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[2.2]Paracyclophane-Derived Chiral P,N-Ligands: Design, Synthesis, and Application in Palladium-Catalyzed Asymmetric Allylic Alkylation

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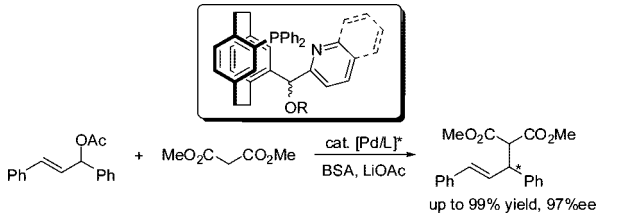

With the idea of tuning structural flexibility and rigidity, several [2.2]paracyclophane-derived P,N-ligands were designed and synthesized. A full investigation of the relationship between the ligands' structures and their abilities to induce asymmetry in palladium-catalyzed asymmetric allylic alkylations of malonates with 1,3-diphenyl 2-propenyl acetate was carried out, and high yields and enantioselectivities (i.e., 99% yield, 97% ee) were observed while using ligands bearing matched planar and central chirality.

Palladium-catalyzed asymmetric allylic alkylation has proven to be a powerful tool for stereoselective C−C bond-formation.[1] Among many chiral ligands designed for this reaction, chiral P,N-ligands have played an important role owing to their steric and electronic asymmetry.[2,3]

Extensive research has been conducted on centrally and axially chiral P,N-ligands, of which representative examples are the PHOX ligands,[2,4] prolinol derived ligands,[5] binaphthyl-based ligands,[6] and the QUINAP-type ligand.[7] Most investigations dealing with ligands possessing planar chirality have focused on ferrocene derivatives.[8] However, the full potential of substituted [2.2]paracyclophanes for asymmetric synthesis has only been realized since ca. the 1990s.[9,10] These compounds are not only highly rigid, but also stable during exposure to high temperatures (up to 200 °C), light, acids, and bases.[9,11] PhanePHOS achieved higher activity and enantioselectivity than BINAP in the preparation of the HIV protease inhibitor Crixivan.[12] N,O-ligands derived from FHPC, AHPC, and BHPC have also been successfully applied to the addition of organozinc reagents to aldehydes and imines.[13] Compared to these successful analogues, P,N-[2.2]paracyclophane ligands are still at an early stage. Pseudo-*gem*-phosphinyl-oxazolinyl[2.2]paracyclophane[14] was the first to be reported, and the pseudo-ortho- and ortho-counterparts[15] were subsequently prepared. All of these ligands were employed in the Pd-catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate and exhibited widely differing activities and enantioselectivities, among which the pseudo-ortho-ligand gave the best result.

We reasoned that if the structural rigidity and flexibility could be further regulated,[16] the performance of the ligands might be improved. Thus P,N-[2.2]paracyclophane ligands **1**−**6**, which use the pyridine or quinoline nitrogen as a donor atom, were

(1) For reviews, see: (a) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. 2. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593−649. (c) Nishibayashi, Y.; Uemura, S. In *Comprehensive Organometallic Chemistry*; Mingos, D. M. P., Crabtree, R. H., Eds.; Elsevier Science: Amsterdam, The Netherlands, 2003; Vol. 11, pp 75−122. (d) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: Chichester, UK, 2004. (e) Zhan Lu, S. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.

(2) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.

(3) (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497–537. (b) Pfaltz, A.; Drury, W. J., III. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5723–5726. (c) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031–1037.

(4) (a) Matt, P. v.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566–568. (b) Matt, P. v.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573–584. (c) Matt, P. V.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265–284. (d) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772. (e) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523–1526.

(5) For examples, see: (a) Mino, T.; Saito, A.; Tanaka, Y.; Hasegawa, S.; Sato, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 1937–1940. (b) Mino, T.; Sato, Y.; Saito, A.; Tanaka, Y.; Saotome, H.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 7979–7984. (c) Jiang, B.; Huang, Z.-G.; Cheng, K.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 942–951.

(6) For examples, see: (a) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073–1083. (b) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343–4346. (c) Stranne, R.; Vasse, J. L.; Moberg, C. *Org. Lett.* **2001**, *3*, 2525–2528.

(7) Doucet, H.; Brown, J. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3775–3784.

(8) For reviews, see: (a) Togni, A. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley: New York, 1998; pp 685−721. (b) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328. (c) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101–3118.

(9) For reviews, see: (a) Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256–1269. (b) Rozenberg, V.; Sergeeva, E.; Hopf, H. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 435−462.

(10) Examples of chiral [2.2]paracyclophane structrues: (a) Rowlands, G. J. *Org. Biomol. Chem.* **2008**, *6*, 1527−1534. (b) Vorontsova, N. V.; Rozenberg, V. I.; Sergeeva, E. V.; Vorontsov, E. V.; Starikova, Z. A.; Lyssenko, K. A.; Hopf, H. *Chem. Eur. J.* **2008**, *14*, 4600–4617.

(11) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3505–3516.

(12) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208.

(13) (a) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113–2116. (b) Dahmen, S.; Bräse, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2845–2850. (c) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119–4122. (d) Dahmen, S.; Bräse, S. *Chem. Commun.* **2002**, 26–27. (e) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941. (f) Danilova, T. I.; Rozenberg, V. I.; Sergeeva, E. V.; Starikova, Z. A.; Bräse, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2013–2019. (g) Danilova, T. I.; Rozenberg, V. I.; Starikova, Z. A.; Bräse, S. *Tetrahedron: Asymmetry* **2004**, *15*, 223–229. (h) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694. (i) Rozenberg, V. I.; Danilova, T. I.; Sergeeva, E. V.; Shouklov, I. A.; Starikova, Z. A.; Hopf, H.; Kühlein, K. *Eur. J. Org. Chem.* **2003**, 432–440.

(14) Wu, X.-W.; Yuan, K.; Sun, W.; Zhang, M.-J.; Hou, X.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 107–112.

(15) Whelligan, D. K.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 4609–4618.

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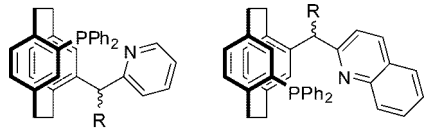
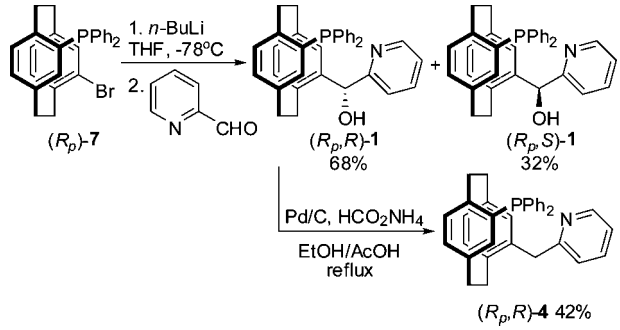
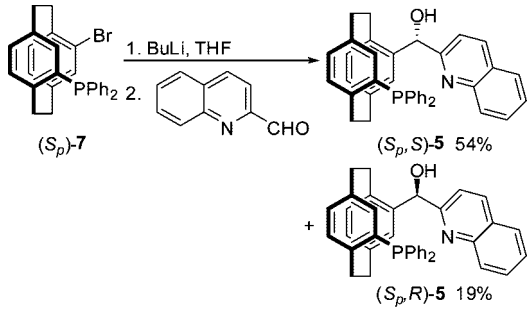


FIGURE 1. Designed [2.2]paracyclophane P,N-chiral ligands.

SCHEME 1. Synthesis of Phosphino−Pyridine Ligands



SCHEME 2. Synthesis of Phosphino−Quinoline Ligands

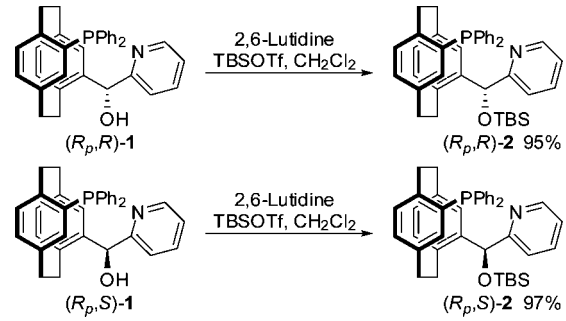


designed (Figure 1).[17] We conjectured that if the pyridine or quinoline ring was attached to the benzylic carbon, which was also a chiral carbon, these structures with adjusted side chains might meet the requirements. Herein, we report the synthesis of ligands **1**−**6**. Matched−mismatched effects were observed when applying them in Pd-catalyzed asymmetric allylic alkylkation reactions.

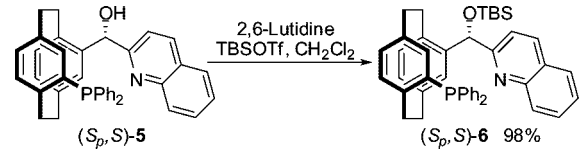
The synthesis started from enantiopure monophosphino [2.2]paracyclophane **7**.[18] Thus, the treatment of (R_p)-**7** with *n*-BuLi followed by the addition of 2-pyridinecarboxaldehyde led to two diastereoisomers, (R_p,*R*)-**1** (68%) and (R_p,*S*)-**1** (32%), which could be readily separated by chromatography (Scheme 1). The relative stereochemistry of (R_p,*R*)-**1** was confirmed by X-ray analysis. Pd/C-catalyzed dehydroxylation of (R_p,*R*)-**1** produced (R_p)-**4**, a structure possessing only planar chirality in 42% yield (Scheme 1).

Beginning with (S_p)-**7**, quenching with 2-quinoline carboxaldehyde after treatment with *n*-BuLi yielded two structurally similar ligands, (S_p,*S*)-**5** (54%) and (S_p,*R*)-**5** (19%), which were also separable by chromatography (Scheme 2).

SCHEME 3. Synthesis of Silylated Phosphino−Pyridine Ligands



SCHEME 4. Synthesis of Silylated Phosphino−Quinoline Ligands



Modifying (R_p,*R*)-**1** and (R_p,*S*)-**1** by silylation with use of TBSOTf/lutidine smoothly generated (R_p,*R*)-**2** in 95% yield and (R_p,*S*)-**2** in 97% yield (Scheme 3).[19]

Silylation of the quinoline ligands also provided the corresponding compounds. However, only (S_p,*S*)-**6** was isolated because (S_p,*R*)-**6** was unstable (Scheme 4).

Direct alkylation of the hydroxyl group of **1** with MeI was not successful due to ylide formation at phosphorus. Thus, the diphenylphosphine group was first protected with sulfur in dicholoromethane, producing (R_p,*R*)-**8** and (R_p,*S*)-**8** in high yield. After respective alkylation with MeI/NaH followed by desulfurization with Raney-Ni of (R_p,*R*)-**8** and (R_p,*S*)-**8**, the alkylated P,N-ligands (R_p,*R*)-**3** and (R_p,*S*)-**3** were obtained. (Scheme 5).[17,20]

With these chiral P,N-ligands in hand, we set out to study their application in the Pd-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate **10** with dimethyl malonate **11** in the presence of BSA/LiOAc.[21] (R_p,*R*)-**1** and (R_p,*S*)-**1** were first employed to explore the reaction conditions and the influence of the planar and central chirality (Table 1, entries 1−8). While the yields are comparable, reactions run in CH_2Cl_2 gave higher enantioselectivities than those in THF. Temperature was not influential since lower temperatures did not provide improved selectivity. A key issue was the configurations of the product **12**, which reversed when the central chirality of the ligand was changed. This reminded us of a matched−mismatched effect. Thus, planar chiral ligand (R_p)-**4** was used to determine the role played by the planar chirality (Table 1, entry 9). (*R*)-**12** with an 86% ee was produced in 55% yield, which showed us that planar chirality could not induce good results alone. The central chiral carbon residing in the ligands was a critical component.

To obtain more evidence about the mechanism, the other ligands were investigated. The reaction carried out with (R_p,*R*)-**2**

(16) (a) Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195–1196. (b) Wu, X.-W.; Zhang, T.-Z.; Yuan, K.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 2357–2365.

(17) Ferrocene based ligands with similar structure: Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089–3092.

(18) Focken, T.; Raabe, G.; Bolm, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1693–1706.

(19) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622–635.

(20) Zhang, W.; Xu, Q.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3161–3169.

(21) (a) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von.Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143–2156. (b) Gihani, E. T. M.; Heaney, H. *Synthesis* **1998**, *35*, 7–375.

SCHEME 5. Synthesis of Alkylated Phosphino−Pyridine Ligands

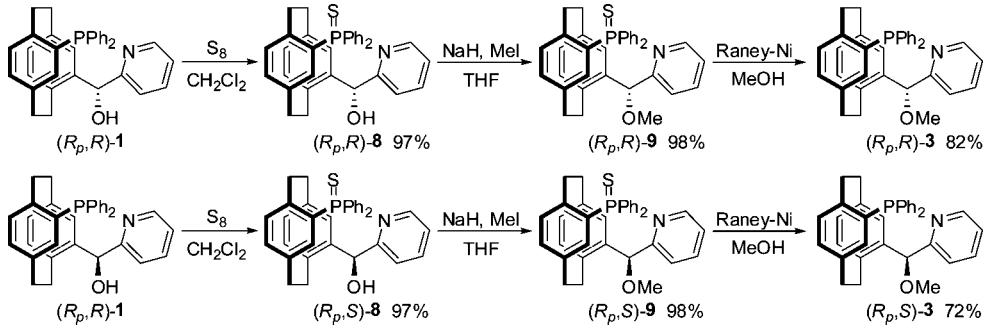
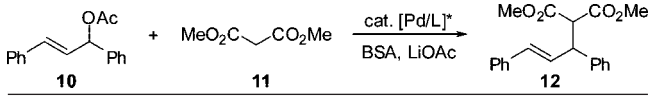


TABLE 1. Results of the Pd-Catalyzed Asymmetric Allylic Alkylation with [2.2]Paracyclophane-Derived Chiral P,N-Ligands



entry	ligands	solvent	temp	time	yield (%)	conf.[b]	ee (%)[c]
1	(R_p,R)-**1**	THF	rt	3.5 h	97	*S*	80
2	(R_p,R)-**1**	THF	−10°C	16 h	98	*S*	86
3	(R_p,S)-**1**	THF	rt	3.5 h	99	*R*	89
4	(R_p,S)-**1**	THF	−10°C	8 h	99	*R*	75
5	(R_p,R)-**1**	CH_2Cl_2	rt	8 h	98	*S*	94
6	(R_p,R)-**1**	CH_2Cl_2	−10°C	8 h	96	*S*	94
7	(R_p,S)-**1**	CH_2Cl_2	rt	8 h	99	*R*	88
8	(R_p,S)-**1**	CH_2Cl_2	−10°C	48 h	81	*R*	87
9	(R_p)-**4**	CH_2Cl_2	rt	48 h	55	*R*	86
10	(R_p,R)-**2**	CH_2Cl_2	rt	5 min	99	*S*	97
11	(R_p,S)-**2**	CH_2Cl_2	rt	48 h	79	*R*	96
12	(R_p,R)-**3**	CH_2Cl_2	rt	72 h	84	*S*	99
13	(R_p,S)-**3**	CH_2Cl_2	rt	20 min	99	*R*	71
14	(S_p,S)-**5**	CH_2Cl_2	rt	30 min	98	*R*	96
15	(S_p,R)-**5**	CH_2Cl_2	rt	30 min	99	*S*	22
16	(S_p,S)-**6**	CH_2Cl_2	rt	24 h	67	*R*	98

[a] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/LiOAc/BSA/10/11 = 2/6/3/300/100/300. [b] Determined by comparison of the retention time of products with that reported by references. [c] Determined by chiral HPLC, ChiralPAK AD-H, 0.8 mL/min, hexane/^{i}PrOH = 80/20.

was very rapid, proceeding to completion within 5 min in high yield (99% yield) and enantioselectivity (97% ee, Table 1, entry 10). In contrast, the reaction with (R_p,S)-**2** as ligand was much slower, although the ee was still high (Table 1, entry 11). Using (R_p,R)-**3** gave 84% yield and 99% ee after 72 h (Table 1, entry 12). When using (R_p,S)-**3**, it took 20 min to furnish a 99% yield and 71% ee (Table 1, entry 13). Quinoline ligands (S_p,S)-**5** and (S_p,R)-**5** afforded comparable yields (98% and 99%) in short times (Table 1, entry 14 and 15), but the ee values were dramatically different (96% ee and 22% ee). The asymmetric induction of (S_p,R)-**5** was obviously much lower than that of its diastereoisomer (S_p,S)-**5**. Finally, (S_p,S)-**6** was tested, and the reaction was slow compared the reaction with unsilylated (S_p,S)-**5**, with only 67% yield achieved after 24 h, but the ee value was still satisfactory (98% ee).

Product configuration and enantioselectivities of all of these reactions proved that both the planar chiral [2.2]paracyclophane unit and the stereogenic center strongly influence the enantioselectivities. Our attention was therefore drawn to the reaction pathway. Two M-type π-allyl complexes[1a] were proposed to be responsible for the different product configurations induced by (R_p,R)-**1** and (R_p,S)-**1** (Figure 2). This model also suits other ligands. Since the W-type complexes (R_p,R)-**1**-**C** and (R_p,S)-**1**-**C** were assumed to have greater steric interference between the two phenyl groups, M-type would be prefered. During

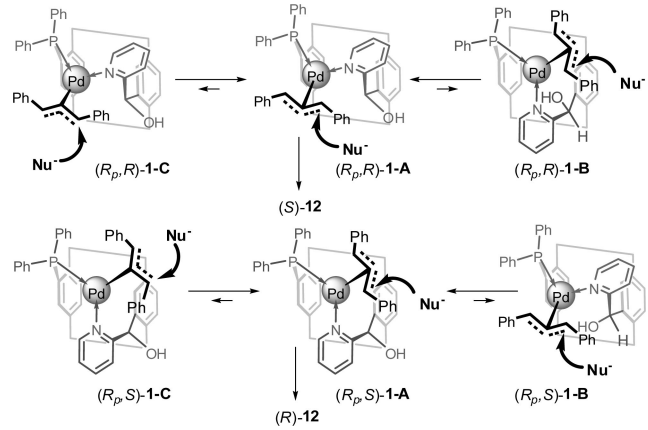


FIGURE 2. Proposed reaction intermediates of the Pd-catalyzed allylic alkylation with ligands (R_p,R)-**1** and (R_p,S)-**1**.

chelation, the pyridine ring rotates to the inner site of the [2.2]paracyclophane to coordinate with palladium, while the hydroxyl group should be away from the [2.2]paracyclophane due to steric considerations. Thus, (R_p,R)-**1**-**A** and (R_p,S)-**1**-**A** are more favored intermediates than (R_p,R)-**1**-**B** and (R_p,S)-**1**-**B**, and (*S*)-**12** and (*R*)-**12** are generated from them, respectively.

In summary, a series of phosphine−pyridine ligands derived from [2.2]paracyclophane were found to be good candidates for asymmetric catalysis. They can easily be prepared from a known enantiopure intermediate. Our pilot study disclosed the high stereoselectivity achieved with these ligands in Pd-catalyzed asymmetric allylic alkylation reactions. The structural flexibility brought by the long side chain and the rigidity originating from the rigid paracyclophane skeleton cooperate to provide a fixed chiral environment, which is supported by analysis of the intermediate π-allyl complexes. Further studies to explore the scope of these ligands in more asymmetric catalytic reactions are currently in progress.

Experimental Section

Typical Procedure for the Asymmetric Allylic Alkylation. Allyl palladium chloride dimer (2.3 mg, 7.0 μmol), ligand (21 μmol), and LiOAc (2 mg) were dissolved in solvent (2 mL), and the solution was stirred at rt for 15 min before 1,3-diphenyl 2-propenyl acetate (88.3 mg, 0.35 mmol) was introduced. The mixture was stirred at rt for another 15 min and changed to the desired temperature before dimethyl malonate (139 mg, 1.05 mmol) and BSA (0.26 mL, 1.05 mmol) were added. The reaction was monitored by TLC. The mixture was quenched by the addition of cold saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc. The organic phase was dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography

on silica gel (petroleum ether/EtOAc = 20/1) to give the product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.16 (m, 10H), 6.50 (d, J = 15.8 Hz, 1H), 6.35 (dd, J = 15.8, 8.5 Hz, 1H), 4.29 (dd, J = 10.8, 8.5 Hz, 1H), 3.98 (d, J = 10.8 Hz, 1H), 3.72 (s, 3H), 3.53 (s, 3H). The ee was determined by chiral HPLC with a ChiralPAK AD-H column, with hexane/*i*-PrOH (80/20) as the mobile phase and a flow rate of 0.8 mL/min (t_R = 12.6 min, t_S = 16.7 min).

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Supporting Information Available: General experimental procedures, compound characterization data, the X-ray structure of (R_p,R)-**1** (CIF file) and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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