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Articles

Versatile Chiral Bidentate Ligands Derived from α-Amino Acids: Synthetic Applications and Mechanistic Considerations in the Palladium-Mediated Asymmetric Allylic Substitutions

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A new class of chiral amidine-phosphine hybrid ligands **7a**,**b**, which are readily accessible from the corresponding α-amino acids, were developed. A versatility for construction of new ligands is desirable, by which a variety of reactions and substrates become applicable. Indeed, a variety of modifications, such as exchange reactions to other amino groups in the amidine skeleton and the production of other types of ligands, are possible using the precursor compounds of **7a**. Thus, novel chiral ligands **7c**,**d**, **8**, **11**, and **13**, which provide sterically and electronically different chiral circumstances, were prepared and used for the palladium-mediated asymmetric allylic substitutions of both acyclic and cyclic compounds. In these reactions, high levels of asymmetric induction were achieved for both substrates. A marked advancement of reactivity and enantioselectivity in palladium-catalyzed asymmetric allylations of 1,3-diphenylpropen-2-yl pivalate **14a** was attained by examination of electronic substituent effects in a new series of chiral P−N and S−N hybrid ligands **8** and **11**. Mechanistic views concerning the enantiodiscriminating step were demonstrated, in which a good correlation between a novel *Pr*/*Mr* concept and the absolute configuration of allylation products are discussed for the prediction of enantioselecting direction. The use of ketene silyl acetals as nucleophiles was investigated and compared with the corresponding harder anionic carbon nucleophiles. The former nucleophiles afforded higher enantioselectivity in asymmetric allylic transformations of **14a**.

Introduction

Palladium-mediated allylic transformations of allyl compounds, alkenes, and conjugated dienes have greatly contributed to the field of synthetic organic chemistry as an effective tool for the construction of C−C and C−X (X = H, heteroatoms) bonds.[1] Extensive investigations on this transformation in terms of reaction types, substrates, and nucleophiles resulted in the establishment of the methodology for useful synthetic applications such as new ring formation via intramolecular cyclization and natural product synthesis.[2] For the asymmetric version, develop-

(1) For pioneering studies, for example, see: (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387. (b) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821. (c) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1650.

(2) Recent reviews including palladium-catalyzed allylic substitutions; see: (a) Wills, M.; Tye, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1109. (b) Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3101. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (d) Williams, J. M. J. *Synlett* **1996**, 705. (e) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic synthesis*; John Wiley & Sons: New York, 1995; p 290. (f) Hayashi, T. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993. (g) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (h) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (i) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

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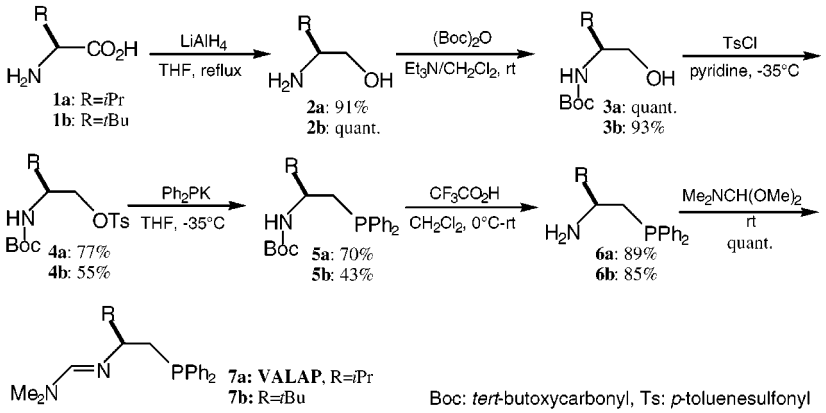
Scheme 1



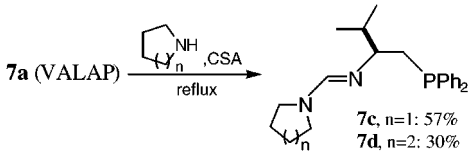
Boc: *tert*-butoxycarbonyl, Ts: *p*-toluenesulfonyl

ment of chiral ligands that can create effective chiral circumstances has opened a way to enantioselective recognition during the bond formation. A number of useful chiral ligands have been prepared to date, by which high levels of catalytic performance have been demonstrated.[2]

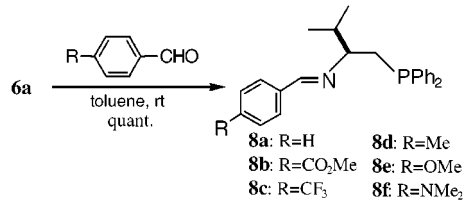
In this area, we have developed new types of chiral ligands derived from easily available α-amino acids in both natural and unnatural types.[3] A new P−N hybrid ligand consisting of phosphine and amidine skeletons **7a** (VALAP) was developed at the initial stage of our investigation. A tight Pd−N chelation could be expected by the more electron-rich imino nitrogen due to the amidine structure in VALAP. Since versatility for a number of reaction types and substrates is an important factor as a design concept, a variety of modifications such as exchange reactions to other amino groups in the amidine skeleton and the production of other types of ligands using the synthetic precursor of VALAP were carried out. The present paper reports the development of a new class of chiral P−N and S−N hybrid ligands **7b**−**d**, **8** and **11** and a diphosphine type auxiliary **13** based on VALAP. Their application to palladium-catalyzed asymmetric allylic alkylations and mechanistic considerations of enantiodiscriminating steps are also described. To extend the scope of enantioselective allylic substitutions, ketene silyl acetals (KSA) were used as a nucleophile, and their synthetic utility is discussed by comparison with "harder" anionic nucleophiles.

Synthesis of New Chiral P−N, S−N Hybrid Ligands. The phosphine−amidine bidentate ligand **7a** (VALAP) was developed at the early stage of our investigation.[3] VALAP was easily accessible from a commercially available α-amino acid, L-valine (**1a**), based on the procedure described for the preparation of a chiral diphosphine ligand, BPPM[4] (Scheme 1).[5] Similarly, the amidine **7b** was prepared from L-*tert*-leucine (**1b**). L-*tert*-Leucinol (**2b**), prepared by the reduction of **1b**, was converted quantitatively into **3b** by protection with di-*tert*-butyl dicarbonate. The sulfonyloxybutane **4b** was derived from **3b** using *p*-toluenesulfonyl chloride. A diphenylphosphino group was introduced by the reaction of **4b** with potassium diphenylphosphide in THF, giving diphenylphosphinobutane **5b**, which was converted into **6b** by deprotection of the amino moiety using trifluoroacetic acid. Finally, the reaction of **6b** and *N*,*N*-dimethylformamide dimethylacetal gave (*S*)-*N*′-[1-[(diphenylphosphino)methyl]-2,2-dimethylpropyl]-*N*,*N*-dimethylmethanimidamide (**7b**).

Scheme 2



Scheme 3



To examine the possibility of sterical and electronical refinement in the structure of ligands as well as introduction of an additional chiral center at the amidine part of VALAP, replacement of the dimethylamino group by other secondary amines was first examined. VALAP was simply treated with pyrrolidine and piperidine at the corresponding reflux temperatures to give the modified amidine ligands **7c**,**d** (Scheme 2). The chiral P−N hybrid ligands **8** consisting of diphenylphosphino and phenyl imino groups with different substituents at the para position were also developed.[6] The ligands **8** were readily prepared in one step by the reaction of **6a** with the corresponding aldehydes (Scheme 3).

In contrast to a number of studies on the P−N hybrid chiral auxiliaries, sulfur-containing hybrid ligands have rarely been used for the transition metal-catalyzed reactions except for a few examples,[7] probably due to their catalyst poisoning property. We previously reported that high enantioselectivity up to 96% ee was achieved by using the S−N hybrid ligands bearing chiral imidazolines in palladium-catalyzed asymmetric allylic substitutions of 1,3-diphenylallyl substrate with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA)-AcOLi. (*S*)-*N*′-[1-[(Phenylthio)methyl]-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide (**11a**), a structure similar to that of VALAP, was prepared through

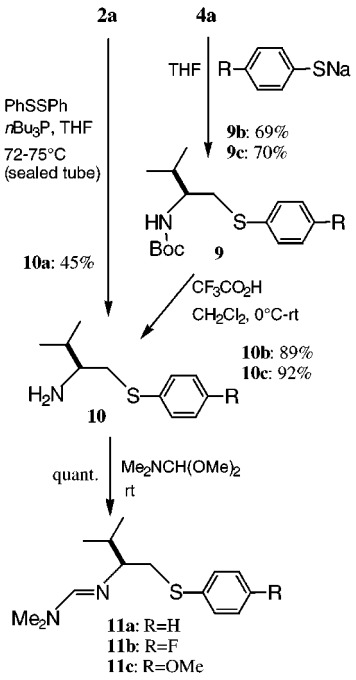
(3) Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3567. Recently, we abbreviated the amidine-phosphine hybrid ligand **7a** derived from L-valine as "VALAP".

(4) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.

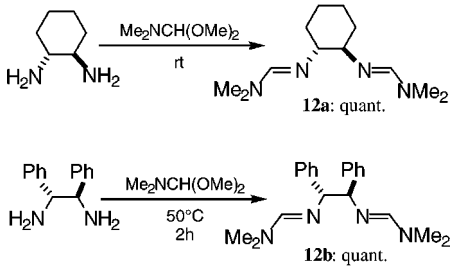
(5) A similar procedure to **10a** was found in a previous publication by Hiroi et al.; see: Hiroi, K.; Haraguchi, M.; Masuda, Y.; Abe, J. *Chem. Lett.* **1992**, 2409.

(6) Saitoh, A.; Misawa, M.; Morimoto, T. *Synlett* **1999**, 483.

Scheme 4



Scheme 5

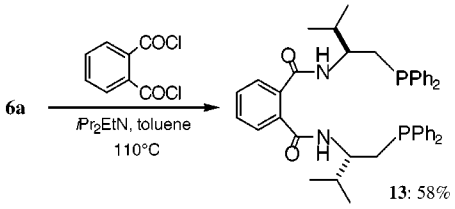


10a[7g] from L-valinol (**2a**). Since thiols bearing phenyl groups with various substituents at the para position were widely available, other ligands **11b**,**c** were also synthesized via two steps after the reaction of **4a** with the corresponding sodium sulfides (Scheme 4).

As one of the structural variation of the amidine-based ligands, diamidine-type auxiliaries **12a**,**b** were then prepared by treatment with *N*,*N*-dimethylformamide dimethylacetal from (1*R*,2*R*)-1,2-diaminocyclohexane and (1*R*,2*R*)-1,2-diphenylethylenediamine, respectively (Scheme 5).

Optically active diphosphine ligands with C_2-symmetry have been proven to create a chiral environment effectively for both substrates and nucleophiles.[8] Thus, we designed a new C_2-symmetric diphosphine ligand **13** as

Scheme 6



an extension of the ligand system based on VALAP.[9] The newly designed ligand **13** was prepared in one step by treatment of **6a** with phthaloyl dichloride (Scheme 6).

Asymmetric Allylic Substitutions of Acyclic Substrates. Bidentate ligands of phosphorus−nitrogen[3,6,10] and sulfur−nitrogen[7] mixed-donors have recently been investigated for which high levels of enantioselection were demonstrated in palladium-catalyzed asymmetric allylic substitutions. In the case of ligands possessing two different donor centers, it is generally accepted that nucleophilic attack to π-allyl complexes occurs predominantly at the allyl terminus trans to better π-acceptors, which must be the phosphino groups in the P−N hybrid ligands.[7d,11] Such a course of the nucleophilic attack provides an advantage to the design of mixed-donor ligands. Among the hybrid ligands, chiral phosphanyldihydrooxazoles, independently developed by several groups,[12] have attracted much attention. The phosphanyldihydrooxazoles, so-called oxazoline ligands, are generally effective for asymmetric allylic replacements of acyclic compounds and Heck-type reactions.[13] Recently, it was also reported that a phosphine−oxazoline ligand with fine-tuning by a cymantrene unit are efficient ligands for asymmetric transformation of cyclic substrates, which has been regarded as one of the most difficult transformations to overcome.[14]

Using the prepared ligands of hybrid type, asymmetric allylic substitutions of 1,3-diphenylpropen-2-yl pivalate (**14a**) and its acetate analogue (reaction 1 in Scheme 7) were first examined. Since the optimized reaction conditions are different in each chiral ligands, effects of

(7) (a) Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015. (b) Frost, C. G.; Williams, J. M. J. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1785. (c) Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 7793. (d) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065. (e) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783. (f) Chesney, A.; Bryce, M. R.; Chubb, R. W. J.; Batsanov, A. S.; Howard, J. A. K. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3185. (g) Anderson, J. C.; James, D. S.; Mathias, J. P. *Tetrahedron*: *Asymmetry* **1998**, *9*, 753. (h) Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256. (i) Boog-Wick, K.; Pregosin, P.; Trabesinger G. *Organometallics* **1998**, *17*, 3254.

(8) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(9) (a) Saitoh, A.; Misawa, M.; Morimoto, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1025. (b) Saitoh, A.; Uda, T.; Morimoto, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4501.

(10) For selected recent articles for P−N hybrid ligands, see: (a) Zhang W.; Yoneda, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3371. (b) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343. (c) Cahill, J. P.; Gulry, P. J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 4301. (d) Widhalm, M.; Mereiter, K.; Bourghida, M. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2983. (e) Burgess, K.; Porte, A. M. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2465. (f) Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1779. (g) Bourghida, M.; Widhalm, M. *Terahedron*: *Asymmetry* **1998**, *9*, 1073. (h) Saitoh, A.; Achiwa, K.; Morimoto, T. *Tetrahedron*: *Asymmetry* **1998**, *9*, 741. (i) Kunz, H.; Glaser, B. *Synlett* **1998**, 53. (j) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1179. (k) Brunel, J. M.; Constantieux, T.; Labande, A.; Lubatti, F.; Buono, G. *Terahedron Lett.* **1997**, *38*, 5971. (l) Sudo, A., Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508. (m) Mino, T.; Imiya, W.; Yamashita, M. *Synlett* **1997**, 583. (n) Gilbertson, S. R.; Chang, C.-W. T. *Chem. Commun.* **1997**, 915.

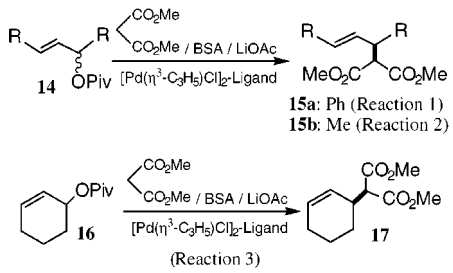
(11) (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523. (b) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2535.

(12) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

(13) (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. (b) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338.

(14) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3047.

Scheme 7



solvents, bases, catalyst amounts, reaction temperature, and reaction time were first investigated in some detail for VALAP and its related ligands **7b**−**d** on the basis of our previously obtained results[3] (Table 1). In the present runs, the absolute configuration of the major enantiomer was determined to be *R* in all cases by the optical rotation and the comparison with HPLC peaks. In terms of base, some difference in the asymmetric induction between the use of dimethyl malonate/BSA and dimethyl sodiomalonate (entries 10 and 12) was observed. The previous work with (*S*)-BINAP also revealed the significant reduction in the enantiomeric excess in the substitution with dimethyl sodiomalonate.[2c,15] In recent studies, most of substitution reactions were conducted according to Trost's procedure[16] using BSA in the presence of metal acetate salts. Under the conditions using dichloromethane (Table 1, entry 1), the alkylated product **15a** was obtained with an excellent level of enantiomeric excess in quantitative yield.[17] Similarly, using the acetate analogue of **14a**, an almost identical level of asymmetric induction (86%, 93% ee) was achieved under the analogous conditions. A remarkable variation of the catalytic activity by the identity of solvents was observed in the reactions using 0.025 equiv of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (Table 1, entries 1−5). The drop of catalytic activity in THF may be assignable to an interaction of the solvent with a key π-allyl complex resulting in reduction of the activity of the cationic palladium complex and/or the coordination ability of the bidentate ligand. In contrast, the excellent catalytic performance was maintained in halogenated solvents even when the amount of catalyst was reduced to 0.01 equiv of the palladium dimer (Table 1, entries 6 and 7). The useful catalytic activity was also demonstrated in the reaction with a considerably small amount of catalyst, 0.005 equiv of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (Table 1, entry 8). From these experiments, dichloromethane was selected as the solvent for VALAP and related ligands. Actually, the reaction in dichloromethane proceeded smoothly within 1 h (Table 1, entry 10). Essentially the same result was obtained regardless of the countercation of the acetate salts (Table 1, entry 9). Lowering the reaction temperature to −30 °C caused slow of the reaction rate without any improvement in ee (Table 1, entries 11 and 13). In addition, the catalytic behavior with the other closely related ligands **7b**−**d** were examined in reaction 1 (Table 1, entries 14−16). The ligand **7b** bearing a large substituent on the chiral center led to lower catalytic performance in comparison with that of VALAP (Table 1, entry 14). Among the oxazoline ligands, replacement of an isopropyl group by a *tert*-butyl group caused opposite effects of improvement or reduction in the enantioselectivity, depending upon kinds of ligands employed.[7a−c,10a,12c] For instance, oxazolinylferrocene ligands of the P−N hybrid type with an isopropyl group on the oxazoline ring demonstrated higher ee than those of a *tert*-butyl analogue.[10a] The ligands having pyrrolidine or piperidine units in the amidine skeleton showed essentially the same result as that of VALAP (Table 1, entries 15 and 16). The effects of amino groups in the amidine skeleton were ambiguous in the present type of reaction, for example, chiral diamidine ligands **12a**,**b** were not so effective (Table 1, entries 17 and 18). A search for more potential asymmetric reactions with respect to this type of ligands is in progress.

The ligands of type **7** were investigated in the reactions with a sterically less demanding acyclic substrate, 3-penten-2-yl pivalate **14b** (reaction 2 in Scheme 7). As summarized in Table 2, the use of VALAP resulted in the production of (*R*)-**15b** in 60% ee (Table 2, entry 2), a comparable level of asymmetric induction as that with a phosphine−oxazoline ligand.[12a] Since it has been reported that improved enantiomeric excess was obtained by employing the ratio of ligand to metal below unity,[10e] the run using the ratio below 1 was attempted, but, no significant improvement was observed with the present ligand (Table 2, entry 3). Despite relatively low catalytic activity, it was suggested that the ligand **7b** having a *tert*-butyl moiety was somewhat effective compared with VALAP in terms of enantioselectivity.

As mentioned before, it has been generally accepted that the nucleophilic attack proceeds predominantly at the allyl terminus trans to a better π-acceptor, which is supposed to be the diphenylphosphino group in the current ligand.[7d,11] In the present systems, the nucleophilic replacement would proceed through the complex **18a** with an M-shaped allyl moiety so as to provide the *R* configuration predominantly (Scheme 8).

Electronic Substituent Effects of Hybrid Ligands 8 and 11 on Asymmetric Allylations of Acyclic Substrates. To get a better understanding of the design of hybrid ligands in asymmetric allylic alkylations, we next examined the electronic effects. Electronic tuning of ligands has been one of our interests in catalytic asymmetric hydrogenations.[18] It is well documented that substituents on the ligands often play key roles electronically in various types of transition metal-catalyzed asymmetric reactions.[19] Several investigations on the electronic effects of ligands have been carried out in

(15) (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (b) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron*: *Asymmetry* **1991**, *2*, 663.

(16) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(17) Commercially available dichloromethane with water content less than 30 ppm (WAKO Chemical) was employed for the present experiments.

(18) For representative articles, see: (a) Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4477. (b) Morimoto, T.; Takahashi, H.; Fujii, K.; Chiba, M.; Achiwa, K. *Chem. Lett.* **1986**, 2061. (c) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1988**, *29*, 4755. (d) Inoguchi, K.; Morimoto, T.; Achiwa, K. *J. Organomet. Chem.* **1989**, *370*, C9. (e) Takahashi, H.; Achiwa, K. *Chem. Lett.* **1989**, 305. (f) Takahashi, H.; Morimoto, T.; Achiwa, K. *J. Synth. Org. Chem., Jpn.* **1990**, *48*, 29. (g) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169.

(19) For instance, for asymmetric hydrogenations, see: (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) RajanBabu, T. V.; Radetich, B.; You K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429. Asymmetric epoxidations, see: (c) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703. (d) Sasaki, H.; Irie, R.; Katsuki, T. *Synlett* **1994**, 356. Asymmetric hydrosilylations, see: (e) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306. Asymmetric hydrocyanations, see: (f) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265. (g) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325.

Table 1. Palladium-Catalyzed Asymmetric Allylic Transformations of 14a Using VALAP and Its Analogues as Ligands in Reaction 1[a]

entry	ligand	solvent	molar equiv of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	base	reaction temp. (°C)	reaction time (h)	yield[b] (%)	ee[c] (%)
1	**VALAP**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	98	95
2	**VALAP**	$ClCH_2CH_2Cl$	0.025	BSA-AcOLi	rt	24	97	94
3	**VALAP**	toluene	0.025	BSA-AcOLi	rt	24	61	91
4	**VALAP**	THF	0.025	BSA-AcOLi	rt	24	53	85
5	**VALAP**	CH_3CN	0.025	BSA-AcOLi	rt	24	11	94
6	**VALAP**	CH_2Cl_2	0.01	BSA-AcOLi	rt	24	93	95
7	**VALAP**	$ClCH_2CH_2Cl$	0.01	BSA-AcOLi	rt	24	90	93
8	**VALAP**	CH_2Cl_2	0.005	BSA-AcOLi	rt	24	74	93
9	**VALAP**	CH_2Cl_2	0.025	BSA-AcONa	rt	24	96	93
10	**VALAP**	CH_2Cl_2	0.025	BSA-AcOLi	rt	1	88	91
11	**VALAP**	CH_2Cl_2	0.025	BSA-AcOLi	−30	24	28	94
12	**VALAP**	THF	0.025	NaH	rt	1	86	71
13	**VALAP**	THF	0.025	NaH	−30	24	26	89
14	**7b**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	67	88
15	**7c**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	94	91
16	**7d**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	92	92
17	**12a**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	8	46
18	**12b**	CH_2Cl_2	0.025	BSA-AcOLi	rt	24	13	33

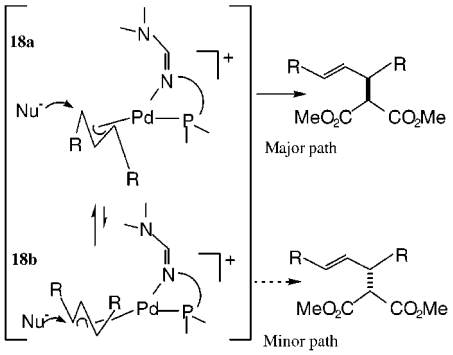
[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**14a**/dimethyl malonate/base = 0.5−2.5/2−10/100/300/300. [b] Isolated yield by preparation TLC on silica gel (toluene/AcOEt = 20:1). [c] The enantiometric excess was determined by HPLC with a chiral column, Daicel Chiralpack AD (*n*-hex/IPA = 20:1).

Table 2. Asymmetric Allylic Substitutions of 14b in Reaction 2[a]

entry	ligand	molar equiv of Pd dimer	molar ratio of ligand/Pd	yield[b] (%)	ee[c] (%)
1	**VALAP**	0.05	2	36	59
2	**VALAP**	0.025	2	27	60
3	**VALAP**	0.025	0.9	29	58
4	**7b**	0.025	2	4	67
5	**7c**	0.025	2	8	54

[a] Molar ratio: $[Pd(\eta^3\text{−}C_3H_5)Cl]_2$/ligand/**14b**/dimethyl malonate/BSA/AcOLi = 2.5−5/4.5−20/100/300/300/5. 3-Penten-2-yl pivalate was derived from commercially available *trans* 3-penen-2-ol (Aldrich). [b] The conversion yield was determined by GLC due to its volatality. [c] The enantiomeric excess was obtained using GLC with a chiral column, CP-Chiralsil-DEX CB.

Scheme 8



asymmetric allylic substitutions.[20] Thus, variations of substituents in a series of ligands **8** and **11** could lead to alternation in the catalytic activity, which provides useful information about development of ligands for different types of catalytic asymmetric transformations. The substitution effect on the catalytic activity was examined by using **14a**, and the results are tabulated. As can be seen from Table 3, clear electronic effects of the substituents in ligands **8** were observed with respect to both the enantioselectivity and the catalytic activity (**8b** < **8c** < **8a** < **8d** < **8e** < **8f**).[6] Among the chiral ligands tested, **8f** bearing a more electron-donating dimethylamino group at the para position on the phenyl group showed a dramatic improvement of catalytic activity together with excellent levels of asymmetric induction, giving **15a** quantitatively (Table 3, entry 6). The allylic substitution proceeded smoothly in the reduction of the catalyst amount to a 0.005 molar equiv of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ while still keeping a high level of the enantiomeric excess (Table 3, entry 7). It was proven that the potential activity of **8f** is superior to that of VALAP. This improved effect was also demonstrated in reaction 3.

Table 3. Effect of Substituents R on Ligands 8 and 11 in Reaction 1[a]

entry	ligand	R	molar equiv of $[Pd(\eta\text{-}C_3H_5)Cl]_2$	yield[b] (%)	ee[c] (%)
1	**8a**	H	0.025	57	52
2	**8b**	CO_2Me	0.025	42	19
3	**8c**	CF_3	0.025	46	38
4	**8d**	CH_3	0.025	76	74
5	**8e**	OMe	0.025	88	85
6	**8f**	NMe_2	0.025	99	92
7	**8f**	NMe_2	0.005	94	89
8	**11a**	H	0.025	75	86
9	**11b**	F	0.025	45	91
10	**11c**	OMe	0.025	93	84

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**14a**/dimethyl malonate/BSA/lithium acetate = 0.5−2.5/2−10/100/300/300/5. [b] Isolated yield by preparative TLC on silica gel. [c] The enantiometric excess was determined by HPLC with a chiral column, Daicel Chiralpack AD.

In contrast to the favorable effect with electron-donating substituents, introduction of electron-withdrawing groups into the ligands afforded detrimental effects. Although the steric influence of the substituents of the ligands should be considered, a net role of the electronic effects by substituents was clearly demonstrated in entries 3 and 4 where the ligands **8c** with a *p*-CF_3 group and **8d** bearing a *p*-CH_3 substituent were used. In this way, the clear evidence of the electronic influence in P−N hybrid ligands on palladium-catalyzed asymmetric allylic transformations could be demonstrated.

It is known that para-substituted styrene derivatives with electron-donating groups such as NMe_2 and OMe

(20) (a) Allen, J. V.; Bower, J. F.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1895. (b) Nomura, N.; Mermet-Bouvier, Y. C.; RajanBabu, T. V. *Synlett* **1996**, 745. (c) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.

Table 4. Asymmetric Allylic Substitutions of 16 in Reaction 3[a]

entry	ligand	molar equiv of Pd dimer	yield[b] (%)	ee[c] (%)
1	**VALAP**	0.05	trace	62
2	**7b**	0.05	24	68
3	**7c**	0.05	11	57
4	**8f**	0.05	25	69
5	**13**	0.025	64	>99

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**16**/dimethyl malonate/BSA/AcOLi = 2.5−5/6−12/100/300/300/5. [b] Isolated yield by preparative TLC on silica gel (toluene/AcOEt = 20/1). [c] Enantiometric excess for **17** was determined by GLC with a CP−Chirasil-DEX CB column.

stabilize cationic palladium(II)−styrene complexes.[21] The electronic effect caused by substituent of ligands in palladium complexes could affect the bond strength between metal−ligand in terms of more effective σ-donation of ligand to palladium than π-back-bonding from the metal. The predominant formation of reactive cationic palladium(II) complex prior to a neutral one in the equilibrium between two intermediate complexes is an essential factor for proceeding a catalytic cycle.[2i] However more cationic palladium(II) complexes activated by electron-withdrawing substituents tend to interact with anionic species such as the pivalate anion produced in the catalytic cycle, to provide neutral complexes. Thus, the free cationic palladium(II) complex stabilized by electron-donating groups might play a key role for the dramatic advancement of catalytic activity.

Variations on catalytic activities in the runs using S−N hybrid ligands **11** might be explained by the stability of the cationic palladium(II) complex in a manner similar to that for the ligands **8**. For instance, introduction of an electron-donating methoxy group would lead to an improvement of catalytic activity by stabilization of the cationic complex (Table 3, entry 10). In contrast to **11c**, the use of **11b** with an electron-withdrawing group exhibited opposite effects on both the catalytic activity and the enantioselectivity.

Asymmetric Allylic Substitutions of Cyclic Allyl Substrates. For the purpose of widespread applicability of the palladium-mediated substitution reaction, we next investigated asymmetric allylic transformations of sterically less demanding cyclic substrates. Among the substrates, asymmetric induction onto the cyclic allyl systems has been regarded as one of the most troublesome processes. Consequently, only a few examples of highly enantioselective induction over 90% ee have been reported to date.[14,22] In the asymmetric allylic transformations of cyclohexen-2-yl pivalate **16** catalyzed by the Pd−VALAP complex (reaction 3, Table 4), (*S*)-**17** was obtained in 62% ee (Table 4, entry 1), which was almost the same value of asymmetric induction as that with chiral phosphanyldihydrooxazoles.[23] The ligands **7b** and **8f** were found to be more effective in reaction 3, giving (*S*)-**17** in 68 and 69% ee, respectively (Table 4, entries 2 and 4). Among a series of the ligands **8** examined, only **8f** demonstrated significantly efficient catalytic activity, by which the electronic effect of substituents was again suggested.

Chiral diphosphine ligands with C_2-symmetry elements possessing a large bite angle induced remarkably high enantioselectivity for sterically less demanding cycloalkenyl substrates.[22a,c] Thus, the newly designed ligand **13** was applied to reaction 3. As expected, **13** exhibited high level of asymmetric induction, to give (*S*)-**17** over 99% ee in 64% yield (Table 4, entry 5),[9] where the versatility of our ligands for the variation of reaction types and substrates was successfully demonstrated. Like the transformation of the acyclic substrates by VALAP, better results were obtained by the use of dichloromethane as a solvent compared with the use of THF. In the latter case, a decrease in the catalytic activity (99% ee, 11% yield) was observed.

Asymmetric Allylic Transformations Using Ketene Silyl Acetals as a Nucleophile. Ordinary anionic species generated from malonates bearing a active methylene group, so-called stabilized soft nucleophiles, have been extensively investigated in the asymmetric allylic alkylations.[2] In contrast, unstabilized "harder" nucleophiles have attracted little attention, probably due to their poor ability of asymmetric induction.[2c,24] With the aim of expanding the scope of asymmetric allylic transformations, we focused on ketene silyl acetals (KSA) **19** as alternative nucleophiles to "harder" anionic species. Since ketene silyl acetals can be readily accessible from esters having α-hydrogen atoms, it is worthy to examine the possibility of KSA as nucleophiles.[25]

Thus, the KSA **19**[26] was used for asymmetric allylic substitutions, represented by reaction 4 using **14a** as the substrate, in place of corresponding harder nucleophiles such as anionic species of monoesters.[10h] The asymmetric substitution by **19** proceeded under usual reaction conditions at room temperature, where excellent levels of catalytic activity were observed (Table 5). The absolute configuration of **20a** was determined by HPLC analysis comparing with an authentic sample of *S*-configuration derived from (*R*)-**15a**.[10h] The reaction conditions discussed in Table 1 were also applicable to the present reaction, in which good yield and enantioselectivity in the production of **20** (Table 5, entries 1 and 9) were achieved using dichloromethane as a solvent compared with THF. Additionally, the analogous ligands **7b**−**d** exhibited comparable levels of asymmetric induction to VALAP, although the catalytic activity was somewhat lowered (Table 5, entries 4−6). Reduction in the yield was also observed with KSA **19b** having cyclohexyl group at R^1

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(22) (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (b) Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem Commun.* **1995**, 1845. (c) Dierkes, P.; Ramdeehul, S.; Barloy, L.; Cian, A. D.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3116.

(23) For asymmetric allylations of cycloalkenyl substrates by phosphanyldihydrooxazoles, see: (a) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595. (b) Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424. By other P−N hybrid ligands, see refs 10g and 15a.

(24) (a) Fiaud, J.-C.; Aribi-Zouioueche, L. *J. Organomet. Chem.* **1985**, *295*, 383. (b) Fiaud, J.-C.; Legros, J.-Y. *Tetrahedron Lett.* **1991**, *32*, 5089. (c) Fotiadu, F.; Cros, P.; Faure, B.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 77.

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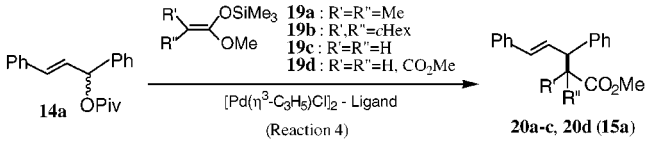
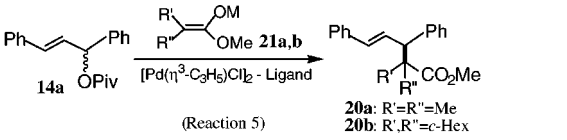
Table 5. Asymmetric Allylic Substitutions Using Ketene Silyl Acetals[a]



entry	ligand	KSA	molar equiv of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	solvent	yield[b] (%)	ee[c] (%)
1	**VALAP**	**19a**	0.025	CH_2Cl_2	78	90
2	**VALAP**	**19a**	0.01	CH_2Cl_2	43	87
3	**VALAP**	**19a**	0.025	THF	13	74
4	**7b**	**19a**	0.025	CH_2Cl_2	17	81
5	**7c**	**19a**	0.025	CH_2Cl_2	30	89
6	**7d**	**19a**	0.025	CH_2Cl_2	45	87
7	**(*S*)-BINAP**	**19a**	0.025	CH_2Cl_2	89	65
8	**(*S*)-BINAP**	**19a**	0.025	THF	6	83
9	**VALAP**	**19b**	0.025	CH_2Cl_2	42	90
10	**VALAP**	**19b**	0.025	THF	17	77
11	**7b**	**19b**	0.025	THF	11	79
12[d]	**VALAP**	**19c**	0.05	CH_2Cl_2		
13	**VALAP**	**19d**	0.025	CH_2Cl_2	93	93
14	**VALAP**	**19d**	0.025	THF	25	78

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**14a**/**19** = 1−5/4−20/100/300. [b] Isolated yield by preparative TLC on silica gel (toluene). [c] The enantiometric excess was determined by using HPLC with a chiral column. Daicel Chiralpak AD (*n*-hex/IPA = 40:1). [d] Reaction time: 85 h.

Table 6. Asymmetric Allylic Substitutions with Ester Enolates 21[a]



entry	enolate	M	solvent	reaction temp (°C)	reaction time (h)	yield[b] (%)	ee[c] (%)
1	**21a**	Li	THF	rt	24	89	59
2	**21a**	Li	THF	rt	1	75	59
3	**21a**	Li	THF	−20	24	73	59
4	**21b**	Li	THF	rt	24	92	57
5	**21a**	*n*-Bu_4N	THF	rt	24	88	12
6	**21a**	*n*-Bu_4N	THF	rt	1	76	13
7	**21a**	*n*-Bu_4N	THF	−20	24	11	14
8	**21a**	*n*-Bu_4N	DME	rt	24	27	14
9	**21**	*n*-Bu_4N	toluene	rt	24	41	25
10	**21a**	*n*-Bu_4N	CH_2Cl_2	rt	24	19	50
11	**21a**	*n*-Hex_4N	THF	rt	24	36	23
12	**21a**	*n*-Hex_4N	toluene	rt	24	2	29
13	**21a**	*n*-Hex_4N	CH_2Cl_2	rt	24	trace	

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**14a**/**21** = 2.5/10/100/300. [b] Isolated yield by preparative TLC on silica gel (toluene). [c] The enantiometric excess was determined by using HPLC with a chiral column, Daicel Chiralpak AD (*n*-hex/IPA = 40:1).

and R^2 (Table 5, entries 9−11), where some repulsive steric interaction between the ligand and the KSA might operate. The generality of this reaction was exhibited by runs using (*S*)-BINAP (Table 5, entries 7 and 8). Finally, no reactions with **19c** occurred even when the amount of the catalyst and the reaction time were increased. This result should originate from the lower nucleophilicity of **19c** compared with **19a**,**b**.

The reactive anionic species might be produced directly from dimethyl malonate in the well-known procedure[16] for the generation of the soft anionic nucleophile in the system of dimethyl malonate, BSA, and acetate salts. When dimethyl malonate was treated with BSA in the presence of AcOLi, formation of carbomethoxy ketene methyltrimethylsilyl acetal **19d** could not be detected by ^{1}H NMR analysis.[10h] This observation implies that BSA does not work as a silylating agent leading to **19d**, but acts as a base. The reaction probably proceeds by the nucleophilic attack of KSA on the π-allyl complex through an interaction of π-orbitals between the π-allyl and the carbon−carbon double bond of KSA. Another possible path is the nucleophilic attack of pivalate anion to the silyl group. The latter possibility might be adopted to the reactions with **19d** because satisfactory conversion was realized regardless of its lower nucleophilicity due to the electron-withdrawing group.

The capability of the imine−phosphine hybrid ligands **8** for the substitution with **19a** was then examined. The reaction using **8a** with no substituents on the phenyl ring afforded only a trace amount of **20a**, whereas the replacement with the stabilized anionic nucleophile yielded **15a** moderately. Although the same result was obtained with **8e**, ligand **8f** with fine electronic tuning was the sole ligand that exerted significant catalytic activity (32%, 67% ee) in the allylic replacement by **19a**. The change in the catalytic activity could support the mechanistic consideration based on the electronic substituent effect of ligands. As mentioned above, it can be considered that stabilization of the cationic palladium(II) complex is a key factor to conduct the reaction, especially in the case of less reactive nucleophiles. Recently, the quantitative investigation on the reactivity between cationic metal electrophiles and noncharged nucleophiles such as KSA and silyl enol ethers was reported, which suggests the reactivity of KSA toward the cationic palladium complex lies near a borderline.[27] Hence, the degree of stabilization of the cationic palladium(II) complex caused by variations of electronic effects of the ligands would result in significant change of catalytic activity.

The soft−hard principle is an interesting subject related to the influence upon the course of nucleophilic displacement reaction. For comparison to the reaction with KSA itself, the reaction with the "harder" ester enolates **21** generated from the reaction of KSA with methyllithium and tetraalkylammonium halides was next examined.

The results are summarized in Table 6, where a considerably different reactivity was demonstrated. The reaction with **21a** in THF resulted in lower enantioselectivity and higher reactivity compared with that using **19a** itself (Table 6, entries 1, 2, 5, and 6). The same behavior was observed in the use of the lithium enolate **21b** (Table 6, entry 4). Again, these results support that the reaction with KSA proceeds through the interaction between π-allylpalladium complex and KSA itself. In the reactions of ester enolates bearing tetraalkylammonium groups as a cationic part, a clear effect of both the size of ion pair and solvents on the reaction was observed. Trost

(26) Ketene methyltrimethylsilyl acetal **19c** was prepared as a 7:3 mixture with a C-silylated compound, methyltrimethylsilyl acetate. Carbomethoxy ketene methyltrimethylsilyl acetal **19d** tends to be hydrolyzed easily. Therefore, the hydrolyzed product dimethyl malonate was removed by distillation just before conducting the asymmetric reaction. For articles referring to the preparation of ketene silyl acetals, see: (a) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59. (b) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67. (c) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, 4311.

and co-workers reported the same trend of reaction influenced by counterions in the reactions of cyclopenten-2-yl acetate.[2c,22a] As expected from the previous study,[22a] the use of dichloromethane as a solvent caused an improvement in ee, probably due to the tightening ion pair or dimerization of enolates (Table 6, entry 10).[28] However, the degree of asymmetric induction was moderate compared with those listed in Table 6. In this way, an effectiveness of the approach employed KSA itself as a nucleophile was reconfirmed.

Mechanistic Views Concerning the Enantiodiscrimination in Allylic Substitutions. Mechanistic studies on the stereochemistry and reaction course of palladium-catalyzed allylic substitutions by soft nucleophiles have been well investigated.[29] The transformation consists of two sequential inversion processes, in which a π-allylpalladium(II) complex is first formed with the inversion through the substitution of the leaving group by a palladium(0) complex, followed by the nucleophilic attack to the allylic position from the site opposite to the metal. Despite the well-established catalytic cycle, reaction pathway, and stereochemistry, a key step for enantiodetermination is still ambiguous for these transformations. Recently, it has been reported that a late transition state (product-like) is a key step in the enantiodiscrimination.[15a,22c,30] Thus, after nucleophilic attack, a rotation occurs to give the Pd(0)−olefin complex, from which the products are released. Osborn and co-workers proposed a theory that the nucleophilic attack to the π-allyl complex and the subsequent rotation to the Pd−olefin complex proceed so as to avoid unfavorable steric repulsion.[22c]

Generally, for applying to various types of chiral ligands, the rotational mechanism for the enantiodetermining step was taken into consideration by the combination with the P/M chirality concept,[31] where the positioning array of four phenyl rings of diphosphine ligands, established by X-ray analysis, closely correlates with the absolute configuration of products in asymmetric hydrogenations.[9] Herein, we illustrate *Pr*(plus region)/*Mr*(minus region) chirality model to classify various chiral ligands and visualize the bulky quadrant in Figure 1. The gray circles are in accordance with the sterically hindered region assignable to quasiequatorial phenyl or bulky substituents.

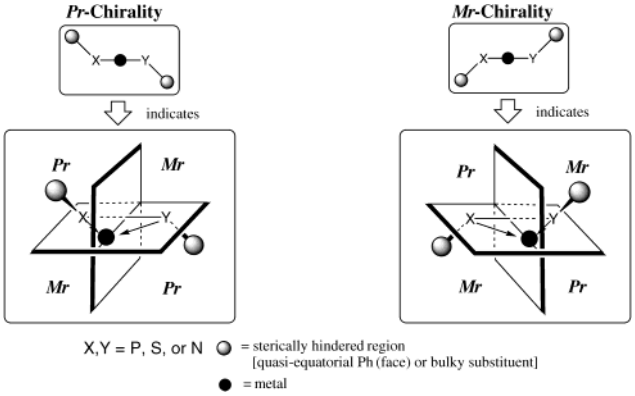


Figure 1. *Pr*/*Pr* chirality model.

Next, the correlation between the *Pr*/*Mr* chirality of ligands and the absolute configuration of products was investigated. Commercially available ligands and recently developed chiral auxiliaries are selected and classified as listed in Table 7, which includes new ligands in this study. (*S*)-BINAP, (*S*,*S*)-Chiraphos, and (*S*,*S*)-Norphos with *Mr* chirality[32] afforded (*R*)-**15a** in reaction 1,[15b] demonstrating a good correlation with the *Pr*/*Mr* chirality (Table 7, entries 4−6). (*S*)-**17** was produced using (*S*)-BINAP under the same conditions as those of entry 1 in Table 4 (Table 7, entry 14). Chiral oxazoline ligands **22a** with *Pr* chirality[11a] provided (*S*)-**15a** (Table 7, entry 3),[12] and (*R*)-**17** was obtained by **22b** (Table 7, entry 12).[14,23a] A C_2-symmetric diamino ligand, (−)-α-isosparteine **23**, which is considered to have *Mr* chirality from its molecular structure, gave the products with the expected configurations (Table 7, entries 7 and 15).[33] (*R*,*R*)-Duthixantphospholane **24** with *Mr* chirality also exhibited reasonable results for both acyclic and cyclic substrates as discussed in the preceding paper by Osborn and co-workers (Table 7, entries 8 and 16).[22c] The use of VALAP and **8f** led to the production of (*R*)-**15a** and (*S*)-**17**, which can correlate with *Mr* chirality of ligands (entries 1, 2, 9, and 10). Actually, from the study on the structure of a rhodium complex bearing a similar type of compound, it was suggested that the equatorial phenyl

(27) Kuhn, O.; Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 343.

(28) It has been demonstrated in the study for X-ray crystal structures of tetraalkylammonium enolates derived from malonates that the enolates present as dimeric structure even if the crystal was formed in DMSO; see: Reetz, M. T.; Hütte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339.

(29) (a) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3416. (c) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem Soc.* **1980**, *102*, 4730. (d) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (e) Åkermark, B.; Bäckvall, J. E.; Lowenborg, A.; Zetterberg, K. *J. Organomet. Chem.* **1979**, *166*, C33. (f) Åkermark, B.; Jutand, A. *J. Organomet. Chem.* **1981**, *217*, C41.

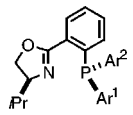
(30) (a) von Matt, P.; Lloyd-Jones, G.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Regger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (b) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108.

(31) (a) Sakuraba, S.; Morimoto, T.; Achiwa, K. *Tetrahedron*: *Asymmetry* **1991**, *2*, 597. The P/M chirality concept was further generalized by Pz(plus zone)/Mz(minus zone) chirality concept in which the course of reaction in asymmetric hydrogenations using chiral bisphospholane ligands could be well explained. (b) Achiwa, K. *Principles and Applications of Chiral Technology*; Industrial Publishing & Consulting: Japan, 1999. (c) Fujie, N.; Matsui, M.; Achiwa, K. *Chem. Pharm. Bull.* **1999**, *47*, 436.

(32) Crystal structures of palladium−BINAP complexes have been elucidated by several groups, in which equatorial phenyl substituents on each phosphorus atom of (*S*)-BINAP are found to occupy the positions assignable to *Mr* chirality; see: (a) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188. (b) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 83. (c) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 5040. (d) Yamaguchi, M.; Yabuki, M.; Yamagishi, T.; Sakai, K.; Tsubomura, T. *Chem. Lett.* **1996**, 241. (e) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. In ref 32b,c, structural studies for palladium−(*S*,*S*)-Chiraphos complexes were presented using multidimensional NMR spectroscopy and MM2 calculations. On the basis of these data, *Mr* chirality of (*S*,*S*)-Chiraphos was pointed out although less equatorial and axial character was demonstrated compared with the palladium−BINAP complex. Moreover, the X-ray crystal structure of rhodium complex with (*R*,*R*)-Chiraphos suggests that the ligand has two equatrial phenyl groups at the *Pr* position; see: Halpern, J. In *Asymmetric Synthesis Vol. 5*; Morruson, J. D., Ed.; Academic Press: New York, 1985. It is reasonable that (*S*,*S*)-Norphos is assigned to have *Mr* chirality from a similarity of molecular structure to (*S*,*S*)-Chiraphos. The results in rhodium-catalyzed asymmetric hydrogenation of *N*-benzoylhydrazone using (*R*,*R*)-Norphos also supported the assignment; see: Yamazaki, A.; Achiwa, I.; Horikawa, K.; Tsurubo, M.; Achiwa, K. *Synlett* **1997**, 455.

(33) Kang, J.; Cho, W. O.; Cho, H. G. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1347.

Table 7. Relationship between *Pr/Mr* Chirality of Ligands and Absolute Configuration of Products in Asymmetric Allylations



22a : Ar^1=Ar^2=Ph
22b : Ar^1=2-biphenylyl, Ar^2=Ph

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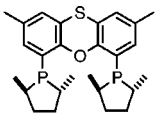

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entry	ligand	*Pr*/*Mr* chirality	substrate[a]	configuration (% ee)	ref
1	**VALAP**	*Mr*	A	*R* (95)	3
2	**8f**	*Mr*	A	*R* (92)	6
3	**22a**	*Pr*	A	*S* (94−98.5)	12
4	**(*S*)-BINAP**	*Mr*	A	*R* (30)	15b
5	**(*S*,*S*)-Chiraphos**	*Mr*	A	*R* (90)	15b
6	**(*S*,*S*)-Norphos**	*Mr*	A	*R* (81)	15b
7	**23**	*Mr*	A	*R* (88)	33
8	**24**	*Mr*	A	*R* (97)	22c
9	**VALAP**	*Mr*	B	*S* (62)	current
10	**8f**	*Mr*	B	*S* (69)	6
11	**13**	*Mr*	B	*S* (>99)	9
12	**22b**	*Pr*	B	*R* (51)	23a
13	**(*S*)-BINAP**	*Mr*	B	*S* (34)	current
14	**23**	*Mr*	B	*S* (62)	33
15	**24**	*Mr*	B	*S* (93)	22c

[a] A: 1,3-diphenylpropen-2-yl acetate or pivalate. B: cyclohexen-2-yl acetate or pivalate.

group belongs to *Mr* chirality.[34] The diphosphine ligand **13**, which affords (*S*)-**17**, is predicted to have *Mr* chirality from the view for VALAP.

The good correlation described above can be explained by mechanistic considerations for an enantiodiscriminating step in C_2-symmetric and heterohybrid ligands as depicted in Figure 2a,b. For the C_2-symmetric ligands, a possible conformation of π-allyl palladium complexes is limited due to the symmetrical element of ligands. Thus, the direction of nucleophilic attack could be controlled to avoid the steric repulsion in the late transition state. In two possible π-allyl complexes of the hybrid ligands, the nucleophilic attack proceeds at the allyl terminus trans to the better π-accepting phosphino group. The predominant π-allyl complex, which leads to a sterically favorable palladium−olefin complex in the late transition state, would exclusively receive the nucleophilic attack.

On the basis of this consideration, it is predicted that the ligand type described in Figure 2c may give a significant effect on the high level of asymmetric induction for cyclic allyl compounds. The phosphine−oxazoline hybrid ligand modified by the cymantrene unit,[14] in which *Pr* chirality on the nitrogen and *Mr* chirality on the phosphorus were demonstrated in the X-ray analysis, could be assigned to the case of Figure 2c. The use of the oxazoline ligand resulted in high levels of asymmetric induction for cycloalkenyl substrates.

As depicted in Figure 2d for the heterohybrid type with the predominant steric effect on the nitrogen site, a possibility through the nucleophilic attack to the allyl terminus trans to the nitrogen may be considered in the case that the steric effect on the nitrogen site is large and the equilibrium between two possible complexes is directed to one side. Actually, an example assignable to the consideration was recently demonstrated in the imine−sulfide hybrid ligand.[7h] In this case, it was clearly shown by the X-ray analysis that the *o*-chlorophenyl group on the imino nitrogen is sterically more effective than the phenyl substituent on the sulfur atom. Although the bond length between the palladium metal and the allyl carbon trans to the sulfide is longer than that trans to the imino nitrogen, the nucleophilic attack may procced at the position trans to the nitrogen by the predominant steric control compared with the electronic effect.

Adaptability of the consideration mentioned above give helpful information for design of effective ligands as well as prediction of the stereochemistry of products in this type of transformations.

Conclusion

It is meaningful to consider that the versatility on designing chiral ligands, which can easily lead to a variety of structural modification, is applicable to different types of reactions and substrates. With this concept, a new class of chiral amidine−phosphine hybrid ligands **7** were first developed by using chiral source of α-amino acids, L-valine and L-*tert*-leucine. A variety of chiral P−N or S−N hybrid ligands **8** and **11** with electronic tuning and a new C_2-symmetric diphosphine ligand **13** were readily prepared from the synthetic precursor of **7a** (VALAP). Replacement of the dimethylamino group by secondary amines such as pyrrolidine and piperidine in the amidine skeleton was successfully demonstrated. In asymmetric allylic substitutions of 1,3-diphenylpropen-2-yl pivalate (**14a**) with the anion of dimethyl malonate, high enantioselectivity of up to 95% ee was achieved using newly developed hybrid ligands. Though the hybrid ligands were less effective to palladium-catalyzed allylic alkylations of sterically less demanding cyclohexen-2-yl pivalate (**17**), extremely high levels of asymmetric induction of over 99% ee were attained by the use of diphosphine ligand **13**. In this way, the versatility of the new ligands was demonstrated.

The electronic influence of ligands on the asymmetric allylations with **8** was investigated and clearly demonstrated that the use of chiral ligand **8f** having a more electron-donating dimethylamino group at the para position on the phenyl group led to a dramatic improvement of catalytic activity together with an excellent level of asymmetric induction.

With the aim of expanding the synthetic scope of asymmetric allylic substitutions, ketene silyl acetals were used as nucleophiles that afforded excellent levels of enantioselective alkylations. This approach can extend not only the utility of asymmetric alkylations but also applicability of the less stabilized "harder" nucleophiles such as anionic species of monoesters in organic synthesis.

In a mechanistic consideration of asymmetric allylic transformations of both acyclic and cyclic allyl substrates, we considered *Pr*(plus region)/*Mr*(minus region) chirality model with respect to the rotational mechanism for the stereodetermining step for applying to various types of chiral ligands, by which a good correlation between the *Pr*/*Mr* chirality of ligands and the direction of enantiodiscrimination at the late transition state was demonstrated.

(34) The X-ray crystal structure of a rhodium complex with a P−N hybrid ligand based on L-valine consisting of bis (4-methylphenyl)-phosphino and 4-methoxybenzylamino groups indicates that the ligand has *Mr* chirality; see: Berger, H.; Nesper, R.; Pregosin, P. S.; Rüegger, H.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 1520.

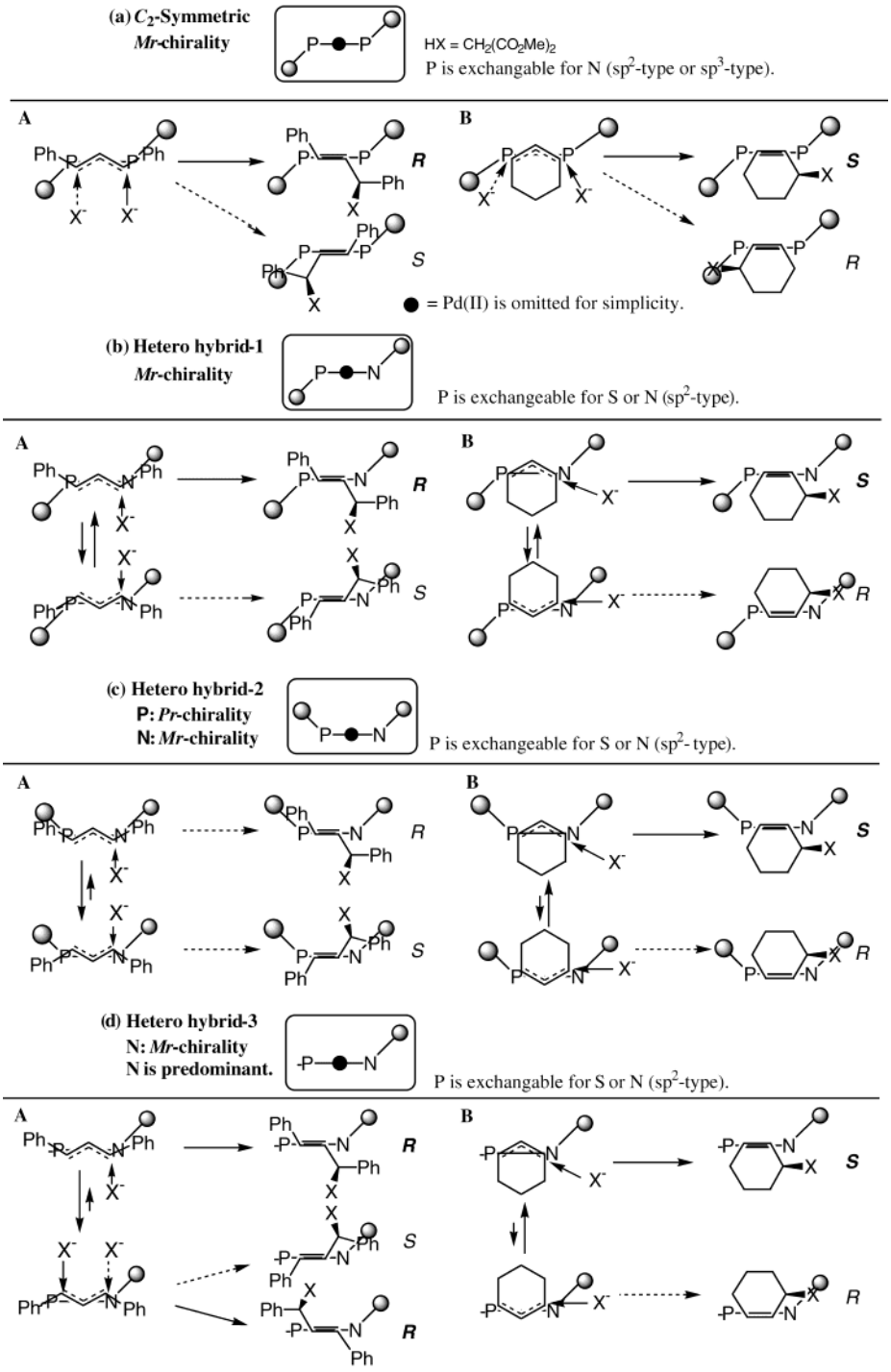

Figure 2. Preferable paths predicted by *Pr*/*Mr* chirality model

In conclusion, we believe the newly developed ligand systems in this study can provide us useful information about the design of chiral ligands. Studies on applying other type of reactions and substrates are in progress.

Experimental Section

General Procedures. ^1H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ solution at 270, 67.8, and 161.7 MHz, respectively. Chemical shift values are expressed in ppm relative to tetramethylsilane for ^1H, $CDCl_3$ for ^{13}C, and phosphoric acid for ^{31}P. IR spectra were obtained using an FT-IR instrument. For fast-atom bombardment (FAB)-MS, the samples were dissolved in 3-nitrobenzyl alcohol matrix, and the measurement was performed using xenone atoms. High-resolution mass spectra (HRMS) were obtained at the Institute for Chemical Research, Kyoto University. Gas chromatographic analysis was performed using an SE-30 capillary column (0.25 mm × 50 m) for a general analysis or Chirasil-DEX CB(0.25 mm × 50 m) for determining the enantiomeric excess of optically active products. High-pressure liquid chromatography (HPLC) with a Daicel Chiralpak AD column was employed to determine the enatiomeric excess. Melting points are uncorrected. Column chromatographic isolation was conducted using silica gel 60 (70−230 mesh, Merck). Silica gel 60 F254 aluminum plates (Merck) were

employed as a thin-layer chromatography (TLC). Silica gel 60 F254 (0.5 and 2 mm, Merck) was used for preparative TLC.

Reagents. In general, all organic reagents were used as received. Dimethyl malonate was distilled in vacuo and dried over molecular sieves. THF was distilled over sodium metal/benzophenone ketyl and used as a peroxide-free solvent. For the catalytic reactions, dehydrated dichloromethane, toluene, and acetonitrile were purchased and degassed before exposure to the reaction. Dehydrated and degassed 1,2-dichloroethane and DME were dried over activated molecular sieves. Pyridine was dried by storing in the presence of sodium hydroxide. Tetrabutylammonium fluoride and terahexylammonium bromide were dried in an oil bath at 70−80 °C under reduced pressure (4 mmHg) prior to use.

General Procedure for 7a,b. The preparation of **3a**−**6a** was documented in the preceding article.[9b]

(*S*)-[1-(Hydroxymethyl)-2,2-dimethylpropyl]carbamic Acid 1,1-Dimethylethyl Ester (3b). To a mixture of L-*tert*-leucinol (**2b**) (1 g, 8.55 mmol) and Et_3N (1.02 g, 10.1 mmol) in CH_2Cl_2 (30 mL) was added di-*tert*-butyl dicarbonate (2.21 g, 10.1 mmol) in an ice-cold bath at 0 °C, followed by stirring at 0 °C for 1 h and at room temperature for 8 h. The reaction mixture was washed with brine and dried over $MgSO_4$. Volatile fractions were removed in vacuo, affording **3a** as a white solid (1.72 g, 93%): $[\alpha]^{23}_D$ +8.5 (*c* 0.4, MeOH); mp 102−103 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.46 (s, 9H), 2.17 (brs, 1H), 3.49 (d, 2H, J = 7.6 Hz), 3.80−3.87 (m, 1H), 4.62 (brs, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 28.4, 33.6, 61.0, 63.2, 79.6; IR (KBr) 3376, 1680, 1562 cm^{-1}; FAB-MS *m*/*z* 218 (MH^+).

(*S*)-[-2,2-Dimethyl-1-[[[(4-methylphenyl)sulfonyl]-oxy]methyl]propyl]carbamic Acid 1,1-Dimethylethyl Ester (4b). *p*-Toluenesulfonyl chloride (1.55 g, 8.12 mmol) dissolved in pyridine (5 mL) was added dropwise to **3b** (1.64 g, 7.56 mmol) in pyridine (15 mL) at −35 °C under argon. The resulting solution was stirred at low temperature for 18 h and in an ice−water bath for 1 h. The excess pyridine was quenched with 10% HCl aqueous solution. The product thus obtained was extracted into AcOEt. The extraction was successively washed with saturated aqueous $NaHCO_3$ and brine. The reaction mixture was dried over $MgSO_4$ and concentrated under vacuum. The product **4b** was isolated as a white wax using silica gel column chromatography eluted by a 20:1 mixture of toluene and AcOEt (1.54 g, 55%): $[\alpha]_D^{26}$ −1.04 (*c* 0.6, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.42 (s, 9H), 3.57−3.64 (m, 1H), 4.04−4.17 (m, 2H), 4.62 (brd, 1H, J = 9.6 Hz), 7.35 (d, 2H, J = 8.2 Hz), 7.79 (d, 2H, J = 8.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 26.7, 28.2, 34.1, 56.8, 69.5, 79.4, 127.9, 129.8, 132.6, 144.9, 155.6; IR (KBr) 3299, 1721, 1537, 1358, 1177 cm^{-1}; FAB-MS *m*/*z* 372 (MH^+).

(*S*)-[1-[(Diphenylphosphino)methyl]-2,2-dimethylpropyl]carbamic Acid 1,1-Dimethylethyl Ester (5b). Potassium diphenylphosphide 0.5 M THF solution (7.9 mL, 3.95 mmol) was added to **4b** (700 mg, 1.89 mmol) in THF (35 mL) at −35 °C under argon. After being stirred for 10 h while cooling was continued, the solution was allowed to warm to room temperature and filtered through Celite. After evaporation of the solvent, **5b** was isolated as a white solid (315 mg, 43%) by silica gel column chromatography using toluene containing 0.5 vol % of Et_3N as the eluent: $[\alpha]^{27}_D$ +43.2 (*c* 0.6, $CHCl_3$); mp 79−81 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.85 (s, 9H), 1.42 (s, 9H), 1.89−1.99, 2.34−2.40 (m, 2H), 3.44−3.56 (m, 1H), 4.29 (d, 1H, J = 10.8 Hz), 7.28−7.45 (m, 10H); IR (KBr) 3410, 1698, 1514 cm^{-1}; FAB-MS *m*/*z* 386 (MH^+).

(*S*)-1-(Diphenylphosphino)-3-methyl-2-butanamine (6b). To a stirred solution of **5b** (250 mg, 0.649 mmol) in CH_2Cl_2 (25 mL) was added trifluoroacetic acid (2.4 mL, 30.9 mmol) in an ice−water bath under argon. The solution was stirred at low temperature for 1 h and room temperature overnight. The resulting solution was quenched with water. The water layer neutralized with aqueous NaOH was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. From the solution dried over $MgSO_4$, the solvent was removed under vacuum, giving **6b** as a viscous liquid (158 mg, 85%): $[\alpha]^{28}_D$ +141.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.71−1.82 (m, 1H), 2.41−2.50 (m, 2H), 7.29−7.52 (m, 10H); IR (neat) 3382, 1591 cm^{-1}; FAB-MS *m*/*z* 285 (MH^+).

(*S*)-*N*′-[1-[(Diphenylphosphino)methyl]-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide, VALAP (7a). A mixture of **6a** (1.90 g, 7 mmol) and *N*,*N*-dimethylformamide dimethylacetal (4.49 g, 5 mL, 37.7 mmol) was stirred at room temperature for 3 h. The reaction was monitored by gas chromatography. After removal of the volatile fractions in vacuo, VALAP **7a** was obtained in a virtually quantitative yield. The product was purified as a colorless viscous liquid by silica gel column chromatography eluted by toluene including 0.5 vol % of Et_3N, followed by checking the purity by using gas chromatography before use: $[\alpha]^{28}_D$ +34.1 (*c* 0.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.6 Hz), 1.73−1.83 (m, 1H), 2.37 (d, 2H, J = 3.5 Hz), 2.67 (s, 6H), 2.69−2.79 (m, 1H), 6.98 (s, 1H), 7.25−7.44 (m, 10 H); ^{31}P{^{1}H} NMR (161.7 MHz, $CDCl_3$, H_3PO_4) δ −17.89; IR (neat) 1651 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{27}N_2P$ 326.1914, found 326.1905.

(*S*)-*N*′-[1-[(Diphenylphosphino)methyl]-2,2-dimethylpropyl]-*N*,*N*-dimethylmethanimidamide (7b). The same procedure as that for **7a** was employed. Viscous liquid: yield quant; $[\alpha]^{27}_D$ +63.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (s, 9H), 2.32 (d, 2H, J = 6.9 Hz), 2.57−2.64 (m, 1H), 2.68 (s, 6H), 6.92(s, 1H), 7.29−7.45 (m, 10H); ^{31}P{^{1}H} NMR (161.7 MHz, $CDCl_3$, H_3PO_4) δ −16.81; IR (KBr) 1649 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{29}N_2P$ 340.2054, found 340.2086.

General Procedure for the Substitution Reactions of the Dimethylamino Group of VALAP with Secondary Amines. The replacement reaction to **7c** is typical.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl]-*N*-[(1-pyrrolidino)methylene]amine (7c). A mixture of VALAP **7a** (250 mg, 0.767 mmol) and pyrrolidine (1.70 g, 2 mL, 24.0 mmol) was degassed and heated in the presence of 10-camphorsulfonic acid (10 mg, 0.0430 mmol) at reflux under argon. The reaction was periodically monitored by gas chromatography. The reaction mixture was stirred overnight and cooled to room temperature. The resulting solution was diluted with toluene, followed by washing the organic phase with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified using silica gel column chromatography eluted by toluene including 0.5 vol % of Et_3N, followed

by checking the purity by using gas chromatography before the use. The modified amidine **7c** was obtained as a viscous liquid (154 mg, 57%): $[\alpha]^{23}_D$ +45.8 (*c* 0.6, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 1.75−1.80 (m, 4H), 2.40 (d, 2H, J = 5.6 Hz), 2.62−2.73 (m, 1H), 3.09−3.20 (m, 4H), 7.21 (s, 1H), 7.27−7.46 (m, 10 H); IR (neat) 1644 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{29}N_2P$ 352.2071, found 352.2093.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl]-*N*-[(1-piperidino)methylene]amine (7d): viscous liquid; yield 30%; $[\alpha]^{25}_D$ +54.9 (*c* 0.4, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.44−1.56 (m, 6H), 1.69−1.82 (m, 1H), 2.36 (d, 2H, J = 6.9 Hz), 2.63−2.74 (m, 1H), 3.00−3.17 (m, 4H), 6.96 (s, 1H), 7.25−7.45 (m, 10 H); IR (neat) 1644 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{31}N_2P$ 366.2227, found 366.2246.

Procedure for Imine−Phosphine Hybrid Ligands (8). (*S*)-1-(Diphenylphosphino)-3-methyl-2-butanamine (**6a**) (400 mL, 1.48 mmol) was reacted with the corresponding benzaldehydes (1.48 mmol) in 3 mL of toluene at room temperature under an argon atmosphere overnight. The solvent was stripped off in vacuo. ^1H NMR spectra of the products showed the quantitative conversion of **6a** to the desirable imine−phosphine hybrid ligands **8**. The hybrid ligands except for **8b** were distilled in vacuo using Kugelrohr before the application to asymmetric reactions.

(*S*)-*N*-Benzylidene-[1-[(diphenylphosphino)methyl]-2-methylpropyl]amine (8a): viscous liquid; $[\alpha]^{25}_D$ +113.4 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 4.3 Hz), 0.93 (d, 3H, J = 4.3 Hz), 1.93−2.05 (m, 1H), 2.49 (d, 2H, J = 6.6 Hz), 2.67 (s, 6H), 2.97−3.07 (m, 1H), 7.21−7.62 (m, 15H), 8.03 (s, 1H); IR (neat) 1644 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{26}NP$ 359.1805, found 359.1791.

(*S*)-*N*-(4-Carbomethoxybenzylidene)-[1-[(diphenylphosphino)methyl]-2-methylpropyl]amine (8b): viscous liquid; $[\alpha]^{24}_D$ +128.4 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz), 0.94 (d, 3H, J = 7.3 Hz), 1.94−2.06 (m, 1H), 2.50 (d, 2H, J = 8.2 Hz), 3.03−3.13 (m, 1H), 3.93 (s, 3H), 7.19−7.46 (m, 10H), 7.63 (d, 2H, J = 8.3 Hz), 8.01 (d, 2H, 8.3 Hz), 8.07 (s, 1H); IR (neat) 1725, 1642 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{28}O_2NP$ 417.1859, found 417.1832.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl)]-*N*-(4-trifluoromethylbenzylidene)amine (8c): viscous liquid; $[\alpha]^{24}_D$ +95.7 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.9 Hz), 1.94−2.06 (m, 1H), 2.50 (d, 2H, J = 8.3 Hz), 3.03−3.14 (m, 1H), 7.20−7.47 (m, 10H), 7.32 (d, 2H, 8.2 Hz), 7.67 (d, 2H, 8.6 Hz), 8.06 (s, 1H); IR (KBr) 1647, 1325 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{25}NF_3P$ 427.1679, found 427.1687.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl)]-*N*-(4-methylbenzylidene)amine (8d): viscous liquid; $[\alpha]^{23}_D$ +105.7 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 5.6 Hz), 0.92 (d, 3H, J = 5.6 Hz), 1.92−2.04 (m, 1H), 2.36 (s, 3H), 2.48 (d, 2H, J = 7.3 Hz), 2.93−3.03 (m, 1H), 7.14−7.51 (m, 14H), 7.98 (s, 1H); IR (neat) 1645 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{28}NP$ 373.1961, found 373.1972.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl)]-*N*-(4-methoxybenzylidene)amine (8e): viscous liquid; $[\alpha]^{26}_D$ +103.9 (*c* 0.6, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 6.3 Hz), 0.92 (d, 3H, J = 6.3 Hz), 1.91−2.05 (m, 1H), 2.48 (d, 2H, J = 6.6 Hz), 2.95−3.05 (m, 1H), 3.83 (s, 3H), 6.87 (d, 2H, J = 8.9 Hz), 7.22−7.56 (m, 1H), 7.95 (s, 1H); IR (neat) 1644, 1252, 1032 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{28}ONP$ 389.1910, found 389.1929.

(*S*)-[1-[(Diphenylphosphino)methyl]-2-methylpropyl)]-*N*-(4-(dimethylamino)benzylidene)amine (8f): white solid; $[\alpha]^{25}_D$ +217.1 (*c* = 1.0, $CHCl_3$); mp 57−58 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 6.4 Hz), 0.91 (d, 6H, J = 6.4 Hz), 1.91−2.03 (m, 1H), 2.47 (d, 2H, J = 8.2 Hz), 2.86−2.93 (m, 1H), 3.00 (s, 6H), 6.66 (d, 2H, J = 8.9 Hz), 7.23−7.51 (m, 12 H), 7.88 (s, 1H); ^{31}P-{^1H} NMR (161.7 MHz, $CDCl_3$, H_3PO_4) δ −19.55; IR (KBr) 1638 cm^{-1}; HRMS(EI) calcd for $C_{26}H_{31}N_2P$ 402.2227, found 402.2233. Anal. Calcd for $C_{26}H_{31}N_2P$: C, 77.58; H, 7.76; N, 6.96. Found: C, 77.63; H, 7.71; N, 6.91.

(*S*)-*N*′-[1-[(Phenylthio)methyl]-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide (11a). A solution of (*S*)-3-methyl-1-(phenylthio)-2-butanamine (**10a**) (212 mg, 1.09 mmol) and *N*,*N*-dimethylformamide dimethylacetal (2.69 g, 3 mL, 22.6 mmol) was stirred at room temperature for 5 h. The reaction was monitored by gas chromatography. Removal of the excess acetal gave **11a** quantitatively. The product was purified by silica gel column chromatography (5:1 mixture of toluene and AcOEt), followed by checking the purity by using gas chromatography before the use: $[\alpha]^{27}_D$ +76.9 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (d, 3H, J = 6.9 Hz), 0.90 (d, 3H, J = 6.9 Hz), 1.74−1.88 (m, 1H), 2.74−2.80 (m, 1H), 2.79 (s, 6H), 3.01 (dd, 1H, J_{BX} = 9.2 Hz, J_{AB} = 12.5 Hz), 3.21 (dd, 1H, J_{AX} = 3.6 Hz, J_{AB} = 12.5 Hz), 7.15 (s, 1H), 7.09−7.33 (m, 4H), 7.95 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.6, 19.9, 33.2, 39.2, 71.2, 125.0, 128.4, 128.5, 137.8, 154.3; IR (neat) 1649 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}N_2S$ 250.1506, found 250.1506.

General Procedure for Preparation of 11b,c from 4b,c. A representative procedure from **4b**,**c** to **11b**,**c** was described by the preparation of **11b**.

(*S*)-[1-[(4-Fluorophenylthio)methyl]-2-methylpropyl]carbamic Acid 1,1-Dimethylethyl Ester (9b). A solution of *p*-fluorothiophenol (700 mg, 5.47 mmol) in THF (3 mL) was added to a suspension of NaH (150 mg, 6.25 mmol, prewashed with *n*-pentane) in THF (15 mL) in an ice−water bath, followed by stirring for 1 h. To the solution was added **4a** (900 mg, 2.53 mmol) in THF (5 mL), and the reaction mixture was stirred at room temperature overnight. Celite filtration and concentration of the filtrate followed by silica gel column chromatography eluted by toluene/AcOEt (20:1) afforded **9b** (546 mg, 69%): white solid; $[\alpha]^{24}_D$ +32.6 (*c* 0.6, $CHCl_3$); mp 84−85 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz), 1.43 (s, 9H), 1.83−1.96 (m, 1H), 2.99 (d, 2H, J = 5.9 Hz), 3.56−3.67 (m, 1H), 4.52 (brd, 1H, J = 10.8 Hz), 6.95−7.04 (m, 2H), 7.36−7.42 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.7, 19.4, 28.4, 30.8, 38.9, 55.1, 79.2, 115.9, 116.2, 131.2, 132.8, 132.9, 155.6, 163.7; IR (KBr) 3304, 1674, 1539, 1175 cm^{-1}; FAB-MS *m*/*z* 314 (MH^+).

(*S*)-1-(4-Fluorophenylthio)-3-methyl-2-butanamine (10b). To a solution of **9b** (515 mg, 1.65 mmol) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (9.12 g, 6.2 mL, 51.9 mmol) in an ice−water bath. After the mixture was stirred at room temperature overnight, water was added. The water phase neutralized with a NaOH aqueous solution and then extracted with CH_2-

Cl_2. The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ and brine, followed by drying over anhydrous $MgSO_4$. The solvent was evaporated to afford the desired amine **10b** as a transparent liquid (313 mg, 89%): $[\alpha]^{23}_D$ +85.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.9 Hz), 1.65−1.77 (m, 1H), 2.68 (d, 2H, J = 9.2 Hz), 3.06−3.16 (m, 1H), 6.98 (d, 1H, J = 8.6 Hz), 7.01 (d, 1H, J = 8.6 Hz), 7.35 (d, 1H, J = 5.3 Hz), 7.38 (d, 1H, J = 5.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.5, 19.2, 32.9, 41.5, 55.3, 115.8, 116.1, 131.1, 132.3, 132.4, 159.9; IR (neat) 3376, 1589, 1227 cm^{-1}; FAB-MS *m*/*z* 214 (MH^+).

(*S*)-*N*′-[1-[(4-Fluorophenylthio)methyl]-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide (11b). A mixture consisting of **10b** (300 mg, 1.51 mmol) and *N*,*N*-dimethylacetamide dimethylacetal (2.69 g, 3 mL, 22.6 mmol) was stirred at room temperature for 5 h. The reaction was monitored by gas chromatography. After removal of the volatile fractions in vacuo, the desired product **11b** was obtained as a viscous liquid quantitatively. The product was exposed to silica gel column chromatography (toluene with 0.5 vol % of Et_3N) before the asymmetric reactions: $[\alpha]^{25}_D$ +62.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz), 1.73−1.86 (m, 1H), 2.68−2.75 (m, 1H), 2.79 (s, 6H), 2.99 (dd, 1H, J_{BX} = 8.9 Hz, J_{AB} = 12.5 Hz), 3.15 (dd, 1H, J_{AX} = 3.6 Hz, J_{AB} = 12.5 Hz), 6.94 (d, 2H, J = 8.6 Hz), 6.96 (d, 2H, J = 8.6 Hz), 7.15 (s, 1H), 7.29 (d, 2H, J = 5.3 Hz), 7.33 (d, 2H, J = 5.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.7, 19.9, 33.3, 37.1, 40.6, 71.5, 115.4, 115.8, 131.2, 131.4, 132.7, 154.4, 159.4; IR (neat) 1649, 1225 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{21}N_2FS$ 268.1411, found 268.1425.

(*S*)-[1-[(4-Methoxyphenylthio)methyl]-2-methylpropyl]carbamic acid 1,1-demethylethyl ester (9c): white solid; yield 70%; mp 74−75 °C; $[\alpha]^{25}_D$ +34.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 1.43 (s, 9H), 1.83−1.96 (m, 1H), 2.95 (d, 2H, J = 5.3 Hz), 3.52−3.63 (m, 1H), 3.79 (s, 3H), 4.54 (brd, 1H, J = 5.4 Hz), 6.84 (d, 2H, J = 8.9 Hz), 7.39 (d, 2H, J = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.7, 19.3, 28.3, 30.8, 39.5, 55.2, 78.9, 114.5, 126.3, 133.5, 155.6, 158.9; IR (KBr) 3382, 1684, 1524, 1246, 1028 cm^{-1}; FAB-MS *m*/*z* 326 (MH^+).

(*S*)-1-(4-Methoxyphenylthio)-3-methyl-2-butanamine (10c): viscous liquid; yield 92%; $[\alpha]^{25}_D$ +85.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz), 1.63−1.75 (m, 1H), 2.62 (d, 2H, J = 7.9 Hz), 3.01−3.10 (m, 1H), 3.80 (s, 3H), 6.84 (d, 1H, J = 8.9 Hz), 7.36 (d, 1H, J = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.5, 19.2, 32.8, 42.2, 55.3, 114.5, 126.2, 133.2, 158.9; IR (neat) 3364, 1593, 1244, 1032 cm^{-1}; FAB-MS *m*/*z* 226 (MH^+).

(*S*)-*N*′-[1-[(4-Methoxyphenylthio)methyl]-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide (11c): viscous liquid; yield quant; $[\alpha]^{24}_D$ +87.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.71−1.84 (m, 1H), 2.66−2.73 (m, 1H), 2.81 (s, 6H), 2.94 (dd, 1H, J_{BX} = 8.6 Hz, J_{AB} = 12.5 Hz), 3.12 (dd, 1H, J_{AX} = 3.6 Hz, J_{AB} = 12.5 Hz), 3.79 (s, 3H), 6.82 (d, 2H, J = 8.9 Hz), 7.15 (s, 1H), 7.31 (d, 2H, J = 8.9 Hz), 7.95 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.7, 19.9, 33.1, 37.0, 41.3, 55.1, 71.3, 114.2, 127.9, 132.1, 154.3, 158.2; IR (neat) 1649, 1244, 1034 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}ON_2S$ 280.1611, found 280.1585.

[1*R*,2*R*-[1α(*E*),2α(*E*)]]-*N*,*N*′-Bis(dimethylaminomethylene)-1,2-cyclohexanediamine (12a). A mixture of (1*R*,2*R*)-1,2-diaminocyclohexane (500 mg, 4.38 mmol) and *N*,*N*-dimethylformamide dimethylacetal (4.49 g, 5 mL, 37.7 mmol) was stirred at room temperature for 3 h. The reaction was followed by gas chromatography. The volatile fractions were stripped off in vacuo, affording **12a** quantitatively. The product was purified as a transparent liquid using Kugelrohr (150−160 °C/4−5 mmHg): $[\alpha]^{25}_D$ −192.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33−1.78 (m, 10H), 2.76 (s, 12H), 7.20 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.5, 34.9, 37.4, 70.1, 155.4; IR (neat) 1651 cm^{-1}; FAB-MS *m*/*z* 225 (MH^+); HRMS (EI) calcd for $C_{12}H_{24}N_4$ 224.2003, found 224.1984.

[1*R*,2*R*-[1α(*E*),2α(*E*)]]-*N*,*N*′-Bis(dimethylaminomethylene)-1,2-diphenylethylenediamine (12b). A solution of (1*R*,2*R*)-1,2-diphenylethylenediamine (100 mg, 0.471 mmol) and *N*,*N*-dimethylformamide dimethylacetal (1.79 g, 2 mL, 15.1 mmol) was stirred in a flask immersed in an oil bath at 50 °C for 2 h. The reaction was monitored by gas chromatography. After removal of the volatile fractions, the diamidine **12b** was produced as white solid quantitatively. The product was recrystallized as a white solid from a mixture of *n*-hexane and AcOEt. Although the ^{13}C NMR spectrum of the product suggests the presence of a minor rotational isomer, the solids were used for the catalytic reaction as it stands: $[\alpha]^{26}_D$ −133.8 (*c* 1.05, $CHCl_3$); mp 99−100 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.82 (s, 12H), 4.15 (s, 2H), 7.03−7.14 (m, 10H), 7.27 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 37.0, 77.5, 125.9, 126.5, 127.4, 128.1, 128.6, 143.1, 144.0, 153.5, 155.3; IR (KBr) 1645 cm^{-1}; FAB-MS *m*/*z* 323 (MH^+); HRMS (EI) calcd for $C_{20}H_{26}N_4$ 322.2160, found 322.2135.

General Procedure for Reactions 1−3. The reaction types 1−3 are typified by the reaction using **14a** as a substrate. A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 0.0109 mmol) and VALAP (14.2 mg, 0.0436 mmol) in CH_2Cl_2 (1 mL, dry and oxygen free) was stirred at room temperature under argon, followed by addition of **14a** (128 mg, 0.436 mmol) in CH_2Cl_2 (1 mL). To the mixture was added a nucleophilic solution prepared in another flask by mixing dimethyl malonate (173 mg, 1.31 mmol) and BSA (266 mg, 1.31 mmol) in the presence of lithium acetate (1.4 mg, 0.0218 mmol) in the solvent (1 mL). The reactions were monitored by TLC. The solution was stirred under the required conditions, and the volatile fractions were removed in vacuo. The residue was purified by preparative TLC (toluene/EtOAc = 20/1).

Representative Procedure for Reaction 4. The reaction catalyzed by the Pd−VALAP complex using **19a** as ketene silyl acetals is described as a representative procedure for the reaction type 4. The palladium chloride dimer, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 0.0109 mmol) and VALAP (14.2 mg, 0.0436 mmol) were combined in CH_2Cl_2 (1 mL, dry and degassed) under argon and stirred at room temperature for 15 min. To the solution was added the allylic pivalate **14a** (128 mg, 0.0436 mmol) in CH_2Cl_2 (1 mL), followed by stirring for 30 min. The resulting catalyst solution was treated with **19a** (228 mg, 1.31 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred under the required conditions, the volatile fractions were stripped off immediately. The residue was purified by preparative TLC using toluene as the eluent.

(*S*)-α,α-Dimethyl-β-(2-phenylethenyl)benzenepropanoic acid methyl ester (20a): $[\alpha]^{26}_D$ −43.1 (*c* 0.7, EtOH) for **20a** with 90% ee; ^{1}H NMR (270 MHz, $CDCl_3$)

δ 1.18 (s, 3H), 1.23 (s, 3H), 3.60 (s, 3H), 3.75 (d, 1H, J = 9.6 Hz), 6.45 (d, 1H, J = 15.8 Hz), 6.60 (dd, 1H, J = 9.6, 16.2 Hz), 7.21−7.41 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.5, 23.2, 47.3, 51.6, 56.9126.3, 126.7, 127.3, 127.7, 128.0, 128.4, 128.6, 128.9, 129.1, 132.5, 137.3, 140.418, 177.3; IR (neat) 1730 cm^{-1}; MS *m*/*z* 294 (M^+), 263, 233, 205, 193, 116; HRMS (EI) calcd for $C_{20}H_{22}O_2$ 294.1621, found 294.1594.

(*S*)-1-(1,3-Diphenyl-2-propenyl)cyclohexanecarboxylic acid methyl ester (20b): $[\alpha]^{25}_D$ −27.4 (*c* 0.3, EtOH) for **20b** with 90% ee; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22−1.33, 1.52−1.63 (m, 8H), 2.10−2.24 (m, 2H), 3.50 (d, 1H, J = 10.8 Hz), 3.57 (s, 3H), 6.41 (d, 1H, J = 16.2 Hz), 6.65 (dd, 1H, J = 9.9, 15.5 Hz), 7.14−7.37 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.5, 23.6, 25.6, 32.0, 32.4, 51.2, 52.6, 58.8, 126.3, 126.7, 127.2, 127.7, 128.0, 128.4, 128.7, 128.9, 129.0, 132.2, 137.4, 140.4, 175.7; IR (neat) 1726 cm^{-1}; MS *m*/*z* 334 (M^+), 303, 275, 193, 116; HRMS (EI) calcd for $C_{23}H_{26}O_2$ 334.1934, found 334.1930.

Representative Procedure for Reaction 5 Using KSA/MeLi. The palladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 0.0109 mmol) was mixed with VALAP (14.2 mg, 0.0436 mmol) in THF (1 mL, dry and degassed) at room temperature for 15 min. The allyl pivalate **14a** (128 mg, 0.0436 mmol) dissolved in THF (1 mL) was added dropwise to the catalyst solution, followed by stirring for 30 min. In another two-necked flask, 1.14 M methyllithium Et_2O solution (1.15 mL, 1.31 mmol) was added to **19a** (228 mg, 1.31 mmol) in THF (2 mL) on an acetone bath at −78 °C. After being stirred for 1 h, the nucleophile solution was treated with the catalyst solution under each reaction condition. The reaction mixture was quenched with water and extracted with Et_2O. After the organic phase was dried over $MgSO_4$, the solution was concentrated. The residue was purified by a preparative TLC using toluene as the eluent.

Representative Procedure for Reaction 5 Using KSA/Tetraalkylammonium Halides. To a catalyst solution consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 0.0109 mmol) and VALAP (14.2 mg, 0.0436 mmol) in THF (1 mL, dry and degassed) was added the allylic pivalate **14a** (128 mg, 0.0436 mmol) in THF (1 mL), followed by stirring at room temperature for 30 min. Under the required reaction temperature, tetrabutylammonium fluoride (341 mg, 1.31 mmol) in THF (1 mL) and **19a** (228 mg, 1.31 mmol) in THF (1 mL) were added dropwise to the catalyst solution continuously. The reaction mixture was worked up in a similar manner as the reaction using KSA/MeLi.

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Supporting Information Available: ^{1}H NMR spectra of compounds **3a**−**7a**, **3b**−**7b**, **7c**,**d**, **8a**−**8f**, **11a**, **9b**−**11b**, **9c**−**11c**, **12a**,**b**, and **20a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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