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Effective Chiral Ferrocenyl Phosphine-Thioether Ligands in Enantioselective Palladium-Catalyzed Allylic Alkylations

Hong Yee Cheung,[a] Wing-Yiu Yu,[a] Terry T. L. Au-Yeung,[a] Zhongyuan Zhou,[a] and Albert S. C. Chan[a,*]

[a] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, People's Republic of China
Fax: (+852)-23-649-932; e-mail: bcachan@polyu.edu.hk

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Abstract: Chiral ferrocene-derived phosphine-thioether mixed donor ligands supported by heterocycles effected the palladium-catalyzed enantioselective allylic alkylations with excellent yields and enantioselectivities (up to 96% *ee*). With cyclic and unsymmetrical allylic acetates as substrate, the corresponding alkylated products with enantioselectivities up to 87% *ee* were obtained. Based on X-ray crystallographic and NMR studies, the origin of the observed enantioselectivities is discussed.

Keywords: allylic alkylation; asymmetric catalysis; enantioselectivity; ferrocenes; phosphine-thioether ligands

Introduction

The design and synthesis of new chiral ligands is a central activity in asymmetric catalysis studies. Extensive efforts have been devoted to developing chiral C_2-symmetrical homobidentate ligands such as P/P, N/N and O/O ligands, and highly effective asymmetric catalysis has been reported using these ligand sets.[1] The development of heterobidentate ligands equipped with a strong and a weak heteroatom pair such as P/N[2] and P/O[3] is receiving increasing attention. Such coordinations have been proved to be effective for achieving high enantioselectivities through steric and electronic differentiations.[4] However, there are few examples on the study of chiral P/S ligands for asymmetric catalysis.[5–10] Unique to this class of ligands, the coordination of the sulfur donor to the metal center would create a stereogenic center at sulfur, near the reaction site in addition to other stereogenic carbon centers.[6] For example, Evans and co-workers showed that phosphinite-thioethers[7] were excellent ligands for the Pd-catalyzed asymmetric allylic substitution of cyclic and acyclic allylic acetates (Figure 1).[7a,b] The same series of ligands was also found to effect Rh-catalyzed asymmetric hydrogenation of dehydroamino acids and asymmetric hydrosilylation of ketones.[7c] Diéguez and Pàmies reported a series of phosphinite-thioether ligands supported by some readily available carbohydrates, and these P/S ligands were effective for asymmetric allylic substitutions[5q] and asymmetric hydrosilylation of ketones.[5r] Extensive studies showed that ferrocene is an appealing building block for designing novel chiral ligands because of the easy implementation of the central and planar chiralities.[8] Enders described a family of enantiopure ferrocenyl P/S ligands which were highly effective for asymmetric allylic substitutions.[9] According to the recent works by Carretero and co-workers,[10] Fesulphos which contained only planar

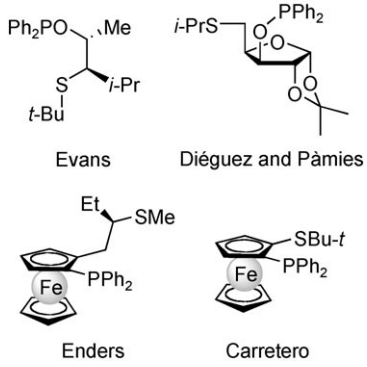


Figure 1. Examples of effective P/S ligands.

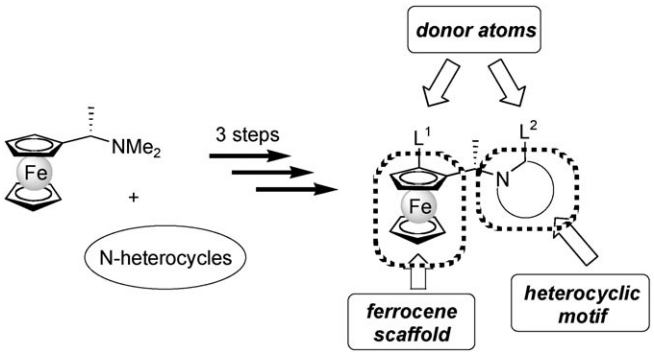


Figure 2. Modular design of bidentate ligands supported by ferrocene and heterocycles.

chirality was developed for enantioselective allylic substitution,[10a,b] ring opening reaction,[10c,d] Diels–Alder reaction,[10e,f] Mannich-type reaction[10g] and 1,3-dipolar cycloaddition.[10h–m]

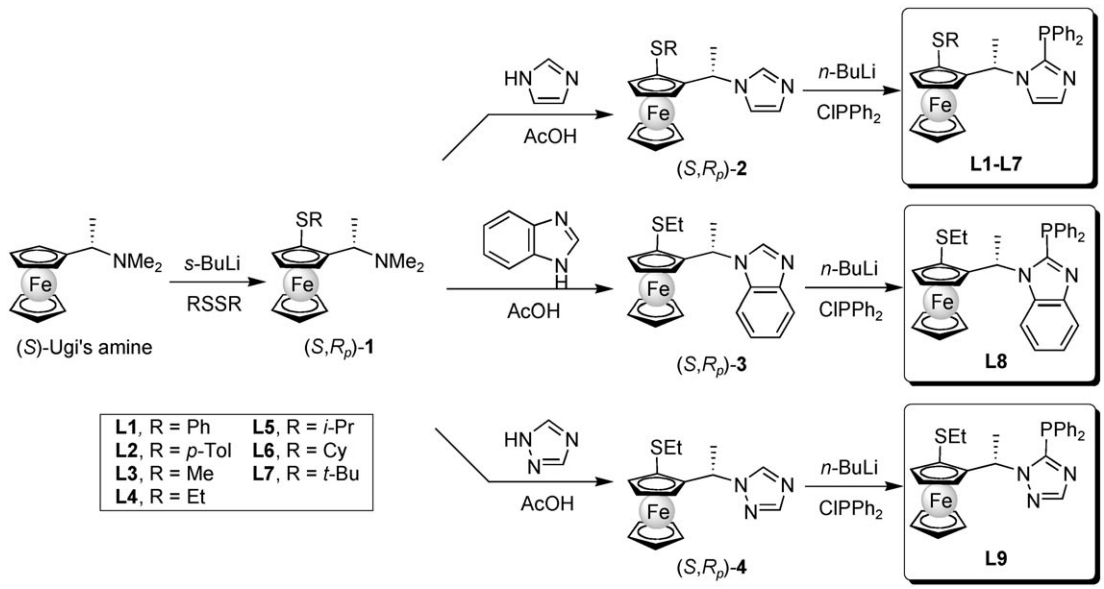
The development of highly efficient and practical chiral ligands for asymmetric C–C bond formation is a long-standing research interest for many scientists. Previously we showed that chiral diphosphine ligands P-Phos[11] with heteroaromatic scaffolds are excellent ligands for asymmetric hydrogenations[12] as well as some C–C bond formation reactions.[13] Notably, these ligands are air-stable compared to the analogous BINAP ligand. Following this approach, we envisioned a new class of ferrocenyl P/S ligands with heterocyclic scaffolds to have good air/moisture stability and to be excellent ligands for asymmetric catalysis. In this work, we describe the preparation of structurally diverse ferrocenyl P/S ligands containing heterocycles using a modular synthetic approach with (*S*)-Ugi's amine as a starting material (Figure 2). Through extensive structure-activity studies, ligand **L8** with a benzimidazole scaffold was found to be highly effective for asymmetric allylic substitutions[14] giving up to 96% *ee*. A related study on the Pd-catalyzed asymmetric intermolecular indole alkylation has been communicated elsewhere.[15]

Results and Discussion

Ligand Synthesis

Ugi's amine has been proven to be a versatile precursor for the preparation of diverse chiral ferrocenyl diphosphine ligands.[16] This is exemplified by the elegant synthesis of Josiphos,[17] BoPhoz[18] and Walphos,[19] etc. While optically pure Ugi's amine was conventionally prepared by resolution of racemic Ugi's amine with tartaric acid[20] or other chiral auxiliaries,[21] we recently developed a highly enantioselective synthesis of (*S*)-Ugi's amine (>99% *ee*) on a 150-gram scale by asymmetric hydrogenation of acetylferrocene, followed by nucleophilic substitution.[12j] By virtue of the synthetic versatility of Ugi's amine, we devised a three-step modular synthetic approach to prepare a library of novel air- and moisture-stable P/S ferrocenyl ligands **L1**–**L9** containing a heterocyclic motif.

As shown in Scheme 1, diastereoselective *ortho*-substitution of (*S*)-Ugi's amine with various disulfides gave amino-thioethers **1**.[22] Treating **1** with imidazole, benzimidazole or 1,2,4-triazole in AcOH afforded optically pure compounds **2**–**4** in good to excellent yields. Lithiation of **2**–**4** followed by trapping with



Scheme 1. Synthesis of P/S ligand **L1**–**L9**.

$ClPPh_2$ afforded ligands **L1**–**L9** in overall 48–76% yields. Ligands **L1**–**L9** are air-stable solids and can be handled and stored without protection from air. The molecular structure and absolute configuration of **L9** has been unambiguously defined as (S,R_p) by X-ray crystallography (See Supporting Information).

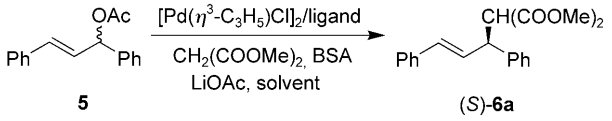
Ligand Screening and Reaction Optimization

To begin the search for effective ligands for the Pd-catalyzed asymmetric allylic alkylation, we employed 1,3-diphenyl-2-propenyl acetate **5** as a model substrate and dimethyl malonate as the nucleophile. The reaction was performed in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand (5 mol%), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 2 equiv.) and a catalytic amount of LiOAc as additive in various solvents (CH_2Cl_2, THF, toluene, MeCN). With ligand **L1**, complete reactions were achieved in polar solvents within 2 h, while only 52% conversion was attained with toluene as solvent (Table 1, entries 1–4). Up to 62% *ee* of (*S*)-**6a** was obtained with MeCN as solvent (entry 4); other solvents such as CH_2Cl_2, THF and toluene produced lower enantioselectivity (37–59% *ee*). Other additives such as NaOAc, KOAc, $Zn(OAc)_2$ and Bu_4NCl showed similar reactivities but slightly lower enantioselectivities (50–52% *ee*).

With MeCN as solvent, we turned to examine the effect of the substituents on the thioether group [R = *p*-Tol (**L2**), Me (**L3**), Et (**L4**), *i*-Pr (**L5**), Cy (**L6**) and *t*-Bu (**L7**)]. Ligand **L2** (R = *p*-Tol) afforded the same level of reactivity and enantioselectivity as **L1** (63% *ee*, entry 5). With smaller primary alkyl substituents such as **L3** (R = Me) and **L4** (R = Et), higher enantioselectivities of 87% and 90% *ee*, respectively, were achieved with complete conversions (entries 6 and 7). Ligands **L5** (R = *i*-Pr) and **L6** (R = Cy) with secondary alkyl substituents led to slightly lower enantioselectivities (81% and 83%, respectively; entries 8 and 9). An *ee* value of 15% was observed when using **L7** containing a *t*-Bu substituent (entry 10). Having found that the ligand **L4** with an ethyl substituent produced higher enantioselectivity, ferrocenyl ligands **L8** and **L9** supported by different heterocycles (benzimidazole and 1,2,4-triazole, respectively) were then examined for this reaction (entries 11 and 13). It was found that **L9** afforded the alkylated product with 82% *ee*, albeit with a shorter time (1 h) for complete reaction (entry 13). However, ligand **L8** supported by benzimidazole furnished the best enantioselectivity of 93% *ee* in 3 h (entry 11). Further improvement to 95% *ee* was attained when the reaction temperature was lowered to 0 °C (entry 12).

With the optimized reaction conditions in hand, the asymmetric allylic alkylation of **5** with different nucleophiles was studied and the results are summarized in Table 2. Excellent reactivities and enantioselectivities

Table 1. Optimization of reaction conditions with ligands **L1**–**L9**.[a]

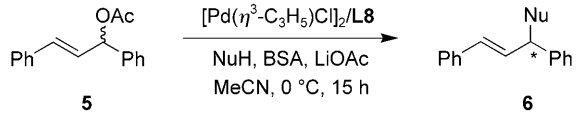


5 (*S*)-**6a**

Entry	Ligand	Solvent	Temp. [°C]	Time [h]	Conv. [%][b]	*ee* [%][c,d]
1	**L1**	CH_2Cl_2	r.t.	2	99	59
2	**L1**	THF	r.t.	2	99	59
3	**L1**	toluene	r.t.	2	52	37
4	**L1**	MeCN	r.t.	2	99	62
5	**L2**	MeCN	r.t.	2	99	63
6	**L3**	MeCN	r.t.	2	99	87
7	**L4**	MeCN	r.t.	2	99	90
8	**L5**	MeCN	r.t.	2	99	81
9	**L6**	MeCN	r.t.	2	99	83
10	**L7**	MeCN	r.t.	2	99	15
11	**L8**	MeCN	r.t.	3	99	93
12	**L8**	MeCN	0	15	99	95
13	**L9**	MeCN	r.t.	1	99	82

[a] *Conditions:* 1,3-diphenyl-2-propenyl acetate **5** (0.1 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand (5 mol%), dimethyl malonate (2 equiv.), BSA (2 equiv.), LiOAc (5 mol%) in solvent (1 mL).
[b] Determined by ^1H NMR analysis of the crude mixture.
[c] Determined by chiral HPLC (see Experimental Section).
[d] Absolute configuration was assigned to be (*S*) by comparison with the literature results.[7]

Table 2. Scope of nucleophiles.[a]



5 **6**

Entry	NuH	Product	Yield [%][b]	*ee* [%][c]
1	MeOOC–CH(–)–COOMe	**6a**	98	95
2	EtOOC–CH(–)–COOEt	**6b**	97	95
3	BnOOC–CH(–)–COOBn	**6c**	95	94
4	EtOOC–C(Bn)(–)–COOEt	**6d**	95	95
5	EtOOC–C(NHCHO)(–)–COOEt	**6e**	94	96
6	MeOC–C(Me)(–)–COMe	**6f**	96	96

[a] *Conditions:* 1,3-diphenyl-2-propenyl acetate **5** (0.1 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), **L8** (5 mol%), NuH (2 equiv.), BSA (2 equiv.), LiOAc (5 mol%) in MeCN (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC (See Experimental Section).

were achieved with both bulky and substituted malonates. The corresponding alkylated products **6a–6e** were obtained in quantitative yields and 94–96% *ee* (entries 1–5). The diketone 3-methyl-2,4-pentanedione was also an effective nucleophile for the Pd-catalyzed allylic alkylation reaction, and adduct **6f** was formed in 96% *ee* with excellent yield (entry 6).

Cyclic and Unsymmetrical Allylic Substrates

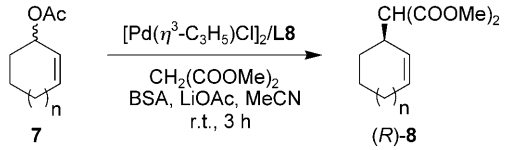
Development of the highly enantioselective allylic alkylation of non-sterically demanding cyclic substrates remains a challenge; few examples with enantioselectivities >90% *ee* have been reported.[7b,23] In this work, the reaction of cyclic allylic acetates **7a–c** of different ring size with dimethyl malonate in the presence of 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 5 mol% **L8** was examined (Table 3). Good to excellent chemical yields were obtained for all cyclic substrates tested. Cycloheptenyl acetate **7c** afforded the alkylated product **8** in 96% yield and 87% *ee* in 3 h at ambient temperature (entry 3).

Many ligands documented in the literature are known to exhibit excellent enantioselectivity for the allylic alkylation of 1,3-diphenyl-2-propenyl acetate **5**; however, they are usually less successful for the reaction with unsymmetrical allylic substrates such as **9** and **11** bearing a larger and a smaller substituent on each terminus. The development of Pd-catalyzed allylic substitution of unsymmetrical substrates with high regioselectivity and enantioselectivity is a current interest since, in the Pd-catalyzed allylic alkylations, nucleophiles would preferentially attack at the least hindered allylic carbon to give achiral linear or less hindered products.[24,25] Recently, bulky and electronically poor phosphorus ligands were found to be efficient in the allylic alkylation of achiral linear or racemic branched allylic acetate **11**, and highly regioselective and enantioselective branched alkylated products **12a** were obtained.[23b,e,24e,g]

To investigate the regio- and enantioselectivity of the allylic substitution of unsymmetrical substrates using our catalyst system, we employed **9** as substrate, which has been extensively studied by Pfaltz and coworkers.[26] It was found that the allylic alkylation of unsymmetrical substrate **9** with 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 5 mol% of **L8** afforded the regioisomers **10a** and **10b** in an 87/13 ratio with excellent yield in 3 h. The less hindered major product **10a** was formed with 43% *ee*. The minor product **10b** was also formed by the nucleophile attacking the more hindered site; a higher enantioselectivity of 71% *ee* was observed (Scheme 2).

Employing the same reaction conditions, cinnamyl acetate **11a** was converted to an inseparable mixture of **12a** and **12b** in 80% total yield (**12a**/**12b** = 68/32), product **12a** was formed in 57% *ee* (Scheme 3). Replacing **11a** with a branched racemic regioisomer **11b**, branched product **12a** was also obtained as the minor isomer (**12a/12b** = 35/65) with improved enantioselectivity (76% *ee*) and 87% total yield.

Table 3. Allylic alkylation of cyclic allylic substrates.[a]



7 (*R*)-**8**

Entry	n	Product	Yield [%][b]	*ee* [%][c,d]
1	0	**8a**	84	76
2	1	**8b**	93	64
3	2	**8c**	96	87

[a] *Conditions:* allylic acetate **7** (0.3 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), **L8** (5 mol%), dimethyl malonate (1.5 equiv.), BSA (1.5 equiv.), LiOAc (5 mol%) in MeCN (1 mL).

[b] Isolated yield.

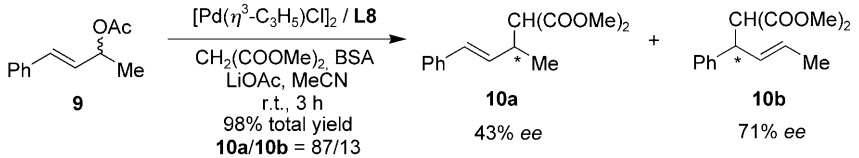
[c] Determined by ^{1}H NMR analysis by using $Eu(hfc)_3$.

[d] Absolute configurations were assigned to be (*R*) by comparison with the literature results.[7]

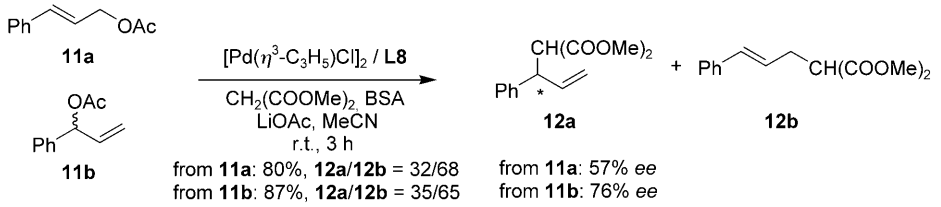
Mechanistic Proposal

In order to gain insight into the allylic substitution reaction, complexes **13a** and **13b** were prepared by reacting $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and $[Pd(\eta^3\text{-}PhC_3H_3Ph)Cl]_2$ with **L8** in CH_2Cl_2, respectively, followed by the addition of $TlPF_6$ to the resulting reaction mixture for counterion exchange (Scheme 4).

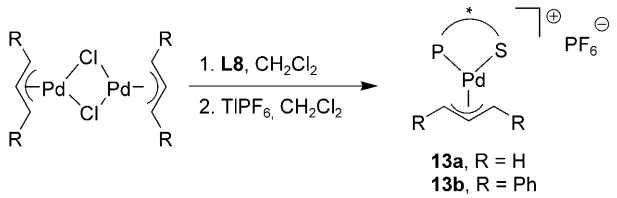
$[Pd(\mathbf{L8})(\eta^3\text{-}C_3H_5)]PF_6$ (**13a**) was recrystallized by slow diffusion of hexane into a CH_2Cl_2 solution, and a single crystal was obtained for X-ray diffraction anal-



Scheme 2. Allylic alkylation of unsymmetrical allylic substrate **9**.



Scheme 3. Allylic alkylation of unsymmetrical allylic substrates **11**.



Scheme 4. Preparation of Pd-(η^3-allyl) complexes **13**.

ysis (Figure 3). However, we failed to prepare a single crystal of [Pd(**L8**)(η^3-PhC_3H_3Ph)]PF_6 (**13b**) despite several attempts. On a ^{31}P NMR study, complex **13a** in CD_2Cl_2 solution showed two peaks at $\delta_P = 11.3$ and 9.8 ppm with an integral ratio of 3.2:1, indicative of the presence of two diastereomeric π-allyl complexes. While chelation of both P- and S-donor atoms of **L8** to the palladium metal center was confirmed by X-ray crystallography, the *endo*- and *exo*-η^3-allyl palladium isomers should account for the occurrence of the two ^{31}P NMR signals.

Selected bond distances and bond angles of the two isomeric *endo*-**13a** and *exo*-**13a** are depicted in Table 4. The Pd atom of **13a** adopted a highly distort-

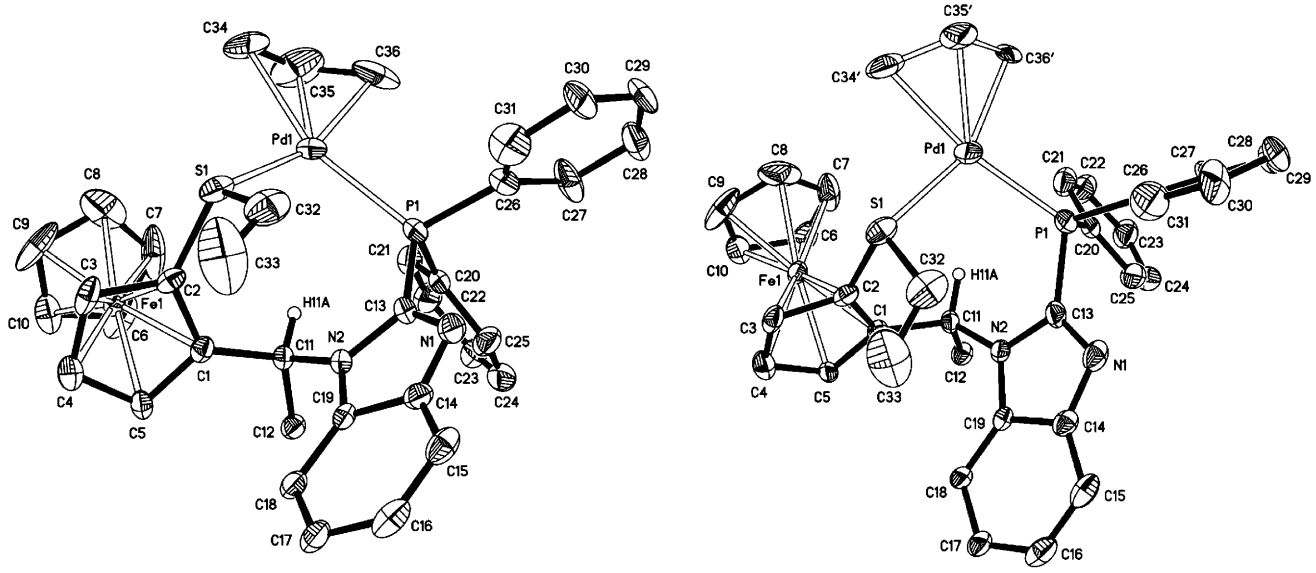


Figure 3. Molecular structures of [Pd(**L8**)(η^3-C_3H_5)]PF_6 complex (**13a**): *endo* isomer (*left*) and *exo* isomer (*right*) (hydrogen atoms and anion are omitted for clarity).

Table 4. Selected bond lengths (Å) and angles (deg) of complex *endo*-**13a** and *exo*-**13a**.

Bond Length (Å)		Bond Angle (deg)	
Pd(1)–P(1)	2.3237(5)	P(1)–Pd(1)–S(1)	105.891(17)
Pd(1)–S(1)	2.3883(5)	C(34)–Pd(1)–C(36)	68.87(11) (*endo*)
Pd(1)–C(34)	2.221(2) (*endo*)	C(34′)–Pd(1)–C(36′)	70.93(11) (*exo*)
Pd(1)–C(35)	2.168(3) (*endo*)	P(1)–Pd(1)–C(36)	91.49(8) (*endo*)
Pd(1)–C(36)	2.179(3) (*endo*)	S(1)–Pd(1)–C(34)	91.75(8) (*endo*)
Pd(1)–C(34′)	2.237(2) (*exo*)	P(1)–Pd(1)–C(36′)	97.20(7) (*exo*)
Pd(1)–C(35′)	2.175(3) (*exo*)	S(1)–Pd(1)–C(34′)	85.99(8) (*exo*)
Pd(1)–C(36′)	2.231(2) (*exo*)	C(36)–Pd(1)–C(34)	68.87(11) (*endo*)
		C(36′)–Pd(1)–C(34′)	70.93(11) (*exo*)

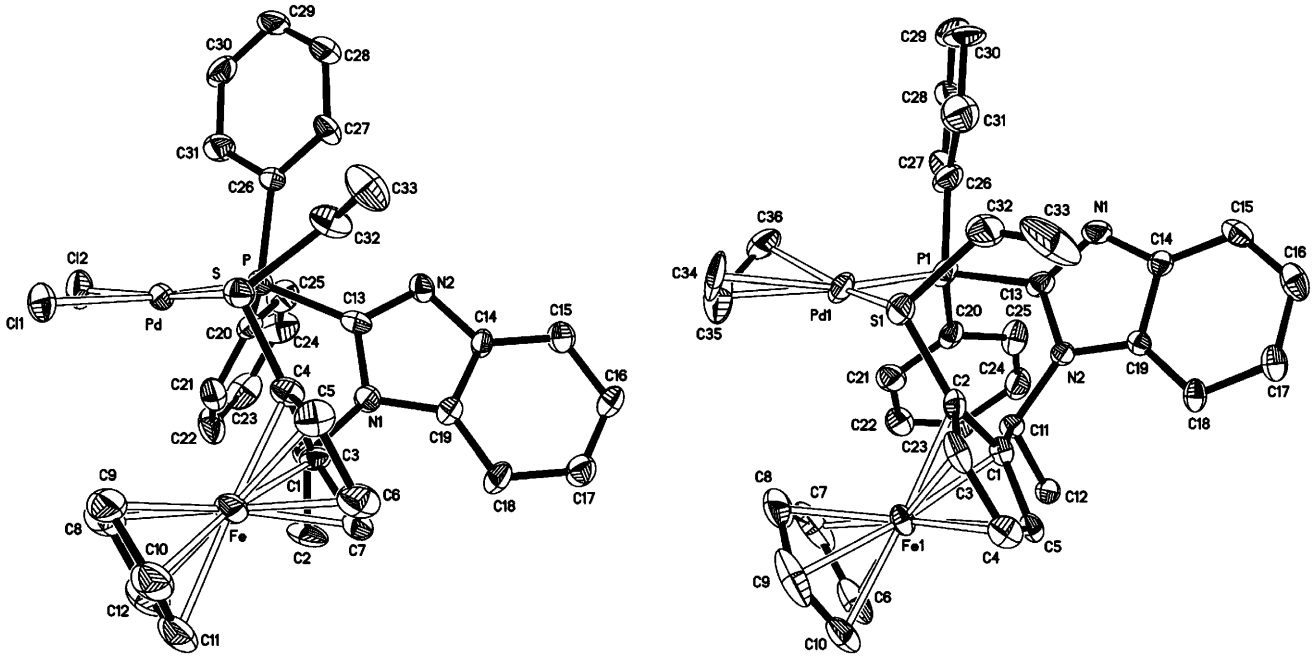


Figure 4. Side view of Pd(**L8**)Cl_2 (*left*) and [Pd(**L8**)(η^3-C_3H_5)]PF_6 (**13a**) (*right*) complexes.

ed square-planar coordination in which the bond angle P(1)–Pd(1)–S(1) is 105.891° and the bond angle C(36)–Pd(1)–C(34) of the *endo*-isomer and C(36′)–Pd(1)–C(34′) of the *exo*-isomer are 68.87° and 70.93°, respectively. The stronger *trans* influence of the phosphine moiety than the thioether group resulted in longer allylic carbon bonds Pd(1)–C(34) with 2.221 Å for *endo*-isomer and Pd(1)–C(34′) with 2.237 Å for the *exo*-isomer. The Pd-allylic carbon distances *trans* to the *S*-donor were found to be shorter: Pd(1)–C(36) = 2.179 Å (*endo*) and Pd(1)–C(36′) = 2.231 Å (*exo*).

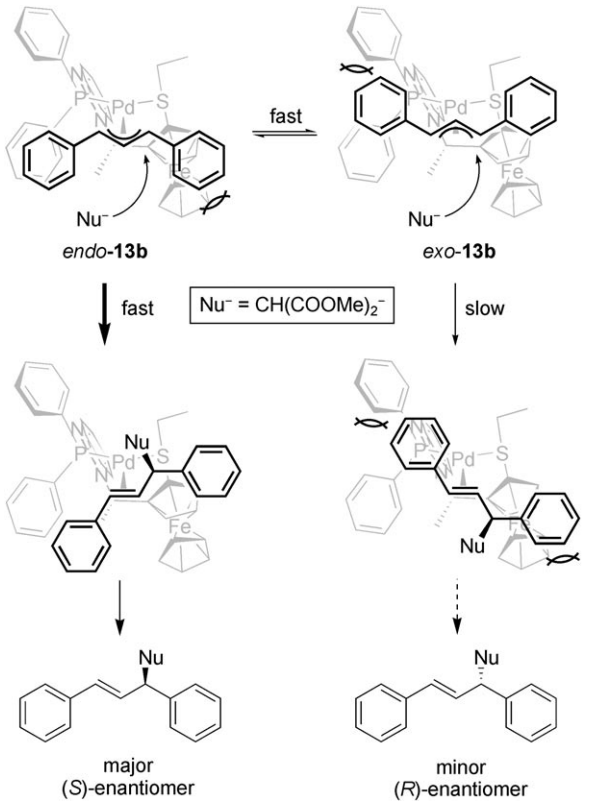
According to VT ^{31}P NMR analysis of **13b** in CD_2Cl_2, two peaks at $\delta_P = 14.8$ and 11.8 ppm were observed with an integral ratio of 1:1 (see Supporting Information). This finding suggested that *endo*- and *exo*-isomers existed equally in rapid equilibrium. However, it should be noted that the *trans* influence of the P-donor is larger than that of the S-donor, nucleophilic addition should occur at the terminal allylic carbon *trans* to P-donor.[5x] Since excellent enantioselectivities (94–96% *ee*) were observed for the allylic substitutions of 1,3-diphenyl-2-propenyl acetate, this implies that one isomer should be more reactive than the other one and the *endo-exo* interconversion must be faster than the nucleophilic addition.

By inspection of the structures of [Pd(**L8**)(η^3-C_3H_5)]PF_6 (**13a**) and Pd(**L8**)Cl_2 (Figure 4), the ferrocene motif should play an important role in the stereochemical control of the product formation. It was found that the lower Cp ring of ferrocene was tilted toward the palladium center. The ferrocene motif is expected to exert some steric interaction for coordination of the 1,3-diphenyl-2-propenyl ligand to the metal center. Yet the ethyl substituent of the thioether group should be more flexible and is oriented away from the palladium center.

The observed enantiofacial selection can be rationalized by a proposed mechanism (Scheme 5). Nucleophilic addition to the *endo*-isomer would result in the relief of steric strain between the allylic phenyl group and the lower Cp ring of the ferrocene motif. Therefore, nucleophilic addition to the *exo*-isomer is probably slower because, upon the nucleophilic addition, a large steric strain would be developed in forming the energetically unfavorable palladium-olefin complex.

Conclusions

In summary, a series of chiral phosphine-thioether mixed donor ligands **L1**–**L9** supported with ferrocene and heterocyclics is described. They are effective in palladium-catalyzed asymmetric allylic alkylations with a variety of allylic substrates and nucleophiles. Excellent yields and enantioselectivities (up to 96% *ee*) were attained. Variation of the substituents of the thioether moiety was crucial in the stereocontrol in the catalysis. The origin of the stereochemical outcome of the alkylated products is discussed with the aid of X-ray crystallography, NMR and observed enantioselectivity. Studies on expanding this class of ligand by further tuning of phosphine-thioether donor sets and heterocyclic scaffolds, as well as development



Scheme 5. Proposed mechanism of the asymmetric allylic alkylation with **L8**.

of other bidentate ligands with this modular framework design, and their applications in other asymmetric catalyses are currently underway.

Experimental Section

General Considerations

All the reactions were carried out under a nitrogen atmosphere using oven-dried glassware. Unless otherwise noted, commercial reagents were used as received without purification. Toluene was distilled from sodium under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2) and hexane were distilled from CaH_2 under a nitrogen atmosphere. Thin layer chromatography was performed on silica gel plates. Silica gel (Merck, 230–400 mesh) was used for flash column chromatography. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian (500 MHz) or Brüker (400 MHz) spectrometer. Chemical shift (δ) are given in ppm and are referenced to residual solvent peaks (^1H NMR and ^{13}C NMR) or to an 85% H_3PO_4 in D_2O externally (^{31}P NMR). Coupling constants (J) were reported in hertz (Hz). Mass spectra and high resolution mass spectra (HR-MS) were obtained on a VG MICROMASS, Fison VG platform, Finnigan Model Mat 95 ST instrument, or Brüker APEX 47e FT-ICR mass spectrometer. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter in a 10 mm cell. Melting points were measured on a Büchi Melting Point B-545 machine. The X-ray crystal structure was determined using a Brüker CCD area detector diffractometer. HPLC analyses were performed on an HP1100 instrument using Chiralcel® OD-H, AD-H and OJ-H columns (0.46 cm diameter × 25 cm length). Compounds **1**–**3**, **L1**–**L8** and Pd(**L8**)Cl_2 were reported elsewhere.[15] [Pd(η^3-PhC_3H_3Ph)Cl]$_2$ was prepared according to the reported procedure.[27]

Ligand Synthesis

1-{(*S*)-1-[(*R*)-2-(Ethylthio)ferrocenyl]ethyl}-1*H*-[1,2,4]-triazole (4): A mixture of thioether **1d** (1 g, 3.15 mmol) and 1,2,4-triazole (1.74 g, 25.2 mmol) in degassed glacial AcOH (11 mL) was stirred at 80 °C for 6 h. The reaction mixture was quenched with an excess of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford compound (S,R_p)-**4**; yield: 94%; red oil; R_f = 0.36 (EtOAc/hexane/Et_3N = 1/1/0.01); $[\alpha]_D^{20}$: +157.7° (c 1.22, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.89 (s, 1H), 7.84 (s, 1H), 5.78 (q, 1H, J = 7.0 Hz), 4.53 (br s, 1H), 4.46–4.45 (m, 1H), 4.34 (t, 1H, J = 2.0 Hz), 4.19 (s, 5H), 2.03–1.96 (m, 1H), 1.89 (d, 3H, J = 7.0 Hz), 1.86–1.79 (m, 1H), 0.89 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.56, 141.54, 88.28, 79.08, 76.09, 70.38, 68.69, 67.57, 53.95, 30.95, 20.81, 14.51; IR (cm^{-1}) 3095, 2977, 2925, 2869, 1666, 1558, 1499, 1453, 1374, 1272, 1195, 1137, 1106, 1051, 1033, 1004, 958, 823, 764, 706, 681, 661; MS (ESI): m/z = 342.04 $[M+H]^+$; HR-MS (ESI): m/z = 342.0749, calcd. for $C_{16}H_{20}N_3SFe$ $[M+H]^+$: 342.0727.

1-{(*S*)-1-[(*R*)-2-(Ethylthio)ferrocenyl]ethyl}-2-(diphenylphosphino)-1*H*-[1,2,4]triazole (L9): To a solution of **4** (0.5 g, 1.47 mmol) in THF (18 mL) was added dropwise n-BuLi (0.92 mL, 1.6 M solution in hexane) at −78 °C, and the mixture was stirred for 30 min under a nitrogen atmosphere. $ClPPh_2$ (291 μL, 1.62 mmol) was then added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for further 4 h at room temperature, and then evaporated under reduced pressure. The residue was purified by flash column chromatography to afford **L9**; yield: 59%, yellow solid; R_f = 0.45 (EtOAc/hexane/Et_3N = 1/3/0.01). A single crystal for X-ray crystallographic analysis was grown by slow diffusion of hexane into a solution of **L9** in CH_2Cl_2. $[\alpha]_D^{20}$: +89.1° (c 1.04, CH_2Cl_2); mp 160–162 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1H), 7.74–7.68 (m, 2H), 7.49–7.46 (m, 2H), 7.38–7.37 (m, 6H), 6.44 (p, 1H, J = 7.0 Hz), 4.61 (s, 1H), 4.41 (s, 1H), 4.35–4.33 (m, 1H), 4.21 (s, 5H), 1.73–1.66 (m, 4H), 1.44–1.37 (m, 1H), 0.70 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.69, 153.55, 152.15, 152.12, 134.51, 134.46, 134.34, 134.17, 133.69, 133.53, 133.46, 133.42, 129.55, 129.36, 128.71, 128.65, 128.40, 128.34, 88.81, 79.01, 75.85, 70.22, 68.55, 68.37, 68.36, 53.69, 53.58, 30.53, 20.69, 14.29; ^{31}P NMR (202 MHz, $CDCl_3$): δ = −35.0; IR: ν = 3072, 3048, 2996, 2977, 2923, 1470, 1436, 1385, 1313, 1278, 1261, 1244, 1217, 1178, 1105, 1090, 1069, 1040, 1029, 1000, 973, 954, 888, 841, 828, 817, 757, 745, 697 cm^{-1}; MS

(ESI): m/z = 526.11 $[M+H]^+$; HR-MS (ESI): m/z = 526.1179, calcd. for $C_{28}H_{29}N_3PSFe$ $[M+H]^+$: 526.1169.

General Procedure for Pd-Catalyzed Asymmetric Allylic Alkylation

A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.91 mg, 2 μmol) and the appropriate ligand (4 μmol) in CH_2Cl_2 (100 μL) was stirred for 15 min under a nitrogen atmosphere in a Teflon-lined screw-capped vial. To this catalyst was added allylic acetate (0.1 mmol) in MeCN (1.0 mL), and the mixture was stirred for further 5 min. After addition of nucleophile (0.2 mmol), BSA (49 μL, 0.2 mmol) and LiOAc (catalytic amount), the reaction mixture was stirred for the corresponding time and temperature indicated. The resulting mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding product.

(*E*)-Methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate (6a):[7b] Yield: 98%, colorless oil. R_f = 0.3 (EtOAc/hexane = 1/9). 95% *ee* by HPLC (Chiralcel AD, *i*-PrOH/hexane = 10/90, 1.0 mL min^{-1}, 254 nm): R_t = 10.7 min (*R*) (minor) and 15.0 min (*S*) (major); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 10H), 6.48 (d, 1H, J = 16.0 Hz), 6.33 (dd, 1H, J = 15.5, 8.5 Hz), 4.26 (dd, 1H, J = 10.5, 8.5 Hz), 3.97 (d, 1H, J = 11.0 Hz), 3.71 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 167.8, 140.2, 136.8, 131.8, 129.1, 128.7, 128.5, 127.9, 127.6, 127.2, 126.4, 57.6, 52.6, 52.4, 49.2; EI-MS: m/z = 324 $[M]^+$.

(*E*)-Ethyl 2-carboethoxy-3,5-diphenylpent-4-enoate (6b):[28] Yield: 97%, colorless oil. R_f = 0.2 (EtOAc/hexane = 1/10). 95% *ee* by HPLC (Chiralcel AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL min^{-1}, 254 nm): R_t = 15.0 min (*R*) (minor) and 20.5 min (*S*) (major); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.17 (m, 10H), 6.48 (d, 1H, J = 16.0 Hz), 6.34 (dd, 1H, J = 15.5, 8.5 Hz), 4.27 (t, 1H, J = 9.5 Hz), 4.17 (q, 2H, J = 7.0 Hz), 3.99–3.92 (m, 3H), 1.20 (t, 3H, J = 7.0 Hz), 1.00 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 167.3, 140.2, 136.8, 131.6, 129.3, 128.6, 128.4, 127.9, 127.4, 127.0, 126.3, 61.5, 61.3, 57.7, 49.2, 14.1, 13.7; EI-MS: m/z = 352 $[M]^+$.

(*E*)-Phenylmethyl 2-carbophenylmethoxy-3,5-diphenylpent-4-enoate (6c):[28] Yield: 95%, colorless oil. R_f = 0.4 (Et_2O/CH_2Cl_2/hexane = 1/1/5). 94% *ee* by HPLC (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL min^{-1}, 254 nm): R_t = 24.1 min (minor) and 29.8 min (major); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 18H), 7.12–7.11 (m, 2H), 6.49 (d, 1H, J = 16.0 Hz), 6.39 (dd, 1H, J = 15.5, 8.5 Hz), 5.17 (dd, 2H, J = 17.5, 12.5 Hz), 5.00 (dd, 2H, J = 17.5, 12.5 Hz), 4.38 (dd, 1H, J = 11.0, 9.0 Hz), 4.13 (d, 1H, J = 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5, 167.1, 140.0, 136.6, 135.1, 135.0, 131.8, 128.9, 128.7, 128.5, 128.4, 128.3, 18.2, 128.1, 128.0, 127.9, 127.5, 127.1, 126.4, 67.3, 67.1, 57.7, 49.2; EI-MS: m/z = 476 $[M]^+$.

(*E*)-Ethyl 2-carboethoxy-2-benzyl-3,5-diphenylpent-4-enoate (6d):[29] Yield: 95%, colorless oil. R_f = 0.5 (Et_2O/CH_2Cl_2/hexane = 1/1/5). 95% *ee* by HPLC (Chiralcel AD-H, *i*-PrOH/hexane = 3/97, 1.0 mL min^{-1}, 254 nm): R_t = 9.4 min (major) and 12.9 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 15H), 6.77 (dd, 1H, J = 15.5, 8.5 Hz), 6.33 (d, 1H, J = 15.5 Hz), 4.29 (d, 1H, J = 9.0 Hz), 4.25–4.11 (m, 2H), 4.02–3.91 (m, 2H), 3.25 (d, 1H, J = 13.5 Hz), 3.10 (d, 1H, J = 13.5 Hz), 1.19 (t, 3H, J = 7.0 Hz), 1.01 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 170.1, 139.3, 137.4, 136.8, 132.1, 130.3, 129.9, 129.5, 128.5, 128.4, 127.8, 127.2, 127.1, 126.7, 126.3, 64.1, 61.1, 61.0, 54.8, 40.9, 13.9, 13.7; EI-MS: m/z = 442 $[M]^+$.

(*E*)-Ethyl 2-carboethoxy-2-formamido-3,5-diphenylpent-4-enoate (6e):[29] Yield: 94%, colorless oil. R_f = 0.5 (EtOAc/hexane = 1/1). 96% *ee* by HPLC (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL min^{-1}, 254 nm): R_t = 15.3 min (major) and 22.5 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (s, 1H), 7.37–7.23 (m, 10H), 6.87 (bs, 1H), 6.77 (dd, 1H, J = 16.0, 7.5 Hz), 6.32 (d, 1H, 16.0 Hz), 4.78 (d, 1H, J = 7.0 Hz), 4.36–4.24 (m, 2H), 4.17–4.01 (m, 2H), 1.27 (t, 3H, J = 7.5 Hz), 1.18 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 166.4, 159.8, 137.8, 137.3, 136.7, 129.5, 128.4, 128.3, 128.2, 127.6, 127.1, 126.4, 68.3, 62.8, 62.5, 53.1, 14.1, 13.9; EI-MS: m/z = 395 $[M]^+$.

(*E*)-3-Acetyl-3-methyl-4,6-diphenyl-5-hexen-2-one (6f):[30] Yield: 96%, colorless oil. R_f = 0.2 (EtOAc/hexane = 1/9). 96% *ee* by HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 10/90, 1.0 mL min^{-1}, 254 nm): R_t = 16.8 min (*S*) (minor) and 23.1 min(*R*) (major); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.18 (m, 10H), 6.46 (d, 1H, J = 15.5 Hz), 6.38 (dd, 1H, J = 15.5, 8.0 Hz), 4.69 (d, 1H, J = 8.5 Hz), 2.15 (s, 3H), 1.93 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.5, 205.7, 139.7, 136.9, 133.2, 129.6, 128.5, 128.3, 127.8, 127.5, 127.0, 126.3, 71.5, 51.5, 27.9, 27.5, 15.8; EI-MS: m/z = 306 $[M]^+$.

(*R*)-Dimethyl 3-cyclopentenylmalonate (8a):[7b] Yield: 84%, colorless oil. R_f = 0.24 (EtOAc/hexane = 1/19). $[\alpha]_D^{20}$: +72.0° (*c* 1.61, CH_2Cl_2); 76% *ee* by ^{1}H NMR using $Eu(hfc)_3$ chiral shift reagent. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82–5.80 (m, 1H), 5.64–5.62 (m, 1H), 3.71 (s, 6H), 3.37–3.34 (m, 1H), 3.26 (d, 1H, J = 9.5 Hz), 2.36–2.29 (m, 2H), 2.14–2.08 (m, 1H), 1.60–1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 169.0, 133.0, 131.3, 56.6, 52.4, 52.3, 45.4, 31.7, 27.7; EI-MS: m/z = 198 $[M]^+$.

(*R*)-Dimethyl 3-cyclohexenylmalonate (8b):[7b] Yield: 93%, colorless oil. R_f = 0.24 (EtOAc/hexane = 1/19). $[\alpha]_D^{20}$: +32.1° (*c* 1.0, CH_2Cl_2); 64% *ee* by ^{1}H NMR using $Eu(hfc)_3$ chiral shift reagent. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76–5.72 (m, 1H), 5.49–5.47 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.25 (d, 1H, J = 9.5 Hz), 2.90–3.84 (m, 1H), 1.98–1.91 (m, 2H), 1.77–1.65 (m, 2H), 1.58–1.49 (m, 1H), 1.37–1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 168.7, 129.6, 127.2, 56.7, 52.3, 52.2, 35.3, 26.5, 24.8, 20.8; EI-MS: m/z = 212 $[M]^+$.

(*R*)-Dimethyl 3-cycloheptenylmalonate (8c):[7b] Yield: 96%, colorless oil. R_f = 0.21 (EtOAc/hexane = 1/19). $[\alpha]_D^{20}$: +7.4° (*c* 1.78, CH_2Cl_2); 86.8% *ee* by ^{1}H NMR using $Eu(hfc)_3$ chiral shift reagent. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82–5.77 (m, 1H), 5.57–5.54 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.44 (d, 1H, J = 8.5 Hz), 3.03–2.99 (m, 1H), 2.12–2.10 (m, 2H), 1.93–1.89 (m, 1H), 1.66–1.56 (m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 168.9, 132.8, 132.7, 56.7, 52.3, 52.2, 39.6, 30.9, 30.1, 28.3, 26.2; EI-MS: m/z = 226 $[M]^+$.

(*E*)-Methyl 2-carbomethoxy-3-methyl-5-phenylpent-4-enoate (10a):[5f,31] Yield: 98% (inseparable mixture with

10b), colorless oil. $R_f = 0.21$ (EtOAc/hexane = 1/10). 43% *ee* by HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL min^{-1}, 254 nm): $R_t = 18.7$ min (major) and 19.8 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$–7.19 (m, 5H), 6.45 (d, 1H, $J = 15.5$ Hz), 6.12 (dd, 1H, $J = 16.0$, 8.5 Hz), 3.75 (s, 3H), 3.67 (s, 3H), 3.40 (d, 1H, $J = 9.0$ Hz), 3.16–3.09 (m, 1H), 1.19 (d, 3H, $J = 6.5$ Hz); EI-MS: $m/z =$ 262 $[M]^+$.

(*E*)-Methyl 2-carbomethoxy-3-phenylhex-4-enonate (10b):[24c] Yield: 98% (inseparable mixture with **10a**), colorless oil. $R_f = 0.21$ (EtOAc/hexane = 1/10). 71% *ee* by HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL min^{-1}, 215 nm): $R_t = 14.9$ min (minor) and 16.0 min (major); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$–7.19 (m, 5H), 5.61–5.53 (m, 2H), 4.04 (dd, 1H, $J = 11.0$, 7.5 Hz), 3.82 (d, 1H, $J = 11.0$ Hz), 3.73 (s, 3H), 3.48 (s, 3H), 1.63 (d, 3H, $J =$ 5.0 Hz); EI-MS: $m/z = 262$ $[M]^+$.

Dimethyl 1-phenyl-2-propenylmalonate (12a):[32] Yield: 87% (inseparable mixture with **12b**), colorless oil. $R_f = 0.21$ (EtOAc/hexane = 1/10). 76% *ee* by HPLC (Chiralcel OJ-H, *i*PrOH/hexane = 3/97, 0.7 mL min^{-1}, 220 nm): $R_t = 44.2$ min (major) and 52.2 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$–7.21 (m, 5H), 6.03–5.96 (m, 1H), 5.14–5.08 (m, 2H), 4.11 (dd, 1H, $J = 11.0$, 8.5 Hz), 3.87 (d, 1H, $J =$ 11.5 Hz), 3.75 (s, 3H), 3.49 (s, 3H); EI-MS: $m/z = 248$ $[M]^+$.

General Procedure for the Synthesis of Pd-allyl Complexes

A mixture of ligand (0.06 mmol) and Pd-allyl complex (0.03 mmol) in CH_2Cl_2 (3 mL) was stirred for 3 h at room temperature under a nitrogen atmosphere. $TlPF_6$ (23 mg, 0.066 mmol) was then added and the solution was stirred overnight at room temperature. The white precipitate was filtered and the filtrate was evaporated under reduced pressure.

$[Pd(L8)(C_3H_5)]PF_6$ (13a): L8 (34.0 mg, 0.06 mmol) and $[Pd(allyl)Cl]_2$ (11.0 mg, 0.03 mmol) were used with in accord with the general procedure. ^{31}P NMR (162 MHz, CD_2Cl_2): $\delta = 11.3$ and 9.8 (3.2:1); HR-MS (ESI): $m/z = 721.0710$, calcd. for $C_{36}H_{36}N_2PSFePd$ $[M-PF_6]^+$: 721.0721.

$[Pd(L8)(PhC_3H_3Ph)]PF_6$ (13b): L8 (34.0 mg, 0.06 mmol) and $[Pd(PhC_3H_3Ph)Cl]_2$ (20.0 mg, 0.03 mmol) were used in accord with the general procedure. ^{31}P NMR (162 MHz, CD_2Cl_2): $\delta = 14.8$ and 11.8 (1:1); HR-MS (ESI): $m/z =$ 873.1365, calcd. for $C_{48}H_{44}N_2PSFePd$ $[M-PF_6]^+$: 873.1347.

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