1,6-Asymmetric Induction during the Conjugate Addition of Arylcopper Reagents to a Chiral Sulfinyl-Substituted Pyrrolyl α,β-Unsaturated Amide

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The asymmetric conjugate addition of arylcopper reagents derived from aryl Grignard reagents and copper(I) iodide to a chiral 1-[2-(*p*-tolylsulfinyl)]pyrrolyl cinnamide proceeded smoothly to give (3*R*)-adducts with high diastereoselectivities (≥92% de) in high yields. Conjugate additions either of the cinnamide with the alkyl Grignard reagent–copper(I) iodide combination or of the crotonamide derivative with aryl Grignard reagent–copper(I) iodide gave moderate to good diastereoselectivities. With these sulfinyl pyrrolyl α,β-unsaturated amides, the chiral auxiliary was efficiently recovered without any loss of optical purity after asymmetric conjugate addition.

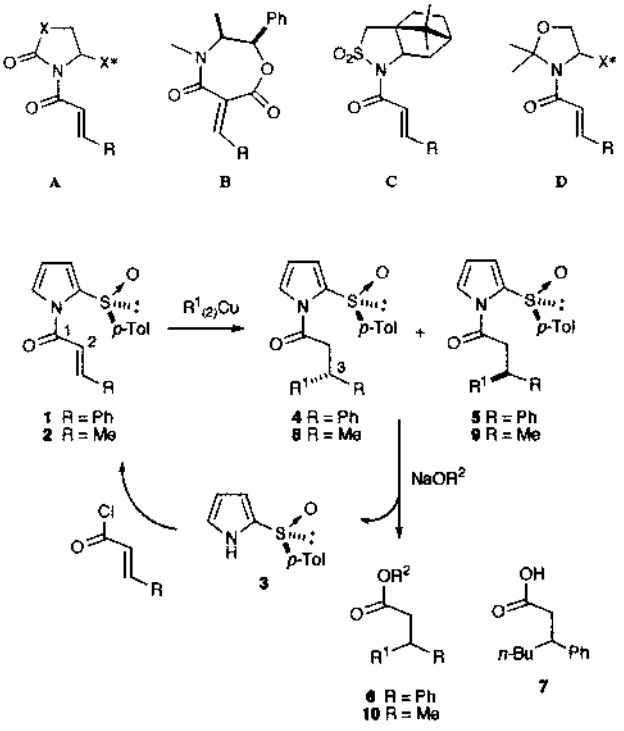
Key words chiral pyrrolyl sulfoxide; conjugate addition; organocopper reagent; remote asymmetric induction; diastereoselectivity

Organocopper conjugate addition to α,β-unsaturated carbonyl systems represents an important area for organic synthesis.[2)] To overcome difficulties encountered with 1,4-addition to unsaturated aldehydes and esters due to competing 1,2-addition and to unsaturated amides owing to low reactivity of the C–C double bond in their carbonyl compounds, Lewis acid- and trimethylsilyl halide-mediated organocopper reagents have been devised. Moreover, to enhance the reactivity of the organocopper reagents, various types of reagents including the higher-order cuprates have also been developed.

Asymmetric organocopper-conjugate addition reactions have been carried out by the use of 1) chiral auxiliaries in either the copper reagent or the α,β-unsaturated carbonyl compound, 2) chiral ligands, 3) a chiral catalyst, or 4) a chiral solvent. Compared with other asymmetric additions of cuprates, methods employing a conjugate acceptor with a chiral auxiliary are most reliable and promising in view of high performance because selectivities in the reactions by other methods are dependent on a large number of factors, including substrate and cuprate structure, solvent,[3)] and the presence of added salts. Asymmetric conjugate addition of organometallic species to α,β-unsaturated enone with a chirally sulfinylated auxiliary has been developed by Posner *et al.*[4)] who reported highly stereoselective 1,4-additions of Grignard reagents with or without a Lewis acid, and organocuprates. On the other hand, studies of asymmetric organocopper-conjugate additions using α,β-unsaturated amides are not common since the amides are essentially inert toward organometallic reagents[5)] unless another activating group is introduced in these molecules. To circumvent the low reactivity of the C–C double bond in these amides, activated amides (X*=chiral auxiliary, X=C, N, O) such as the *N*-enoyl lactams[6)] (A, B) and the *N*-enoyl sultams[7)] (C), or the use of trimethylsilyl chloride (TMSCl) as an additive for the amide (D)[8)] have been devised to date.

In the course of our studies on asymmetric reactions using chiral sulfoxides, we recently reported the highly diastereoselective Diels–Alder reaction of α,β-unsaturated amides **1** and **2**, which are obtained, respectively, from a chiral sulfinyl auxiliary **3** and (*E*)-cinnamoyl- and crotonoyl chloride.[9)] Encouraged by the excellent results with both the reactivity and the diastereoselectivity of **1** in the cycloaddition, we were intrigued by the conjugate addition of an organocopper reagent to these amides. To evaluate the reactivity and selectivity in organocopper-conjugate addition, we planned the reaction using the α,β-unsaturated amides. Here we describe the diastereoselective conjugate addition of organocopper reagents to **1** and **2** with a remote chiral auxiliary **3**.[10)]

First, we undertook the conjugate addition of methylcopper and dimethyl cuprate derived from methyllithium and copper(I) iodide to cinnamide **1** (Chart 1). The results are



a: R^1 = Me; R^2 = Me; **b**: R^1 = *i*-Pr; R^2 = *i*-Pr; **c**: R^1 = *n*-Bu, R^2 = Me
d: R^1 = *t*-Bu, R^2 = Me; **e**: R^1 = C_2H_3, R^2 = Me; **f**: R^1 = 2-MeC_6H_4, R^2 = Me
g: R^1 = 4-MeC_6H_4, R^2 = Me (for **6**), Et (for **10**); **h**: R^1 = 1-$C_{10}H_7$, R^2 = Me

Chart 1

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Table 1. Conjugate Addition of the Organometallic Reagent to Pyrrolyl Cinnamide **1** at −30 °C in THF

Entry	Organometallic reagent (equimolar)	Additive	(eq used)	Reaction time (h)	Yield (%)[a] of **4a**+**5a**	de (%)[b]
1	MeCu·LiI (4)	—		1.5	0[c]	—
2	MeCu·LiI (4)	TMSCl/TMEDA[d]	5/4.4	1.5	0[c]	—
3	MeCu·LiI (3)	$BF_3 \cdot Et_2O$	3	20	0[c]	—
4	$Me_2CuLi \cdot LiI$ (3)	—		1.5	0[c]	—
5	Me_3Al (3)	$Ni(acac)_2$[e]	0.05	1	(90)	−16
6	MeCu·MgBrI (2)	$AlCl_3$	1	26	32[f]	34
7	MeCu·MgBrI (2)	—		1	74	26
8	$Me_2CuMgBr \cdot MgBrI$ (3)	—		1	96	38

a) Isolated yields (calculated yield on the basis of ^{1}H-NMR analysis in parentheses). A small amount of **3** was also produced. *b*) De, **4a** in excess is epimeric to **5a**, was determined by ^{1}H-NMR analysis of the crude product. The negative sign indicates that the diastereoisomer **5a** in excess is epimeric to **4a**. *c*) Starting material was decomposed to **3**. *d*) TMEDA=tetramethylethylenediamine. *e*) Ni(acac)$_2$=nickel(II) acetylacetonate. The reaction was carried out at 0 °C. The product was obtained in capricious yield. *f*) A considerable amount (≤70%) of starting material **1** was recovered unchanged.

Table 2. Conjugate Addition of the Organocopper Reagent to Pyrrolyl Amide at −30 °C in THF

Entry	Amide	Type of organometallic reagent	(Equimolar)	Reaction time (h)	Yield (%)[a] of **4** (or **8**)+**5** (or **9**)	de (%)[b]
1	**1**	iso-$Pr_2CuMgBr \cdot MgBrI$	(2)	5	54	34[c]
2	**1**	*n*-$Bu_2CuMgBr \cdot MgBrI$	(2)	1.5	80	36[c]
3	**1**	*tert*-$Bu_2CuMgCl \cdot MgClI$	(3)	1	90	52[d]
4	**1**	$(C_2H_3)_2CuMgBr \cdot MgBrI$[e]	(3)	1	80	73[c]
5	**1**	$(2\text{-}MeC_6H_4)Cu \cdot MgBrI$	(2)	1	75	95[d]
6	**1**	$(2\text{-}MeC_6H_4)_2CuMgBr \cdot MgBrI$	(2)	1	76	93[d]
7	**1**	$(4\text{-}MeC_6H_4)Cu \cdot MgBrI$	(3)	1	76	94[c]
8	**1**	$(4\text{-}MeC_6H_4)_2CuMgBr \cdot MgBrI$	(2)	1	71	94[c]
9	**1**	$(1\text{-}C_{10}H_7)Cu \cdot MgBrI$[f]	(2)	1	87	93[d]
10	**1**	$(1\text{-}C_{10}H_7)_2CuMgBr \cdot MgBrI$	(2)	1	79	92[d]
11	**2**	$(2\text{-}MeC_6H_4)_2CuMgBr \cdot MgBrI$	(3)	2	83	78[d]
12	**2**	$(4\text{-}MeC_6H_4)_2CuMgBr \cdot MgBrI$	(3)	2	87	54[c]
13	**2**	$(1\text{-}C_{10}H_7)_2CuMgBr \cdot MgBrI$	(3)	2	79	92[c]

a) Isolated yield. A small amount of **3** was also produced in <10% yield. *b*) De, **4** (or **8**) in excess is epimeric to **5** (or **9**). *c*) Determined by chiral HPLC analysis of **6** (or **10**). Sulfoxides **1** and **2** with 98—100% ee were employed for the reaction. *d*) Determined by ^{1}H-NMR analysis of the crude product. *e*) C_2H_3=vinyl. *f*) 1-$C_{10}H_7$=1-naphthyl.

summarized in Table 1. Attempts to perform the conjugate addition with these cuprates gave no adduct, resulting in decomposition to sulfinyl pyrrole **3** during the reaction. This impasse was not improved with the addition of a Lewis acid[11] such as boron trifluoride or trimethylsilyl halide under some reaction conditions (Table 1, entries 1—4). It has been reported that, in a certain case, nickel-catalyzed conjugate addition of trimethylaluminum is superior to the copper-catalyzed conjugate addition. Unfortunately some attempts of nickel-catalyzed conjugate addition by trimethylaluminum[12] gave no better results, while the diastereoselectivity was reversed (Table 1, entry 5). We next turned to the use of methyl Grignard reagent instead of methyllithium, because higher selectivity was observed using organomagnesium species with more coordinating ability than organolithiums, and the organocuprates generated from Grignard reagent afford better results in diastereoselectivity and yields than the use of the cuprates obtained from organolithiums.[6a] In contrast to the results with the copper reagent derived from organolithium reagent, the copper reagents generated from Grignard reagent underwent conjugate addition smoothly to give the products **4a** and **5a** in good yield. However, two diastereoisomeric products **4a** and **5a** were produced with low diastereoselectivity (Table 1, entries 6—8). Under milder reaction conditions (−70 °C), the reaction was sluggish and gave poor yields. Usually 2—3 equimolar of the organocopper reagent was employed in the reactions in tetrahydrofuran (THF) as solvent. The difference between the alkyl- and the dialkylcopper has no significant influence on the asymmetric induction. Smaller amounts of the reagent led to a prolonged reaction time and gave low yields. Further optimization of the reaction conditions with different additives and/or solvent resulted in low yields and poor diastereoselectivities.

Absolute stereochemistry at the newly created carbon center of the major product **4a** was determined by transformation of **4a** into the known ester **6a** by alcoholysis. At this stage, the sulfinyl auxiliary **3** was recovered without any loss of optical purity. The diastereoisomeric excesses (de's) in these conjugate additions were estimated by the integration of pertinent signals (1.19 and 1.27 ppm for methyls) of **4a** and **5a** in the ^{1}H-NMR spectrum. Enantiomeric excess (ee) values comparable with those of de were obtained by chiral HPLC analysis of **6a**.

Since the Grignard reagent/copper iodide system generally has proven to afford the best results, we decided to use similar conditions for the conjugate addition of other dialkyl-, aryl-, and diarylcopper reagents to **1** (Table 2). The conjugate addition with dialkyl copper reagents gave poor to moderate diastereoselectivities, although the reaction of divinyl cuprate afforded good selectivity (73% de). On the other hand, with arylcopper and diarylcopper reagents generated from Grignard reagents, the reaction of **1** was also complete within a

few hours at −30 °C to afford the product **4f**—**h** as the major product with high diastereoselectivity and in high yields. With the crotonamide **2**, reactions of the diarylcopper reagents gave moderate to good diastereoselectivities.

The diastereoselectivities were determined by ^{1}H-NMR analysis of the crude mixture and/or by chiral HPLC analysis of the resulting ester **6b**—**h** obtained by alcoholysis of the product mixture. Upon alcoholysis, the chiral auxiliary **3** was recovered without loss of optical purity in quantitative yield. For the reactions with the (di)alkylcopper reagent, addition of a cold (−30 °C) solution of **1** and **2** was preferable in the view of the high reproducibility of the diastereoselectivity,[13] while a similar reaction with the (di)aryl copper reagents did not decrease the diastereoselectivity by addition of the substrate at ambient temperature.

The absolute stereochemistry at the newly created carbon center of the major products **4** and **8** was determined by transformation of the adducts into the known esters (**6**, **10**) or the acid **7**, accompanied by efficient removal of the chiral auxiliary **3** without loss of optical purity. In the case of **6g**, the absolute configuration was unequivocally established by X-ray analysis of **4g**. It is assumed that major isomers **4f**, **h**, and **8f** have the same relative stereochemistry as other major products.

An analytical sample for detection of the diastereoisomeric products **4f**—**h** and **5f**—**h** was prepared as follows: deoxygenation of isomerically almost pure products **4f**—**h**, obtained by recrystallization, with Zn/$TiCl_4$ afforded the corresponding sulfide, which was oxidized with *m*-chloroperoxybenzoic acid (*m*-CPBA) to afford **4f**—**h** and the enantiomers of **5f**—**h** as roughly a 1 : 1 mixture (see Experimental section). The diastereoisomeric relationship of **4** with **5** was thus confirmed by this reaction sequence. The diastereoselectivities were estimated by the integration of pertinent signals (methyls and/or arylmethyls) of **4** and **5**, or **8** and **9** in the ^{1}H-NMR spectrum. In some cases, however, diastereoselectivities were estimated by chiral HPLC analysis of **6** and **10** because of inefficient baseline separation of the corresponding signals in the ^{1}H-NMR spectrum.

Although further study is necessary to disclose the reaction mechanism, the high diastereoselectivity observed in the 1,4-addition of arylcopper reagents is consistent with previous proposals.[2,6] Since it is assumed that the conjugate addition takes place *via* the *s-cis* conformation[6] of α,β-unsaturated tertiary amide **1**, a diarylcopper reagent, which would be dimeric,[14] could attack preferentially from the C(3)-*Re* face of transition state A, affording **4** as shown in Fig. 1. As described previously in the stereochemical outcome of the Diels–Alder reaction of **1** (and **2**), some Lewis acids such as ZnX_2 had little chelating effect, except for lanthanoid triflates that have a large ion radii. In a similar manner, with arylcopper reagents (*e.g.*, $Ar_2Cu\cdot MgBr\cdot MgBrI$), the salt MgBrI should coordinate with the sulfinyl oxygen in monodentate form. Alternatively, transition state B, which would arise due to such an intramolecular nonbonded S–O interaction,[15] is also possible; however, the observed diastereoselectivities were not consistent. When the de values obtained for (di)alkylcopper reagents were compared to those observed for (di)arylcopper reagents, a sterically bulky substituent has no significant influence on the asymmetric induction. However, attachment of an aromatic substituent to the β-position

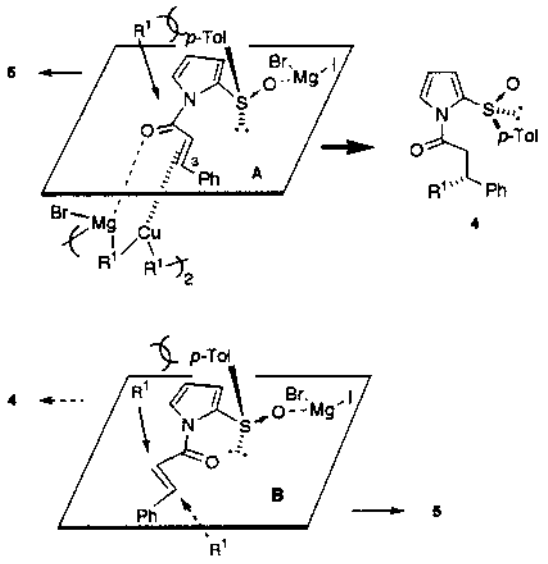

Fig. 1

of the enone moiety (*i.e.*, the cinnamoyl group) and the choice of (di)arylcopper reagents may be important to achieve excellent diastereoselectivity, since the reaction of the crotonoyl derivative **2** resulted in moderate to good selectivities. The high diastereoselectivities in the reaction of **1** with (di)arylcoppers may reflect the π-attractive interaction[16] between the π system of the phenyl portion in the enone moiety and the C=C bond of divinyl- and (di)arylcoppers.

In summary, we have shown that asymmetric 1,4-addition of arylcopper reagents to the α,β-unsaturated amides with a chiral sulfinyl auxiliary proceeds smoothly to give the addition product with high diastereoselectivity in high yield. With this amide, 1,6-asymmetric induction has been achieved, and the chiral auxiliary was recovered without any loss of optical purity.

Experimental

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Boiling points for bulb-to-bulb distillation indicate bath temperature. IR spectra were recorded as film or KBr disk on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H-NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as internal standard, on a JEOL JNM-GX270 (270 MHz) or EX-400 (400 MHz) spectrometer. The following abbreviations are used: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of dd (ddd), multiplet (m), and broad (br). *J*-Values are given in Hz. Mass spectra were taken with a JEOL JMS-D300 or JMS-SX102A spectrometer. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. The symbol S_s expresses that the absolute configuration of the sulfinyl center is *S*. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents on a rotary evaporator under reduced pressure. Dry THF and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. *m*-CPBA was used after purification by washing with phosphate buffer, pH 7.5, according to the literature method.[17] TLC analyses were performed using Merck precoated Silica $60F_{254}$ plates (0.2 mm). Column chromatography was carried out on Merck silica (70—230 mesh) or Merck silica (230—400 mesh). Chiral HPLC analyses were performed using a chiral column (4.6×250 mm). Peak ratios by HPLC were determined with an integrator (Shimadzu Chromatopac C-R6A). 1-Naphthylmagnesium bromide was prepared from 1-bromonaphthalene and magnesium in toluene/THF by the literature method.[18] Methyllithium (diethyl ether solution) and other Grignard reagents (THF solution) were purchased commercially. Grignard reagents were diluted with THF to the appropriate concentrations and titrated[19] prior to use.

Typical Procedure for Preparation of 4 and 5 from 1 (Table 2, Entry

8) To a sonicated suspension of Cu(I)I (248 mg, 1.3 mmol) in dry THF (20 ml) cooled at −30 °C was added *p*-tolylmagnesium bromide (2.6 mmol, 6.6 ml of a 0.39 mol dm^{-3} solution in THF) dropwise. After 0.5 h, a solution of **1**[9] (200 mg, 0.6 mmol, 98% ee) in dry THF (10 ml) was added dropwise, and the yellow solution was stirred for 1 h at the same temperature. The reaction mixture was then quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (30 ml×3). The combined extracts were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography on silica using hexane–AcOEt (3 : 1) as eluent to give a mixture of **4g** and **5g** (182 mg, 71%). Minor diastereoisomer **5g** was not clearly separable in the ^{1}H-NMR spectrum of the product mixture. The product ratio was thus determined by chiral HPLC analysis of the methyl ester **6g** by methanolysis. An analytical sample of **4g** for X-ray analysis was obtained by recrystallization from AcOEt.

For determination of the product ratio by ^{1}H-NMR analysis, an analytical sample of **4** and **5** was prepared by the following sequence. Treatment of the original product mixture of **4a**—**e** and **5a**—**e** (**4** enriched) or an essentially pure **4f**—**h** after recrystallization with Zn–$TiCl_4$ afforded the corresponding sulfide, which was oxidized with *m*-CPBA to produce **4** and *ent*-**5** (the enantiomer of **5**) in a rough ratio of 1 : 1. Since all the ^{1}H-NMR signals of the mixture of **4** and *ent*-**5** were spectroscopically applicable to those of the crude mixture of **4** and **5**, the diastereoisomeric relationship of the product was thus confirmed.

1-[(*R*)-3-Phenyl-3-(*p*-tolyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4g**): mp 187—189 °C (AcOEt); $[\alpha]_D^{21}$ −95.8° (*c*=0.74, $CHCl_3$) for >99% de, 97% ee; ^{1}H-NMR (270 MHz) δ: 2.28 (3H, s, Me), 2.36 (3H, s, Me), 3.39 (1H, dd, *J*=16.6, 7.7, C<u>H</u>H), 3.45 (1H, dd, *J*=16.6, 7.3, CH<u>H</u>), 4.59 (1H, t, *J*=7.3, C<u>H</u>CH_2), 6.39 (1H, t, *J*=3.3, pyrrole), 6.9—7.3 (13H, m, ArH), 7.51 (2H, d, *J*=8.1, *p*-Tol). IR cm^{-1} (KBr) 1720 (C=O), 1037 (S→O). MS *m/z* 427 (M^+), 410, 189, 181, 157. *Anal.* Calcd for $C_{27}H_{25}NO_2S$: C, 75.86; H, 5.90; N, 3.28. Found: C, 75.68; H, 5.90; N, 3.22.

Crystal data for **4g**: M_w=427.56, monoclinic, space group $P2_1$ (No 4), *a*=11.146(1) Å, *b*=7.905(1) Å, *c*=12.860(2) Å, β=92.10(1)°, *V*=1132.3 (2) Å^3, *Z*=2, μ=1.66 cm^{-1}, D_c=1.254 g cm^{-3}, *F*(000)=452.00. Data ware collected with a maximum 2θ of 54.9° at 123 K on a Rigaku RAXIS-RAPID diffractometer with Mo/$K\alpha$ radiation (λ=0.71069 Å). Of a total of 5581 reflection data which were collected, 2763 were unique (R_{int}=0.066); equivalent reflections were merged. Convergence to the final *R* values of *R*=0.092, R_1=0.058, and R_w=0.102 [$I>0.10\sigma(I)$] was achieved using 2557 reflections and 280 variable parameters. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC-153070).

1-[(*S*)-3-Phenyl-3-(*p*-tolyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5g**): ^{1}H-NMR (270 MHz) δ: 2.29 (3H, s, Me), 2.36 (3H, s, Me), 3.40 (2H, d, *J*=7.3, CH_2), 4.59 (1H, t, *J*=7.3, CHC<u>H</u>$_2$), 6.39 (1H, t, *J*=3.3, pyrrole), 6.9—7.3 (13H, m, ArH), 7.51 (2H, d, *J*=8.1, *p*-Tol).

1-[(*R*)-3-Phenylbutanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4a**): mp 103—106 °C (from hexane/AcOEt) (3*R*+3*S* mixture). IR cm^{+1} (KBr) 1706 (C=O), 1043 (S→O). ^{1}H-NMR (400 MHz) δ: 1.19 (3H, d, *J*=7.0, Me), 2.36 (3H, s, Me), 2.86 (1H, dd, *J*=15.8, 8.4, C<u>H</u>H), 3.00 (1H, dd, *J*=15.8, 5.9, CH<u>H</u>), 3.31 (1H, m, CH), 6.38 (1H, t, *J*=3.3, pyrrole), 7.04 (1H, dd, *J*=3.3, 1.8, pyrrole), 7.05—7.30 (8H, m, ArH), 7.61 (2H, d, *J*=8.4, *p*-Tol). Electron impact (EI)-MS *m/z* 351 (M^+), 335, 334, 189, 157, 105. *Anal.* Calcd for $C_{21}H_{21}NO_2S$: C, 71.78; H, 6.02; N, 3.56. Found: C, 71.57; H, 6.22; N, 3.85.

1-[(*S*)-3-Phenylbutanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5a**): ^{1}H-NMR (400 MHz) δ: 1.27 (3H, d, *J*=7.0, Me), 2.39 (3H, s, Me), 2.90 (1H, dd, *J*=16.0, 8.1, C<u>H</u>H), 2.97 (1H, dd, *J*=16.0, 6.6, CH<u>H</u>), 3.32 (1H, m, CH), 6.37 (1H, t, *J*=3.3, pyrrole), 7.04 (1H, dd, *J*=3.3, 1.8, pyrrole), 7.05—7.30 (5H, m, Ph), 7.13 (1H, dd, *J*=3.3, 1.8, pyrrole), 7.18 (2H, d, *J*=8.4, *p*-Tol), 7.56 (2H, d, *J*=8.4, *p*-Tol).

1-[(*S*)-3-Phenyl-4-methylpetanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4b**): mp 77—100 °C (from hexane/AcOEt) (3*R*+3*S* mixture). IR cm^{-1} (KBr) 1715 (C=O), 1039 (S→O). ^{1}H-NMR (270 MHz) δ: 0.69, 0.85 (each 3H, d×2, each *J*=6.8, Me×2), 1.8—1.9 (1H, m, CH), 2.36 (3H, s, Me), 2.85—3.2 (3H, m, CH, CH_2), 6.37 (1H, t, *J*=3.3, pyrrole), 6.9—7.3 (9H, m, ArH), 7.56 (2H, d, *J*=8.1, *p*-Tol). EI-MS *m/z* 379 (M^+), 363, 331, 189, 157, 91. *Anal.* Calcd for $C_{23}H_{25}NO_2S$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.61; H, 6.51; N, 3.68.

1-[(*R*)-3-Phenyl-4-methylpetanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5b**): ^{1}H-NMR (270 MHz) δ: 0.73, 0.94 (3H×2, d×2, each *J*=6.8, Me×2), 1.8—1.9 (1H, m, CH), 2.34 (3H, s, Me), 2.85—3.2 (3H, m, CH, CH_2), 6.36 (1H, t, *J*=3.3, pyrrole), 6.9—7.3 (9H, m, ArH), 7.45 (2H, d, *J*=8.1, *p*-Tol).

1-[(*R*)-3-Phenylheptanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4c**): mp 97—100 °C (from hexane) (3*R*+3*S* mixture). IR cm^{-1} (KBr) 1704 (C=O), 1034 (S→O). ^{1}H-NMR (400 MHz) δ: 0.80 (3H, t, *J*=7.3, Me), 1.0—1.3 (4H, m, CH_2CH_2), 1.5—1.6 (2H, m, CH_2), 2.35 (3H, s, Me), 2.9—3.0 (2H, m, CH_2CO), 3.05—3.2 (1H, m, C<u>H</u>Ph), 6.36 (1H, t, *J*=3.3, pyrrole), 7.0—7.3 (9H, m, ArH), 7.53 (2H, d, *J*=8.1, *p*-Tol). EI-MS *m/z* 393 (M^+), 377, 189, 157, 91. *Anal.* Calcd for $C_{24}H_{27}NO_2S$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.86; H, 6.91; N, 3.53.

1-[(*S*)-3-Phenylheptanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5c**): ^{1}H-NMR (400 MHz) δ: 0.78 (3H, t, *J*=7.3, Me), 1.0—1.3 (4H, m, CH_2CH_2), 1.5—1.6 (2H, m, CH_2), 2.36 (3H, s, Me), 2.9—3.0 (2H, m, CH_2CO), 3.05—3.2 (1H, m, C<u>H</u>Ph), 6.37 (1H, t, *J*=3.3, pyrrole), 7.0—7.3 (9H, m, ArH), 7.60 (2H, d, *J*=8.1, *p*-Tol).

1-[(*S*)-4,4-Dimethyl-3-phenylpentanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4d**): mp 149—151 °C (from hexane/AcOEt) (3*R*+3*S* mixture). IR cm^{-1} (KBr) 1712 (C=O), 1042 (S→O). ^{1}H-NMR (400 MHz) δ: 0.84 (9H, s, Me), 2.35 (3H, s, Me), 3.0—3.2 (3H, m, CH_2, CH), 6.41 (1H, t, *J*=3.5, pyrrole), 6.95—7.4 (9H, m, ArH), 7.51 (2H, d, *J*=8.2, *p*-Tol). EI-MS *m/z* 393 (M^+), 345, 254, 189, 157. *Anal.* Calcd for $C_{24}H_{27}NO_2S$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.01; H, 6.96; N, 3.45.

1-[(*R*)-4,4-Dimethyl-3-phenylpentanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5d**): ^{1}H-NMR (400 MHz) δ: 0.85 (9H, s, Me), 2.32 (3H, s, Me), 3.0—3.2 (3H, m, CH_2CO), 6.39 (1H, t, *J*=3.3, pyrrole), 6.95—7.4 (9H, m, ArH), 7.34 (2H, d, *J*=8.2, *p*-Tol).

1-[(*S*)-3-Phenylpent-4-enoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4e**): mp 115—126 °C (from hexane/AcOEt) (3*R*+3*S* mixture) IR cm^{-1} (KBr) 1723 (C=O), 1044 (S→O). ^{1}H-NMR (400 MHz) δ: 2.37 (3H, s, Me), 3.1 (2H, m, CH_2), 3.9 (1H, m, CH), 4.82 (1H, d, *J*=17.2, CH=), 4.94 (1H, d, *J*=10.4, CH=), 5.86 (1H, ddd, *J*=17.2, 10.4, 7.0, CH=), 6.40 (1H, t, *J*=3.3, pyrrole), 7.0—7.4 (9H, m, ArH), 7.60 (2H, d, *J*=8.1, *p*-Tol). EI-MS *m/z* 363 (M^+), 315, 224, 189, 157, 117. *Anal.* Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.47; H, 5.89; N, 3.79.

1-[(*R*)-3-Phenylpent-4-enoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5e**): ^{1}H-NMR (400 MHz) δ: 2.36 (3H, s, Me), 3.1 (2H, m, CH_2), 3.9 (1H, m, CH), 4.99 (1H, d, *J*=17.2, CH=), 5.06 (1H, d, *J*=10.4, CH=), 5.95 (1H, ddd, *J*=17.2, 10.4, 6.8, CH=), 6.41 (1H, t, *J*=3.3, pyrrole), 7.0—7.4 (9H, m, ArH), 7.55 (2H, d, *J*=8.1, *p*-Tol).

1-[(*R*)-3-Phenyl-3-(*o*-tolyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4f**): mp 122—123 °C (from Et_2O). $[\alpha]_D^{22}$ −171.1° (*c*=0.94, $CHCl_3$) for 94% de, 97% ee. IR cm^{-1} (KBr) 1712 (C=O), 1040 (S→O). ^{1}H-NMR (270 MHz) δ: 2.19 (3H, s, Me), 2.34 (3H, s, Me), 3.39 (1H, dd, *J*=16.3, 7.3, CHC<u>H</u>H), 3.45 (1H, dd, *J*=16.3, 7.7, CHCH<u>H</u>), 4.52 (1H, dd, *J*=7.7, 7.3, C<u>H</u>CH_2), 6.39 (1H, t, *J*=3.3, pyrrole), 7.0—7.3 (13H, m, ArH), 7.46 (2H, d, *J*=8.2, *p*-Tol). EI-MS *m/z* 427 (M^+), 410, 189, 181, 157. *Anal.* Calcd for $C_{27}H_{25}NO_2S$: C, 75.86; H, 5.90; N, 3.28. Found: C, 75.59; H, 5.85; N, 3.40.

1-[(*S*)-3-Phenyl-3-(*o*-tolyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5f**): ^{1}H-NMR (270 MHz) δ: 2.23 (3H, s, Me), 2.37 (3H, s, Me), 3.40 (2H, d, *J*=7.3, CH_2), 4.79 (1H, t, *J*=7.3, C<u>H</u>CH_2), 6.38 (1H, t, *J*=3.3, pyrrole), 7.0—7.3 (13H, m, ArH), 7.53 (2H, d, *J*=8.2, *p*-Tol).

1-[(*R*)-3-Phenyl-3-(1-naphthyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**4h**): mp 77—80 °C (from hexane/EtOAc). $[\alpha]_D^{26}$ −133.2° (*c*=0.93, $CHCl_3$) for 92% de, 97% ee. IR cm^{-1} (KBr) 1718 (C=O), 1040 (S→O). ^{1}H-NMR (270 MHz) δ: 2.32 (3H, s, Me), 3.55 (2H, d, *J*=7.3, CH_2), 5.45 (1H, t, *J*=7.3, C<u>H</u>CH_2), 6.39 (1H, t, *J*=3.3, pyrrole), 7.0—8.0 (16H, m, ArH), 7.71 (2H, d, *J*=8.1, *p*-Tol). EI-MS *m/z* 463 (M^+), 446, 217, 189, 157. *Anal.* Calcd for $C_{30}H_{25}NO_2S$: C, 77.73; H 5.44; N 3.02. Found: C, 77.25; H, 5.41; N, 2.95. EI-HR-MS Calcd for $C_{30}H_{25}NO_2S$ 463.1606. Found 463.1612.

1-[(*S*)-3-Phenyl-3-(1-naphthyl)propanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**5h**): ^{1}H-NMR (270 MHz) δ: 2.37 (3H, s, Me), 3.56 (2H, d, *J*=7.3, CH_2), 5.44 (1H, t, *J*=7.3, C<u>H</u>CH_2), 6.40 (1H, t, *J*=3.3, pyrrole), 7.0—8.0 (16H, m, ArH), 7.73 (2H, d, *J*=8.1, *p*-Tol).

Typical Procedure for Preparation of 8 and 9 from 2 (Table 2, Entry 13) To a sonicated suspension of Cu(I)I (324 mg, 1.7 mmol) in dry THF (20 ml) cooled at −10 °C was added 1-naphthylmagnesium bromide (3.4 mmol, 6.4 ml of a 0.53 mol dm^{-3} solution in toluene/THF) dropwise. After being stirred for 0.5 h at that temperature, the mixture was cooled down to −30 °C, and a solution of **2** (155 mg, 0.57 mmol, >98% ee) in dry THF (3 ml) was added dropwise *via* a cannula. The dark green solution was stirred for 1 h at the same temperature. The reaction mixture was then quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (20 ml×3). The combined extracts were washed with brine, dried, and concentrated. It was difficult to determine the exact de value, which appeared to be >90%, due to inefficient baseline separation in the signals of the ^{1}H-NMR spectrum. The de value (92%) was finally estimated by chiral HPLC analysis of the ester **10h** derived from the crude mixture of **8h** and **9h**. The crude mixture was purified by flash chromatography

on silica using hexane–AcOEt (3 : 1) as eluent to give a mixture of **8h** and **9h** (179 mg, 79%). An analytical sample of **8h** was obtained by recrystallization from hexane–AcOEt. The diastereoisomeric relationship between **8h** and **9h** was confirmed in a manner similar to the reaction sequence for **4** and **5**.

1-[(*S*)-3-(1-Naphthyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**8h**): mp 114—119 °C (from hexane/AcOEt), $[\alpha]_D^{20}$ −104.7° (c=1.51, $CHCl_3$) for >99% ee, >99% de. IR cm^{-1} (KBr) 1714 (C=O), 1041 (S→O). ^{1}H-NMR (400 MHz) δ: 1.43 (3H, d, J=7.0, Me), 2.34 (3H, s, Me), 3.06 (1H, dd, J=16.5, 8.8, CHH), 3.16 (1H, dd, J=16.5, 5.1, CHH), 4.2 (1H, m, CH), 6.39 (1H, t, J=3.3, pyrrole), 7.04 (1H, dd, J=3.3, 1.8, pyrrole), 7.13 (2H, d, J=8.1, *p*-Tol), 7.18 (1H, dd, J=3.3, 1.8, pyrrole), 7.2—8.1 (7H, m, ArH), 7.55 (2H, d, J=8.1, *p*-Tol). EI-MS m/z 401 (M^+), 384, 262, 189, 157, 155, 153. *Anal.* Calcd for $C_{25}H_{23}NO_2S$: C, 74.78; H, 5.77; N, 3.49. Found: C, 74.56; H, 5.96; N, 3.34.

1-[(*R*)-3-(1-Naphthyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**9h**): ^{1}H-NMR (400 MHz) δ: 1.29 (3H, d, J=7.0, Me), 2.37 (3H, s, Me), 2.96 (1H, dd, J=16.3, 9.5, CHH), 3.18 (1H, dd, J=16.3, 3.9, CHH), 4.2 (1H, m, CH), 6.37 (1H, t, J=3.4, pyrrole), 7.04 (1H, dd, J=3.4, 1.7, pyrrole), 7.10 (1H, dd, J=3.4, 1.7, pyrrole), 7.25 (2H, d, J=8.1, *p*-Tol), 7.2—8.1 (7H, m, ArH), 7.65 (2H, d, J=8.1, *p*-Tol).

1-[(*S*)-3-(*o*-Tolyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**8f**): mp 128—130 °C (from hexane/AcOEt) (3*S*+3*R* mixture). IR cm^{-1} (KBr) 1713 (C=O), 1036 (S→O). ^{1}H-NMR (400 MHz) δ: 1.23 (3H, d, J=7.0, Me), 2.24, 2.36 (each 3H, each s, Me), 2.94 (1H, dd, J=16.1, 7.8, C(O)CHH), 2.98 (1H, dd, J=16.1, 6.4, C(O)CHH), 3.3 (1H, m, CH), 6.41 (1H, t, J=3.5, pyrrole), 7.04 (1H, dd, J=3.5, 1.7, pyrrole), 7.05—7.25 (4H, m, ArH), 7.15 (2H, d, J=8.3, *p*-Tol), 7.19 (1H, dd, J=3.5, 1.7, pyrrole), 7.53 (2H, d, J=8.3, *p*-Tol). EI-MS m/z 365 (M^+), 348, 189, 157, 119. *Anal.* Calcd for $C_{22}H_{23}NO_2S$: C, 72.30; H, 6.34; N, 3.83. Found: C, 72.03; H, 6.40; N, 3.73.

1-[(*R*)-3-(*o*-Tolyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**9f**): ^{1}H-NMR (400 MHz) δ: 1.14 (3H, d, J=7.0, Me), 2.32, 2.37 (each 3H, each s, Me), 2.87 (1H, dd, J=16.1, 8.8, C(O)CHH), 2.98 (1H, dd, J=16.1, 4.4, C(O)CHH), 3.3 (1H, m, CH), 6.40 (1H, t, J=3.5, pyrrole), 7.05 (1H, dd, J=3.5, 1.7, pyrrole), 7.05—7.2 (5H, m, ArH), 7.22 (2H, d, J=8.3, *p*-Tol), 7.62 (2H, d, J=8.3, *p*-Tol).

1-[(*S*)-3-(*p*-Tolyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**8g**): mp 107—110 °C (from hexane/AcOEt) (3*S*+3*R* mixture). IR cm^{-1} (KBr) 1709 (C=O), 1041 (S→O). ^{1}H-NMR (400 MHz) δ: 1.24 (3H, d, J=7.0, Me), 2.30 (3H, s, Me), 2.35 (3H, s, Me), 2.89 (1H, dd, J=15.8, 8.1, C(O)CHH), 2.95 (1H, dd, J=15.8, 6.4, C(O)CHH), 3.3 (1H, m, HC-Me), 6.38 (1H, t, J=3.3, pyrrole), 6.9—7.15 (6H, m, ArH), 7.18 (2H, d, J=8.1, *p*-Tol), 7.57 (2H, d, J=8.1, *p*-Tol). EI-MS m/z 365 (M^+), 348, 189, 157, 119. *Anal.* Calcd for $C_{22}H_{23}NO_2S$: C, 72.30; H, 6.34; N, 3.83. Found: C, 72.13; H, 6.44; N, 3.75.

1-[(*R*)-3-(*p*-Tolyl)butanoyl]-2-[(S_s)-(*p*-tolylsulfinyl)]pyrrole (**9g**): ^{1}H-NMR (400 MHz) δ: 1.18 (3H, d, J=7.0, Me), 2.30 (3H, s, Me), 2.36 (3H, s, Me), 2.84 (1H, dd, J=15.8, 8.4, C(O)CHH), 2.99 (1H, dd, J=15.8, 5.5, C(O)CHH), 3.3 (1H, m, HC-Me), 6.38 (1H, t, J=3.3, pyrrole), 6.9—7.15 (6H, m, ArH), 7.22 (2H, d, J=8.1, *p*-Tol), 7.62 (2H, d, J=8.1, *p*-Tol).

Typical Procedure for Alcoholysis of Adduct To a solution of the crude mixture of **4e** and **5e** (74 mg, 0.2 mmol) in dry THF (10 ml) cooled in an ice-bath was added NaOMe (0.25 mmol, 0.25 ml of a 1 mol dm^{-3} solution in MeOH) dropwise. After being stirred for 0.5 h at that temperature, the mixture was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (10 ml×3). The extracts were washed with brine, dried, and concentrated. The crude product was purified by column chromatography on silica using hexane–AcOEt (4 : 1→0 : 1) as eluent to give the ester **6e** (29 mg, 74%) and the sulfinyl pyrrole **3** (38 mg, 90%, >98% ee). **6e**: A colorless oil, bp 130—140 °C (2.7 kPa). $[\alpha]_D^{25}$ −6.3° (c=0.41, $CHCl_3$) for 73% ee. lit.[20] $[\alpha]_D^{24}$ −3.7° (c=0.41, $CHCl_3$) for *S* configuration; lit.[21] $[\alpha]_D$ +3.7° (c=1.07, $CHCl_3$) for *S* configuration. Chiral HPLC: Chiralcel OJ, 254 nm, hexane–2-propanol: 500 : 1; 1.0 ml/min; (*S*): 25.9 min, (*R*): 20.7 min. A racemic sample for chiral HPLC was prepared by the method reported in the literature.[22]

Methyl (*R*)-3-Phenylbutanoate (**6a**): 80% yield. A colorless oil, bp 130—140 °C (2.7 kPa). $[\alpha]_D^{25}$ −14.1° (c=0.51, $CHCl_3$) for 37% ee. Chiral HPLC: Chiralcel OD, 254 nm, hexane–2-propanol: 200 : 1; 0.5 ml/min; (*R*): 15.6 min, (*S*): 44.0 min. lit.[23] $[\alpha]_D^{22}$ +30.3° (c=1.10, $CHCl_3$) for *S* configuration. lit.[24] $[\alpha]_D$ −8.5° (c=2.12, EtOH) for *R* configuration.

Isopropyl (*S*)-3-Phenyl-4-methylpentanoate (**6b**): 87% yield. A colorless oil, $[\alpha]_D^{25}$ −10.5° (c=0.44, $CHCl_3$) for 34% ee. lit.[25] $[\alpha]_D^{20}$ −23° (c=1.19, $CHCl_3$) for 98% ee. Chiral HPLC: Chiralcel OD, 254 nm, hexane–2-propanol: 200 : 1; 0.5 ml/min; (*S*): 9.7 min, (*R*): 10.9 min.

Methyl (*S*)-4,4-Dimethyl-3-phenylpentanoate (**6d**): 80% yield. A colorless oil, bp 140—150 °C (2.7 kPa). $[\alpha]_D^{25}$ −5.7° (c=1.07, $CHCl_3$), for which the ee value was not determined because a racemic sample was inseparable on some chiral HPLC columns. lit.[26] $[\alpha]_D^{25}$ −23.32° (neat) for 97.5% optical purity.

Methyl (*R*)-3-Phenyl-3-(*o*-tolyl)propanoate (**6f**): 97% yield. A colorless oil, bp 175—180 °C (0.6 kPa). $[\alpha]_D^{26}$ −65.6° (c=0.55, $CHCl_3$) for 91% ee. IR cm^{-1} (neat) 1739 (C=O). ^{1}H-NMR (270 MHz) δ: 2.28 (3H, s, Me), 3.03 (2H, d, J=8.1, CH_2), 3.58 (3H, s, OMe), 4.75 (1H, t, J=8.1, CH), 7.1—7.3 (9H, m, ArH). EI-MS m/z 254 (M^+), 181, 179, 165, 83. EI-HR-MS Calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1299. Chiral HPLC: OD-H, 254 nm, hexane–2-propanol: 100 : 1; 1.0 ml/min; (*R*): 10.8 min, (*S*): 9.0 min. A racemic sample for chiral HPLC was prepared under similar reaction conditions by the procedure reported in the literature.[11a)]

Methyl (*R*)-3-Phenyl-3-(*p*-tolyl)propanoate (**6g**): 93% yield. A colorless oil, bp 190—200 °C (0.5 hPa); mp 46.5—47.5 °C. $[\alpha]_D^{22}$ −2.7° (c=0.72, $CHCl_3$) for 97% ee. IR cm^{-1} (neat) 1739 (C=O). ^{1}H-NMR (270 MHz) δ: 2.29 (3H, s, Me), 3.04 (2H, d, J=8.1, CH_2), 3.58 (3H, s, OMe), 4.52 (1H, t, J=8.1, CH), 7.08 (2H, br d, J=8.4, *p*-Tol), 7.12 (2H, br d, J=8.4, *p*-Tol), 7.15—7.32 (5H, m, Ph). EI-MS m/z 254, (M^+), 194, 181, 165. EI-HR-MS Calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1316. Chiral HPLC: Chiralcel OD-H, 254 nm, hexane–2-propanol: 100 : 1; 1 ml/min; (*R*): 7.3 min; (*S*): 11.7 min. A racemic sample for chiral HPLC was prepared under similar reaction conditions by the procedure reported in the literature.[11a)]

Methyl (*R*)-(3-Phenyl)-3-(1-naphthalene)propanoate (**6h**): 91% yield. A colorless oil, $[\alpha]_D^{26}$ −12.5° (c=0.67, $CHCl_3$) for 90% ee. ^{1}H-NMR (270 MHz) δ: 3.17, 3.18 (each 1H, each dd, J=15.6, 8.1; 15.6, 7.3, CH×2), 3.59 (3H, s, Me), 5.38 (1H, t, J=8.1, CH), 7.1—7.5 (9H, m, ArH), 7.7—7.9 (2H, m, ArH), 8.1—8.2 (1H, m, ArH). Chiral HPLC: Chiralcel OD-H, 254 nm, hexane–2-propanol: 100 : 1, 1.0 ml/min; (*R*): 35.4 min, (*S*): 19.6 min. lit.[27] (±)-**6h**: mp 67 °C.

Methyl (*S*)-3-(*o*-Tolyl)butanoate (**10f**): 85% yield. A colorless oil, bp 115—120 °C (4.0 hPa). $[\alpha]_D^{26}$ +12.2° (c=2.4, $CHCl_3$) for 78% ee. IR cm^{-1} (neat) 1739 (C=O). ^{1}H-NMR (400 MHz) δ: 1.25 (3H, d, J=7.0, Me), 2.36 (3H, s, Me), 2.52 (1H, dd, J=15.4, 8.6, CH), 2.62 (1H, dd, J=15.4, 6.4, CH), 3.5 (1H, m, CH), 3.61 (3H, s, OMe), 7.0—7.2 (4H, m, ArH). Chiral HPLC: Chiralpak AS, 245 nm, hexane–2-propanol: 800 : 1, 0.3 ml/min; (*S*): 17.5 min; (*R*): 18.9 min. lit. (±)-**10f**: bp 132—140 °C (12 hPa);[28] bp 82—86 °C (2.0 hPa).[29]

Ethyl (*S*)-3-(*p*-Tolyl)butanoate (**10g**): 84% yield. A colorless oil, $[\alpha]_D^{20}$ +13.6° (c=2.17, $CHCl_3$) for 54% optical purity. lit.[30] $[\alpha]_D$ +25.4° (c=2.17, $CHCl_3$) for 100% ee. lit.[31] $[\alpha]_D$ +25.0° (c=2.17, $CHCl_3$) (bp 130—135 °C (2.0 hPa)).

Methyl (*S*)-3-(1-Naphthyl)butanoate (**10h**): 81% yield. A colorless oil, bp 170—180 °C (3.3 hPa). $[\alpha]_D^{20}$ −7.48° (c=0.81, EtOH) for 92% ee. lit.[32] $[\alpha]_D^{25}$ +4.27° (c=2.9, EtOH) for 60% ee (*R* configuration). lit.[33] $[\alpha]_{365}^{25}$ +36.15° (c=3.02, PhH) (bp 148 °C (2.0 hPa)). Chiral HPLC: Chiralcel OJ, 254 nm, hexane–2-propanol: 499 : 1; 1.0 ml/min; (*R*): 18.9 min; (*S*): 21.8 min. A racemic sample for chiral HPLC was prepared by the method reported in the literature.[34]

(*R*)-3-Phenylheptanoic Acid (7) Ester **6c**[23] obtained in 86% yield was subjected to hydrolysis as follows. A mixture of **6** (51 mg, 0.23 mmol) with aqueous KOH (2.5 ml, 5 mmol, 2 mol dm^{-3} solution) in dioxane (3 ml) was heated at reflux for 6 h. After being cooled, the reaction mixture was acidified with 15% HCl and the aqueous layer was then extracted with Et_2O (10 ml×3). The combined extracts were washed with brine, dried, and concentrated. Flash chromatography on silica using hexane–EtOAc–AcOH (80 : 20 : 1) gave **7** (29 mg, 61%), as a colorless oil, $[\alpha]_D^{20}$ −4.63° (c=1.42, $CHCl_3$) for 30% optical purity. lit.[23] $[\alpha]_D^{22}$ +15.2° (c=1.03, $CHCl_3$) for *S* configuration. lit.[35] $[\alpha]_D^{25}$ −27.8° (neat) for >95% ee.

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