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Synthesis of novel ferrocenylphosphine-amidine ligands with central and planar chirality and their diastereomeric effect in Pd-catalyzed asymmetric allylic alkylation

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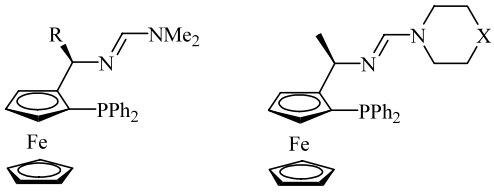
Abstract—Some novel ferrocenylphosphine-amidine ligands with central and planar chirality were prepared from (R,S_p)-PPFNH$_2$-R **3** and its diastereomer (S,S_p)-PPFNH$_2$ **3a**. The efficiency and diastereomeric impact of these ferrocenylphosphine-amidine ligands in the palladium-catalyzed asymmetric allylic substitution was examined, and up to 96% e.e. with 98% yield was achieved by the use of ligand (R,S_p)-**4a** with a methyl group in the amidino moiety. The results also indicated that (R)-central chirality and (S_p)-planar chirality in these ferrocenylphosphine-amidine ligands were matched for the palladium-catalyzed asymmetric allylic alkylation.

1. Introduction

Chiral ferrocene based ligands incorporating both planar and central chirality have found widespread application in asymmetric catalysis.[1] A large array of these ferrocenyl ligands was derived from *N*,*N*-dimethyl-1-ferrocenylethylamine and its analogues.[1,2] The key step in synthesizing these ferrocenyl ligands involves the highly diastereoselective *ortho*-lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine and its analogues followed by introduction of an appropriate electrophile.[3] As a consequence, the resulting ferrocenes are diastereoisomers, containing elements of both planar and central chirality, and having (R,S_p)- or (S,R_p)-configurations. This is why there are few reports involving the synthesis of chiral ferrocenyl ligands with (S,S_p)- or (R,R_p)-configurations and their application in catalytic asymmetric reactions.[4] Recently, we have developed a novel family of ferrocenylphosphine-amidine ligands **1** and **2** with (R,S_p)-configurations and found that they were effective ligands for the palladium-catalyzed asymmetric allylic alkylation.[5] Following this preliminary research, herein we wish to report the synthesis of some new (R,S_p)-ferrocenylphosphine-amidine ligands with a methyl group in the amidino moiety and describe the details of this reaction using all of these ferrocenylphosphine-amidine ligands. In order to investigate the impact of diastereomeric ferrocenyl ligands in the catalytic asymmetric reactions, the first synthesis of (S,S_p)-PPFNH$_2$ was carried out, and the efficiency of its amidine derivatives in Pd-catalyzed asymmetric allylic alkylation was also examined.



(R,S_p)-**1a**: R = Me;
(R,S_p)-**1b**: R = Et;
(R,S_p)-**1c**: R = Ph

(R,S_p)-**2a**: X = O;
(R,S_p)-**2b**: X = CH_2

2. Results and discussion

2.1. Synthesis of ferrocenylphosphine-amidine ligands (R,S_p)-1, (R,S_p)-2 and (R,S_p)-4

In order to investigate the influence of the substituent in the amidino moiety in asymmetric catalysis, the synthesis of novel modified ferrocenylphosphine-amidine ligands was first performed, which is outlined in Scheme 1. As we have reported, the synthesis of these ligands is straightforward, treatment of (R,S_p)-

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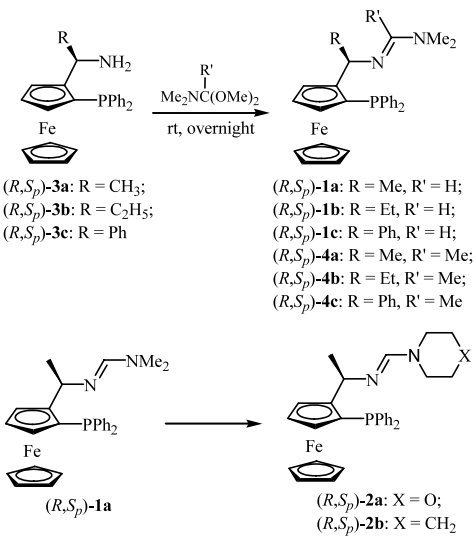


Scheme 1. Preparation of chiral ferrocenylphosphine-amidines **1**, **2** and **4**.

$PPFNH_2$-R **3**[6] with *N*,*N*-dimethylformamide dimethyl acetal or *N*,*N*-dimethylacetamide dimethyl acetal at room temperature gave the target ferrocenylphosphine-amidines **1** and **4** in good yields, respectively.

The dimethylamino group of amidines was easily replaced by other secondary amines. This exchange reaction was carried out by simply mixing compound **1a** and a large excess of morpholine or piperidine in the presence of a catalytic amount of 10-camphorsulfonic acid at the corresponding reflux temperature to give the modified amidine ligands **2a** and **2b** in 88 and 56% yield, respectively.

2.2. Synthesis of (S,S_p)-$PPFNH_2$ 3a and its amidine derivatives (S,S_p)-1a and (S,S_p)-4a

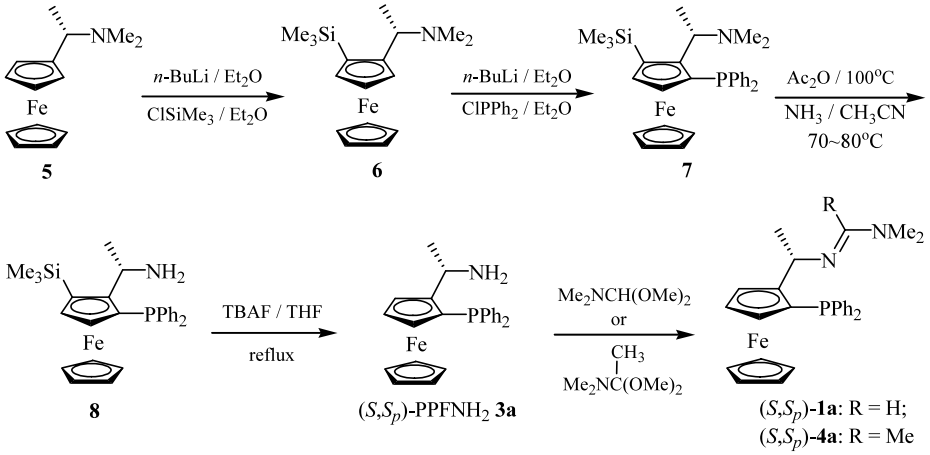
In order to examine the effect of diastereomeric ligands in the catalytic reactions, (S,S_p)-$PPFNH_2$ and its derivatives were then prepared. The synthetic procedure is outlined in Scheme 2. The initial step in the synthesis involved the introduction of a trimethylsilyl protected group in the *ortho*-position of *N*,*N*-dimethyl-1-ferrocenylethylamine **5** (FA).[3a] Further metallation of (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(trimethylsilyl)ferrocenyl]ethylamine **6** by *n*-BuLi, followed by diphenylphosphination with chlorodiphenylphosphine gave (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)-ferrocenyl]ethylamine **7** according to the method described by Hayashi and Kumada et al.[3b] After the reaction of dimethylamine **7** with Ac_2O at 100°C followed by treatment with a large excess of ammonia in methanol or acetonitrile in an autoclave at 80°C, the dimethylamino group of **7** was substituted by a primary amino group to form the key intermediate, (*S*)-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)ferrocenyl]-ethylamine **8**, which was easily purified by recrystallization from 2-propanol. Desilylation of primary amine **8** was accomplished by treatment with a solution of tetrabutylamminum fluride (TBAF) in THF to give (*S*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **3** [(S,S_p)-$PPFNH_2$] in nearly quantitative yields.

According to above-described method, treatment of (S,S_p)-$PPFNH_2$ **3** with *N*,*N*-dimethylformamide dimethyl acetal and *N*,*N*-dimethylacetamide dimethyl acetal gave corresponding ferrocenylphosphine-amidine ligands (S,S_p)-**1a** and (S,S_p)-**4a** in good yields, respectively.

2.3. Pd-catalyzed asymmetric allylic alkylation

The chiral ferrocenylphosphine-amidine ligands were then applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate **9a** or acetate **9b** with dimethyl malonate (Scheme 3).[7] This reaction was carried out in toluene in the presence of 2.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5 mol% of chiral ligand, a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of metal acetate.

Initially, the optimization of reaction conditions was examined by use of ligand (R,S_p)-**1a**. Results were listed

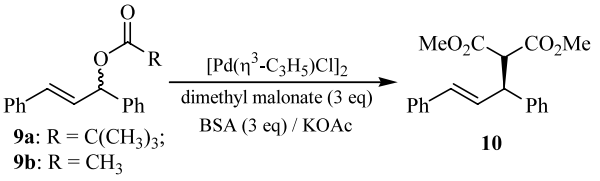


Scheme 2. Synthesis of (S,S_p)-**3a** and its amidine derivatives (S,S_p)-**1a** and (S,S_p)-**4a**.

Table 1. Asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate **9b** or pivalate **9a** using amidine ligand (R,S_p)-**1a**[a]

Entry	Substrate	Additive salt	Solvent	Temp. (°C)	Yield (%)[b]	e.e. (%)[c] (config.)[d]
1	**9b**	KOAc	Toluene	25	93	87 (*S*)
2	**9a**	KOAc	Toluene	25	96	92 (*S*)
3	**9a**	NaOAc	Toluene	25	90	88 (*S*)
4	**9a**	LiOAc	Toluene	25	99	84 (*S*)
5	**9a**	CsOAc	Toluene	25	94	92 (*S*)
6	**9a**	KOAc	Toluene	25	84	91 (*S*)[e]
7	**9a**	KOAc	CH_2Cl_2	25	31	65 (*S*)
8	**9a**	KOAc	THF	25	79	83 (*S*)
9	**9a**	KOAc	Benzene	25	98	90 (*S*)
10	**9a**	KOAc	Et_2O	25	99	88 (*S*)
11	**9a**	KOAc	Toluene	40	99	87 (*S*)
12	**9a**	KOAc	Toluene	10	83	79 (*S*)[f]

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 equiv.), (R,S_p)-**1a** (0.05 equiv.), dimethyl malonate (3.0 equiv.), BSA (3.0 equiv.) and a catalytic amount of additive salts.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralpak AD column (eluent: hexanes/2-propanol = 9 /1, 1.0 mL/min).
[d] Determined by chiroptical comparison with the reported data, see: Ref. 10.
[e] The reaction was carried out by using 1.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.5 mol% ligand.
[f] The reaction was carried out for 48 h.



Scheme 3. Pd-catalyzed asymmetric allylic alkylation.

in Table 1. The reaction was first carried out in toluene by use of 1,3-diphenylprop-2-en-1-yl acetate **9b** as substrate and KOAc as base, and 87% e.e. with 93% yield was obtained (entry 1). Replacing **9b** with **9a** as substrate, enantioselectivity was remarkably raised to 92% e.e. with 96% yield (entry 2). The effect of the bases was next evaluated. Using sodium acetate or lithium acetate instead of potassium acetate gave the product in 90 and 99% yields with 88 and 84% e.e., respectively (entries 3 and 4). The use of cesium acetate gave comparable enantioselectivity (92% e.e.) (entry 5 versus entry 2). The reduction of the amount of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ from 0.02 to 0.01 mol equivalent caused a decrease in the reaction rate, and only a slight drop in enantioselectivity (entry 6). The effect of solvents on this reaction was also investigated and a remarkable variation in the catalytic activity on the nature of solvents was observed: CH_2Cl_2, which is usually a good solvent for the Pd-catalyzed allylic alkylation, was proved to be not so good for our catalytic system, and only 65% e.e. with 31% yield was obtained (entry 7). The reaction proceeded at a low reaction rate with moderate enantioselectivity in THF (entry 8). When the reaction was carried out in benzene or Et_2O, somewhat lower enantioselectivity with slightly increased yield was obtained (entries 9 and 10). Increasing the reaction temperature to 40°C resulted in low enantioselectivity (entry 11), while lowering the reaction temperature to 10°C decreased both enantioselectivity and reactivity (entry 12).

Table 2. Asymmetric allylic alkylation of allylic pivalate **9a** using ligands **1**, **2** and **4**[a]

Entry	Ligand	Yield (%)[b]	E.e. (%)[c] (config.)[d]
1	(R,S_p)-**1a**	96	92 (*S*)
2	(R,S_p)-**1b**	98	94 (*S*)
3	(R,S_p)-**1c**	61	37 (*S*)
4	(R,S_p)-**2a**	91	81 (*S*)
5	(R,S_p)-**2b**	90	65 (*S*)
6	(R,S_p)-**4a**	98	96 (*S*)
7	(R,S_p)-**4b**	97	95 (*S*)
8	(R,S_p)-**4c**	71	42 (*S*)

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 equiv.), **L*** (0.05 equiv.), dimethyl malonate (3.0 equiv.), BSA (3.0 equiv.) and a catalytic amount of KOAc.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralpark AD column.
[d] Determined by chiroptical comparison with the reported data, see: Ref. 10.

From the reaction conditions screening experiments, we then selected **9a** as substrate, toluene as solvent, and potassium acetate as base for investigating the influence of ligands on the catalytic activity and enantioselectivity, and the results are summarized in Table 2. Of ligands **1a**–**1c** with different substituents R on the stereogenic carbon center, the ligand **1b** (R = Et) exhibited the best enantioselectivity (94% e.e.) (entry 2), while the ligand **1c** (R = Ph) gave the product with unexpected low yield and enantioselectivity (entry 3). For ligands **2a**–**2b** with a morpholino or piperidino substituting in place of dimethylamino group, both yield and enantioselectivity were decreased significantly (entries 4 and 5). It is interesting that ligands **4a**–**c** exhibited higher enantioselective induction than their corresponding analogues **1a**–**c** without a methyl group in the amidino moiety (entries 6 ~ 8 versus entries 1 ~ 3). The difference between the results obtained from ligands **1** and **4** could be explained by a 'locking-in'

effect of the amidino group in **4**/Pd complexes, recently reported by Reetzs et al.[8] In contrast, the amidino groups of **1**/Pd complexes rotate more freely, resulting in a decreased secondary effect of the amino group on the catalytic reaction.[9] When ligand **4a** was used in the catalytic reaction, up to 96% ee with 98% yield was obtained (entry 6). The absolute configuration of product **10** from these reactions established as *S* by comparing the specific rotation with a literature value.[10]

2.4. The diastereomeric effects in Pd-catalyzed asymmetric allylic alkylation using ferrocenylphosphine-amidine ligands

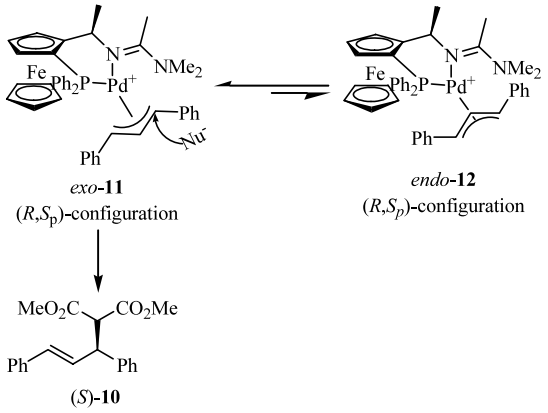
In contrast to the extensive use of ferrocene based ligands with (R,S_p)- or (S,R_p)-configuration, there are few reports involving the preparation and application of chiral ferrocenyl ligands with (S,S_p)- or (R,R_p)-configurations derived from *N*,*N*-dimethyl-1-ferrocenylethylamine **5** partly due to the difficult synthesis of these compounds.[4] After having synthesized amidine ligands (S,S_p)-**1a** and (S,S_p)-**4a**, we next investigated the diastereomeric impact of ferrocenyl ligands in the palladium-catalyzed asymmetric allylic alkylation. The results are summarized in Table 3. All of these ferrocenylphosphine-amidine ligands exhibited high enantioselectivity. Compared to (R,S_p)-**1a** and (R,S_p)-**4a**, however, (S,S_p)-**1a** and (S,S_p)-**4a** showed lower enantioselectivity but gave the alkylation product **10** with the same configuration (entries 2 and 4 versus entries 1 and 3). This result indicates that (R)-central chirality and (S_p)-planar chirality were matched in these ferrocenylphosphine-imine ligands for the palladium-catalyzed asymmetric allylic alkylation.

The mechanism of asymmetric induction with this type of ligand is rationalized on the basis of the stereochemical results obtained (Scheme 4). Concluded from the above-results, the planar chirality of ferrocenyl units in these P,N ligands has the key influence on the Pd-catalyzed asymmetric allylic alkylation, and controls the configuration of the allylic alkylation production. According to the recent research by Guiry et al.,[11] in the conformational equilibrium of sterically favored

Table 3. The diastereomeric effects in Pd-catalyzed asymmetric allylic alkylation using ferrocenylphosphine-amidine ligands[a]

Entry	Ligand	Yield (%)[b]	E.e. (%)[c] (config.)[d]
1	(R,S_p)-**1a**	96	92 (*S*)
2	(S,S_p)-**1a**	94	88 (*S*)
3	(R,S_p)-**4a**	98	96 (*S*)
4	(S,S_p)-**4a**	93	91 (*S*)

[a] The reactions were carried out using pivalate **9a** as a substrate in toluene in the presence of 2.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5 mol% of chiral ligand, 3 equiv. of dimethyl malonate, 3 equiv. of BSA and a catalytic amount of KOAc at rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralpark AD column.
[d] Determined by chiroptical comparison with the reported data, see: Ref. 10.



Scheme 4. The conformational equilibrium of sterically favored π-allyl palladium complexes *exo*-**11** and *endo*-**12**.

π-allyl palladium complexes *exo*-**11** and *endo*-**12**,[12] complex *exo*-**11** would be formed preferentially due to the predominated role of the planar chirality of the ferrocenyl units on the 1,3-diphenylallyl orientation through interactions between the diphenylphosphinoferrocene unit and the allylic fragment, no matter the central chirality is (R)- or (S)-configuration. The structure of Pd/**4a** complex prepared in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (R,S_p)-**4a** was monitored by spectroscopic methods, and ^{31}P NMR spectrum showed two peaks at 27.6 and 21.7 ppm in a ratio of 19.9:1, indicating that one diastereomer formed preferentially. The decreased enantioselectivity obtained by the use of ligand (S,S_p)-enantiomers could be due to the dismatched (S)-central chirality, which resulted in the decreased ratio of *exo*:*endo* diastereomers. The nucleophile attacks the allylic terminus *trans* to the phosphorus atom in the major diastereomer *exo*-**11**, from the back side of the palladium catalyst in the π-allyl system as designated in **11**,[13] affording the product (S)-**10**.

3. Conclusion

In conclusion, we have extended our research in developing novel ferrocenylphosphine-amidine ligands and prepared some novel phosphine-amidine ligands **4** with a methyl group in amidino moiety from (R,S_p)-PPFNH$_2$-R **3**. The efficiency of ferrocenylphosphine-amidine ligands **1**, **2** and **4** in the palladium-catalyzed asymmetric allylic alkylation was examined, and up to 96% e.e. with 98% yield was achieved by the use of ligand **4a**. The results also indicated that the existence of a methyl group in the amidino unit in the ferrocenylphosphine-amidine ligands was favorable to obtain high enantioselectivity in this reaction. In order to examine the effect of diastereomeric ligands in the catalytic reactions, (S,S_p)-PPFNH$_2$ **3a** and its amidine derivatives (S,S_p)-**1a** and (S,S_p)-**4a** were then prepared. The results indicated that (R)-central chirality and (S_p)-planar chirality in these ferrocenylphosphine-amidine ligands are matched for the palladium-catalyzed asymmetric allylic alkylation. Further application and modification of ligands are in progress.

4. Experimental

4.1. General methods

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a HORIBA SEPA-200 high sensitive polarimeter. The ^{1}H NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. The ^{31}P NMR spectra were recorded using a BRUKER DRX 400 system with 85% phosphoric acid as the external standard. Enantiomeric excesses (% e.e.) were determined by HPLC (Agilent 1100 series) analysis. All experiments were carried out under an argon atmosphere. All solvents were dried using standard procedures. 1,3-Diphenyl-2-propenyl pivalate **9a** was derived from the reaction of 1,3-diphenylprop-2-en-1-ol with pivaloyl chloride in pyridine. 1,3-Diphenyl-2-propenyl acetate **9b** was prepared according to the reported method.[14] PPFNH$_2$-R **3** were prepared according to literature's procedure.[6] (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)ferrocenyl]ethylamine **7** was synthesized according to the procedure reported by Hayashi, et al.[3b]

4.2. General procedure for the synthesis of ferrocenylphosphine-amidine ligands (R,S_p)-1 and (R,S_p)-4

A mixture of (R,S_p)-PPFNH$_2$-R (1.0 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.35 g, 1.5 ml, 11.3 mmol) or *N*,*N*-dimethylacetamide dimethyl acetal (1.50 g, 11.3 mmol) was stirred at room temperature. TLC periodically monitored the reaction. After the reaction was complete, the volatile fractions were removed in vacuo. The residue was purified by silica gel column chromatography modified by 2.0% of Et$_3$N.

4.2.1. Preparation of (*R*)-*N*-(dimethylaminomethylene)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine 1a. Recrystallized from *n*-hexane to afford a golden solid, yield 81.0%; mp 98–100°C; $[\alpha]_{25}^{D}=-427$ (*c* 0.11, CHCl$_3$); ^{1}H NMR (CDCl$_3$) 1.56 (d, $J=6.8$ Hz, 3H), 2.21 (s, 6H), 3.70 (s, 1H), 3.97 (s, 5H), 4.25 (s, 1H), 4.56 (m, 1H), 4.60 (s, 1H), 7.07–7.52 (m, 11H); ^{31}P NMR δ −22.8. HRMS calcd for $C_{27}H_{29}FeN_2P$+H 469.1490, found 469.1494.

4.2.2. Preparation of (*R*)-*N*-(dimethylaminomethylene)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]propylamine 1b. Yellow foam solid, yield 78.7%; $[\alpha]_{25}^{D}=-450$ (*c* 0.22, CHCl$_3$); ^{1}H NMR (CCl$_4$) δ 1.01–1.05 (m, 3H), 1.84–2.25 (m, 2H), 2.36 (s, 6H), 3.79 (s, 1H), 4.03 (s, 5H), 4.14–4.17 (m, 1H), 4.33 (s, 1H), 4.62 (s, 1H), 7.13–7.60 (m, 11H); ^{31}P NMR δ −22.4. HRMS calcd for $C_{28}H_{31}FeN_2P$+H 483.1652, found 483.1650.

4.2.3. Preparation of (*R*)-*N*-(dimethylaminomethylene)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine 1c. Recrystallized from *n*-hexane to afford yellow needle solid yield 86.1%; mp 106–107°C; $[\alpha]_{D}^{25}=-330$ (*c* 0.20, CHCl$_3$); ^{1}H NMR (CCl$_4$) δ 2.44 (s, 6H), 3.86 (s, 5H), 4.27–4.30 (m, 2H), 4.80 (s, 1H), 5.53–5.54 (m, 1H), 7.19–7.75 (m, 15H); ^{31}P NMR δ −22.6. HRMS calcd for $C_{32}H_{31}FeN_2P$ 530.1573, found 530.1578.

4.2.4. Preparation of (*R*)-*N*-(dimethylaminoethylene)-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine 4a. Recrystallized from *n*-hexane to afford orange solid, yield 86.7%; mp 108–109°C; $[\alpha]_{D}^{25}=-402$ (*c* 0.10, CHCl$_3$); ^{1}H NMR (DMSO-d^6) δ 1.33 (d, $J=4.0$ Hz, 3H), 1.75 (s, 3H), 2.26 (s, 6 H), 3.63 (s, 1H), 3.97 (s, 5H), 4.29 (s, 1H), 4.51 (s, 1H), 4.65–4.66 (m, 1H), 6.99–7.03 (m, 2H), 7.16–7.19 (m, 3H), 7.41 (s, 3H), 7.46–7.48 (m, 2H); ^{31}P NMR δ −21.4. HRMS calcd for $C_{28}H_{31}FeN_2P$ 482.1574, found 482.1574.

4.2.5. Preparation of (*R*)-*N*-(dimethylaminoethylene)-[(*S*)-2-(diphenylphosphino)ferrocenyl]propylamine 4b. Orange viscous liquid, yield 57.4%; $[\alpha]_{D}^{25}=-431$ (*c* 0.10, CHCl$_3$); ^{1}H NMR (DMSO-*d*^{6}) δ 0.75–0.79 (t, $J=7.2$ Hz, 3H), 1.54–1.61 (m, 1H), 1.68 (s, 3H), 2.14–2.19 (m, 1H), 2.29 (s, 6H), 3.58 (s, 1H), 3.96 (s, 5H), 4.26 (s, 1H), 4.33–4.36 (m, 1H), 4.49 (s, 1H), 6.98–7.00 (m, 2H), 7.17–7.19 (m, 3H), 7.40 (s, 3H), 7.45–7.48 (m, 2H); ^{31}P NMR δ −20.9. HRMS calcd for $C_{29}H_{33}FeN_2P$+H 497.1808, found 497.1812.

4.2.6. Preparation of (*R*)-*N*-(dimethylaminoethylene)-[(*S*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine 4c. Yellow viscous liquid, yield 71.1%; $[\alpha]_{D}^{25}=-345$ (*c* 0.20, CHCl$_3$); ^{1}H NMR (DMSO-*d*^{6}) δ 1.65 (s, 3H), 2.34 (s, 6 H), 3.72 (s, 1H), 3.74 (s, 5H), 4.09 (s, 1H), 4.26 (s, 1H), 5.61 (s, 1H), 7.08–7.10 (m, 2H), 7.21–7.24 (m, 4H), 7.32–7.36 (m, 2H), 7.42–7.43 (m, 3H), 7.53–7.55 (m, 4H); ^{31}P NMR δ -21.5. HRMS calcd for $C_{33}H_{33}FeN_2P$+H 545.1808, found 545.1810.

4.3. Synthesis of modified amidine ligands (R,S_p)-2

4.3.1. Preparation of (*R*)-1-[(*S*)-2-(diphenylphosphino)-ferrocenyl]-*N*-[(4-morpholino)methylene]ethylamine 2a. A mixture of **3a** (390 mg, 0.833 mmol) and morpholine (2.27 g, 2.3 ml, 26.0 mmol) was refluxed under argon in the presence of 10-camphorsulfonic acid (10 mg, 0.043 mmol). The reaction was periodically monitored by TLC. After 8 h at reflux temperature. The resulting solution was then diluted with toluene (20 ml), following 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 by silica gel column chromatography eluted by a 4:1 mixture of hexane and acetate including 10% Et$_3$N to give a yellow solid. The crude product was recrystallized from *n*-hexane to give **4a** (374 mg, 88.0% yield) as a golden needle solid; mp 179–180°C; $[\alpha]_{D}^{25}=-482$ (*c* 0.11, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 1.58 (d, $J=6.8$ Hz, 3H), 2.69 (m, 4H), 3.29 (m, 4H), 3.76 (s, 1H), 3.96 (s, 5H), 4.29 (s, 1H), 4.61 (br, 2H), 7.07–7.53 (m, 11H); ^{31}P NMR δ −23.3. HRMS calcd for $C_{29}H_{31}FeN_2OP$+H 511.1601, found 511.1597.

4.3.2. Preparation of (*R*)-1-[(*S*)-2-(diphenylphosphino)-ferrocenyl]-*N*-[(1-piperidino)methylene]ethylamine 2b. **4b** was afforded as a yellow solid in a similar procedure as **4a**, yield 56.0%; mp 96–98°C; $[\alpha]_D^{25}=-470$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (m, 4H), 1.29 (br, 2H), 1.57 (d, $J=6.4$ Hz, 3H), 2.60 (br, 4H), 3.74 (s, 1H), 3.95 (s, 5H), 4.27 (s, 1H), 4.57 (m, 1H), 4.61 (s, 1H), 7.07–7.53 (m, 11H); ^{31}P NMR δ -23.0. HRMS calcd for $C_{30}H_{33}FeN_2P$+H 509.1809, found 509.1803.

4.4. Synthesis of (*S*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine 3a

4.4.1. Preparation of (*S*)-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)ferrocenyl]ethylamine 8. (*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)ferrocenyl]ethylamine **7** (1.03 g, 2.0 mmol) was sealed in an air-free tube with acetic anhydride (2.0 mL). The tube was heated to 100°C for 2 h. After cooling to rt, the reaction mixture was poured into 150 mL of 15% aqueous potassium carbonate with vigorous stirring. Oily material was extracted with Et_2O (30 mL×2). The ether extract was washed with 5.0% HCl (20 mL×2), 5.0% K_2CO_3 (20 mL×2), and brine (50 mL×1), and then dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel, hexanes:ethyl acetate, 30:1) to give an orange oil. The resulting oil was then dissolved in a solution of 10 mL 25% aqueous NH_3 in 20 mL of CH_3CN. The mixture was then placed in a 100 mL autoclave and heated at 70–80°C for 8 h. The reaction mixture was diluted with 10 mL of CH_2Cl_2, and the solvent was evaporated. The residue was purified by column chromatography on a silica gel column (hexanes:ethyl acetate, 10:1 to 4:1) to give orange viscous liquid 0.59 g, which was solidified on standing. The resulting solid was purified by recrystallization from 2-propanol to give 0.38 g (40.2% yield) of (*S*)-1-[(*R*)-2-trimethylsilyl-(*S*)-5-(diphenylphosphino)-ferrocenyl]ethylamine **8**. mp 118–119°C; $[\alpha]_D^{25}=-342$ (*c* 0.10, $CHCl_3$); ^1H NMR (DMSO-d^6) δ 0.28 (s, 9H), 1.01 (d, $J=6.8$ Hz, 3H), 1.64 (br, 2H), 3.89–3.90 (m, 1H), 3.95 (s, 5H), 4.21–4.25 (m, 2H), 7.11–7.15 (m, 2H), 7.24–7.29 (m, 3H), 7.42–7.43 (m, 3H), 7.51–7.56 (m, 2H); ^{31}P NMR δ –22.1.

4.4.2. Synthesis of (*S*)-1-[(*S*)-2-(diphenylphosphino)-ferrocenyl]ethylamine 3a. (*S*)-1-[(*R*)-2-Trimethylsilyl-(*S*)-5-(diphenylphosphino)ferrocenyl]ethylamine **8** (121 mg, 0.25 mmol) was dissolved in 5.0 mL of a 1.0 mol/L solution of tetrabutylammunim fluride (TBAF) in THF. After 3 h reflux, the mixture was concentrated in vacuo to afford a red oil, which was extracted with Et_2O (10 mL×2). The resulting organic layer was washed with water (10 mL×2), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel modified by 2% Et_3N, elution by hexanes:ethyl acetate:Et_3N, 20:10:1 to 10:20:1) to give 94 mg (91.0% yield) of (*S*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(S_p)-**3a**] as an orange crystals. Mp 127–128°C; $[\alpha]_D^{25}=-341$ (*c* 0.11, $CHCl_3$); ^1H NMR (DMSO-d^6) δ 0.78 (d, $J=6.4$ Hz, 3H), 3.34 (br, 2H), 3.72 (s, 1H), 4.02 (s, 1H), 4.02 (s, 5H), 4.31 (s, 1H), 4.60 (s, 1H), 7.10–7.13 (m, 2H), 7.25–7.29 (m, 3H), 7.43 (s, 3H), 7.50–7.52 (m, 2H); ^{31}P NMR δ –23.2.

4.5. General procedure for the synthesis of amidine ligands (S,S_p)-1a and (S,S_p)-4a

A mixture of (S,S_p)-PPFNH$_2$ **3a** (413 mg, 1.0 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.35 g, 1.5 ml, 11.3 mmol) or *N*,*N*-dimethylacetamide dimethyl acetal (1.50 g, 11.3 mmol) was stirred at room temperature. TLC periodically monitored the reaction. After the reaction was complete, the volatile fractions were removed in vacuo. The residue was purified by silica gel column chromatography modified by 2.0% of Et_3N (eluent, hexanes:ethyl acetate:Et_3N, 10:10:1).

4.5.1. Preparation of (*S*)-*N*-(dimethylaminomethylene)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine 1a. Orange foam solid, yield 81.3%; $[\alpha]_D^{25}=-161$ (*c* 0.19, MeOH); ^1H NMR (DMSO-d^6) δ 0.86 (d, $J=6.4$ Hz, 3H), 2.84 (s, 6H), 3.66 (s, 1H), 3.90 (s, 5H), 4.28 (s, 1H), 4.28–4.30 (m, 1H), 4.54 (s, 1H), 7.12–7.15 (m, 2H), 7.24–7.31 (m, 3H), 7.42 (s, 3H), 7.49–7.53 (m, 2H), 7.56 (s, 1H); ^{31}P NMR δ –22.6. HRMS calcd for $C_{27}H_{29}N_2PFe$+H 469.1490, found 469.1503.

4.5.2. Preparation of (*S*)-*N*-(dimethylaminoethylene)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine 4a. Orange foam solid, yield 85.8%; $[\alpha]_D^{25}=-142$ (*c* 0.28, MeOH); ^1H NMR (DMSO-d^6) δ 0.79 (d, $J=6.4$ Hz, 3H), 1.90 (s, 3H), 2.89 (s, 6H), 3.61 (s, 1H), 3.87 (s, 5H), 4.27–4.28 (m, 1H), 4.46–4.49 (m, 1H), 4.65 (s, 1H), 7.14–7.18 (m, 2H), 7.26–7.30 (m, 3H), 7.40–7.41 (m, 3H), 7.47–7.51 (m, 2H); ^{31}P NMR δ -22.5. HRMS calcd for $C_{28}H_{31}FeN_2P$+H 483.1652, found 483.1626.

4.6. General procedure for asymmetric allylic alkylations

A solution of [Pd(η^3-C_3H_5)Cl]$_2$ (3.7 mg, 0.010 mmol) and chiral phosphine-amidine **1**, **2** or **4** (0.025 mmol) in toluene (1.5 mL) was stirred at room temperature for 1 h under argon. To this Pd-catalyst was added allylic pivalate **9a** or acetate **9b** (0.50 mmol) in toluene (1.5 mL), followed by dimethyl malonate (170 uL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 0.37 mL, 1.5 mmol), and a catalytic amount of KOAc sequentially. After stirring at rt for 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate, 8:1) to afford a pure product **10**. The enantiomeric excess was determined by HPLC (Chiralpak AD, hexanes:2-propanol=90:10, 1.0 mL/min). The absolute configuration was assigned by the comparison of the specific rotation with a literature value.[10]

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References

1. (a) Hayashi, T. In *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995; p. 105; (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1999**, *9*, 2377–2407; (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1999; (d) Bolm, C.; Muniz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491–493; (e) Zhang, W.; Shimanuki, T.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *J. Org. Chem.* **1999**, *64*, 6247–6251; (f) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285; (g) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483–1484; (h) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467; (i) Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195–1196; (j) Longmire, J. M.; Wang, B.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 5435–5439; (k) Deng, W.-P.; You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W.; Sun, J. *J. Am. Chem. Soc.* **2001**, *123*, 6508–6519; (l) Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* **2001**, 2360–2361; (m) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *1*, 149–151; (n) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684–4695; (o) Xiao, L.; Weissensteiner, W.; Kitzler, R.; Widhalm, M. *J. Org. Chem.* **2002**, *67*, 2206–2214; (p) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982–7994; (q) Lotz, M.; Kramer, G.; Knochel, P. *Chem. Commun.* **2002**, 2546–2547; (r) Priego, J.; Mancheno, G. O.; Cabrera, S.; Arrayas, R. G.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512–2513; (s) Priego, J.; Mancheno, O. G.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346–1353; (t) Kloetzing, R. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 255–264.
2. (a) Almena Perea, J. J.; Borner, A.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073–8076; (b) Cho, D.-J.; Jeon, S.-J.; Kim, H.-S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833–3848; (c) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212–3215; (d) Almena Perea, J. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375–384; (e) Song, J.-H.; Cho, D.-J.; Jeon, S.-J.; Kim, Y.-H.; Kim, T.-J. *Inorg. Chem.* **1999**, *38*, 893–896; (f) Fukuzawa, S.; Tsuchiya, D.; Sasamoto, K.; Hirano, K.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877–2883; (g) Kang, J.; Lee, J. H.; Kim, J. B.; Kim, G. J. *Chirality* **2000**, *12*, 378–382; (h) Kang, J.; Lee, J. H.; Choi, J. S. *Tetrahedron: Asymmetry* **2001**, *12*, 33–35; (i) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. *Org. Lett.* **2002**, *4*, 2421–2424.
3. (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393; (b) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138–1151.
4. (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718; (b) Hayashi, T.; Konoshi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.
5. Hu, X.; Chen, H.; Hu, X.; Dai, H.; Bai, C.; Wang, J.; Zheng, Z. *Tetrahedron Lett.* **2002**, *43*, 9179–9182.
6. (a) Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2503–2506; (b) Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687–1693; (c) Kim, T.-J.; Lee, H.-Y.; Ryu, E.-S.; Park, D.-K.; Cho, C. S.; Shim, S. C.; Jeong, J. H. *J. Organomet. Chem.* **2002**, *649*, 258–267; (d) Tu, T.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C.; Yu, Y.-H.; Sun, J. *Organometallics* **2003**, *22*, 1255–1265.
7. For recent development of P, N ligands in Pd-catalyzed asymmetric allylic alkylation: (a) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231 and references cited therein; (b) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, 65, 7807–7813; (c) Mino, T.; Tanaka, Y.; Sakamoto, M.; Fujita, T. *Heterocycles* **2000**, *53*, 1485–1488; (d) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193–1198; (e) Wang, Y.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4153–4162; (f) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206–215; (g) Mino, T.; Shiotsuki, M.; Yamamoto, N.; Suenaga, T.; Sakamoto, M.; Fujita, T.; Yamashita, M. *J. Org. Chem.* **2001**, *66*, 1795–1797; (h) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837–4839; (i) Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 5553–5555; (j) You, S.-L.; Zhu, X.-Z.; Lou, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471–7472; (k) Mino, T.; Kashihara, K.; Yamashita, M. *Tetrahedron: Asymmetry* **2001**, *12*, 287–291; (l) Mino, T.; Tanaka, Y.; Akita, K.; Anada, K.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2001**, *12*, 1677–1682; (m) Mino, T.; Tanaka, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2435–2440; (n) Fukuda, T.; Takehara, A.; Iwao, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2793–2799; (o) Mino, T.; Ogawa, T.; Yamashita, M. *Heterocycles* **2001**, *55*, 453–456; (p) Stranne, R.; Vasse, J.-L.; Moberg, C. *Org. Lett.* **2001**, *3*, 2525–2528; (q) Wang, Y.; Li, X.; Ding, K. *Tetrahedron Lett.* **2002**, *43*, 159–161; (r) Wu, X.-W.; Yuan, K.; Sun, W.; Zhang, M.-J.; Hou, X.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 107–112; (s) Mino, T.; Ogawa, T.; Yamashita, M. *J. Organomet. Chem.* **2003**, *664*, 122–126.
8. Reetz, M. T.; Haderlein, G.; Angermund, K. *J. Am. Chem. Soc.* **2000**, *122*, 996–997.
9. Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227–4240.
10. von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568.

11. Farrel, A.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 4209–4217.
12. Nomenclature note: the *endo*-isomer is defined here as that allyl configuration in which the central allyl proton points above the plane of the P–Pd–N chelate.
13. (a) Akermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679–682; (b) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M. *Tetrahedron Lett.* **1994**, *35*, 1523–1526; (c) Allen, J. V.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065–2072; (d) Dawson, G. I.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535–2546; (e) Anderson, J. C.; James, D. S.; Mathias, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 753–756.
14. Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046.