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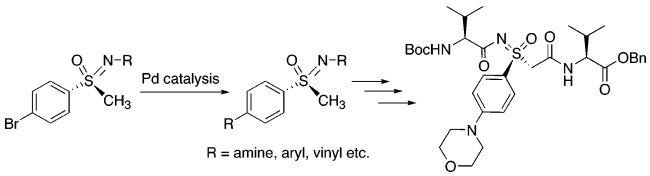
Synthesis and Palladium-Catalyzed Coupling Reactions of Enantiopure *p*-Bromophenyl Methyl Sulfoximine

Gae Young Cho, Hiroaki Okamura, and Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Str. 1, D-52056 Aachen, Germany

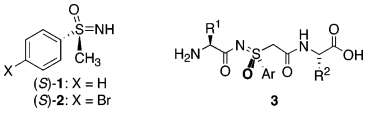
carsten.bolm@oc.rwth-aachen.de

Received November 19, 2004



The asymmetric synthesis and chemical modification of *p*-bromophenyl methyl sulfoximine (**2**) is described. Starting from *p*-bromophenyl menthyl sulfinate (**5**), enantiopure **2** can be obtained in a short reaction sequence involving a well-established substitution reaction followed by stereospecific imination with *O*-mesitylenesulfonylhydroxylamine (MSH). Palladium-catalyzed Buchwald/Hartwig, Suzuki, and Stille coupling reactions allow a broad variation of the sulfoximine aryl group, which is otherwise difficult to achieve. The incorporation of a *p*-morpholino-substituted derivative into a pseudotripeptide demonstrates the applicability of the novel sulfoximine derivatives.

In recent years, sulfoximines have been widely used as building blocks in chiral ligands[1,2] and structural units in pseudopeptides.[3,4] All of those applications require enantiopure sulfoximines.[5] For their preparation two approaches have been commonly used. The first one involves the synthesis of racemic sulfoximines, which are then resolved into their enantiomers.[6] The second relies on the stereospecific imination of enantiopure sulfoxides.[7,8] Both ways have the disadvantage that they are rather limited in scope and that only a narrow range of enantiopure sulfoximines can be accessed. For that reason, many applications of sulfoximines utilize phenyl methyl sulfoximine (**1**) as starting material, since this compound is readily available by the resolution process.[6] Unfortunately, attempts to expand the scope of this type of enantiomer separation remained largely unsuccessful.[9] By the sulfoxide imination route a larger variety of enantiopure sulfoximines can be prepared, but in this case the limitation stems from the fact that each sulfoximine requires the intermediacy of the corresponding sulfoxide, and often those compounds are not easy to prepare in enantiopure form either.[10] In the context of our studies on sulfoximine-containing pseudopeptides (such as **3**)[3] we became particularly interested in the modification of the aryl group of sulfoximines. By varying the electronic (and steric) properties of this substituent we hoped to be able to fine-tune the chemical stability of the pseudopeptides toward peptidases and eventually develop interesting candidates for a prodrug approach. Furthermore, sulfoximine derivatives with modified aryl groups would also be of interest for the synthesis of novel ligands, since in several cases sulfoximines with substituted aryls showed improved properties in catalytic asymmetric reactions compared to their phenyl analogues.[2c,d]



With the intention to develop a more flexible synthetic strategy, which allowed the introduction of a high structural diversity, we focused our attention on the search of a single key intermediate, which should readily be available on a large scale and easily be modified. On that basis, *p*-bromophenyl methyl sulfoximine (**2**) was

* To whom correspondence should be addressed. Fax: (Int.) +49 241 809 2391. Phone: (Int.) +49 241 809 4675.

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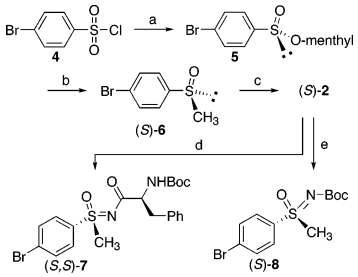
10.1021/jo047940c CCC: $30.25
Published on Web 02/10/2005

SCHEME 1[a]



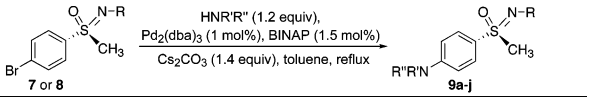
[a] Reagents and conditions: (a) (−)-menthol, $P(OMe)_3$, Et_3N, CH_2Cl_2; (b) CH_3MgBr, toluene, 5 °C; (c) MSH, CH_2Cl_2, rt; (d) (*S*)-Boc-PheOH, DCC, HOBt, CH_2Cl_2 rt; (e) $(Boc)_2O$, NaH, THF, rt.

identified as the target compound. The bromo substituent in the para position was expected to allow the introduction of various other groups by palladium catalysis, and the synthesis of **2** appeared practical, since Naso and coworkers recently prepared the corresponding sulfoxide **6** in enantiopure form.[11] Here, we report on the realization of this concept. Enantiopure **2** was synthesized by a short reaction sequence and subsequent palladium-catalyzed Buchwald/Hartwig,[12] Suzuki,[13] and Stille couplings[14] led to various para-substituted sulfoximines. One of those modified derivatives was finally incorporated into a pseudopeptidic structure.

Following Naso's protocol,[11] *p*-bromophenyl menthyl sulfinate (**5**) was prepared by reaction between *p*-bromobenzenesulfonyl chloride (**4**) and (−)-menthol in the presence of trimethyl phosphite as reducing agent (Scheme 1). The diastereomer with *S*-configuration at the stereogenic center of sulfur was isolated by crystallization and subsequently treated with methylmagnesium bromide affording (*S*)-*p*-bromophenyl methyl sulfoxide [(*S*)-**6**]. Finally, imination of (*S*)-**6** with MSH gave sulfoximine (*S*)-**2** in 86% yield with >99% ee (after crystallization).

To demonstrate the potential introduction of functional groups at the imine nitrogen, (*S*)-**2** was coupled with (*S*)-*N*-Boc-phenylalanine and treated with Boc-anhydride to give amino acid derivative (*S,S*)-**7** (96% yield) and *N*-Boc-protected (*S*)-**8** (74% yield), respectively.[15]

TABLE 1. Palladium-Catalyzed (Buchwald/Hartwig) Aminations of 7 and 8 with Amino Derivatives



entry	educt	HNR′R″	product[a]	yield (%)[b]	entry	educt	HNR′R″	product	yield (%)
1	(*S,S*)-**7**	$BnNH_2$	(*S,S*)-**9a**	98 (88)	6	*rac*-**8**	$BnNH_2$	*rac*-**9f**	94
2[c]	(*S,S*)-**7**		(*S,S*)-**9b**	92 (18)	7[c]	*rac*-**8**		*rac*-**9g**	79
3	(*S,S*)-**7**	$PhNH_2$	(*S,S*)-**9c**	99 (92)	8	*rac*-**8**	$PhNH_2$	*rac*-**9h**	96
4[c]	(*S,S*)-**7**		(*S,S,S*)-**9d**	95 (99)	9	*rac*-**8**		*rac*-**9i**	81
5	(*S,S*)-**7**	$H_2NNHBoc$	(*S,S*)-**9e**	87 (73)[d]	10[c]	*rac*-**8**		*rac*-**9j**[e]	72

[a] In reactions with (*S,S*)-**7** and Cs_2CO_3 diastereomers were formed (see text). [b] Values for reactions with K_2CO_3 instead of Cs_2CO_3 are given in parentheses. Single diastereomers were obtained in these reactions (see text). [c] Reaction conditions: $Pd(OAc)_2$ (2 mol %), BINAP (4 mol %), and Cs_2CO_3 (1.4 equiv), toluene, reflux. [d] A 1:1 mixture of diastereomers was obtained with both bases Cs_2CO_3 and K_2CO_3. [e] As a mixture of diastereomers.

As chemical transformations of **7** and **8** (and with the intention to increase the electron-donating ability of the sulfoximine aryl group) we first investigated palladium-catalyzed (Buchwald/Hartwig) amination reactions (Table 1). Although (*S*)-**8** could be prepared in good yield, racemic **8** was used in most of the reactivity studies. An optimization of various reaction parameters revealed that a combination of $Pd_2(dba)_3$, BINAP, and Cs_2CO_3 was the best system for the coupling reactions with primary amines. For the reactions with morpholine (Table 1, entries 2 and 7) use of $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ proved superior. The same trend was found in reactions of sulfoximine (*S*)-**1** with (*S,S*)-**7** and *rac*-**8** (Table 1, entries 4 and 10). There, with $Pd(OAc)_2$ as metal source the corresponding products (*S,S,S*)-**9d** and *rac*-**9j** were obtained in 95 and 72% yield, respectively. Applying $Pd_2(dba)_3$ in the coupling of (*S,S*)-**7** and sulfoximine (*S*)-**1** gave the product in only 40% yield. Most reactions proceeded to completion within less than 24 h and gave high yields.

Although the yields in the palladium-catalyzed amine couplings were satisfying, another aspect of the transformation was problematic. Thus, under the reaction conditions described above, (*S,S*)-**7** was converted well, but unfortunately a significant amount of epimerization (ca. 40%) occurred. Since the diastereomers could not be separated by column chromatography, the application of the new amino-substituted sulfoximines as building blocks in pseudopeptide synthesis appeared to be critical. On the basis of previous results,[16] we assumed that the loss of the stereochemical integrity involved the amino acid part of the products. To confirm this hypothesis, (*S*)-**9h** [the coupling product of (*S*)-**8** and aniline] was specifically converted into both diastereomers of **9c** (Scheme 2), and a comparison of the product NMR spectra confirmed the assumed formation of (*S,S*)-**9c** and

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(15) The ^1H NMR spectra of sulfoximines coupled to *N*-Boc-phenylalanine indicated the presence of rotamers in a ratio of ca. 6:1. For example, compound (*S,S*)-**7** showed two separate sets of signals at 5.14/4.97 ppm and 4.60−4.55/4.41 ppm for the N*H* and C*H*N protons, respectively. Only one set of signals was found in a spectrum taken at 55 °C (in $CDCl_3$).

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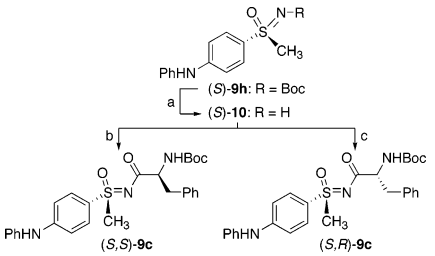
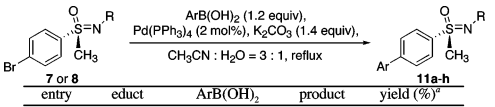
SCHEME 2[a]



[a] Reagents and conditions: (a) TFA/CH_2Cl_2 = 1:3; (b) (*S*)-Boc-Phe-OH, DCC, HOBt, CH_2Cl_2; (c) (*R*)-Boc-Phe-OH, DCC, HOBt, CH_2Cl_2.

TABLE 2. Palladium-Catalyzed (Suzuki) Couplings of 7 and 8 with Boronic Acids



entry	educt	$ArB(OH)_2$	product	yield (%)[a]
1	(*S,S*)-**7**		(*S,S*)-**11a**	79 (>10:1)
2	(*S,S*)-**7**	MeO	(*S,S*)-**11b**	90 (–)[b]
3	(*S,S*)-**7**		(*S,S*)-**11c**	75 (8:1)
4	(*S,S*)-**7**	H_3COC	(*S,S*)-**11d**	70 (>10:1)[c]
5	*rac*-**8**		*rac*-**11e**	95
6	*rac*-**8**	MeO	*rac*-**11f**	90
7	*rac*-**8**		*rac*-**11g**	93
8	*rac*-**8**	H_3COC	*rac*-**11h**	97

[a] The epimer ratio is given in parentheses. [b] Single stereoisomer. [c] After recrystallization dr > 30:1.

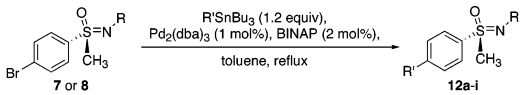
(*S,R*)-**9c** in the palladium-catalyzed coupling starting from (*S,S*)-**7**.

Suspecting that the epimerization was most likely caused by the base (Cs_2CO_3) in toluene under reflux, a brief base screening was performed which revealed that K_2CO_3 could also be applied in the coupling reactions. As shown by the data presented in Table 1 (entries 1−5), a slight decrease in yield had to be accepted in some cases, but most significantly, with K_2CO_3 as base the epimerization was suppressed. Only in the coupling with *tert*-butyl carbazate (entry 5) were two diastereomers of **9e** still observed.

Next, palladium-catalyzed (Suzuki) couplings of **7** and **8** with boronic acids were investigated. For both compounds, a system consisting of $Pd(PPh_3)_4$ and K_2CO_3 in acetonitrile/water (3:1) proved optimal. Under those conditions, the base-induced epimerization of products stemming from (*S,S*)-**7** was reduced to a minimum (Table 2).

Attempts to use $Pd(OAc)_2$, P(*o*-Tol)$_3$, and K_2CO_3 in dioxane in Suzuki-type couplings of **8** gave **11** in lower yields. Interestingly, with the same catalyst system reactions between (*S,S*)-**7** and *p*-biphenylboronic acid led to the coupling product **11a** in 91% yield. In this case, however, more of the undesired epimer [(*S,R*)-**11a**] was formed (dr = 1.6:1). Other reagent combinations {[$Pd(PPh_3)_4$] and Cs_2CO_3 in CH_3CN/water or [$Pd(PPh_3)_4$] and K_2CO_3 in DME/water} led to lower yields of **11a** (69 and 71%, respectively). Furthermore, both the yield and the degree of epimerization appeared to be affected by the ratio of acetonitrile and water. For example, **11c** was obtained as an 11:1 mixture of diastereomers in 42% yield when the ratio of CH_3CN/water was 1:1. In a 3:1 mixture of these solvents, however, the yield of **11c** increased to 75% and the dr was now 8:1 (Table 2, entry 3).

TABLE 3. Palladium-Catalyzed (Stille) Coupling Reactions of 7 and 8

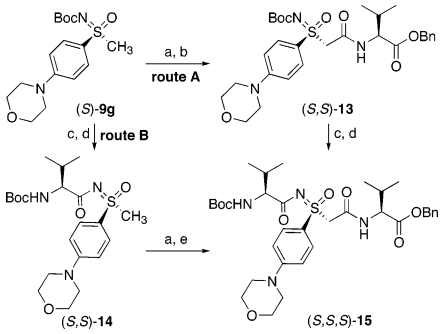


entry	educt	R'$SnBu_3$	product	yield (%)	entry	educt	R'$SnBu_3$	product	yield (%)
1	(*S,S*)-**7**	$SnBu_3$	(*S,S*)-**12a**	97	6	*rac*-**8**	$SnBu_3$	*rac*-**12f**	98
2	(*S,S*)-**7**	Ph–$SnBu_3$	(*S,S*)-**12b**	98	7	*rac*-**8**	Ph–$SnBu_3$	*rac*-**12g**	96
3	(*S,S*)-**7**	OEt, $SnBu_3$	(*S,S*)-**12c**	87	8	*rac*-**8**	Ph—≡—$SnBu_3$	*rac*-**12h**	94
4	(*S,S*)-**7**	Ph—≡—$SnBu_3$	(*S,S*)-**12d**	86	9	*rac*-**8**	$SnBu_3$	*rac*-**12i**	89
5	(*S,S*)-**7**	$SnBu_3$	(*S,S*)-**12e**	91					

To introduce other unsaturated functional groups in the para position of the sulfoximine aryl, palladium-catalyzed Stille coupling reactions with **7** and **8** were examined. As shown in Table 3, all reactions proceeded well giving the corresponding products **12** in high yields (up to 98%). No epimerization was observed. As ligand BINAP was more effective than P(*t*-Bu)$_3$ and P(*o*-Tol)$_3$. In most reactions full conversion was achieved in less than 24 h.

After having established that a broad range of compounds with various substituents in the para position of the sulfoximine aryl group was accessible by this coupling route, the attention was focused on the incorporation of the novel building blocks into pseudopeptidic structures. As representative substrate morpholino-substituted sulfoximine (*S*)-**9g** was chosen. This compound was regarded as particularly interesting, since the amino substitutent in the para position was expected to have a significant electronic effect on the sulfoximine unit. Furthermore, amine protonation could enhance the water solubility of such modified pseudopeptides. To allow a comparison with our previous studies,[3a,b] both α-amino acids next to the new sulfoximine unit in target compound **15** were protected valines. To our surprise, the standard reaction sequence for the synthesis of pseudopeptides of this type (route A) involving carboxylation of (*S*)-**9g** at the sulfoximine methyl group followed by DCC coupling of the resulting ammonium salt with the α-amino acid benzyl ester proved inefficient here giving (*S,S*)-**13** in only 14% yield (Scheme 3). Deprotection of (*S,S*)-**13** at the sulfoximine nitrogen, and subsequent DCC coupling with *N*-Boc-valine gave (*S,S,S*)-**15** in 67% yield over two steps. The alternative reaction sequence for the synthesis of **15**, route B, in which the sulfoximine nitrogen is first connected with *N*-Boc-valine and the carbon chain then extended by carboxylation, also required significant optimization. In this case, the second step was the most critical one. Thus, the Boc cleavage and the subsequent DCC coupling of the resulting NH-sulfoximine (not shown) proceeded well and gave (*S,S*)-**14** in good yield (88% over two steps). The following carboxylation of (*S,S*)-**14** and the subsequent DCC coupling of the resulting ammonium salt with benzyl-protected valine, however, gave (*S,S,S*)-**15** in only 16% yield. After an extensive

SCHEME 3[a]



[a] Reagents and conditions: (a) LCHIPA, THF, −78 °C, then CO_2; (b) (*S*)-H-Val-OBn, DCC, DMAP, CH_2Cl_2; (c) TFA/CH_2Cl_2 = 1:3; (d) (*S*)-Boc-Val-OH, DCC, HOBt, CH_2Cl_2; (e) (*S*)-H-Val-OBn, EEDQ, DMAP, CH_2Cl_2.

search for new conditions (involving the use of other bases such as *n*-BuLi and KHMDS for the metalation before the introduction of CO_2 and the exchange of DCC by EDC and HBTU)[17] it was found that the best yield could be achieved when the standard carboxylation protocol with LCHIPA (lithium cyclohexylisopropyl amide) as base was applied and when the following reaction with the benzyl-protected valine was performed in the presence of EEDQ[17] as coupling reagent. Under these conditions pseudotripeptide (*S,S,S*)-**15** was obtained in 55% yield over two steps [starting from (*S,S*)-**14**].

In conclusion, we have synthesized enantiomerically pure *p*-bromophenyl methyl sulfoximine (**2**) and used it as a key intermediate for the preparation of a variety of novel sulfoximines with a functionalized aryl group. Palladium-catalyzed Buchwald/Hartwig, Suzuki, and Stille coupling reactions gave the corresponding products in high yields. By fine-tuning of the reaction conditions the observed epimerization in couplings of (*S,S*)-**7** was mimimized. Finally, the potential application of these new sulfoximines in the synthesis of pseudotripeptides was demonstrated. Further investigations are now focused on incorporating these products into other peptidic structures and ligands for asymmetric catalysis.

Experimental Section

General Procedure (GP 1) for the Palladium-Catalyzed Amination of (*S,S*)-7 and *rac*-8. A solution of (*S,S*)-**7** (96 mg, 0.2 mmol) or *rac*-**8** (100 mg, 0.3 mmol), amine (1.2 equiv), potassium carbonate or cesium carbonate (1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) or palladium(II) acetate (2 mol %), and *rac*-BINAP (1.5 equiv/Pd) in toluene (0.2 M) was heated to reflux under argon until the starting material completely disappeared (TLC analysis). After the mixture was cooled to room temperature, aq HCl (1 N, ca. 20 mL) and ethyl acetate (ca. 30 mL) were added, and the organic phase was separated, dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (SiO_2).

Synthesis of (*S,S*)-9a. Following GP 1 using (*S,S*)-**7**, benzylamine, K_2CO_3, *rac*-BINAP, and $Pd_2(dba)_3$ gave 89.2 mg (88%) of (*S,S*)-**9a** as a colorless oil (and as a single isomer): $[\alpha]_D$ −32.4 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, J = 8.8 Hz), 7.38−7.15 (m, 10H), 6.62 (d, 2H, J = 8.8 Hz), 5.20 (d, 1H, J = 8.0 Hz), 5.02 (s, br, 1H), 4.55 (dd, 1H, J = 5.8, 13.2 Hz), 4.38 (s, br, 2H), 3.27 (s, 3H), 3.24−3.07 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.7, 155.2, 152.4, 137.6, 137.2, 129.7, 129.1, 128.8, 128.1, 127.7, 127.2, 126.4, 123.8, 112.2, 79.1, 57.4, 47.4, 44.5, 38.7, 28.3; IR (neat, cm^{-1}) 3376, 2978, 1706, 1596; MS (CI, *m/z*) 508 (MH^+). Anal. Calcd for $C_{28}H_{33}N_3O_4S$: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.03; H, 6.59; N, 8.22.

General Procedure (GP 2) for Palladium-Catalyzed Suzuki Coupling of (*S,S*)-7 and *rac*-8. To a mixture of (*S,S*)-**7** (96 mg, 0.2 mmol) or *rac*-**8** (100 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (2 mol %) in acetonitrile (3 mL) was added the aryl boronic acid (1.2 equiv), followed by K_2CO_3 (1.5 equiv) in H_2O (1 mL). The mixture was heated to reflux until the starting material was completely consumed (TLC analysis). After being cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was separated, dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (SiO_2).

Synthesis of 11a. Following GP 2 using (*S,S*)-**7** and 4-biphenylboronic acid gave 89.5 mg (78%) of **11a** as a white solid and as a mixture of diastereomers (>10:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, 2H, J = 8.5 Hz), 7.73−7.71 (m, 2H), 7.67−7.56 (m, 6H), 7.42−7.38 (m, 2H), 7.34−7.29 (m, 1H), 7.23−7.13 (m, 5H), 5.12 (d, 1H, J = 7.7 Hz), 4.57−4.52 (m, 1H), 3.30/3.24 (s, 3H), 3.21−3.04 (m, 2H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 146.5, 141.7, 140.1, 137.6, 137.2, 136.7, 129.7, 128.9, 128.2, 128.0, 127.8, 127.7, 127.0, 126.5, 79.3, 57.4, 44.1, 38.6, 28.3 (signal pairs of diastereomers are indicated by /; two C_{aryl} signals could not be assigned); IR (neat, cm^{-1}) 3375, 2928, 1648, 1501; MS (CI, *m/z*) 555 (MH^+). Anal. Calcd for $C_{33}H_{34}N_2O_4S$: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.67; H, 6.18; N, 4.75.

General Procedure (GP 3) for Palladium-Catalyzed Stille Coupling of (*S,S*)-7 and *rac*-8. Under argon, (*S,S*)-**7** (96 mg, 0.2 mmol) or *rac*-**8** (100 mg, 0.3 mmol), $Pd_2(dba)_3$ (1 mol %), and *rac*-BINAP (2.2 mol %) were dissolved in toluene (2 mL). After addition of the stannane (1.2 equiv), the mixture was heated to reflux until the starting material was completely consumed (TLC analysis). The solution was concentrated in vacuo, and the resulting product was isolated by column chromatography (SiO_2).

Synthesis of (*S,S*)-12a. Following GP 3 using (*S,S*)-**7** and tributyl(vinyl)tin gave 86.4 mg (97%) of (*S,S*)-**12a** as a white solid and as a single isomer: mp 153−154 °C; $[\alpha]_D$ −41.42 (*c* 1.26, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 2H, J = 8.2 Hz), 7.56 (d, 2H, J = 8.5 Hz), 7.29−7.20 (m, 5H), 6.76 (dd, 1H, J = 11.0, 17.6 Hz), 5.92 (d, 1H, J = 17.6 Hz), 5.48 (d, 1H, J = 11.0 Hz), 5.16 (d, 1H, J = 7.4 Hz), 4.61−4.56 (m, 1H), 3.33 (s, 3H), 3.25−3.08 (m, 2H), 1.41(s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 143.2, 137.2, 136.9, 135.0, 129.7, 128.2, 127.5, 127.1, 126.5, 118.4, 79.2, 57.4, 44.1, 38.6, 28.4; IR (neat, cm^{-1}) 3384, 2930, 1623, 1525; MS (CI, *m/z*) 429 (MH^+). Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.33; H, 6.70; N, 6.48.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 "Asymmetric Synthesis by Chemical and Biological Methods" and the "Graduiertenkolleg" (GRK) 440 "Methods in Asymmetric Synthesis". H.O. is grateful to the Alexander von Humboldt Foundation for a postdoctoral fellowship. We also thank Dr. J. Runsink for helping in the interpretation of the ^{1}H NMR spectra.

Supporting Information Available: Full experimental details and spectral characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047940C

(17) HBTU: *O*-Benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate. EEDQ: 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate.