New Bisphosphine Ligands for Palladium-Catalyzed Desymmetrization of *meso*-Cyclopent-2-en-1,4-diol Biscarbamate

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Abstract: A new class of bisphosphine ligands (**5**, **6**) with a cyclobutane backbone have been designed and synthesized on the basis of a privileged C_2 scaffold of head-to-head coumarin dimer, among which ligand **5a** was found to show excellent activity and enantioselectivity in Pd-catalyzed desymmetrization of the biscarbamate of *meso*-cyclopent-2-en-1,4-diol, affording oxazolidin-2-one in up to 90% yield with 97% ee.

Key words: C_2-symmetric, bisphosphine, palladium, desymmetrization, *meso*-diols

The enantiopure anti head-to-head coumarin dimer (–)-**1**[1] is a highly strained but readily accessible compound which, upon lactone-opening reactions, can be easily transformed into various C_2 symmetric cyclobutane-containing bisphosphine ligands, such as **2**[2] and **3**.[3,4] Despite the facts of excellent asymmetric induction of ligand **3** and its PEG-supported analogues in Pd-catalyzed asymmetric allylic substitutions of acyclic substrate,[4] ligand **3** exhibited poor enantioselective control of palladium-catalyzed desymmetrization of *meso*-cyclopent-2-ene-1,4-diol derivative (25% ee). As an extension of our research to the development of new bisphosphine ligands for asymmetric catalysis on the basis of privileged C_2 scaffold of **1**,[3,4] in the present letter, we report our preliminary results on the synthesis of a new class of bisphosphine ligands (**5**, **6**) having cyclobutane backbone, which can be considered as the structural analogues of Trost's ligand **4**.[5] Among the new ligands developed in this work, ligand **5a** was found to show excellent activity and enantioselectivity in Pd-catalyzed desymmetrization of the biscarbamate of *meso*-cyclopent-2-en-1,4-diol, affording oxazolidin-2-one in up to 90% yield with 97% ee.

The key intermediates for the syntheses of bisphosphine ligands **5a** and **5b**, chiral diamines **11a** and **11b**, were prepared with an overall yield of 70% and 68%, respectively, by following the reaction sequences as shown in Scheme 1. As we described previously, the enantiopure *anti*-head-to-head coumarin dimer (–)-**1** could be easily obtained in large scale by optical resolution of the corresponding racemic coumarin dimer through molecular complexation with TADDOL.[3,4] One of the advantages of this coumarin dimer was its high functionality. Lactone-opening reaction of (–)-**1** with Me_2SO_4 afforded the corresponding diesters (**7**) in excellent yields.[6] Hydrolysis of **7** followed by treatment with thionyl chloride[7] and subsequent condensation with anhydrous ammonia gas in chloroform gave the diamide **9**, which was converted through **10** to the target diamine **11a** by Hoffmann rearrangement using phenyl iodosylacetate [$PhI(OAc)_2$]

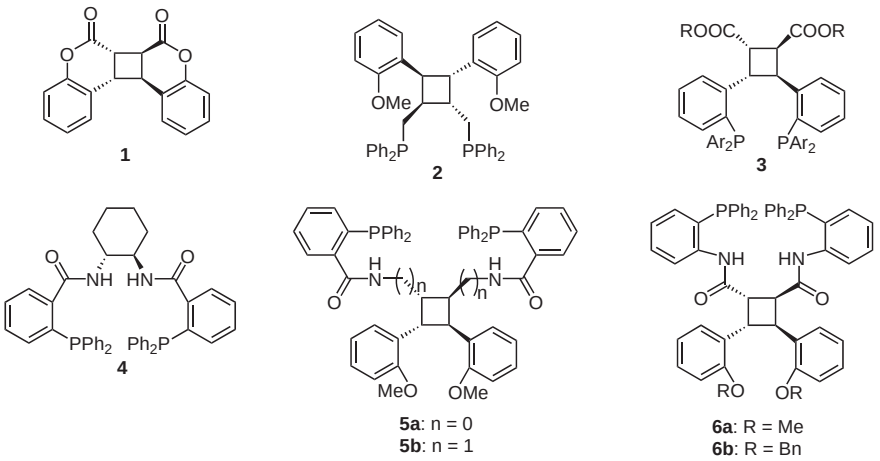

Figure 1

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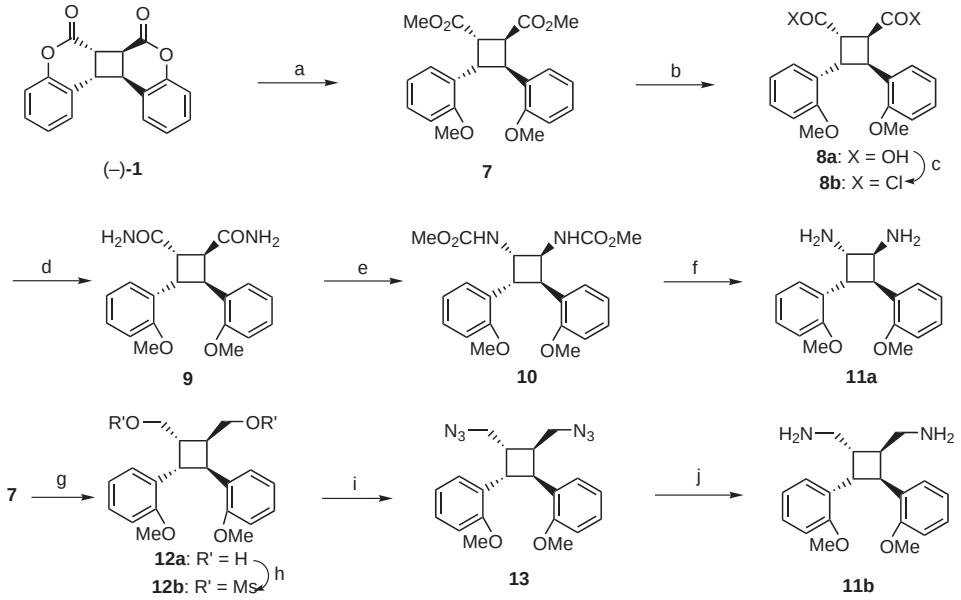


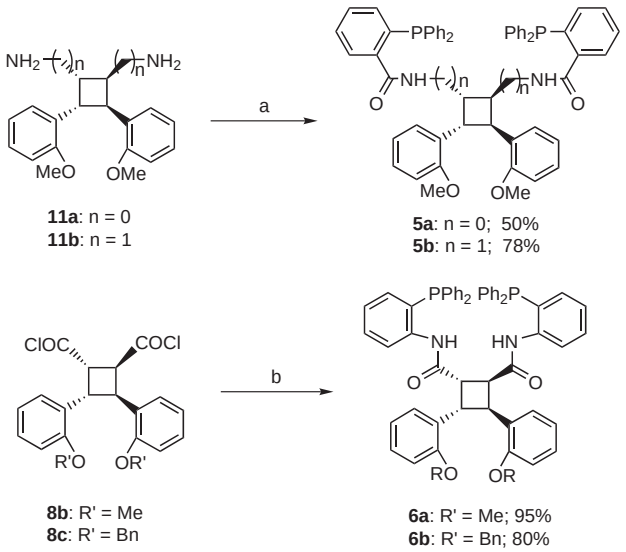
Scheme 1 Synthesis of chiral 1,2-diamine **11a** and chiral 1,4-diamine **11b**. *Reagents and conditions*: a) Me_2SO_4, aq KOH, acetone, >95%; b) MeOH, aq KOH, reflux, then 2 N HCl, >95%; c) $SOCl_2$, benzene, reflux; d) $CHCl_3$, NH_3 (g), r.t., >99%; e) KOH, 2 equiv $PhI(OAc)_2$, MeOH, 0 °C, reflux, 83.3%; f) aq KOH, MeOH, reflux, 48h, >95%; g) 8 equiv $LiAlH_4$, Et_2O, 95%; h) 4 equiv MsCl, Et_3N, CH_2Cl_2, 90%; i) 10 equiv NaN_3, DMF, reflux, 98%; j) Pd/C, H_2 (1 atm), 86%.

in alkaline methanol. On the other hand, synthesis of chiral 1,4-diamine **11b**, a more flexible counterpart of **11a**, was accomplished via a four-step reaction procedure starting from **7** (Scheme 1). Reduction of the ester functionalities of **7** with lithium aluminum hydride gave diol **12a**, which was mesylated on the hydroxyl groups to yield the corresponding dimesylate **12b**. Nucleophilic substitution of **12b** with sodium azide, followed by Pd/C catalytic hydrogenation at ambient pressure, afforded the desired chiral 1,4-diamine **11b**.

With the chiral diamines **11a**,**b** in hand, the transformation to the target chiral biphosphine ligands **5a**,**b** was quite straightforward. Condensation of **11a**,**b** with 2-(diphenylphosphino)benzoic acid (DPPBA)[8] in the presence of DCC and a catalytic amount of DMAP proceeded smoothly affording bisphosphines **5a**[9] and **5b**[10] in 50% and 78% yields, respectively (Scheme 2).

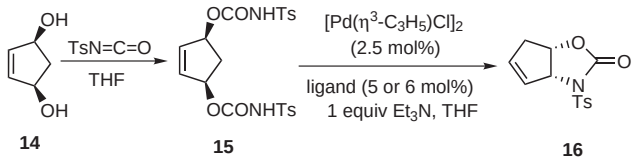
To investigate the possible influences of different amide linkage on the asymmetric induction capability of this type of bisphosphine ligands, two other chiral bisphosphine ligands **6a**,**b**, which have similar *trans*-cyclobutane backbones as that of **5a** or **5b** but with inversed amide linkages, were subsequently prepared. By following Trost's procedure,[11] condensation of the corresponding dichlorides **8b** or **8c** (prepared by following the similar procedure for the preparation of **8b**) with 2-(diphenylphosphino)aniline (DPPA)[12] (Scheme 2) afforded **6a**[13] and **6b**[14] as white solids in 95% and 80% yield, respectively.

Palladium-catalyzed desymmetrization of *meso*-alkenediols or their derivatives (Scheme 3) was developed by Trost et al.[5,11] and has been successfully used in the synthesis of a number of biologically significant products.[15]



Scheme 2 Synthesis of bisphosphine ligands **5a**,**b** and **6a**,**b**. *Reagents and conditions*: a) 2.4 equiv DPPBA, 3 equiv DCC, DMAP, CH_2Cl_2, r.t.; b) 3 equiv DPPA, CH_2Cl_2, r.t.

The reaction is formally an intramolecular allylic substitution reaction of a *meso*-substrate with two enantiotopic leaving groups.[5a] Owing to its mechanically well-defined nature, the reaction was also often adopted as a standard test reaction for chiral ligands designed for use in asymmetric allylic substitution reactions.[5,16] Given these facts, we moved on to examine the enantiodiscrimination abilities of our chiral bisphosphines **5a**,**b** and **6a**,**b** in palladium-catalyzed desymmetrization of *meso*-cyclopent-2-en-1,4-diol bis(carbamate) **15**,[17] and the results obtained were summarized in Table 1.



Scheme 3 Palladium-catalyzed desymmetrization of *meso*-alkene-diols or their derivatives.

The reaction was initially conducted in a one-pot fashion, i.e., using the in situ generated bis(carbamate) **15** (from equal molar amounts of the corresponding *meso*-diol and tosyl isocyanate) directly in the desymmetrization reaction with the palladium catalyst of ligand **5a** (entry 1). It was found that ligand **5a** showed remarkably high activity and very good enantioselectivity in the titled reaction, affording the oxazolidinone **16** in 61% isolated yield and 89% ee within two hours at 0 °C. Encouraged by this result, we turned to studying the reactions with isolated biscarbamate **15** as substrate. Under the otherwise identical conditions, the isolated yield of the reaction using pure biscarbamate **15** was much higher (quantitative) than that of the one-pot reaction using in situ prepared **15**, albeit the enantioselectivity of the product **16** remained at the same level (entry 2 vs. entry 1). Remarkably, the flexible ligand **5b** exhibited a drastically lowered enantiodiscriminating capability for this reaction, produced almost racemic product in 81% yield under the otherwise identical conditions (entry 3). This can be rationalized by the fact that ligand **5b** is considerably more flexible than **5a** owing to the presence of extra methylene moieties, which should in principle give rise to more transition state structures (or conformations) competing with each other,[5a] thus leading to the significantly poorer enantiocontrol performance. It is interesting to note that for the 'invertomer' ligands **6a**,**b**, the reaction proceeded in high yields and moderate ee values, but the sense of product configuration was opposite to that obtained by the 'normal' ligand **5a** (entries 4, 5 vs. entries 1, 2). This phenomenon has also been reported for ligand **4** and its analogue in the literature,[18] indicating that the asymmetric induction capabilities of these ligands are highly sensitive to the subtle changes in the ligand structures. Finally, the temperature effect on the enantioselectivity of this reaction was examined using ligands **5a** and **6a** (entries 6–11). In both series, the reaction rate decreases with the lowering of the temperature, accompanied by an enhancement of the enantioselectivity (entries 2 vs. 6–8 or entries 4, 9–11). When the reaction was conducted at –60 °C, high enantioselectivity up to 97% ee was achieved with ligand **5a** (entry 8), whereas the 'invertomer' ligand **6a** gave the allylic product **16** in 78% ee with an opposite configuration (entry 11).

In summary, new C_2-symmetric chiral bisphosphine ligands with different skeleton flexibilities (**5a** vs. **5b**) or different amide linkages (**6a**,**b** vs. **5a**,**b**) were synthesized starting from enantiopure *anti*-head-to-head coumarin dimer (–)-**1**. These Trost-type ligands were tested as chiral inducers in Pd-catalyzed desymmetrization of *meso*-cyclopent-2-en-1,4-diol biscarbamate (**15**), affording the allylic substitution product oxazolidinone **16** in excellent yields and various degrees of enantioselectivities (up to 97% ee with ligand **5a**). The enantiodiscrimination capabilities of this type of ligands were found to be highly sensitive to the subtle changes in the ligand structures, with

Table 1 Pd-Catalyzed Enantioselective Intramolecular Cyclization of *meso*-Biscarbamate **15** Using Trost-Type Bisphosphine Ligands **5** and **6**[a]

Entry	Ligand	Temp (°C)	Time (h)	Yield (%)[c]	ee (%)[d]	Config[e]
1[b]	**5a**	0	2	61	89	3*R*,4*S*
2	**5a**	0	2	>99	88	3*R*,4*S*
3	**5b**	0	2	81	8	3*S*,4*R*
4	**6a**	0	2	>99	63	3*S*,4*R*
5	**6b**	0	2	>99	35	3*S*,4*R*
6	**5a**	–15	12	>99	93	3*R*,4*S*
7	**5a**	–30	12	98	94	3*R*,4*S*
8	**5a**	–60	18	90	97	3*R*,4*S*
9	**6a**	–15	12	92	78	3*S*,4*R*
10	**6a**	–30	12	>99	75	3*S*,4*R*
11	**6a**	–60	18	89	78	3*S*,4*R*

[a] Molar ratio of **15**:Et_3N:[π-allylPdCl]$_2$:ligand = 1:1:0.025:0.06; ligands **5**, **6** used were all of *S*,*S*,*S*,*S* configuration.
[b] One-pot reaction.
[c] Isolated yield.
[d] The ee values were determined by HPLC on a Chiralcel AD column.
[e] The absolute configurations of **16** were assigned to be 3*R*,4*S* and 3*S*,4*R*, respectively, based on their optical rotations.

the rigid **5a** giving considerably superior performance to its flexible counterpart **5b**. This fact suggests that a broad space of structural modifications is still possible for further ligand optimizations. Extension of the substrate scope in this reaction and utilization of the present catalyst system in other types of asymmetric reactions are currently in progress in this laboratory.

Acknowledgment

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(9) **Synthesis of (*S*,*S*,*S*,*S*)-5a.**
Anhyd CH_2Cl_2 (4 mL) was added to the diamine **11a** (0.06 g, 0.2 mmol), 2-(diphenylphosphino)benzoic acid (0.15 g, 0.48 mmol), DCC (0.12 g, 0.6 mmol) and 5 mol% DMAP. The resultant yellow, chalky mixture was stirred at r.t. until TLC indicated complete reaction. The mixture was filtered through Celite to remove dicyclohexylurea, and the filter cake was washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated in vacuo and chromatographed on silica gel with EtOAc–hexane (1:2) as eluent to afford diamide **5a** as an amorphous white solid (0.08 g, 50%). $[\alpha]_D^{20}$ –26.0 (*c* 1.02, $CHCl_3$). IR (KBr): ν = 2930, 2852, 1654, 1628, 1584, 1493, 1460, 1435, 1328, 1245, 1027, 745, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 6 H), 4.42 (d, *J* = 8.4 Hz, 2 H), 5.13 (br, 2 H), 6.15 (d, *J* = 8.4 Hz, 2 H), 6.87–7.51 (m, 36 H). ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = –10.04. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.78, 158.13, 141.06, 140.74, 138.52, 138.35, 137.98, 137.68, 134.97, 134.29, 134.01, 133.74, 130.54, 129.05, 128.81, 128.71, 128.57, 127.17, 126.69, 121.14, 110.66, 55.72, 52.75, 40.29. MS (EI): *m/z* (%) = 305 (100), 285 (45), 306 (29), 56 (28), 91 (25), 57 (24), 147 (24), 277 (20). MS (ESI): *m/z* = 875.1 (100) $[M^+ + 1]$. HRMS (MALDI): *m/z* calcd for $C_{56}H_{49}O_4N_2P_2$ $[M^+ + 1]$: 875.3162; found: 875.3144.

(10) **Synthesis of (*S*,*S*,*S*,*S*)-5b.**
Following the same procedure for the preparation of (*S*,*S*,*S*,*S*)-**5a**, reaction of (*S*,*S*,*S*,*S*)-**11b** with 2-(diphenylphosphino)benzoic acid afforded (*S*,*S*,*S*,*S*)-**5b** as a white solid (yield 78%). $[\alpha]_D^{20}$ –32.2 (*c* 1.04, $CHCl_3$). IR (KBr): ν = 2929, 1627, 1584, 1531, 1492, 1461, 1435, 1245, 1026, 747, 696, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.69–2.73 (m, 2 H), 2.98–3.07 (m, 2 H), 3.25–3.33 (m, 2 H), 3.83 (s, 6 H), 4.30 (d, *J* = 6.6 Hz, 2 H), 6.29 (br, 2 H), 6.78–7.44 (m, 36 H). ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = –8.86. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.50, 157.65, 141.95, 141.61, 137.10, 137.00, 136.30, 136.04, 134.29, 134.23, 134.18, 134.01, 133.90, 130.34, 129.21, 129.05, 128.95, 128.84, 128.79, 128.34, 127.96, 127.92, 127.68, 120.90, 109.82, 55.49, 41.82, 39.52, 36.73. MS (ESI): *m/z* (%) = 903.45 (100) $[M^+ + 1]$. HRMS (FT): *m/z* calcd for $C_{58}H_{52}O_4N_2NaP_2$ $[M^+ + Na]$: 925.3295; found: 925.3277.

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(13) **Synthesis of (*S*,*S*,*S*,*S*)-6a.**
Anhyd $CHCl_3$ (5 mL) was added to the freshly prepared dichloride **8b** (0.2 mmol) and 2-(diphenylphosphino)aniline (0.17 g, 0.6 mmol). The resultant yellow mixture was stirred at r.t. until TLC indicated complete reaction. The mixture was concentrated in vacuo and chromatographed on silica gel with EtOAc–hexane (1:3) as eluent to afford diamide **6a** as an amorphous white solid (0.16 g, 95%). $[a]_D^{20}$ –36.9 (*c* 1.09, $CHCl_3$). IR (KBr): ν = 3302, 1671, 1574, 1506, 1494, 1434, 1289, 1248, 1028, 746, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.66–3.81 (m, 8 H), 4.79–4.89 (m, 2 H), 6.61–7.54 (m, 36 H), 7.90–8.10 (m, 2 H). ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = –21.27. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.59, 157.44, 141.73, 141.47, 135.97, 135.87, 135.19, 135.10, 134.15, 134.10, 133.90, 133.84, 133.65, 130.23, 129.44, 129.18, 129.06, 128.98, 128.15, 127.62, 127.53, 126.97, 126.83, 124.88, 122.68, 120.83, 110.06, 55.76, 55.72, 45.73, 39.53. MS (ESI): *m/z* (%) = 875.5 (100) $[M^+ + 1]$. HRMS (FT): *m/z* calcd for $C_{56}H_{49}O_4N_2P_2$ $[M^+ + 1]$: 875.3162; found: 875.3163.

(14) Following the same procedure for the preparation of **6a**, reaction of **8c** with 2-diphenylphosphino)aniline afforded (*S*,*S*,*S*,*S*)-**6b** as a white solid (yield 80%). $[\alpha]_D^{20}$ –28.7 (*c* 1.00, $CHCl_3$). IR (KBr): ν = 1682, 1575, 1508, 1450, 1434, 1288, 1244, 745, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.70–3.74 (m, 2 H), 4.96–5.01 (m, 4 H), 5.17 (d, *J* = 12.3 Hz, 2 H), 6.68–7.54 (m, 46 H), 7.90–8.10 (m, 2 H). ^{31}P NMR (121.46 MHz, $CDCl_3$): δ = –21.32. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.46, 156.41, 154.96, 141.77, 141.51, 137.54, 136.13, 136.03, 135.10, 135.00, 134.13, 133.87, 133.80, 133.55, 130.44, 130.27, 129.37, 129.04, 128.97, 128.94, 128.90, 128.84, 128.09, 127.92, 127.84, 127.71, 127.21, 127.14, 124.88, 122.81, 121.27, 111.76, 70.24, 70.19, 45.95, 39.70. MS (ESI): *m/z* (%) = 1027.35 (30) $[M^+ + 1]$. HRMS (FT): *m/z* calcd for $C_{68}H_{56}O_4N_2P_2Na$ $[M^+ + Na]$: 1049.3608; found: 1049.3616.

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(17) **A General Procedure for Pd-Catalyzed Intramolecular Cyclization of *meso*-Biscarbamate 15.**
To a Schlenk tube containing $[Pd(C_3H_5)Cl]_2$ (1.3 mg, 0.0036 mmol, 2.5 mol%) and chiral ligand **5a** (0.009 mmol, 6.0 mol%) was added dried THF (2 mL), and the mixture was stirred at r.t. for 30 min. Then, addition of biscarbamate **15** (74.8 mg, 0.15 mmol) was followed by Et_3N (0.024 mL, 0.15 mmol). The resulting clear solution stirred at the indicated temperature for the stated times, and then was quenched with a sat. aq NH_4Cl solution (5 mL). The aqueous phase was extracted with Et_2O, the combined organic phase was separated and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was submitted to flash chromatography on silica gel with hexane–EtOAc (3:1) as eluent to product (3*R*,4*S*)-**16** as a colorless oil in 90% yield. $[\alpha]_D^{20}$ –136.6 (*c* 0.90, $CHCl_3$); 97% ee. IR (KBr): ν = 1771, 1355, 1191, 1172, 1146, 1090, 707, 663, 609, 562, 542 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.67–2.69 (m, 1 H), 2.82–2.84 (m, 1 H), 5.11 (ddd, *J* = 8.3, 5.8, 1.8 Hz, 1 H), 5.29 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.02–6.04 (m, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H). MS (ESI): *m/z* (%) = 279.95 (5) [M^+ + 1]. HRMS (FT): *m/z* calcd for $C_{13}H_{14}NO_4S$ [M^+ + 1]: 280.0638; found: 280.0636. The ee was determined with HPLC on a Chiralcel AD column, flow rate: 1.0 mL/min, *n*-hexane–*i*-PrOH = 85:15, 30.6 min (3*S*,4*R*), 36.6 min (3*R*,4*S*); λ = 254 nm.

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