2615.
124. Ogasawara, M.; Murakami, H.; Furukawa, T.; Takahashi, T.; Shibata, N. *Chem. Commun.* **2009**, 7366.
125. Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.
126. Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217.
127. Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764.
128. Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takahashi, T.; Lin, W. *Org. Lett.* **2005**, *7*, 2881.
129. Ogasawara, M. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 100.
130. Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. *Chem. Lett.* **2002**, 140.
131. Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.-I.; Naota, T. *Org. Lett.* **2005**, *7*, 5837.
132. Imada, Y.; Nishida, M.; Naota, T. *Tetrahedron Lett.* **2008**, *49*, 4915.
133. Trost, B. M.; Frandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.
134. For a review, see: Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59.
135. Lowe, G. *J. Chem. Soc., Chem. Commun.* **1965**, 411.
136. Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1.
137. For a review, see: Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

138. Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447.
139. Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837.
140. Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927.
141. For a review, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
142. For a representative example, see: Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507.
143. For a representative example, see: Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310.
144. For a representative example, see: Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103.
145. For a representative example, see: Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521.
146. For a representative example, see: Raheen, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.
147. For a representative example, see: Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.
148. For a representative example, see: Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.
149. For a representative example, see: Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689.
150. For a representative example, see: Shi, M.; Ma, G.-N.; Gao, J. *J. Org. Chem.* **2007**, *72*, 9779.
151. For a representative example, see: Abermil, N.; Masson, G.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12596.
152. For a representative example, see: Abermil, N.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 4648.
153. For a representative example, see: Yukawa, T.; Seelig, B.; Xu, Y.; Morimoto, H.; Matsunaga, S.; Berkessel, A.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11988.
154. Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534.
155. Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616.
156. Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155.
157. For a review, see: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
158. Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570.
159. Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.
160. Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103.
161. Nemoto, T.; Tamura, S.; Sakamoto, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1751.
162. Dong, Y.; Teesdale-Spittle, P.; Hoberg, J. O. *Tetrahedron Lett.* **2005**, *46*, 353.
163. Nemoto, T.; Yamamoto, E.; Franzén, R.; Fukuyama, T.; Wu, R.; Fukamachi, T.; Kobayashi, H.; Hamada, Y. *Org. Lett.* **2010**, *12*, 872.
164. Duan, J.-A.; Williams, I. D.; Che, C.-T.; Zhou, R.-H.; Zhao, S.-X. *Tetrahedron Lett.* **1999**, *40*, 2593.
165. Liu, B. P. L.; Chong, E. Y. Y.; Cheung, F. W. K.; Duan, J.-A.; Che, C.-T.; Liu, W. K. *Biochem. Pharmacol.* **2005**, *70*, 287.
166. For an example of total synthesis of racemic tangutorine, see: Putkonen, T.; Tolvanen, A.; Jokela, R. *Tetrahedron Lett.* **2001**, *42*, 6593.
167. For an example of total synthesis of racemic tangutorine, see: Luo, S.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709.
168. For an example of total synthesis of racemic tangutorine, see: Ho, T.-L.; Chen, C.-K. *Helv. Chim. Acta* **2006**, *89*, 122.
169. For an example of total synthesis of racemic tangutorine, see: Salame, R.; Gravel, E.; Leblanc, K.; Poupon, E. *Org. Lett.* **2009**, *11*, 1891.
170. For a review on catalytic asymmetric epoxidation, see: Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.
171. For a review on catalytic asymmetric epoxidation, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; p 231.
172. David, H.; Dupuis, L.; Guillerez, M.-G.; Guibé, F. *Tetrahedron Lett.* **2000**, *41*, 3335.
173. Kawanobe, T.; Iwamoto, M.; Kogami, K.; Matsui, M. *Agric. Biol. Chem.* **1987**, *51*, 791.
174. Zhang, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1434.
175. For the pioneering work on Ir-catalyzed allylic substitutions, see: Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263.
176. For the pioneering work on Ir-catalyzed allylic substitutions, see: Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647.
177. For the pioneering work on Ir-catalyzed allylic substitutions, see: Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525.
178. For a review, see: Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.
179. Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737.
180. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.
181. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.
182. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Shu, C.; Leiner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797.
183. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426.
184. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896.
185. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631.
186. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Weihohen, R.; Dahnz, A.; Tverskoy, O.; Helmchen, G. *Chem. Commun.* **2005**, 3541.
187. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621.
188. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Weihohen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546.
189. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949.
190. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.
191. Weix, D. J.; Markovic, D.; Ueda, M.; Hartwig, J. F. *Org. Lett.* **2009**, *11*, 2944.
192. For a representative example of Ir-catalyzed asymmetric allylic amination, see: Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917.
193. Nemoto, T.; Sakamoto, T.; Fukuyama, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 4977.
194. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025.
195. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Bartels, A.; Helmchen, G. *Chem. Commun.* **1999**, 741.
196. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun.* **1999**, 2289.
197. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054.
198. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197.
199. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Kinoshita, N.; Marx, K. H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* **2004**, *69*, 7960.
200. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529.
201. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.
202. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Streiff, S.; Welter, C.; Schelwiss, M.; Lipowsky, G.; Miller, N.; Helmchen, G. *Chem. Commun.* **2005**, 2957.
203. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192.
204. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596.
205. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Onodera, G.; Watabe, K.; Matsubara, M.; Oda, K.; Kezuka, S.; Takeuchi, R. *Adv. Synth. Catal.* **2008**, *350*, 2725.
206. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918.
207. For a representative example of Ir-catalyzed asymmetric allylic alkylation, see: Giacomina, F.; Riat, D.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1156.
208. For a representative example of Ir-catalyzed asymmetric allylic etherification, see: Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794.
209. For a representative example of Ir-catalyzed asymmetric allylic etherification, see: Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204.
210. For a representative example of Ir-catalyzed asymmetric allylic etherification, see: Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707.
211. For a representative example of Ir-catalyzed asymmetric allylic etherification, see: Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928.
212. For a catalytic asymmetric synthesis of paroxetine, see: Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.
213. For a catalytic asymmetric synthesis of paroxetine, see: Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.
214. For a catalytic asymmetric synthesis of paroxetine, see: Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.
215. For a catalytic asymmetric synthesis of paroxetine, see: Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305.
216. For a catalytic asymmetric synthesis of paroxetine, see: Koech, P. K.; Krische, M. J. *Tetrahedron* **2006**, *62*, 10594.
217. For a catalytic asymmetric synthesis of paroxetine, see: Ito, M.; Sakaguchi, A.; Kobayashi, C.; Ikariya, T. *J. Am. Chem. Soc.* **2007**, *129*, 290.
218. For a catalytic asymmetric synthesis of paroxetine, see: Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.* **2007**, 728.
219. For a catalytic asymmetric synthesis of paroxetine, see: Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389.
220. For a catalytic asymmetric synthesis of paroxetine, see: Valero, G.; Schimer, J.; Cisarova, I.; Vesely, J.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2009**, *50*, 1943.
221. For a catalytic asymmetric synthesis of paroxetine, see: Kim, M.-h.; Park, Y.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2010**, *12*, 2826.
222. Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.

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