New Types of Soluble Polymer-Supported Bisphosphine Ligands with a Cyclobutane Backbone for Pd-Catalyzed Enantioselective Allylic Substitution Reactions

Dongbo Zhao, Jie Sun, and Kuiling Ding*[a]

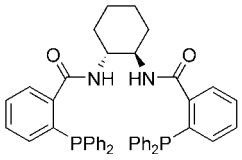
Dedicated to Professor Changtao Qian on the occasion of his 70th birthday

Abstract: A highly efficient and practical optical resolution of *anti* head-to-head racemic coumarin dimer **7** has been achieved by molecular complexation with TADDOL, (−)-**8**, through a hydrogen bonding interaction to afford the corresponding two enantiomers, (−)- and (+)-**7**, in 70 and 75% yields, respectively, with >99% *ee*. Starting from enantiopure (−)-**7**, a new type of C_2-symmetric bisphosphine ligand (*S*,*S*,*S*,*S*)-**3** with a cyclobutane backbone has been synthesized in good yield by facile transformations. The asymmetric induction efficiency of these chiral bisphosphine ligands in Pd-catalyzed asymmetric allylic substitution reactions was evaluated. Under the experimental conditions, the allylic substitution products could be obtained in excellent yields (up to 99%) and enantioselectivities (up to 98.9% *ee*). By taking advantage of the high enantioselectivity of this catalytic reaction and the easily derivable carboxylate groups on the cyclobutane backbone of ligand (*S*,*S*,*S*,*S*)-**3**, a new type of analogous ligand (*S*,*S*,*S*,*S*)-**4** as well as the MeO-PEG-supported soluble ligand (*S*,*S*,*S*,*S*)-**5** (PEG = polyethylene glycol) have also been synthesized and utilized in asymmetric allylic substitution reactions. In particular, the MeO-PEG supported (*S*,*S*,*S*,*S*)-**5b** had a synergistic effect on the enantioselectivity of the reaction compared with its nonsupported precursor (*S*,*S*,*S*,*S*)-**4c**, affording the corresponding allylation products **14a** and **14b** with excellent enantioselectivities (94.6 and 97.2% *ee*, respectively). Moreover, the Pd complex of (*S*,*S*,*S*,*S*)-**5b** could easily be recovered and recycled several times without significant loss of enantioselectivity and activity in the allylic substitution reactions.

Keywords: allylic substitutions · asymmetric catalysis · bisphosphine · immobilization · optical resolution · P ligands · palladium · soluble polymers

Introduction

The asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] The development of chiral ligands is crucial if high enantioselectivity of catalytic asymmetric reactions is to be achieved.[2] Therefore, the design of novel chiral ligands has been an eternal theme in the research of asymmetric catalysis. Because some C_2-symmetric bisphosphine ligands (such as BINAP[3] and Trost's ligand (**1**)[4]) have shown excellent asymmetric induction in many kinds of asymmetric reactions, we are interested in the development of a new type of C_2-symmetric bisphosphine ligand (**3**), which has a cyclobutane backbone and carboxylate functional groups and which can be considered an analogue of **1** and **2**.[5] Herein, we report the synthesis of bisphosphine ligands **3** and **4** and their polyethylene glycol(PEG)-supported derivatives **5**, as well as their application in Pd-catalyzed asymmetric allylic substitution reactions.[6] Meanwhile, an efficient and practical resolution of *anti* head-to-head racemic coumarin dimer



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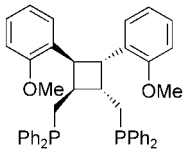

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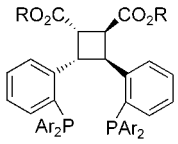

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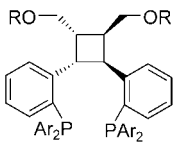

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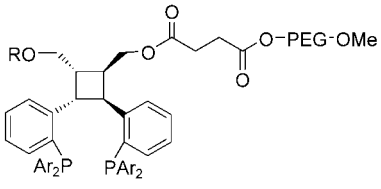

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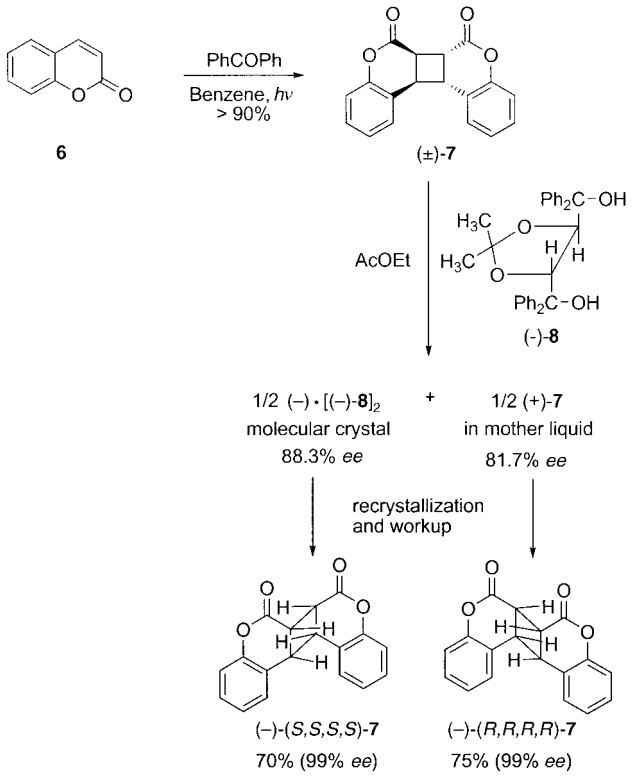
(±)-**7** has also been achieved by molecular complexation with (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (TADDOL, (−)-**8**) to give enantiopure **7**, a key intermediate in the synthesis of **3**–**5**.

Results and Discussion

Practical optical resolution of *anti* head-to-head racemic coumarin dimer (±)-7: As shown in Scheme 1, the preparation of *anti* head-to-head racemic coumarin dimer (±)-**7** was



Scheme 1. Optical resolution of coumarin dimer **7** by molecular complexation with TADDOL (−)-**8**.

carried out by following a literature method;[7] coumarin **6** was irradiated in benzene solution in the presence of benzophenone as a sensitizer to give (±)-**7** in >90% yield (0.2 mol scale). Although the optical resolution of (±)-**7** could be achieved by stepwise recrystallization of its diastereomers formed with enantiopure α-phenylethylamine, acidic hydrolysis, and recyclization of the hydroxy carboxylic acid,[8] the process is somewhat convoluted. The direct synthesis of enantiopure (*S*,*S*,*S*,*S*)-**7** through topochemically controlled [2+2] photodimerization of coumarin **6** included in a TADDOL ((−)-**8**) host in the solid state or in an aqueous suspension was recently reported by Toda and co-workers to give (−)-(*S*,*S*,*S*,*S*)-**7** in 99% yield with 100% *ee*.[9] Despite the difficulties associated with the large-scale preparation of (−)-(*S*,*S*,*S*,*S*)-**7** by using this strategy, the perfect molecular recognition between (−)-**8** and (−)-**7** in the product prompted us to utilize TADDOL (−)-**8**, which is readily available,[10] as a chiral host to resolve the two enantiomers of **7** by molecular complexation through hydrogen bonding. Thus, by heating a mixture of an equimolar amount of (±)-**7** and the resolving agent (−)-**8** in ethyl acetate and then cooling the homogeneous solution to room temperature molecular crystals of (−)-**8** and (−)-**7** were formed with (−)-**7** in 88.3% *ee*. The crystals that precipitated were collected by filtration and washed with ethyl acetate; these crystals were characterized as 2:1 molecular crystals of (−)-**8** and (−)-**7** by ^{1}H NMR spectroscopy. The enantiomeric excess of the opposite enantiomer [(+)-**7**] remaining in the mother liquor was 81.7%. Further recrystallization of the molecular crystals (−)-**7**·[(−)-**8**]$_2$ from ethyl acetate afforded enantiopure (−)-**7**·[(−)-**8**]$_2$ in 70% yield. Decomposition of the molecular crystals (−)-**7**·[(−)-**8**]$_2$ with DMF gave (−)-**7** in 99% yield. The absolute configuration of (−)-**7** was assigned as *S*,*S*,*S*,*S* by comparison of its optical rotation with that reported in the literature.[9a] The enantiomeric excess of (+)-**7** in the mother liquor could be further enriched to 99% by further recrystallization from ethanol and then recyclization in AcOH.

Synthesis of bisphosphine ligands (*S*,*S*,*S*,*S*)-3a–h with a cyclobutane backbone: With the enantiopure **7** in hand, we extended its application to the synthesis of a new type of C_2-symmetric bisphosphine ligand **3**. As shown in Scheme 2, heating an ethanolic solution of (*S*,*S*,*S*,*S*)-**7** resulted in lactone ring-opening to give ethyl ester (*S*,*S*,*S*,*S*)-**9a** in quantitative yield. Treatment of (*S*,*S*,*S*,*S*)-**9a** with $(CF_3SO_2)_2O$ in the presence of Et_3N gave the ditriflate derivative (*S*,*S*,*S*,*S*)-**10a** in 97.3% yield. Compound (*S*,*S*,*S*,*S*)-**10a** underwent a coupling reaction with diarylphosphine oxides in the presence of Pd(OAc)$_2$/dppp (dppp = 1,3-bis(diphenyl-phosphino)propane) and diisopropylethylamine to give the corresponding 1,2-bis(2-diarylphosphinoylphenyl)cyclobutane derivatives (*S*,*S*,*S*,*S*)-**11a–f** in good-to-excellent yields. The target bisphosphine ligands (*S*,*S*,*S*,*S*)-**3a–f** could be easily obtained by the reduction of their oxides (*S*,*S*,*S*,*S*)-**11a–f** with $HSiCl_3$ in the presence of *N*,*N*-dimethylaniline in 74–91% yields.

Two analogous ligands (*S*,*S*,*S*,*S*)-**3g,h** were also designed and synthesized following a similar procedure to that used for the preparation of (*S*,*S*,*S*,*S*)-**3a–f**. As shown in Scheme 2, the preparation of methyl ester derivative (*S*,*S*,*S*,*S*)-**3g** was quite simple and the total yield from the enantiopure coumarin dimer was >70%. In contrast, the coupling reaction of benzyl ester (*S*,*S*,*S*,*S*)-**10c** with diphenylphosphine oxides in the presence of Pd(OAc)$_2$/dppp produced a lot of benzyldiphenylphosphine oxide ($PhCH_2P(O)Ph_2$) in addition to the expected phosphine oxide (*S*,*S*,*S*,*S*)-**11h**. The total yield for the last two steps including C–P bond formation and $HSiCl_3$ reduction of the phosphine oxide was only 30%.

Application of bisphosphine ligands (*S*,*S*,*S*,*S*)-3a–f in Pd-catalyzed enantioselective allylic substitution: Pd-catalyzed enantioselective allylic substitution is one of the most important C–C or C–N bond-forming reactions in modern asymmetric catalysis.[4,11] To demonstrate the asymmetric induction efficiency of the chiral ligands (*S*,*S*,*S*,*S*)-**3a–f**, Pd-catalyzed enantioselective allylic substitution was taken as the

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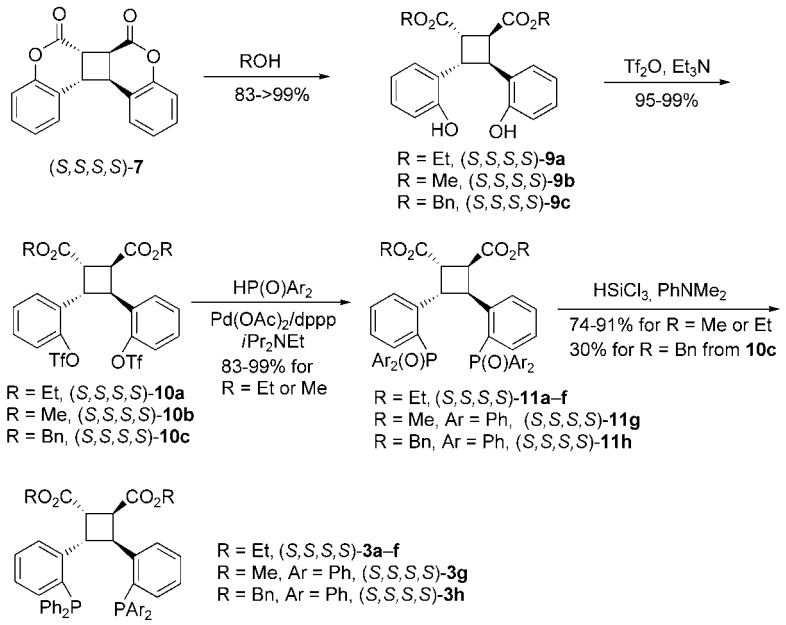
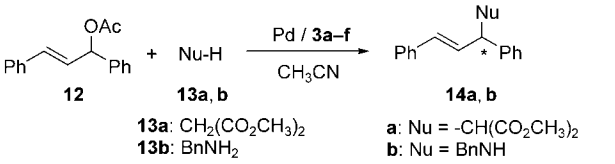


Scheme 2. Transformation of enantiopure coumarin dimer (*S*,*S*,*S*,*S*)-**7** to a new type of chiral bisphosphine ligands (*S*,*S*,*S*,*S*)-**3a–h**: **a**) Ar = C_6H_5, R = Et; **b**) Ar = 4-$MeOC_6H_4$, R = Et; **c**)Ar = 4-*t*BuC_6H_4, R = Et; **d**) Ar = 3-MeC_6H_4, R = Et; **e**) Ar = 3,5-$(Me)_2C_6H_3$, R = Et; **f**) Ar = 4-MeC_6H_4, R = Et; **g**) Ar = C_6H_5, R = Me; **h**) Ar = C_6H_5, R = Bn.

model reaction. Accordingly, 1,3-diphenylprop-2-enyl acetate (**12**) was employed as the substrate, and dimethyl malonate **13a** or benzylamine **13b** was utilized as the nucleophile. As shown in Table 1, all of the chiral ligands [(*S*,*S*,*S*,*S*)-**3a–f**] showed excellent asymmetric induction in the model reaction to give the corresponding allylation products in 91–99% yield and with 95.6–98.9% *ee*. These results clearly demonstrate that this type of bisphosphine ligands (*S*,*S*,*S*,*S*)-**3a–f** with cyclobutane backbone are very promising in asymmetric catalysis.

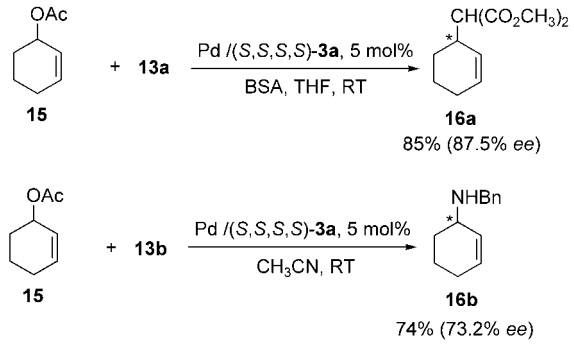
The use of this catalyst system was extended to the allylic substitution of cyclic substrate **15**[11e–h]; the reaction proceeded smoothly to give the corresponding cyclic allylation products **16a** and **16b** in good yields (74–85%) and enantioselectivities (73.2–87.5% *ee*) by using 5 mol% of the catalyst (Scheme 3). These results combined with those obtained above indicate that this type of ligand is particularly useful in Pd-catalyzed allylic substitution reactions, which encouraged us to further investigate their structure–property relationship and immobilization in asymmetric catalysis.

Table 1. Pd-catalyzed enantioselective allylic substitution reactions using bisphosphine ligands **3a–f**.[a]



Entry	Ligand	Base	NuH	Product	Yield [%][b]	*ee* [%][c]
1	**3a**	BSA	**13a**	**14a**	99	96.8
2	**3b**	BSA[d]	**13a**	**14a**	99	98.0
3	**3c**	BSA[d]	**13a**	**14a**	99	97.5
4	**3c**	BSA	**13a**	**14a**	99	98.9
5	**3d**	BSA[d]	**13a**	**14a**	99	96.1
6	**3e**	BSA[d]	**13a**	**14a**	99	97.3
7	**3f**	BSA[d]	**13a**	**14a**	99	95.8
8	**3a**	–	**13b**	**14b**	99	95.6
9	**3b**	–	**13b**	**14b**	91	96.2
10	**3c**	–	**13b**	**14b**	97	96.2
11	**3d**	–	**13b**	**14b**	96	96.4
12	**3e**	–	**13b**	**14b**	94	96.7
13	**3f**	–	**13b**	**14b**	91	97.5

[a] The molar ratio of **12**/NuH/[{(η-allyl)PdCl}$_2$] /**3** = 1:2:0.025:0.06. All the ligands **3a–f** used were of the *S*,*S*,*S*,*S* configuration. [b] Yield of isolated product. [c] The enantiomeric excesses were determined by HPLC on a Chiralcel OJ or AD column. The absolute configurations of **14a** and **14b** were assigned as *S* and *R*, respectively, based on their optical rotations. [d] BSA (2 equiv) was added in the presence of LiOAc (5 mol%).



Scheme 3. Pd-catalyzed enantioselective allylic substitution reactions of cyclohex-2-enyl acetate using bisphosphine ligand (*S*,*S*,*S*,*S*)-**3a**.

The impact of carboxylate groups on the enantioselectivity of the allylic substitutions: The investigation into the relationship between the carboxylate groups on the cyclobutane backbone of the bisphosphine ligands and the enantioselectivity of the reaction will provide useful information regarding their immobilization on an organic polymer support by taking advantage of the easily derivable carboxylic groups. To investigate the impact of the ester groups of the chiral ligands **3** on their asymmetric induction, ligands (*S*,*S*,*S*,*S*)-**3a** or (*S*,*S*,*S*,*S*)-**3g**,**h** were submitted to Pd-catalyzed enantioselective allylic substitution of **12** with dimethyl malonate **13a** and benzylamine **13b**, respectively, under the optimized conditions indicated in Table 1. As shown in Figure 1, the enan-

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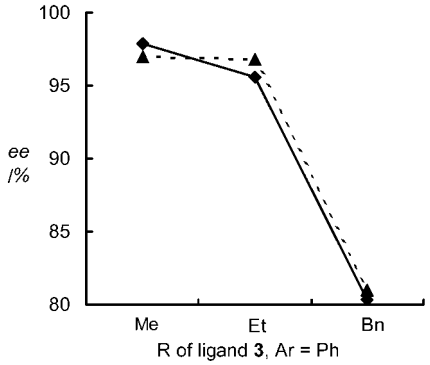
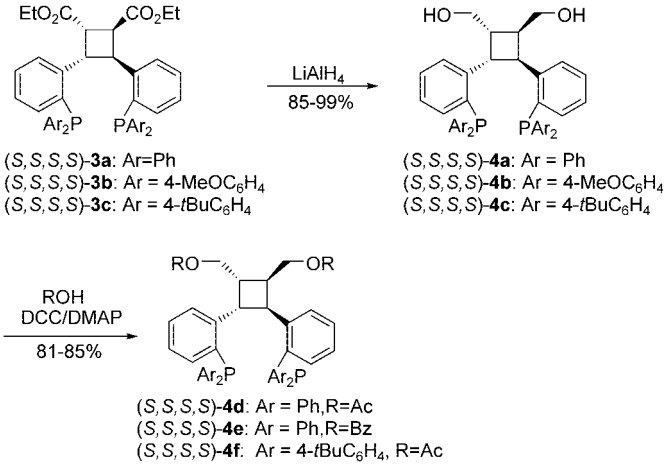


Figure 1. The influence of the ester groups of the ligands **3** on the enantioselectivities of Pd-catalyzed allylic substitution reactions of **12** with dimethyl malonate **13a** (dotted line) and benzylamine **13b** (solid line).

tioselectivities of both reactions dramatically decreased as the size of the ester groups was increased. When the bisphosphine ligand (*S*,*S*,*S*,*S*)-**3h**, which contains benzyl ester groups on the cyclobutane backbone, was used, the enantioselectivities of the reactions dropped to around 80%. This substituent effect on the enantioselectivities of the reactions might cause a reduction in the enantioselectivity of the reaction when this type of ligand is immobilized on a large polymer support by the formation of an ester link. Therefore, we decided to investigate the effect of modifying the ligands by reducing the carboxylate groups to hydroxymethyl moieties ((*S*,*S*,*S*,*S*)-**4a**–**c**), which can also be easily immobilized on a polymer support containing a carboxylic group.

Synthesis of analogous bisphosphine ligands (*S*,*S*,*S*,*S*)-4a–f with a cyclobutane backbone and their application in enantioselective allylic substitutions: As shown in Scheme 4, the



Scheme 4. Modification of bisphosphine ligands by reduction of ethoxycarbonyl groups followed by esterification.

reduction of ethoxycarbonyl functional groups in (*S*,*S*,*S*,*S*)-**3a**–**c** using $LiAlH_4$ resulted in the formation of the corresponding hydroxymethyl analogues (*S*,*S*,*S*,*S*)-**4a**–**c** in 85–99% yields. The structure of (*S*,*S*,*S*,*S*)-**4a** was confirmed by X-ray crystal structural analysis (Figure 2).[12] The molecule of (*S*,*S*,*S*,*S*)-**4a** adopts a C_2-symmetric geometry. Evidently, the two chelating phosphorus atoms in the ligand have a

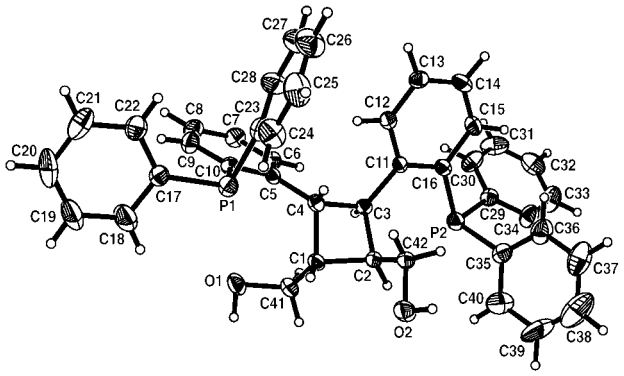


Figure 2. Molecular structure of (*S*,*S*,*S*,*S*)-**4a** (ORTEP drawing; 30% probability thermal ellipsoids).

trans configuration. The distance between them is 7.673 Å. There is no intramolecular hydrogen-bonding interaction between the two *trans*-hydroxymethyl groups. The reaction of (*S*,*S*,*S*,*S*)-**4a** with an excess of acetic acid or benzoic acid in the presence of 4-dimethylaminopyridine (DMAP) using dicyclohexylcarbodiimide (DCC) as condensation reagent afforded the corresponding acetate and benzoate derivatives (*S*,*S*,*S*,*S*)-**4d** and -**4e** in 81 and 85% yields, respectively. Similarly, (*S*,*S*,*S*,*S*)-**4f** could be obtained from (*S*,*S*,*S*,*S*)-**4c** in 85% yield.

As summarized in Table 2, the analogous bisphosphine ligands (*S*,*S*,*S*,*S*)-**4a**–**f** showed good to excellent asymmetric induction in Pd^{II}-catalyzed allylic substitution reactions with similar activities to those of (*S*,*S*,*S*,*S*)-**3a**–**h** when the ligands contain hydroxymethyl ((*S*,*S*,*S*,*S*)-**4a**—-**c**) or carboxylate groups ((*S*,*S*,*S*,*S*)-**4d**–**f**) on the cyclobutane backbone. The absolute configurations of the products obtained using li-

Table 2. Pd-catalyzed enantioselective allylic substitution reactions using bisphosphine ligands **4**.[a]

Entry	Ligand	Base	NuH	Product	Yield [%][b]	*ee* [%][c]
1	**4a**	BSA[d]	**13a**	**14a**	81.3	86.8
2	**4b**	BSA[d]	**13a**	**14a**	>99	80.9
3	**4c**	BSA[d]	**13a**	**14a**	>99	90.8
4	**4d**	BSA[d]	**13a**	**14a**	>99	89.9
5	**4e**	BSA[d]	**13a**	**14a**	>99	81.8
6	**4f**	BSA[d]	**13a**	**14a**	>99	89.3
7	**4a**	–	**13b**	**14b**	>99	84.7
8	**4b**	–	**13b**	**14b**	90.3	88.1
9	**4c**	–	**13b**	**14b**	>99	87.0
10	**4d**	–	**13b**	**14b**	>99	96.4
11	**4e**	–	**13b**	**14b**	66.5	98.7
12	**4f**	–	**13b**	**14b**	78.8	90.7

[a] The molar ratio of **12**/NuH/$[\eta$-allylPdCl$]_2$/**4**=1:2:0.025:0.06. All the ligands **4a**–**f** used were of *S*,*S*,*S*,*S* configuration. [b] Yield of isolated product. [c] The enantiomeric excesses were determined by HPLC on a Chiralcel OJ or AD column. The absolute configurations of **14a** and **14b** were assigned as *S* and *R*, respectively, based on their optical rotations. [d] BSA (2 equiv) was added.

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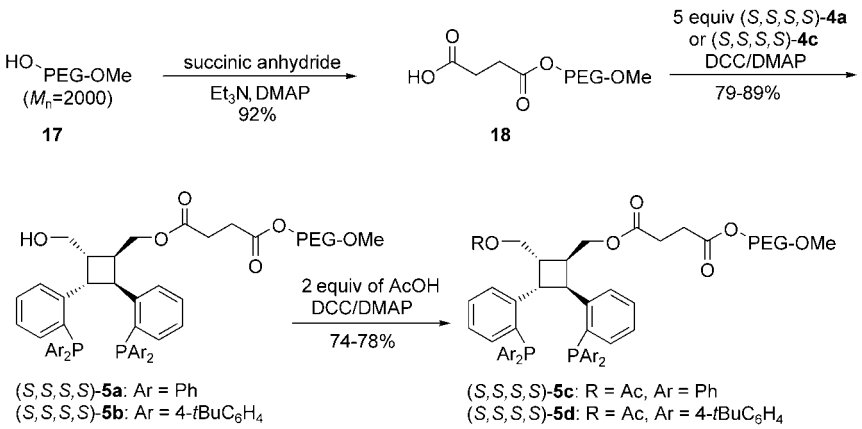
gands (*S*,*S*,*S*,*S*)-**4a–f** were the same as those attained with ligands (*S*,*S*,*S*,*S*)-**3a–h**, which illustrates that the substituents on the cyclobutane backbone only have a small impact on the sign of the asymmetric induction in the catalysis. The protection of hydroxy groups of (*S*,*S*,*S*,*S*)-**4a** with acetate could improve the enantioselectivities of the allylic substitution reactions (Table 2, entries 1, 7 versus 4, 10, respectively), particularly when using benzylamine as the nucleophile. The performance of the benzoate derivative (*S*,*S*,*S*,*S*)-**4e** was inferior to that of the acetate analogue (*S*,*S*,*S*,*S*)-**4d** (Table 2, entry 5 versus 4), although the enantioselectivity of allylic amination could be as high as 98.7% using (*S*,*S*,*S*,*S*)-**4e**, which has a relatively low catalytic activity (Table 2, entry 11). Therefore, acetate might be an ideal protecting group in the PEG-supported ligand (*S*,*S*,*S*,*S*)-**5**. The convenient preparation of ligands (*S*,*S*,*S*,*S*)-**4a** and (*S*,*S*,*S*,*S*)-**4c** and their facile esterification as well as the synergistic effect of the ester groups of the ligands on the enantioselectivity of the reactions have provided an excellent opportunity for anchoring the hydroxymethyl ligands (*S*,*S*,*S*,*S*)-**4a–c** on polymeric supports that possess carboxylic acid functional groups.



Scheme 5. Synthesis of MeO-PEG-supported bisphosphine ligands (*S*,*S*,*S*,*S*)-**5a–d**.

Synthesis of MeO-PEG-supported bisphosphine ligands (*S*,*S*,*S*,*S*)-5a–d for enantioselective allylic substitution reactions—homogeneous catalysis and heterogeneous recovery of the catalyst: Although significant developments in homogeneous asymmetric catalysis have been achieved in recent decades,[1] its application has been limited mainly due to problems with the separation and recycling of the expensive chiral catalyst. To overcome these problems, the immobilization of homogeneous catalysts on insoluble polymer supports has received considerable attention, which has made the recovery and reuse of the catalysts possible, as well as their adaptation to continuous-flow-type processes.[13] However, the immobilization of the chiral catalysts on insoluble supports often results in lower activities and enantioselectivities than those observed for their homogeneous counterparts. Alternatively, homogeneous catalysts can be achieved by utilizing soluble polymer supports in the immobilization, and which may have catalytic activities and stereoselectivities similar to those of the homogeneous parent systems.[14] When the reaction is completed, the catalyst can be separated by either solvent or heat precipitation, membrane filtration or size-exclusion chromatography. Owing to the high order of asymmetric induction of ligands (*S*,*S*,*S*,*S*)-**4** in Pd-catalyzed allylic substitution reactions, as well as the easy modification of hydroxy groups on the cyclobutane backbone of the ligands, we decided to prepare a new type of soluble polymer-supported bisphosphine ligand (*S*,*S*,*S*,*S*)-**5** for use in Pd-catalyzed enantioselective allylic substitution by using polyethylene glycol monomethyl ether (MeO-PEG) as the support.

As shown in Scheme 5, a MeO-PEG based-support (MeO-PEG-$O_2CCH_2CH_2CO_2H$, **18**) containing a carboxylic acid end group was prepared by the reaction of MeO-PEG (M_n=2000, **17**) with succinic anhydride in the presence of Et_3N according to the literature procedure.[15i] The condensation of support **18** with (*S*,*S*,*S*,*S*)-**4a** or -**4c** in the presence of DCC/DMAP as condensation reagent afforded the monoester (*S*,*S*,*S*,*S*)-**5a** or (*S*,*S*,*S*,*S*)-**5b** in 79 and 89% yields, respectively. An excess (5 equiv) of (*S*,*S*,*S*,*S*)-**4a** or (*S*,*S*,*S*,*S*)-**4c** was employed to ensure the complete conversion of support **18** and a 1:1 ratio of support and bisphosphine unit in the anchored (*S*,*S*,*S*,*S*)-**5a** and (*S*,*S*,*S*,*S*)-**5b**. The separation and purification of (*S*,*S*,*S*,*S*)-**5a** and (*S*,*S*,*S*,*S*)-**5b** was quite convenient. After removal of dicyclohexylurea (DCU), which was formed in the reaction, by simple filtration, the filtrate was concentrated to dryness under reduced pressure, and then a minimum amount of dichloromethane was added to the crude product to ensure the complete dissolution of the residue. Addition of diethyl ether allowed the precipitation of supported ligands (*S*,*S*,*S*,*S*)-**5a** or (*S*,*S*,*S*,*S*)-**5b** as white solids. This procedure was repeated three times to guarantee products of high purity. Their ^{1}H NMR, ^{31}P NMR, and MALDI-TOF spectra (Figure 3) were consistent with the expected structures and demonstrated the high purity of the ligands (*S*,*S*,*S*,*S*)-**5a** and (*S*,*S*,*S*,*S*)-**5b**. The unreacted starting hydroxymethyl derivatives, (*S*,*S*,*S*,*S*)-**4a** and (*S*,*S*,*S*,*S*)-**4c**, were readily recovered from the filtrate by column chromatography on silica gel. The remaining hydroxy group of (*S*,*S*,*S*,*S*)-**5a** and (*S*,*S*,*S*,*S*)-**5b** could be further protected with acetate by the reaction with two equivalents of acetic acid following the same procedures as those used for the preparation and purification of (*S*,*S*,*S*,*S*)-**5a** and (*S*,*S*,*S*,*S*)-**5b** to afford (*S*,*S*,*S*,*S*)-**5c** and (*S*,*S*,*S*,*S*)-**5d** in 78 and 74% yields, respectively.

With the MeO-PEG-supported ligands (*S*,*S*,*S*,*S*)-**5a**–(*S*,*S*,*S*,*S*)-**5d** in hand, we next investigated their asymmetric induction and the impact of the MeO-PEG support on the

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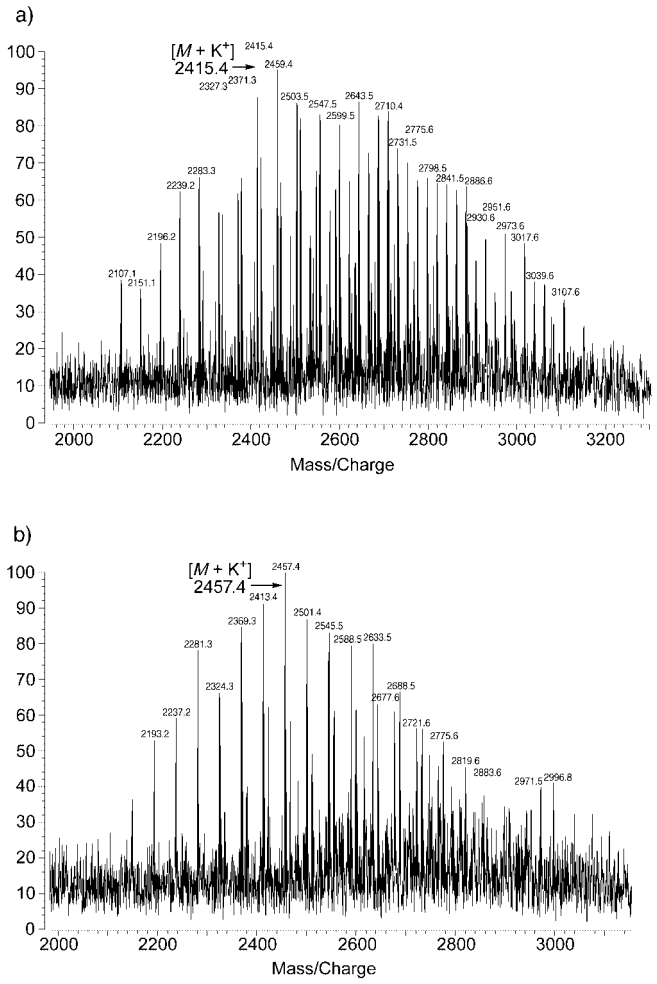

Figure 3. MALDI-TOF spectra of MeO-PEG-supported ligands a) (*S*,*S*,*S*,*S*)-**5a** and b) (*S*,*S*,*S*,*S*)-**5c**.

enantioselectivity of the Pd-catalyzed allylic substitution of **12** with dimethyl malonate **13a** or benzylamine **13b**. As shown in Table 3, ligand (*S*,*S*,*S*,*S*)-**5b** gave the best performance for the reactions in terms of both reactivity and enantioselectivity (Table 3, entries 2 and 6). It is evident that the coupling of the MeO-PEG support to the dihydroxy bisphosphine (*S*,*S*,*S*,*S*)-**4c** (ligand (*S*,*S*,*S*,*S*)-**5b**) significantly improved the enantioselectivities from 90.8 and 87.0 % *ee* to 94.7 and 97.3 % *ee*, respectively (entries 3 and 9 in Table 2 versus entries 2 and 6 in Table 3), which demonstrates the synergistic effect of the polymeric support on the enantioselectivity of the reaction. On the other hand, the acetate-protected analogue (*S*,*S*,*S*,*S*)-**5d** exhibited reduced enantioselectivity compared with (*S*,*S*,*S*,*S*)-**5b** (Table 3, entries 4 and 8 versus entries 2 and 6, respectively). The other advantage of the present catalyst system is the convenient recovery of the catalyst. After the reaction was complete, diethyl ether was added to the reaction mixture and the catalyst precipitated as a yellow solid. Simple filtration afforded the catalyst in >90 % recovery and the flash chromatography of the filtrate conveniently afforded the product.

Recyclablity of the Pd complex of the MeO-PEG-supported ligand (*S*,*S*,*S*,*S*)-5b in allylic substitution reactions: On the basis of the findings mentioned above, we then examined the reusability of the recovered Pd complex of (*S*,*S*,*S*,*S*)-**5b** in enantioselective allylic alkylation and amination reactions in order to demonstrate further advantages of this type of ligands. After the first run of the reaction, diethyl ether was added to the reaction mixture so that the catalyst formed a precipitate which was filtered off under an argon atmosphere and washed with diethyl ether three times. The recovered catalyst was submitted to the next catalytic reaction without any further addition of Pd. The recovered catalyst could be recycled with only a slight loss in the activity and enantioselectivity of the allylic alkylation reaction (from 94.6 % *ee* in the first run to 86.0 % *ee* in the fourth run; Table 4, entries 1–4). In particular, the recovered catalyst could be reutilized nine times in the allylic amination reaction with high enantioselectivities (89.5–97.2 % *ee*; Table 4, entries 5–13) although the catalytic activity diminished gradually after the fifth run (Table 4, entries 10–13). These results demonstrate that the MeO-PEG-bound ligand

Table 3. Pd-catalyzed enantioselective allylic substitution reactions using MeO-PEG-supported bisphosphine ligands **5a–d**.[a]

Entry	Ligand	Base	NuH	Product	Yield [%][b]	*ee* [%][c]
1	**5a**	BSA[d]	**13a**	**14a**	45.4	85.4
2	**5b**	BSA[d]	**13a**	**14a**	>99	94.7
3	**5c**	BSA[d]	**13a**	**14a**	84.3	90.1
4	**5d**	BSA[d]	**13a**	**14a**	61.0	87.5
5	**5a**	–	**13b**	**14b**	97.8	96.4
6	**5b**	–	**13b**	**14b**	>99	97.3
7	**5c**	–	**13b**	**14b**	>99	96.4
8	**5d**	–	**13b**	**14b**	>99	90.8

[a] The molar ratio of **12**/NuH/$[\eta$-allylPdCl$]_2$/**5** = 1:3:0.025:0.06. All the ligands **5a–d** used were of *S*,*S*,*S*,*S* configuration. [b] Yield of isolated product. [c] The enantiomeric excesses were determined by HPLC on a Chiralcel OJ or AD column. The absolute configurations of **14a** and **14b** were assigned as *S* and *R*, respectively, based on their optical rotations. [d] BSA (3 equiv) was added.

Table 4. Recyclability of the Pd complex of (*S*,*S*,*S*,*S*)-**5b** in allylic substitution reactions.[a]

Entry	Ligand	Base	NuH	Product	Yield [%][b]	*ee* [%][c]
1[d]	**1st**	1	**13a**	**14a**	>99	94.6
2[d]	**2nd**	4	**13a**	**14a**	>99	93.8
3[d]	**3rd**	8	**13a**	**14a**	>99	91.7
4[d]	**4th**	16	**13a**	**14a**	88.3	86.0
5	**1st**	<0.5	**13b**	**14b**	>99	97.2
6	**2nd**	0.5	**13b**	**14b**	>99	93.4
7	**3rd**	<1	**13b**	**14b**	>99	89.5
8	**4th**	1	**13b**	**14b**	>99	91.0
9	**5th**	2	**13b**	**14b**	95.9	92.2
10	**6th**	12	**13b**	**14b**	>99	91.8
11	**7th**	20	**13b**	**14b**	63.6	90.5
12	**8th**	30	**13b**	**14b**	69.0	89.6
13	**9th**	30	**13b**	**14b**	81.0	91.1

[a] The molar ratio of **12**:NuH:$[\{(\eta$-allyl)PdCl$\}_2]$: (*S*,*S*,*S*,*S*)-**5b** = 1:3:0.025:0.06. [b] Yield of isolated product. [c] The enantiomeric excesses were determined by HPLC on a Chiralcel OJ or AD column. The absolute configurations of **14a** and **14b** were assigned as *S* and *R*, respectively, based on their optical rotations. [d] BSA (3 equiv) was added.

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(*S*,*S*,*S*,*S*)-**5b** has the advantage of easy recovery and reutilization in asymmetric allylic substitution reactions in addition to its facile preparation.

Conclusions

In summary, a highly efficient and practical optical resolution of *anti* head-to-head racemic coumarin dimer **7** by molecular complexation with TADDOL **8** through hydrogen bonding and a convenient transformation of enantiopure (−)-**7** to a new type of C_2-symmetric bisphosphine ligands (*S*,*S*,*S*,*S*)-**3** have been achieved. The asymmetric induction efficiency of these chiral bisphosphine ligands in Pd-catalyzed asymmetric allylic substitution reactions was evaluated. Under the experimental conditions, the allylic substitution products were obtained in excellent yields (up to 99%) and enantioselectivities (up to 98.9% *ee*). By taking advantage of the high enantioselectivity of the catalytic reaction and the easily derivable carboxylate groups on the cyclobutane backbone of ligands **3**, a new type of analogous ligands (*S*,*S*,*S*,*S*)-**4**, as well as MeO-PEG-supported soluble ligands (*S*,*S*,*S*,*S*)-**5** have also been synthesized and utilized in asymmetric allylic substitution reactions. In particular, the MeO-PEG support in ligand (*S*,*S*,*S*,*S*)-**5b** displayed a synergistic effect on the enantioselectivity of the reaction compared with its precursor (*S*,*S*,*S*,*S*)-**4c**, affording the corresponding allylation products **14a** and **14b** with excellent enantioselectivities (94.6 and 97.2% *ee*, respectively). Moreover, the Pd complex of (*S*,*S*,*S*,*S*)-**5b** could be easily recovered and recycled several times without significant loss of enantioselectivity and activity of the allylic substitution reactions. Accordingly, this new strategy for efficient and practical optical resolution of *anti* head-to-head racemic coumarin dimer **7**, the excellent asymmetric induction of the chiral ligands **3**–**5** developed on the basis of enantiopure **7**, as well as the high functional capacity of coumarin dimer **7** and bisphosphine ligands **3** and **4** disclosed in this work will definitely stimulate further research on the uses of enantiopure **7** as a privileged scaffold for the synthesis of various chiral ligands or chiral polymers for use in asymmetric catalysis or for other aspects.

Experimental Section

General considerations: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 spectrometer at 25 °C. The chemical shifts are given in ppm with TMS ($\delta = 0$ ppm) and the residue signal of $CDCl_3$ ($\delta = 77$ ppm) as the internal standards for ^{1}H and ^{13}C NMR spectroscopy, respectively. The ^{31}P NMR spectra were recorded on a Bruker AM300 instrument in $CDCl_3$ with 85% H_3PO_4 as the external reference and the 19F NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 instrument. Melting points were measured on an XT-4 apparatus and are uncorrected. Optical rotations were measured on a PE-341 automatic polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Liquid chromatographic analyses were conducted on a JASCO 1580 system. The IR spectra were measured on a Rio-Rad FTS-185 spectrometer using KBr pellets. EI and ESI mass spectra were obtained on HP5989A and Mariner LC-TOF spectrometers, respectively. HRMS spectra were determined on a Kratos Concept, Q-Tof micro or APEXIII 7.0 TESLA FTMS instrument. MALDI-TOF mass spectra were taken on a PerSeptive Biosystems Voyager DE-STR equipped with a 337 nm nitrogen laser. Elemental analyses were performed on an Elemental VARIO EL apparatus. All the experiments sensitive to moisture or air were carried out under argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Dichloromethane and CH_3CN were freshly distilled from calcium hydride and THF, diethyl ether, and toluene from sodium benzophenone ketyl.

Racemic *anti* head-to-head coumarin dimer 7: The preparation of the *anti* head-to-head racemic coumarin dimer (±)-**7** was carried out by following a literature method in 0.2 mol scale;[7] coumarin **6** was irradiated in benzene solution in the presence of benzophenone as a sensitizer.

Optical resolution of 7 by molecular complexation with (−)-TADDOL ((−)-8): By heating a mixture of an equimolar amount of (±)-**7** and the resolving agent (−)-**8** in ethyl acetate and then cooling the homogeneous solution to room temperature molecular crystals of (−)-**8** and (−)-**7** were formed with (−)-**7** in 88.3% *ee*. The crystals that precipitated were collected by filtration and washed with ethyl acetate; these crystals were characterized as 2:1 molecular crystals of (−)-**8** and (−)-**7** by ^{1}H NMR spectroscopy. The enantiomeric excess of the opposite enantiomer ((+)-**7**) remaining in the mother liquor was 81.7%. Further recrystallization of the molecular crystals (−)-**7**·[(−)-**8**]$_2$ from ethyl acetate afforded enantiopure (−)-**7**·[(−)-**8**]$_2$ in 70% yield. (−)-**7**·[(−)-**8**]$_2$: m.p. 220–222 °C (lit.:[9a] 228–232 °C); $[\alpha]_D^{21} = -72.0$ ($c = 1.00$ in C_6H_6); $[\alpha]_{435}^{21} = -157.5$ ($c = 1.00$ in C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.05$ (s, 12H), 3.89–3.95 (m, 8H), 4.60 (s, 4H), 7.10–7.60 (m, 48H) ppm; elemental analysis calcd (%) for $C_{80}H_{72}O_{12}$: C 78.41, H 5.92; found: C 78.58, H 5.84.

Treatment of the 1:2 complex (−)-**7**·[(−)-**8**]$_2$ (10.00 g) with DMF/H_2O (5:1; 50 mL) gave a 1:1 complex of (−)-**8** and DMF as colorless needles in 99% yield (8.60 g). (−)-**8**·DMF: M.p. 211–212 °C; $[\alpha]_D^{20} = -76.2$ ($c = 1.02$ in C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.03$ (s, 6H), 3.85 (s, 3H), 4.29 (br, 2H), 4.57 (s, 2H), 7.20–7.60 (m, 20H) ppm; EI-MS (70 eV): *m*/*z* (%): 105 (100), 183 (63), 207 (50), 208 (29), 77 (23), 237 (20), 179 (19), 225 (17); IR (KBr): $\nu = 3256$, 2929, 2901, 1652, 1495, 1414, 1388, 1370, 1333, 1243, 1221, 1207, 1168, 1102, 1082, 1054, 1016, 886, 769, 743, 701, 667, 641, 561, 507 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{37}NO_5$: C 75.67, H 6.91, N 2.60; found: C 75.66, H 6.86, N 2.62.

The filtrate containing optically pure (−)-**7** was concentrated under reduced pressure to give (−)-**7** in quantitative yield. (−)-(*S*,*S*,*S*,*S*)-**7**: M.p. 168.5–169 °C; $[\alpha]_D^{21} = -9.0$ ($c = 1.00$ in C_6H_6); $[\alpha]_{435}^{21} = -65.8$ ($c = 1.00$ in C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 3.85$–3.95 (m, 4H), 7.10–7.40 (m, 8H) ppm; IR (KBr): $\nu = 1760$, 1490, 1450, 775, 765 cm^{-1}. (+)-(*R*,*R*,*R*,*R*)-**7**: M.p. 168.5–169 °C; $[\alpha]_D^{21} = +9.0$ ($c = 1.00$ in C_6H_6); $[\alpha]_{435}^{21} = +65.8$ ($c = 1.00$ in C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 3.85$–3.95 (m, 4H), 7.10–7.40 (m, 8H) ppm; IR (KBr): $\nu = 1760$, 1490, 1450, 775, 765 cm^{-1}.

The complex (−)-**8**·DMF (5.40 g) was dissolved in ethyl acetate (15 mL) and washed with water (3 × 8 mL). The organic phase was then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give TADDOL (−)-**8** in >99% yield. M.p. 195–196 °C; $[\alpha]_D^{21} = -87.0$ ($c = 1.00$ in C_6H_6); $[\alpha]_{435}^{21} = -183.0$ ($c = 1.00$ in C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.00$ (s, 6H), 3.95 (s, 2H), 4.60 (s, 2H), 7.20–7.60 (m, 20H) ppm; IR (KBr): $\nu = 3437$, 3211, 3091, 3059, 3025, 2988, 2891, 1494, 1462, 1447, 1382, 1371, 1243, 1222, 1191, 1170, 1096, 1080, 1047, 1016, 889, 759, 740, 698, 666, 639, 554, 507 cm^{-1}. The recovered resolving reagent could be used directly in the next run of the optical resolution of (±)-**7** without any change in its efficiency.

(−)-(*S*,*S*,*S*,*S*)-9a: A suspension of the *anti* head-to-head coumarin dimer (−)-(*S*,*S*,*S*,*S*)-**7** (5.0 g, 17.1 mmol) in ethanol (160 mL) was refluxed for 48 h. The solution was concentrated and dried in vacuo to obtain the product (*S*,*S*,*S*,*S*)-**9a** as a white solid (6.57 g, 99%). M.p. 159–161 °C (lit.:[9b] 174–175 °C); $[\alpha]_D^{20} = -129.2$ ($c = 1.01$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 0.83$ (t, $J = 7.1$ Hz, 6H), 3.05 (br, 1H), 3.71–3.91 (m, 6H), 4.87 (d, $J = 8.36$ Hz, 2H), 6.66–7.06 (m, 8H), 8.85 (br, 1H) ppm; IR (KBr): $\nu = 3341$, 3070, 3039, 2981, 2937, 2905, 1691, 1607, 1596, 1507, 1455, 1413, 1373, 1336, 1315, 1281, 1247, 1217, 1186, 1121, 1086, 1035, 936, 864, 855, 754, 732, 642, 471 cm^{-1}; the enantiomeric excess was determined by HPLC on a Chiralcel OJ column by using hexane/2-

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propanol (90:10) as eluent, flow rate = 1.2 mL min^{-1}, UV detection at λ = 220 nm, t_{R1} = 14.8 min (*R*,*R*,*R*,*R* isomer), t_{R2} = 20.0 min (*S*,*S*,*S*,*S* isomer).

(−)-(*S*,*S*,*S*,*S*)-9b: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**9a**, the reaction of (−)-(*S*,*S*,*S*,*S*)-**7** with MeOH afforded (*S*,*S*,*S*,*S*)-**9b** as an amorphous white solid (98% yield). $[\alpha]_D^{20} = -160.0$ (c = 1.00 in THF); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.40 (s, 6H), 4.04 (d, J = 8.7 Hz, 2H), 4.96 (d, J = 8.7 Hz, 2H), 6.76–7.12 (m, 8H) ppm; IR (KBr): ν = 3509, 3346, 1725, 1708, 1610, 1595, 1506, 1453, 1436, 1367, 1355, 1336, 1324, 1300, 1264, 1227, 1208, 1187, 1173, 1152, 1136, 1104, 1089, 1029, 896, 763, 750, 479 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 146 (100), 775 (80), 149 (63), 118 (48), 212 (44), 147 (36), 148 (30), 178 (22), 115 (20), 356 ([*M*]$^+$, 1).

(−)-(*S*,*S*,*S*,*S*)-9c: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**9a**, the reaction of (−)-(*S*,*S*,*S*,*S*)-**7** with BnOH using $TiCl_4$ (10 mol%) as a catalyst afforded (*S*,*S*,*S*,*S*)-**9c** as a white solid (84% yield). M.p. 106–110 °C; $[\alpha]_D^{20} = -68.4$ (c = 1.01 in THF); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 2.86 (s, 1H), 4.04 (d, J = 9.3 Hz, 2H), 4.60 (d, J = 12.3 Hz, 2H), 4.84 (d, J = 12.3 Hz, 2H), 5.07 (d, J = 9.0 Hz, 2H), 6.71–7.25 (m, 18H) ppm; EI-MS (70 eV): *m*/*z* (%): 91 (100), 146 (95), 118 (61), 79 (32), 108 (27), 147 (26), 77 (22), 107(21); IR (KBr): ν = 3053, 2980, 1722, 1605, 1586, 1509, 1477, 1464, 1435, 1369, 1328, 1303, 1266, 1216, 1159, 1134, 1093, 1070, 1035, 998, 745, 695, 546, 497, 416 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{28}O_6$: C 75.57, H 5.55; found: C 75.31, H 5.49.

(−)-(*S*,*S*,*S*,*S*)-10a: Trifluoromethanesulfonic anhydride (0.41 mL, 2.4 mmol) was slowly added to a solution of (*S*,*S*,*S*,*S*)-**9a** (0.384 g, 1.0 mmol) and Et_3N (0.675 mL, 4.8 mmol) in dried CH_2Cl_2 (3 mL) at −78 °C. The reaction mixture was stirred for 1 h, and then warmed to room temperature. After the removal of the solvent under reduced pressure, the resulting residue was submitted to chromatographic separation on silica gel using hexane/EtOAc (5:1) as eluent to give (*S*,*S*,*S*,*S*)-**10a** as a white solid (0.63 g, 97%). M.p. 73–75 °C; $[\alpha]_D^{20} = -59.7$(c = 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.86 (t, J = 7.1 Hz, 6H), 3.85 (q, J = 7.1 Hz, 4H), 3.93 (d, J = 4.4 Hz, 2H), 4.92 (d, J = 4.4 Hz, 2H), 7.20–7.40 (m, 8H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −74.4 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.82, 147.75, 130.62, 129.18, 128.55, 128.44, 121.11, 120.67, 116.43, 60.80, 43.79, 38.01, 13.61 ppm; EI-MS (70 eV): *m*/*z* (%): 127 (38), 147 (54), 175 (100), 181 (45), 210 (98), 501 (39), 574 ([*M*]$^+$, 30); IR (KBr): ν = 2980, 1728, 1708, 1492, 1454, 1420, 1404, 1373, 1343, 1319, 1250, 1226, 1204, 1142, 1076, 1047, 1035, 941, 894, 876, 826, 786, 771, 743, 729, 620, 607, 573, 520, 481 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{22}O_{10}F_6S_2$: C 44.44, H 3.42; found; C 44.47, H 3.45.

(−)-(*S*,*S*,*S*,*S*)-10b: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**10a**, the reaction of (*S*,*S*,*S*,*S*)-**9b** with Tf_2O afforded (*S*,*S*,*S*,*S*)-**10b** as a white solid (99% yield). M.p. 54–56 °C; $[\alpha]_D^{20} = -74.6$ (c = 0.99 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.37 (s, 6H), 3.98 (d, J = 9.0 Hz, 2H), 4.93 (d, J = 9.0 Hz, 2H), 6.26–7.38 (m, 8H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −74.5 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.26, 147.66, 130.40, 129.25, 128.43, 128.38, 121.03, 120.64, 116.41, 51.69, 43.83, 37.97 ppm; IR (KBr): ν = 1734, 1489, 1452, 1423, 1406, 1338, 1290, 1251, 1218, 1162, 1139, 1078, 908, 861, 817, 769, 745, 648, 628, 603 cm^{-1}; ESI-MS [*M*$^+$ H]: 621.3.

(−)-(*S*,*S*,*S*,*S*)-10c: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**10a**, the reaction of (*S*,*S*,*S*,*S*)-**9c** with Tf_2O afforded (*S*,*S*,*S*,*S*)-**10c** as a white solid (95% yield). $[\alpha]_D^{20} = -28.1$ (c = 1.25 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 4.02 (d, J = 8.7 Hz, 2H), 4.76 (d, J = 12.3 Hz, 2H), 4.86 (d, J = 12.3 Hz, 2H), 4.92 (d, J = 8.7 Hz, 2H), 7.05–7.27 (m, 18H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −74.3 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.26, 147.66, 130.40, 129.25, 128.43, 128.38, 121.03, 120.64, 116.41, 51.69, 43.83, 37.97 ppm; IR (KBr): ν = 1729, 1490, 1453, 1421, 1404, 1382, 1332, 1250, 1216, 1139, 1078, 904, 863, 769, 697, 605 cm^{-1}; ESI-MS [*M*$^+$+Na]: 731.1; HRMS (FT): calcd for $C_{34}H_{26}O_{10}NaF_6$ [*M*$^+$+Na]: 731.1322; found: 731.1317.

(−)-(*S*,*S*,*S*,*S*)-11a: DMSO (6 mL) and diisopropylethylamine (1.8 mL, 10.0 mmol) were added to a mixture of (*S*,*S*,*S*,*S*)-**10a** (0.648 g, 1.0 mmol), diphenylphosphine oxide (0.808 g, 4.0 mmol), $Pd(OAc)_2$ (24.0 mg, 0.10 mmol), and dppp (74.8 mg, 0.15 mmol) and the mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with water twice and then with brine. The organic phase was dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The resulting residue was submitted to chromatographic separation on silica gel using EtOAc as eluent to give (*S*,*S*,*S*,*S*)-**11a** as an amorphous solid (0.74 g, 99%). $[\alpha]_D^{20} = -95.7$ (c = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.86 (t, J = 7.13 Hz, 6H), 2.95 (d, J = 4.3 Hz, 2H), 3.72 (q, J = 5.8 Hz, 4H), 5.38 (d, J = 4.3 Hz, 2H), 7.00–7.80 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 31.1 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.19, 142.34, 142.24, 133.16, 133.10, 132.98, 132.57, 132.21, 132.17, 132.08, 132.04, 131.73, 132.61, 131.21, 129.13, 129.00, 128.51, 128.35, 126.31, 126.14, 60.04, 44.80, 42.30, 42.23, 13.79 ppm; IR (KBr): ν = 3582, 3420, 3056, 2985, 2939, 1709, 1653, 1591, 1438, 1372, 1313, 1232, 1178, 1140, 1116, 1099, 1069, 1033, 998, 769, 753, 736, 725, 697, 554, 546, 511, 490 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 201 (70), 303 (80), 431 (43), 485 (45), 579 (36), 633 (92),679 (100), 680 ([*M*$^+$], 34),752 (4); HRMS (EI): calcd for $C_{46}H_{42}O_6P_2$ [*M*$^+$]: 752.2457; found: 752.2439.

(−)-(*S*,*S*,*S*,*S*)-11b: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10a** with bis(4-methoxyphenyl)phosphine oxide afforded (*S*,*S*,*S*,*S*)-**11b** as an amorphous a white solid (88% yield). $[\alpha]_D^{20} = -75.9$ (c = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.81 (t, J = 6.7 Hz, 6H), 3.04 (d, J = 6.7 Hz, 2H), 3.05–3.81 (m, 16H), 5.36 (d, J = 6.7 Hz, 2H), 6.87–7.65 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 12.5 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.19, 162.10, 162.06, 162.02, 142.39, 142.29, 133.94, 133.79, 133.48, 133.03, 132.83, 132.12, 131.72, 131.74, 129.13, 129.00, 126.10, 125.93, 125.02, 124.85, 123.56, 123.39, 113.93, 113.76, 59.86, 55.16, 44.72, 42.21, 42.14, 29.52, 14.00, 13.80 ppm; IR (KBr): ν = 3423, 3063, 2976, 2840, 1720, 1598, 1570, 1504, 1464, 1442, 1407, 1369, 1338, 1296, 1255, 1177, 1118, 1025, 935, 830, 801, 757, 729, 664, 622, 551, 458 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 261 (100), 363 (62), 575 (41), 611 (66), 612 (27), 700 (46), 799 (82), 800 (37),872 (8); HRMS (EI): calcd for $C_{50}H_{50}O_{10}P_2$ [*M*$^+$]: 872.2880; found: 872.2879.

(−)-(*S*,*S*,*S*,*S*)-11c: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10a** with bis(4-*tert*-butylphenyl)phosphine oxide afforded (*S*,*S*,*S*,*S*)-**11c** as an amorphous white solid (92% yield). $[\alpha]_D^{20} = -69.0$ (c = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.87 (t, J = 11.9 Hz, 6H), 1.32 (s, 36H), 2.99 (d, J = 7.3 Hz, 2H), 3.71 (m, 4H), 5.40 (d, J = 7.3 Hz, 2H), 7.03–7.68 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 12.6 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.22, 154.87, 154.83, 154.79, 142.62, 142.51, 133.17, 133.10, 133.00, 132.09, 131.96, 131.88, 131.74, 130.37, 130.29, 129.30, 129.17, 129.00, 128.89, 126.19, 126.02, 125.44, 125.30, 125.28, 59.90, 44.54, 42.39, 42.31, 34.91, 31.13, 31.09, 29.64, 13.93 ppm; IR (KBr): ν = 3439, 3062, 2964, 2928, 2870, 1726, 1599, 1498, 1465, 1444, 1394, 1366, 1308, 1264, 1189, 1137, 1114, 1093, 1038, 1018, 829, 802, 751, 613, 592, 567, 520, 490 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 313 (53), 415 (59), 653 (40), 663 (78), 804 (64), 903 (96), 904 (100), 976 (23), 903 (96); HRMS (EI): calcd for $C_{62}H_{74}O_6P_2$ [*M*$^+$−COOEt]: 903.4671; found: 903.4665.

(−)-(*S*,*S*,*S*,*S*)-11d: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10a** with di(3-tolyl)phosphine oxide afforded (*S*,*S*,*S*,*S*)-**11d** as an amorphous white solid (97% yield). $[\alpha]_D^{20} = -80.8$ (c = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.86 (t, J = 6.7 Hz, 6H), 2.34 (s, 3H), 2.38 (s, 3H), 2.96 (d, J = 8.6 Hz, 2H), 3.73 (q, J = 8.4 Hz, 4H), 5.33 (d, J = 8.5 Hz, 2H), 6.98–7.66 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 12.7 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.74, 142.17, 142.06, 138.08, 138.05, 137.92, 137.90, 133.05, 132.84, 132.67, 132.41, 132.29, 132.19, 132.11, 132.06, 131.81, 131.698, 131.49, 129.09, 129.04, 128.96, 128.91, 128.77, 128.07, 127.93, 127.90, 126.00, 125.83, 59.61, 44.62, 42.18, 42.10, 21.13, 13.67 ppm; IR (KBr): ν = 2980, 1722, 1592, 1477, 1444, 1370, 1307, 1222, 1174, 1114, 1036, 871, 785, 697, 559, 464 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 229 (58), 331 (49), 580 (56), 690 (51), 734 (59), 735 (96), 736 (100), 737 (36), 808 (18); HRMS (EI): calcd for $C_{50}H_{50}O_6P_2$ [*M*$^+$]: 808.3083; found: 808.3076.

(−)-(*S*,*S*,*S*,*S*)-11e: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10a** with di(3,5-xylyl)phosphine oxide afforded (*S*,*S*,*S*,*S*)-**11e** as an amorphous white solid (95% yield). $[\alpha]_D^{20} = -99.4$ (c = 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.86 (t, J = 7.3 Hz, 6H), 2.29 (s, 12H), 2.32 (s, 12H), 2.93 (d, J = 4.3 Hz, 2H), 3.75 (q, J = 6.7 Hz, 4H), 5.24 (d, J = 4.3 Hz, 2H), 7.00–7.40 (m, 20H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 31.0 ppm;

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^{13}C NMR (75 MHz, $CDCl_3$) : δ = 171.02, 142.36, 142.26, 138.16, 138.10, 137.99, 137.93, 133.27, 133.13, 132.98, 131.96, 131.77, 129.81, 129.76, 129.69, 129.63, 128.97, 126.19, 126.02, 59.89, 45.01, 42.46, 21.25, 13.90 ppm; IR (KBr): ν = 3012, 2980, 1723, 1600, 1444, 1369, 1307, 1274, 1185, 1129, 1037, 871, 850, 693, 582, 525, 423 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 257 (55), 359 (33), 360 (43), 608 (68), 746 (35), 791 (90), 792 (100), 793 (48), 864 (24); HRMS (EI): calcd for $C_{54}H_{58}O_6P_2$ [M^+]: 864.3709; found: 864.3733.

(−)-(*S*,*S*,*S*,*S*)-11f: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10a** with di(4-tolyl)phosphine oxide afforded (*S*,*S*,*S*,*S*)-**11f** as an amorphous white solid (83% yield). $[\alpha]_D^{20}$ = −72.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.86 (t, *J* = 7.3 Hz, 6H), 2.40 (s, 12H), 3.04 (d, *J* = 7.0 Hz, 2H), 3.73 (m, 4H), 5.38 (d, *J* = 7.0 Hz, 2H), 6.95–7.65 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 12.7 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.25, 142.57, 142.47, 141.97, 141.93, 141.87, 133.20, 133.12, 132.95, 132.25, 132.12, 131.84, 130.44, 130.30, 129.22, 129.14, 129.05, 128.90, 126.14, 125.97, 59.97, 44.81, 42.37, 42.29, 29.64, 21.59, 13.87, 0.97 ppm; IR (KBr): ν = 2962, 2925, 2854, 1724, 1602, 1500, 1444, 1399, 1369, 1309, 1262, 1216, 1184, 1114, 1099, 1036, 807, 756, 725, 659, 634, 620, 545, 524, 459 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 91 (43), 226 (67), 229 (100), 245 (84), 331 (35), 579 (41), 688(29), 735 (66), 808 (12); HRMS (EI): calcd for $C_{50}H_{50}O_6P_2$ [M^+]: 808.3083; found: 808.3085.

(−)-(*S*,*S*,*S*,*S*)-11g: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10b** with diphenylphosphine oxide afforded (*S*,*S*,*S*,*S*)-**11g** as an amorphous white solid (98% yield). $[\alpha]_D^{20}$ = −50.0 (*c* = 1.06 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.95 (d, *J* = 9.0 Hz, 2H), 3.23 (s, 6H), 5.33 (d, *J* = 8.7 Hz, 2H), 6.91–7.75 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 31.5 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.50, 142.27, 142.18, 133.28, 133.20, 133.14, 133.02, 132.73, 132.31, 132.28, 132.22, 132.17, 132.09, 132.04, 131.91, 131.75, 131.71, 131.64, 131.60, 131.37, 128.93, 128.80, 128.54, 128.51, 128.38, 128.35, 126.39, 126.22, 51.15, 45.14, 42.39, 42.32 ppm; IR (KBr): ν = 1728, 1437, 1189, 1135, 1117, 1100, 751, 721, 696, 553, 514 cm^{-1}; ESI-MS [M^++H]: 825.2; HRMS (FT): calcd for $C_{44}H_{38}O_6P_2Na$ [M^++Na]: 747.2036; found: 747.2044.

(−)-(*S*,*S*,*S*,*S*)-11h: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**11a**, the reaction of (*S*,*S*,*S*,*S*)-**10c** with diphenylphosphine oxide afforded a mixture of the by-product $BnP(O)Ph_2$ and (*S*,*S*,*S*,*S*)-**11h**. Isolation of the desired pure (*S*,*S*,*S*,*S*)-**11h** proved to be very difficult. The mixture was directly used in subsequent reduction to (−)-(*S*,*S*,*S*,*S*)-**3h** without further purification (see synthesis of (−)-(*S*,*S*,*S*,*S*)-**3h**) To get an unambiguous identification of compound (*S*,*S*,*S*,*S*)-**11h**, however, its pure form was obtained in quantitative yield by oxidation of (−)-(*S*,*S*,*S*,*S*)-**3h** with 30% H2O2 in THF. The spectroscopic data are as follows: $[\alpha]_D^{20}$ = −75.8 (*c* = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.05 (d, *J* = 8.7 Hz, 2H), 4.43 (d, *J* = 8.4 Hz, 2H), 4.57 (d, *J* = 12.3 Hz, 2H), 4.74 (d, *J* = 12.3 Hz, 2H), 6.90–7.70 (m, 38H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = 31.3 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.11, 141.39, 141.28, 134.40, 132.22, 132.14, 132.11, 131.44, 131.27, 131.24, 131.14, 131.10, 130.73, 130.60, 128.11, 127.98, 127.55, 127.50, 127.38, 127.34, 127.21, 127.02, 125.47, 125.31, 65.37, 43.73, 41.53, 41.45, 28.67 ppm; IR (KBr): ν = 1723, 1438, 1306, 1262, 1186, 1160, 1134, 1116, 1100, 1071, 1027, 752, 722, 695, 553, 513 cm^{-1}; ESI-MS [M^++H]: 877.3; HRMS (FT): calcd for $C_{56}H_{46}O_6P_2Na$ [M^++Na]: 899.2662; found: 899.2667.

(−)-(*S*,*S*,*S*,*S*)-3a: $HSiCl_3$ (2.85 mL, 25.0 mmol) was added to a solution of (*S*,*S*,*S*,*S*)-**11a** (0.752 g, 1.0 mmol) and $PhNMe_2$ (7.2 mL, 25.0 mmol) in dried toluene (8 mL) at 0 °C. The reaction mixture was stirred for 0.5 h, and then heated at 100 °C with stirring for an additional 12 h. The reaction was quenched at room temperature with concentrated aqueous $NaHCO_3$. The mixture was filtered through Celite, and the filtrate was extracted with diethyl ether, washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was submitted to chromatographic separation on silica gel using hexane/EtOAc (10:1) as eluent to give an amorphous white solid (0.53 g, 74%). $[\alpha]_D^{20}$ = −111.2 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.77 (t, *J* = 7.2 Hz, 6H), 3.72 (m, 6H), 5.21 (d, *J* = 3.3 Hz, 2H), 6.70–7.40 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −13.2 ppm; EI-MS (70 eV): *m*/*z* (%): 183 (12), 201 (19), 287 (23), 471 (11), 535 (100), 536 (26), 563 (9), 580 (9); IR (KBr): ν = 3053, 2980, 1722, 1605, 1586, 1509, 1477, 1464, 1435, 1369, 1328, 1303, 1266, 1216, 1159, 1134, 1093, 1070, 1035, 998, 745, 695, 546, 497, 416 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{42}O_4P_2$: C 76.65, H 5.87; found: C 76.59, H 5.93.

(−)-(*S*,*S*,*S*,*S*)-3b: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**3a**, the reduction of (*S*,*S*,*S*,*S*)-**11b** afforded (*S*,*S*,*S*,*S*)-**3b** as an amorphous white solid (80% yield). $[\alpha]_D^{20}$ = −69.0 (*c* = 1.22 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.73 (t, *J* = 7.3 Hz, 6H), 3.58–3.80 (m, 18H), 5.05 (d, *J* = 4.3 Hz, 2H), 6.63–7.25 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −16.5 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.43, 160.13, 160.05, 141.18, 140.87, 138.55, 138.36, 135.85, 135.61, 135.56, 135.33, 132.00, 127.99, 127.52, 127.42, 126.83, 126.73, 126.52, 114.12, 114.01, 113.92, 59.81, 54.93, 54.88, 43.59, 42.25, 41.95, 29.46, 13.64 ppm; IR (KBr): ν = 3055, 2836, 1722, 1594, 1568, 1498, 1463, 1441, 1369, 1305, 1286, 1248, 1177, 1135, 1095, 1031, 827, 797, 752, 531, 501, 419 cm^{-1}; ESI-MS [M^++H]: 841.5; HRMS (FT): calcd for $C_{50}H_{51}O_8P_2$ [M^++H]: 841.3053; found: 841.3033.

(−)-(*S*,*S*,*S*,*S*)-3c: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**3a**, the reduction of (*S*,*S*,*S*,*S*)-**11c** afforded (*S*,*S*,*S*,*S*)-**3c** as an amorphous white solid (91% yield). $[\alpha]_D^{20}$ = −67.8 (*c* = 0.99 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.75 (t, *J* = 6.7 Hz, 6H), 1.31 (s, 18H), 1.33 (s, 18H), 3.65–3.76 (m, 4H), 3.82 (d, *J* = 4.3 Hz, 2H), 5.18 (d, *J* = 4.3 Hz, 2H), 6.72–7.69 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −15.9 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.70, 151.64, 151.56, 141.85, 141.52, 138.17, 137.99, 134.25, 133.98, 133.93, 133.67, 133.27, 133.14, 132.85, 132.73, 128.26, 126.86, 126.56, 126.53, 125.51, 125.41, 125.34, 59.99, 43.84, 43.78, 42.42, 42.12, 34.63, 34.60, 31.31, 31.24, 13.83 ppm; IR (KBr): ν = 2964, 2904, 2869, 1725, 1600, 1510, 1494, 1463, 1393, 1365, 1331, 1305, 1268, 1142, 1094, 1084, 1037, 1016, 923, 827, 752, 592, 560 cm^{-1}; ESI-MS [M^++H]: 945.8; HRMS (FT) calcd for $C_{62}H_{75}O_4P_2$ [M^++H]: 945.5135; found: 945.5138.

(−)-(*S*,*S*,*S*,*S*)-3d: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**3a**, the reduction of (*S*,*S*,*S*,*S*)-**11d** afforded (*S*,*S*,*S*,*S*)-**3d** as an amorphous white solid (76% yield). $[\alpha]_D^{20}$ = −70.6 (*c* = 1.04 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.77 (t, *J* = 6.7 Hz, 6H), 2.31 (s, 6H), 2.32 (s, 6H), 3.67–3.79 (m, 6H), 5.18 (d, *J* = 4.3 Hz, 2H), 6.76–7.51 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −13.2 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.45, 141.71, 141.38, 137.91, 137.81, 137.76, 137.65, 137.57, 137.38, 136.41, 136.26, 135.90, 135.77, 135.08, 134.77, 134.45, 132.64, 131.52, 131.28, 131.06, 130.84, 129.39, 129.41, 128.98, 128.37, 128.25, 128.14, 126.87, 126.50, 59.90, 43.87, 42.50, 42.18, 21.30, 13.65 ppm; IR (KBr): ν = 3422, 3056, 2980, 2925, 2870, 1721, 1592, 1489, 1477, 1444, 1405, 1370, 1332, 1307, 1246, 1219, 1174, 1136, 1114, 1036, 998, 925, 872, 784, 758, 697, 566, 559, 464 cm^{-1}; ESI-MS [M^++H]: 777.5; HRMS (ESI) calcd for $C_{50}H_{51}O_4P_2$ [M^++H]: 777.3263; found: 777.3235.

(−)-(*S*,*S*,*S*,*S*)-3e: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**3a**, the reduction of (*S*,*S*,*S*,*S*)-**11e** afforded (*S*,*S*,*S*,*S*)-**3e** as an amorphous white solid (74% yield). $[\alpha]_D^{20}$ = −131.9 (*c* = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.70 (t, *J* = 6.7 Hz, 6H), 2.16 (s, 12H), 2.20 (s, 12H), 3.66 (m, 6H), 5.25 (d, *J* = 4.2 Hz, 2H), 6.60–7.00 (m, 20H); ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −12.5 ppm; IR (KBr): ν = 3396, 2980, 2921, 2862, 1723, 1600, 1467, 1444, 1370, 1307, 1274, 1182, 1130, 1073, 1037, 872, 851, 757, 723, 693, 581, 525, 468 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 343 (14), 416 (8), 555 (23), 591 (100), 592 (30), 593 (9), 727 (8), 759 (10); elemental analysis calcd (%) for $C_{54}H_{58}O_4P_2$: C 77.86, H 7.02; found: C 77.66, H 7.18.

(−)-(*S*,*S*,*S*,*S*)-3f: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**3a**, the reduction of (*S*,*S*,*S*,*S*)-**11f** afforded (*S*,*S*,*S*,*S*)-**3f** as an amorphous white solid (76% yield). $[\alpha]_D^{20}$ = −76.4 (*c* = 0.75 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.79 (t, *J* = 9.2 Hz, 6H), 2.38 (s, 6H), 2.35 (s, 6H), 3.66–3.80 (m, 6H), 5.17 (d, *J* = 3.6 Hz, 2H), 6.71–7.29 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = −15.2 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.67, 141.71, 141.38, 138.56, 138.07, 137.88, 134.54, 134.27, 133.99, 133.36, 133.24, 132.76, 132.64, 132.54, 129.37, 129.28, 129.18, 128.24, 126.87, 126.71, 126.64, 60.03, 43.87, 43.82, 42.48, 42.17, 29.67, 21.34, 13.76 ppm; IR (KBr): ν = 2958, 2924, 2854, 1723, 1497, 1463, 1441, 1369, 1304, 1215, 1186, 1160, 1093, 1036, 806, 750, 628, 508 cm^{-1}; ESI-MS [M^++H]: 777.5; HRMS (FT) calcd for $C_{50}H_{51}O_4P_2$ [M^++H]: 777.3263; found: 777.3257.

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(−)-(*S,S,S,S*)-3g: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**3a**, the reduction of (*S,S,S,S*)-**11g** afforded (*S,S,S,S*)-**3g** as an amorphous white solid (75% yield). $[\alpha]_D^{20} = -110.5$ ($c = 1.02$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 3.25$ (s, 6H), 3.72 (d, $J = 9.0$ Hz, 2H), 5.23 (d, $J = 7.5$ Hz, 2H), 6.83–7.41 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -13.2$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.94$, 141.74, 141.40, 137.14, 136.65, 136.51, 136.04, 135.90, 134.49, 134.22, 134.14, 133.87, 132.88, 128.68, 128.56, 128.47, 128.42, 128.32, 127.05, 126.54, 126.46, 51.11, 44.17, 44.11, 42.59, 42.26 ppm; IR (KBr): $\nu = 2947$, 1728, 1434, 1334, 1305, 1161, 1026, 744, 696, 498 cm^{-1}; ESI-MS [M^++H]: 693.2; HRMS (FT) calcd for $C_{44}H_{38}O_4P_2Na$ [M^++Na]: 715.2138; found: 715.2168.

(−)-(*S,S,S,S*)-3h: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**3a**, the reduction of (*S,S,S,S*)-**11h** afforded (*S,S,S,S*)-**3h** as an amorphous white solid (yield of the last two steps from (*S,S,S,S*)-**10c**, 30%). $[\alpha]_D^{20} = -109.0$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): $\delta = 3.79$ (d, $J = 9.0$ Hz, 2H), 4.57 (d, $J = 12.3$ Hz, 2H), 4.74 (d, $J = 12.3$ Hz, 2H), 5.22–5.25 (m, 2H), 6.72–7.38 (m, 38H); ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -13.4$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.56$, 141.57, 141.24, 137.71, 137.52, 136.44, 136.29, 135.77, 135.63, 135.35, 134.58, 134.47, 134.38, 134.20, 134.11, 132.79, 128.75, 128.68, 128.61, 128.52, 128.49, 128.37, 128.26, 127.97, 127.13, 126.58, 66.42, 43.96, 42.73, 42.40 ppm; IR (KBr): $\nu = 3053$, 1723, 1435, 1301, 1216, 1157, 1133, 1026, 1001, 744, 695, 499 cm^{-1}; ESI-MS [M^++H]: 845.3; HRMS (FT) calcd for $C_{56}H_{47}O_4P_2$ [M^++H]: 845.2944; found: 845.2963.

(−)-(*S,S,S,S*)-4a: Compound (*S,S,S,S*)-**1a** (1.07 g, 1.5 mmol) in Et_2O (20 mL) was added to a Schlenk tube containing $LiAlH_4$ (0.46 g, 12.0 mmol) and dried Et_2O (30 mL) at 0°C. The mixture was stirred for 10 min, and then the reaction was quenched with water. The precipitate was filtered and washed with CH_2Cl_2 three times. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting amorphous white solid was recrystallized in EtOAc to give (−)-(*S,S,S,S*)-**4a** as white crystals (0.80 g, 85%). M.p. 190.0–191.0°C; $[\alpha]_D^{20} = -88.4$ ($c = 0.975$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.58$ (d, $J = 6.3$ Hz, 2H), 3.31–3.44 (m, 4H), 4.62 (d, $J = 6.3$ Hz, 2H), 6.67–7.41 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -12.7$ ppm; IR (KBr): $\nu = 3360$, 3047, 1584, 1432, 1066, 1032, 762, 750, 741, 695 cm^{-1}; EI-MS (70 eV): *m/z* (%): 451 (100), 287 (92), 549 (92), 183 (90), 363 (66), 361 (55), 559 (54), 471 (42); elemental analysis calcd (%) for $C_{42}H_{38}O_2P_2$: C 79.23, H 6.02; found: C 79.01, H 6.10.

Crystal data: $C_{42}H_{38}O_2P_2$, formula weight 636.66, orthorhombic, space group $P2_12_12_1$, $a = 8.0449(12)$, $b = 16.257(2)$, $c = 26.605(4)$ Å, $V = 3479.5(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.215$ g cm^{-3}, $F(000) = 1344$, $\mu(Mo_{K\alpha}) = 1.60$ cm^{-1}. Data collection and refinement: diffraction data were measured in the range $2\theta_{max} = 2.94$–56.62°. A total of 7797 unique reflections with positive intensities were recorded. The final refinement, based on F^2, converged at $R = 0.0490$ ($wR_2 = 0.0873$) for 3284 observations having $I_o > 2\sigma(I_o)$ and $R = 0.1299$ ($wR_2 = 0.1053$) for 7797 unique data. At convergence, $S = 0.342$ and $\Delta\rho = -0.205$ e Å^{-3}.

(−)-(*S,S,S,S*)-4b: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**4a**, the reduction of (*S,S,S,S*)-**3b** afforded (*S,S,S,S*)-**4b** as an amorphous white solid (99% yield). $[\alpha]_D^{20} = -47.4$ ($c = 0.97$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.82$ (br, 2H), 2.59 (d, $J = 6.0$ Hz, 2H), 3.34–3.39 (m, 4H), 3.79 (s, 6H), 3.83 (s, 6H), 4.53 (d, $J = 6.0$ Hz, 2H), 6.56–7.30 (m,24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -16.7$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.34$, 160.28, 141.97, 141.66, 138.25, 138.07, 135.97, 135.68, 135.56, 135.28, 132.36, 128.31, 127.54, 127.44, 126.67, 126.57, 126.52, 126.45, 126.36, 114.34, 114.30, 114.23, 114.19, 63.16, 55.29, 55.14, 55.10, 40.66, 40.60, 39.96, 39.71, 29.28 ppm; IR (KBr): $\nu = 2926$, 1594, 1567, 1498, 1461, 1440, 1285, 1247, 1177, 1095, 1029, 827, 797, 747, 532 cm^{-1}; ESI-MS [M^++H]: 757.3; HRMS (FT) calcd for $C_{46}H_{47}O_6P_2$ [M^++H]: 757.2842; found: 757.2833.

(−)-(*S,S,S,S*)-4c: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**4a**, the reduction of (*S,S,S,S*)-**3c** afforded (*S,S,S,S*)-**4c** as an amorphous white solid (95% yield). $[\alpha]_D^{20} = -47.6$ ($c = 1.02$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.32$ (s, 18H), 1.36 (s, 18H), 2.57 (d, $J = 7.5$ Hz, 2H), 3.36–3.39 (m, 4H), 4.51 (d, $J = 7.5$ Hz, 2H), 6.64–7.42 (m,24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -14.9$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.96$, 151.92, 142.32, 142.00, 137.80, 137.62, 134.34, 134.07, 133.84, 133.58, 132.92, 132.81, 132.71, 132.34, 132.22, 128.39, 126.36, 125.57, 125.49, 63.26, 48.91, 40.78, 40.71, 40.06, 39.81, 34.63, 34.59, 33.87, 31.28, 31.19, 31.06, 25.56, 24.90 ppm; IR (KBr): $\nu = 3384$, 3055, 2963, 2868, 1494, 1463, 1392, 1363, 1268, 1201, 1084, 1031, 1016, 827, 751, 591, 560 cm^{-1}; EI-MS (70 eV): *m/z* (%): 546 (100), 775 (80), 774 (66), 57 (62), 399 (57), 640 (51), 641 (51), 477 (50), 860 (33), 861 (30) [M^++H]; HRMS (EI) calcd for $C_{58}H_{70}O_2P_2$ [M^+]: 860.4851; found: 860.4828.

(−)-(*S,S,S,S*)-4d: AcOH (80.0 μL, 1.38 mmol) was added to a mixture of (*S,S,S,S*)-**4a** (0.175 g, 0.276 mmol), DCC (0.285 g, 1.38 mmol) and DMAP (0.017 g, 0.138 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 12 h and the precipitated urea was removed by filtration through Celite. The filtrate was concentrated under reduced pressure and then submitted to chromatographic separation on silica gel using hexane/EtOAc (5:1) as eluent to give an amorphous white solid (0.143 g, 81%). $[\alpha]_D^{20} = -65.0$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.78$ (s, 6H), 2.75 (d, $J = 7.5$ Hz, 2H), 3.85–3.88 (m, 4H), 4.71 (d, $J = 7.5$ Hz, 2H), 6.67–7.42 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -12.0$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.92$, 141.99, 141.66, 136.76, 136.59, 136.49, 136.35, 135.93, 135.79, 134.59, 134.32, 133.90, 133.649, 132.958, 128.957, 128.908, 128.751, 128.658, 128.560, 126.73, 126.64, 64.33, 40.18, 39.93, 37.41, 37.34, 20.73 ppm; IR (KBr): $\nu = 3056$, 2925, 2853, 1739, 1590, 1463, 1437, 1368, 1238, 1187, 1116, 1031, 917, 748, 722, 697, 546 cm^{-1}; EI-MS (70 eV): *m/z* (%): 536 (100), 535 (86), 537 (33), 550 (31), 549 (27), 287 (20), 472 (20), 471 (19), 720 (7) [M^+]; HRMS (EI) calcd for $C_{46}H_{42}O_4P_2$ [M^+]: 720.2509; found: 720.2534.

(−)-(*S,S,S,S*)-4e: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**4d**, the esterification of (*S,S,S,S*)-**4a** with benzoic acid afforded (*S,S,S,S*)-**4e** as an amorphous white solid (85% yield). $[\alpha]_D^{20} = -88.3$ ($c = 0.875$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.84$–2.88 (m, 2H), 3.96 (t, $J = 9.0$ Hz, 2H), 4.21 (t, $J = 9.0$ Hz, 2H), 4.85 (d, $J = 7.0$ Hz, 2H), 6.72–7.90 (m, 38H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -12.8$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.68$, 141.93, 141.61, 137.32, 137.15, 136.73, 136.59, 135.97, 135.83, 134.94, 134.67, 134.36, 134.10, 133.28, 132.97, 130.43, 129.90, 129.22, 129.18, 129.07, 128.98, 128.89, 128.79, 128.44, 127.03, 65.18, 40.31, 40.03, 38.21, 38.14, 30.41, 29.95 ppm; IR (KBr): $\nu = 2925$, 2854, 1717, 1435, 1315, 1264, 1176, 1112, 1070, 1026, 804, 745, 711, 696, 545, 501 cm^{-1}; ESI-MS [M^++H]: 845.3; HRMS (FT) calcd for $C_{56}H_{47}O_4P_2$ [M^++H]: 845.2944; found: 845.2938.

(−)-(*S,S,S,S*)-4f: Following the same procedure as described above for the preparation of (*S,S,S,S*)-**4d**, the esterification of (*S,S,S,S*)-**4c** with AcOH afforded (*S,S,S,S*)-**4f** as an amorphous white solid (85% yield). $[\alpha]_D^{20} = -90.5$ ($c = 0.99$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.30$ (s, 18H), 1.38 (s, 18H), 1.79 (s, 6H), 2.67 (d, $J = 6.0$ Hz, 2H), 3.80–3.85 (m, 4H), 4.64 (d, $J = 6.0$ Hz, 2H), 6.70–7.42 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -14.3$ ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.81$, 151.94, 151.88, 141.72, 141.40, 137.58, 137.40, 134.40, 134.13, 133.64, 133.38, 132.90, 132.78, 132.64, 132.46, 132.35, 128.26, 126.50, 125.63, 125.54, 125.46, 64.43, 39.96, 39.71, 37.18, 37.11, 34.62, 34.58, 31.27, 31.17, 20.76 ppm; IR (KBr): $\nu = 2963$, 2905, 2869, 1743, 1494, 1462, 1390, 1364, 1269, 1236, 1084, 1032, 1016, 827, 751, 582, 560 cm^{-1}; ESI-MS [M^++H]: 946.5; HRMS (FT) calcd for $C_{62}H_{75}O_4P_2$ [M^++H]: 945.5135; found: 945.5137.

MeO-PEG-O$_2$CCH$_2$CH$_2$CO$_2$H (18):[15i] NEt_3 (1.40 mL, 10.0 mmol) was added to a mixture of poly(ethylene glycol) methyl ether (MeO-PEG, $M_n = 2000$, 2.0 g, 1.0 mmol), succinic anhydride (0.50 g, 5.0 mmol), and DMAP (0.122 g, 1.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 12 h and the precipitated urea was removed by filtration through Celite. The filtrate was concentrated under reduced pressure and then the residue was dissolved in CH_2Cl_2 (2 mL). Et_2O (50 mL) was added slowly to the solution with vigorous stirring at 0°C. The precipitate formed was isolated by filtration and then dried over P_2O_5 in vacuo to give the MeO-PEG derivative **18** (1.93 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.59$–2.67 (m, 4H), 3.38 (s, 3H), 3.39–3.77 (polyethylene glycol peaks), 4.21–4.23 (m, 2H) ppm; IR (KBr): $\nu = 2889$, 2695, 1967, 1737, 1648, 1468, 1361, 1344, 1281, 1243, 1150, 1113, 1060, 964, 842, 529 cm^{-1}.

(−)-(*S,S,S,S*)-5a: DCC (1.40 g, 0.63 mmol) was added to a mixture of **18** (0.125 g, 0.059 mmol), (*S,S,S,S*)-**4a** (0.20 g, 0.313 mmol) and DMAP (0.004 g, 0.0313 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stir-

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red for 12 h and the precipitated urea was removed by filtration through Celite. The filtrate was concentrated under reduced pressure and then dissolved in CH_2Cl_2 (2 mL). Et_2O (50 mL) was added slowly to the mixture with vigorous stirring at 0 °C. The precipitate formed was isolated by filtration as a white solid and purified by repeated precipitation from diethyl ether as mentioned above. The solids obtained were then dried over P_2O_5 in vacuo to give (−)-(*S*,*S*,*S*,*S*)-**5a** (0.144 g, 89 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.36$ (t, $J = 6.0$ Hz, 2H), 2.50 (t, $J = 6.0$ Hz, 2H), 2.60–2.70 (m, 2H), 3.38 (s, 3H), 3.65–3.71 (polyethylene glycol peaks), 4.18–4.21 (m, 2H), 4.57–4.60 (m, 2H), 6.60–7.37 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -12.391$, −12.558 ppm; IR (KBr): $\nu = 3474$, 3053, 2887, 2742, 2696, 1967, 1736, 1585, 1468, 1436, 1361, 1344, 1281, 1242, 1149, 1112, 1061, 964, 843, 747, 699, 505 cm^{-1}; MALDI-MS [M^++K]: 2415.4.

(−)-(*S*,*S*,*S*,*S*)-5b: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**5a**, the esterification of (*S*,*S*,*S*,*S*)-**4c** with **18** afforded (*S*,*S*,*S*,*S*)-**5b** as a white solid (78.6 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.30$ (s, 18H), 1.34 (s, 18H), 2.39–2.43 (m, 2H), 2.51–2.56 (m, 2H), 2.64–2.67 (m, 2H), 3.38 (s, 3H), 3.65–3.71 (polyethylene glycol peaks), 4.22–4.26 (m, 2H), 4.52 (d, $J = 7.0$ Hz, 2H), 6.60–7.41 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -14.6$, −14.8 ppm; IR (KBr): $\nu = 3447$, 2949, 2887, 2742, 2696, 1967, 1735, 1700, 1653, 1599, 1559, 1467, 1394, 1361, 1344, 1281, 1242, 1149, 1114, 1060, 964, 947, 842, 756, 638, 614, 591, 562, 528 cm^{-1}; MALDI-MS [M^++K]: 2691.6.

(−)-(*S*,*S*,*S*,*S*)-5c: AcOH (3.0 μL, 0.0516 mmol) was added to a mixture of (*S*,*S*,*S*,*S*)-**5a** (0.07 g, 0.0258 mmol), DCC (0.011 g, 0.0516 mmol), and DMAP (0.002 g, 0.013 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 12 h and the precipitated urea was removed by filtration through Celite. The filtrate was concentrated under reduced pressure and then dissolved in CH_2Cl_2 (2 mL). Et_2O (50 mL) was slowly added to the mixture with vigorous stirring at 0 °C. The precipitate was isolated by filtration as a white solid and purified by repeated precipitation from diethyl ether as mentioned above. The solids obtained were then dried over P_2O_5 in vacuo to give (−)-(*S*,*S*,*S*,*S*)-**5c** (0.056 g, 78.2 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.79$ (s, 3H), 2.31–2.38 (m, 2H), 2.49–2.54 (m, 2H), 2.73 (d, $J = 7.0$ Hz, 2H), 3.38 (s, 3H), 3.65–3.71 (polyethylene glycol peaks), 4.24 (t, $J = 4.8$ Hz, 2H), 4.70 (d, $J = 7.0$ Hz, 2H), 6.68–7.72 (m, 28H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -12.0$, −12.7 ppm; IR (KBr): $\nu = 2887$, 1738, 1627, 1467, 1436, 1361, 1344, 1281, 1242, 1149, 1112, 1060, 964, 842, 747, 698 cm^{-1}; MALDI-MS [M^++K]: 2457.4.

(−)-(*S*,*S*,*S*,*S*)-5d: Following the same procedure as described above for the preparation of (*S*,*S*,*S*,*S*)-**5c**, the esterification of (*S*, *S*, *S*, *S*)-**5b** with AcOH afforded (*S*,*S*,*S*,*S*)-**5d** as a white solid (73.6 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.31$ (s, 18H), 1.35 (s, 18H), 1.74–1.77 (m, 3H), 2.40–2.56 (m, 4H), 2.65–2.67 (m, 2H), 3.38 (s, 3H), 3.65–3.71 (polyethylene glycol peaks), 4.22–4.26 (m, 2H), 4.50–4.52 (m, 2H), 6.00–7.68 (m, 24H) ppm; ^{31}P NMR (121.46 MHz, $CDCl_3$): $\delta = -14.27$, −14.73 ppm; IR (KBr): $\nu = 3855$, 3328, 2888, 2742, 1968, 1736, 1627, 1598, 1467, 1395, 1361, 1344, 1281, 1243, 1149, 1114, 1061, 964, 842, 756, 639, 613, 591, 567, 528 cm^{-1}; MALDI-MS [M^++K]: 2736.7.

Representative procedure for the allylic substitution using dimethyl malonate as a nucleophile: Dried CH_3CN (2 mL) was added to a Schlenk tube containing [{Pd(C_3H_5)Cl}$_2$] (1.3 mg, 0.0036 mmol, 2.5 mol %) and chiral ligand (−)-(*S*,*S*,*S*,*S*)-**3** (0.009 mmol, 6.0 mol %) and the mixture was stirred at room temperature for 30 min. Then, 1,3-diphenylprop-2-en-1-yl acetate **12** (37.8 mg, 0.15 mmol) was added to the reactor and the mixture was stirred for an additional 10 min. Dimethyl malonate **13a** (35.2 μL, 0.30 mmol) and *N*,*O*- bis(trimethylsilyl)acetamide (78.0 μL, 0.30 mmol) were finally added to the reaction mixture. The reaction process was monitored by TLC and the resulting mixture was diluted with diethyl ether (5 mL) and quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered through Celite and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel using hexane/EtOAc (5:1) as eluent to give the product (*S*)-**14a**[6] as a colorless oil (see Table 1 for yields). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 3.52$ (s, 3H), 3.70 (s, 3H), 3.95 (d, $J = 10.8$ Hz, 1H), 4.23–4.30 (m, 1H), 6.30 (dd, $J = 8.8$, 15.8 Hz, 1H), 6.44 (d, $J = 15.8$ Hz, 1H), 7.20–7.32 (m, 10H); the enantiomeric excess was determined by HPLC on a Chiralpak AD column using hexane/2-propanol (90:10) as eluent, flow rate = 1.0 mL min^{-1}, UV detection at $\lambda = 254$ nm, $t_{R1} = 9.5$ min (*R* isomer), $t_{R2} = 12.9$ min (*S* isomer).

Representative procedure for the allylic substitution using benzylamine as the nucleophile: Dried CH_3CN (2 mL) was added to a Schlenk flask containing [{Pd(C_3H_5)Cl}$_2$] (1.3 mg, 0.0036 mmol, 2.5 mol %) and chiral ligand (−)-(*S*,*S*,*S*,*S*)-**3** (0.009 mmol, 6.0 mol %). The mixture was stirred at room temperature for 30 min and then 1,3-diphenylprop-2-en-1-yl acetate **12** (37.8 mg, 0.15 mmol) was added. The mixture was stirred for an additional 10 min. Benzylamine **13b** (36.2 μL, 0.30 mmol) was introduced to the reactor through a microsyringe. The reaction process was monitored by TLC. After completion of the reaction, the product was purified by flash chromatography using hexane/EtOAc (10:1) as eluent to yield (*R*)-**14b**[6] as a colorless oil (see Table 1 for yields). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 3.75$–3.81 (m, 2H), 4.43 (d, $J = 7.4$ Hz, 1H), 6.31 (dd, $J = 7.4$, 15.9 Hz, 1H), 6.58 (d, $J = 15.9$ Hz, 1H), 7.17–7.45 (m, 15H) ppm; the enantiomeric excess was determined by HPLC on a Chiralcel OJ column using hexane/2-propanol (93:7) as eluent, flow rate = 0.6 mL min^{-1}, UV detection at $\lambda = 254$ nm, $t_{R1} = 18.8$ min (*S* isomer), $t_{R2} = 21.8$ min (*R* isomer).

(*R*)-Dimethyl cyclohex-2-enylmalonate (16a):[6] Compound **16a** was prepared in 85 % yield. $[\alpha]_D^{20} = +32.0$ ($c = 1.21$ in CH_2Cl_2); 87.5 % *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.26$–1.81 (m, 4H), 1.96–2.06 (m, 2H), 2.86–2.95 (m, 1H), 3.29 (d, $J = 9.6$ Hz, 1H), 3.75 (s, 6H), 5.52 (dd, $J = 2.3$, 9.9 Hz, 1H), 5.74–5.82 (m, 1H); the enantiomeric excess was determined by HPLC on a Chiralcel OB-H column using hexane/2-propanol (90:10(, flow rate = 0.8 mL min^{-1}, UV detection at $\lambda = 230$ nm, $t_{R1} = 8.3$ min (*R* isomer), $t_{R2} = 10.8$ min (*S* isomer).

(*R*)-*N*-Benzyl(cyclohex-2-enyl)amine (16b):[6] Compound **16b** was prepared in 74 % yield. $[\alpha]_D^{20} = +45.6$ ($c = 0.99$ in CH_2Cl_2); 73.2 % *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.43$–2.00 (m, 6H), 3.21–3.25 (m, 1H), 3.80–3.89 (m, 2H), 5.75 (m, 2H), 7.2–7.4 ppm (m, 5H); the enantiomeric excess was determined by HPLC on a Chiralcel OB-H column using hexane/2-propanol (95:5), flow rate = 0.5 mL min^{-1}, UV detection at $\lambda = 230$ nm, $t_{R1} = 11.0$ min (*R* isomer), $t_{R2} = 12.2$ min (*S* isomer).

General procedure for the recycling experiment with MeO-PEG-bound ligand 5b: The reaction was performed in a glove box under a nitrogen atmosphere. After completion of the reaction, most of the CH_3CN was removed under reduced pressure and the residue was treated with diethyl ether (50 mL) at −20 °C. The precipitated polymeric catalyst was collected by filtration and then washed with Et_2O (2 × 10 mL). The recycled catalyst was submitted to the next run of the reaction and the catalyst loading was kept at 5 mol % Pd. The filtrate collected was purified by flash chromatography in order to determine the yield and enantiomeric excess of the reaction.

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[1] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience, New York, **1994**; b) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**; c) *Comprehensive Asymmetric Catalysis*, *Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; d) *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, New York, **2001**.

[2] H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, *Vol. I–II*, VCH, Weinheim, **1993**.

[3] T. Ohkuma, M. Kitamura, R. Noyori in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, pp. 1–110.

[4] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.

[5] a) M. Hayashi, Y. Hashimoto, H. Takezaki, Y. Watanabe, K. Saigo, *Tetrahedron: Asymmetry* **1998**, *9*, 1863–1866; for other reports on the synthesis of bisphosphine ligands with cyclobutane backbones,

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see: b) D. Haag, H.-D. Scharf, *J. Org. Chem.* **1996**, *61*, 6127–6135; c) T. Morimoto, N. Nakajima, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 75–78; d) R. Glaser, J. Blumenfeld, M. Twaik, *Tetrahedron Lett.* **1977**, *18*, 4639–4642; e) R. Glaser, M. Twaik, S. Geresh, J. Blumenfeld, *Tetrahedron Lett.* **1977**, *18*, 4635–4638.

[6] The synthesis of **3a–f** and their application in Pd-catalyzed allylic substitutions were reported in a previous communication, see: D. Zhao, K. Ding, *Org. Lett.* **2003**, *5* 1349–1351.

[7] C. H. Krauch, S. Farid, G. O. Schenck, *Chem. Ber.* **1966**, *99*, 625–633.

[8] K. Saigo, N. Yonezawa, K. Sekimoto, M. Hasegawa, K. Ueno, H. Nakanishi, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1000–1005.

[9] a) K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, *Angew. Chem.* **1999**, *111*, 3733–3736; *Angew. Chem. Int. Ed.* **1999**, *38*, 3523–3525; b) K. Tanaka, F. Toda, *J. Chem. Soc., Perkin Trans. 1* **1992**, 943–944.

[10] a) D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954–974; b) for a comprehensive review on TADDOL chemistry, see: D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96–142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138.

[11] For reviews, see: a) A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis, Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 833–884. See also ref. [4]. For selected examples, see: b) B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343; c) P. V. Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614–616; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566–568; d) W.-P. Deng, S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, J. Sun, *J. Am. Chem. Soc.* **2001**, *123*, 6508–6519. For examples of reaction systems using cyclic substrates, see: e) B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089–4090; f) S. Kudis, G. Helmchen, *Angew. Chem.* **1998**, *110*, 3210–3212; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047–3050; g) S. R. Gilbertson, D. Xie, *Angew. Chem.* **1999**, *111*, 2915–2918; *Angew. Chem. Int. Ed.* **1999**, *38*, 2750–2752; h) D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagne, *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.

[12] CCDC-239002 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] For comprehensive reviews on supported catalysts for enantioselective reactions, see: a) *Chiral Catalyst Immobilization and Recycling* (Eds.: D. E. de Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; for recent reviews on chiral catalyst immobilization, see: b) C. E. Song, S. Lee, *Chem. Rev.* **2002**, *102*, 3495–3524; c) Q. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385–3466; d) D. E. de Vos, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, *102*, 3615–3640; e) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274; f) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; g) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494.

[14] For recent examples of polymer-supported catalysts for asymmetric allylation, see: a) Y. Uozumi, H. Tanaka, K. Shibatomi, *Org. Lett.* **2004**, *6*, 281–283; b) Y. Ribourdouille, G. D. Engel, M. Richard-Plouet, L. H. Gade, *Chem. Commun.* **2003**, 1228–1229; c) M. M. Dell′Anna, P. Mastrorilli, C. F. Nobile, G. P. Suranna, *J. Mol. Catal.* **2003**, *201*, 131–135; d) B. M. Trost, Z. Pan, J. Zambrano, C. Kujat, *Angew. Chem.* **2002**, *114*, 4885–4887; *Angew. Chem. Int. Ed.* **2002**, *41*, 4691–4693; e) C.-E. Song, J.-W. Yang, E.-J. Roh, S.-G. Lee, J.-H. Ahn, H. Han, *Angew. Chem.* **2002**, *114*, 4008–4010; *Angew. Chem. Int. Ed.* **2002**, *41*, 3852–3854; f) Y. Uozumi, K. Shibatomi, *J. Am. Chem. Soc.* **2001**, *123*, 2919–2920; g) K. Hallman, C. Moberg, *Tetrahedron: Asymmetry* **2001**, *12*, 1475–1478; h) T. Hashizume, K. Yonehara, K. Ohe, S. Uemura, *J. Org. Chem.* **2000**, *65*, 5197–5201; i) K. Hallman, E. Macedo, K. Nordström, C. Moberg, *Tetrahedron: Asymmetry* **1999**, *10*, 4037–4046; j) Y. Uozumi, H. Danjo, T. Hayashi, *Tetrahedron Lett.* **1998**, *39*, 8303–8306; k) P. Gamez, B. Dunjic, F. Fache, M. Lemaire, *Tetrahedron: Asymmetry* **1995**, *6*, 1109–1116; l) P. Gamez, B. Dunjic, F. Fache, M. Lemaire, *J. Chem. Soc. Chem. Commun.* **1994**, 1417–1418; m) Y. Akiyama, S. Kobayashi, *Angew. Chem.* **2001**, *113*, 4008–4010; *Angew. Chem. Int. Ed.* **2001**, *40*, 3577–3579; M. Reggelin, M. Schultz, M. Holbach, *Angew. Chem.* **2002**, *114*, 1684–1687; *Angew. Chem. Int. Ed.* **2002**, *41*, 1614–1617.

[15] For PEG-supported chiral catalysts for other asymmetric reactions including hydrogenation and reduction, see: a) X. Li, W. Chen, W. Hems, F. King, J. Xiao, *Org. Lett.* **2003**, *5*, 4559–4561; b) C. Saluzzo, T. Lamouille, D. Herault, M. Lemaire, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1841–1844; c) Q. Fan, G. Deng, C. Lin, A. S. C. Chan, *Tetrahedron: Asymmetry* **2001**, *12*, 1241–1247; d) P. Guerreiro, V. Ratovelomanana-Vidal, J.-P. Genet, P. Dellis, *Tetrahedron Lett.* **2001**, *42*, 3423–3426; e) Q. Fan, G. Deng, X. Chen, W. Xie, D. Jiang, D. Liu, A. S. C. Chan, *J. Mol. Catal. A: Chem.* **2000**, *159*, 37–43; for asymmetric dihydroxlation and epoxidation, see: f) R. W. Flood, T. P. Geller, S. A. Petty, S. M. Roberts, J. Skidmore, M. Volk, *Org. Lett.* **2001**, *3*, 683–686; g) T. S. Reger, K. D. Janda, *J. Am. Chem. Soc.* **2000**, *122*, 6929–6934; h) P. Wentworth Jr., K. D. Janda, *Chem. Commun.* **1999**, 1917–1924; i) C. Bolm, A. Gerlach, *Angew. Chem.* **1997**, *109*, 773–775; *Angew. Chem. Int. Ed.* **1997**, *36*, 741–743; j) H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 7632–7633; for cycloaddition and aldol reactions, see: k) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160–3166; l) M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171–173; m) M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045–2048; n) M. Reggelin, V. Brenig, C. Zur, *Org. Lett.* **2000**, *2*, 531–533; for asymmetric addition of diethylzinc to aldehydes, see: o) U. K. Anyanwu, D. Venkataraman, *Tetrahedron Lett.* **2003**, *44*, 6445–6448; p) C. Bolm, N. Hermanns, A. Classen, K. Muniz, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795–1798.

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