Enantioselective Friedel–Crafts type addition of indoles to nitro-olefins using a chiral hydrogen-bonding catalyst – synthesis of optically active tetrahydro-β-carbolines

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The enantioselective Friedel–Crafts addition of indoles to nitro-olefins using chiral hydrogen-bonding bis-sulfonamides as the catalysts has been developed. The reactions, in the presence of only 2 mol% catalyst, generally proceed in high yields and with enantioselectivities up to 64% ee, and the enantiomeric excess can be improved to >98% ee by recrystallization. Various synthetic transformations of the Friedel–Crafts adducts are demonstrated: the nitro group can easily be reduced to the corresponding amine and the product obtained can undergo a stereocontrolled Pictet–Spengler cyclization to give, for example, enantiopure tetrahydro- β -carbolines. The X-ray structure of the chiral bis-sulfonamides has been determined and based on these structures the mechanism for the stereoselectivity in the reaction is discussed.

Introduction

The addition of heteroaromatic compounds to nitro-olefins, the Friedel–Crafts type Michael reaction, is an important reaction in organic chemistry because valuable synthetic building blocks are obtained by this aromatic electrophilic substitution.^{1,2} These reactions are normally performed in a non-enantioselective fashion using Lewis acid-³ or organo-catalysis.⁴

Recently, it has been shown that hydrogen-bonding interactions play a crucial role in some organocatalytic enantioselective reactions.⁵ However, hydrogen-bonding-catalyzed Friedel– Crafts type alkylation to nitro-olefins is still an unexplored field compared with the enantioselective Michael addition to nitroolefins catalyzed, for example, by L-proline and its derivatives,⁶ chiral urea⁷ and cinchona alkaloids.⁸

Vicinal diamine derivatives attract extensive investigation in asymmetric synthesis due to their important role as a chiral ligand in Lewis acid complexes.⁹ Chiral bis-sulfonamide catalysts are easily prepared from chiral diamines¹⁰ and potentially activate the oxygen atoms of the nitro-olefin *via* a hydrogenbonding interaction with the acidic hydrogen atoms. This paper presents the catalytic, enantioselective Friedel–Crafts type reaction of nitrostyrenes **1** to heteroaromatic compounds **2** catalyzed by chiral vicinal diamine derivatives – bis-sulfonamide (**4**) – as the chiral hydrogen bond donors [eqn. (1)].



The Friedel–Crafts products (3) formed by this reaction are potential starting materials for many biologically active compounds, *e.g.* physostigmine,¹¹ that is isolated from seeds of *Physostigma venenosum* (Calabar beans) and serves as a clinically useful anticholinergic drug.¹²

Results and discussion

The reaction of β -nitrostyrene **1a** with *N*-methyl indole **2a** was studied for different chiral hydrogen bond catalysts under various reaction conditions [eqn. (2)].¹³



Some representative examples for the reaction catalyzed by the bis-sulfonamides **4** are presented in Table 1.

The results in Table 1 show that without catalyst no reaction was observed between β -nitrostyrene **1a** and N-methyl indole 2a (Table 1, entry 1). Using only 2 mol% of 4a as the catalyst, the desired Friedel-Crafts product 3a was obtained with high conversion and up to 26% ee at room temperature (entry 2). Replacement of catalyst 4a with 4b-d led to a clear decrease in both conversion and enantioselectivity of the Friedel-Crafts reaction (entries 3-5), whereas the use of the less acidic hydrogen bond catalyst 4e did not yield the desired product (entry 6). A number of other solvents were also successfully applied to the catalytic enantioselective Friedel-Crafts reaction (entries 7–10). Decreasing the reaction temperature to -24 °C led to an increase of the enantioselectivity of product 3a to 43% ee (entry 11). Lowering the temperature further to -40 °C did not improve the enantioselectivity; however, lower conversion was found (entry 12). Application of a catalyst loading of 1 and 0.5 mol% did not affect the enantioselectivity of the reaction, but longer reaction times were required to maintain the high conversion (entries 13, 14).



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Table 1 Result for the enantioselective Friedel–Crafts reaction of β -nitrosytrene **1a** with *N*-methyl indole **2a** catalyzed by bis-sulfonamides **4** under various reaction conditions

Entry	Catalyst	Solvent	$T/^{\circ}C$	Time/h	Conversion (%) ^a	Ee (%) ^b
1		CH ₂ Cl ₂	rt	16	0	
2	4a	CHCl ₃	rt	18	100	26
3	4b	CHCl ₃	rt	40	64	4
4	4c	CHCl ₃	rt	40	65	0
5	4d	CHCl ₃	rt	40	72	4
6	4 e	CH ₂ Cl ₂	rt	16	0	
7	4 a	CH ₂ Cl ₂	rt	18	100	21
8	4 a	ClCH ₂ CH ₂ CH	rt	18	98	26
9	4 a	THF	rt	18	35	18
10	4a	Toluene	rt	18	95	27
11	4a	CH ₂ Cl ₂	-24	40	85	43
12	4 a	CH ₂ Cl ₂	-40	40	65	43
13 ^c	4 a	Toluene	-24	60	90	46
14^{d}	4 a	CHCl ₃	-24	96	83	47

The 1,2-diphenyltrifluoromethanesulfonamide **4a** catalyzed Friedel–Crafts reaction [eqn. (3)] proceeded well for various nitro-olefins **1** and the results are presented in Table 2.



First, it is worthy to note that the reaction also proceeded well in the presence of 50 mg silica gel as a mild heterogeneous catalyst and that the corresponding product was isolated in 97% yield (Table 1, entry 1).¹⁵ In toluene, nitrostyrene **1a** reacted with *N*-methyl indole **2a** to give 91% yield and up to 50% ee (entry 2). The reaction proceeded with good yield and moderate enantioselectivity for nitrostyrene having electron-withdrawing groups (**1b,c**) (entries 3, 4). However, introduction of electron-rich substituents on the phenyl group in the nitrostyrene **1d** resulted in lower enantioselectivity (entry 5). When the β -substituent was heteroaryl, moderate enantiomeric excess of the corresponding product was observed (entries 6, 7), whereas alkyl-substituents at the β -position of the nitro-olefin dramatically decreased the enantioselectivity of the reaction (entries 8, 9).

Table 2 Results for the catalytic, enantioselective Friedel–Crafts reaction of β -nitro-olefins **1** with *N*-methyl indole **2a** in the presence of 2 mol% **4a** as the catalyst

Entry	Substrate	Solvent	$T/^{\circ}C$	Yield ^a (%)	$Ee^{b,c}$ (%)
1^d	1a	CHCl ₃	rt	97 (3a)	
2	1a	Toluene	-24	91 (3a)	50
3	1b	CHCl ₃	-24	62 (3b)	45 (51)
4	1c	CHCl ₃	-24	53 (3c)	40 (46)
5	1d	CHCl ₃	-24	66 (3d)	32 (33)
6	1e	CHCl ₃	-24	63 (3e)	40 (40)
7	1f	CHCl ₃	-24	77 (3f)	43 (45)
8	1g	Toluene	-24	56 (3g)	11 (23)
9	1ĥ	Toluene	-24	84 (3h)	19 (20)

^{*a*} Isolated yield. ^{*b*} Ee of the isolated product determined by chiral stationary HPLC. ^{*c*} The ee value in parentheses is the enantiomeric excess before column chromatography.¹⁴ ^{*d*} Silica gel 50 mg.

The results for the reaction of β -nitrostyrene **1a** with the indoles **2b–f** catalyzed by 2 mol% **4a** in CHCl₃ [eqn. (4)] are shown in Table 3. It appears from the results in Table 3 that changing from *N*-methyl-protected indole (**2a**) to the unprotected indole (**2b**), the high yield was maintained, but the enantioselectivity was eroded (entry 1). Other indoles with a more bulky protecting group on the nitrogen atom were also applied in the Friedel–Crafts reaction; however, neither the yield nor the enantiomeric excess of the corresponding product was improved (entries 2, 3). However, *N*-methyl-5-methoxy-indole **2e** reacted with **1a** to give **3l** in high yield (87%) and good enantioselectivity (64% ee) (entry 4). According to entry 5 (Table 3) the chloro-substituted indole **2f** does furnish the product **3m** in only 27% yield.



The Friedel–Crafts adducts obtained can be recrystallized in Et₂O/hexane giving these compounds as optically pure, as shown for **3a**. Furthermore, the nitro group in, for example, **3a** can easily be reduced by Pd/C in the presence of NH_4CO_2H , followed by reaction with methyl chloroformate to the corresponding amide **6** in high yield and without significant loss of enantiomeric excess (Scheme 1).

Another important synthetically useful aspect of the reaction is that the corresponding optically enriched Friedel–Crafts adduct can be applied in substrate-controlled Pictet–Spengler

Table 3 Results for the catalytic enantioselective Friedel–Crafts reaction of β -nitro-olefins 1a with methyl indole 2 in the presence of 2 mol% 4a as the catalyst

Entry	Substrate	T∕°C	Yield ^a (%)	Ee ^{<i>b</i>,<i>c</i>} (%)
1	2b	-24	86 (3i)	15 (11)
2	2c	-24	20 (3j)	36 (35)
3	2d	-24	37 (3k)	13 (26)
4	2e	-40	87 (3l)	63 (64)
5	2f	-24	27 (3m)	40 (43)

^{*a*} Isolated yield. ^{*b*} Ee of the isolated product determined by chiral stationary HPLC. ^{*c*} The ee value in parentheses is the enantiomeric excess before column chromatography.¹⁴



Scheme 1 Reduction of the nitro functionality and proection of the amino functionality.

cyclization¹⁶ to form tetrahydro-β-carboline and tetrahydroisoquinoline ring systems, which are key building blocks for natural and synthetic compounds possessing important biological activities.¹⁷ By reduction of **3a** (99% ee) with Pd/C and NH₄CO₂H, followed by treatment with benzaldehyde and TFA, it was found that the original chirality in **3a** controlled the stereochemistry of the newly formed stereogenic center in the acid-catalyzed Pictet–Spengler reaction to give **7** as major diastereoisomer (dr = 5 : 1). Finally, *N*-Boc protection, or reaction with *p*-chlorobenzoyl chloride, gave **8a** or **8b**, respectively, of which the absolute configuration of the latter has been characterized by X-ray analysis (Scheme 2). On the basis of the absolute configuration of the compound obtained in the reaction of **7** with *p*-chlorobenzoyl chloride the stereochemical outcome was assigned to be (*S*).



Scheme 2 Synthetic transformations of optically active 3a.

In an attempt to try to understand the induction of enantioselectivity in the reaction, we have obtained the X-ray structures of the bis-sulfonamide catalysts **4a–d**. The structure of **4a**, which gives the highest enantioselectivity, is shown in Fig. 1.

An interesting change in structure of the bis-sulfonamide catalysts 4a-d, which might be related to the enantioselectivity introduced by the catalysts, is found when comparing the dihedral angle N-C-C-N. This dihedral angle in 4a is found to be 64.2° , whereas the same dihedral angle in 4b is only 19.4°. The use of 4a as the catalyst can give up to 64% ee, whereas 4b provides a nearly racemic product. Furthermore, we have also tried to crystallize a 1 : 1 mixture of the bis-sulfonamide catalyst 4a and nitrostyrene 1a under various conditions in order to try to obtain structural information about the catalyst-substrate



Fig. 1 X-Ray structure of the bis-sulfonamide catalyst 4a.

intermediate.¹⁸ Unfortunately, these crystallization experiments gave separate crystallization of 4a and 1a.

We have used the structure of the bis-sulfonamide catalyst **4a** in an attempt to understand the enantioinduction in the reaction. By the coordination of nitrostyrene as proposed in Fig. 2, the *Re*-face of the alkene is shielded by the phenyl-substituents in the chiral catalyst, leaving the *Si*-face available for approach of the indole. Owing to the relatively large N-C-C-N dihedral angle in catalyst **4a** (64.2°), the amino hydrogen atoms are enantiotopic, whereas for catalyst **4b**, in which the dihedral angle N-C-C-N is only 19.4°, the amino hydrogen atoms are probably 'less enantiotopic' compared to catalyst **4a**. For the interaction of nitrostyrene with catalyst **4b**, the smaller N-C-C-N dihedral angle could then lead to an intermediate in which the substituents at the chiral carbon atoms shield the *Re*-face of the substrate to a lesser extent compared with the bissulfonamide catalyst having a large N-C-C-N dihedral angle.



Fig. 2 Proposed interaction of nitrostyrene with one of the amino hydrogen atoms in bis-sulfonamide catalyst **4a** (the hydrogen atoms in the catalyst are omitted, with the exception of those at the chiral carbon atoms and the nitrogen atoms).

Conclusion

We have shown that chiral hydrogen-bonding bis-sulfonamides are effective catalysts for the enantioselective Friedel–Crafts addition of indoles to nitro-olefins. The reactions proceed with only 2 mol% of the catalyst and the optically active Friedel– Crafts adducts are obtained in high yields and with enantioselectivities up to 64% ee, and the enantiomeric excess can be improved to >98% ee by recrystallization. The scope of the development is demonstrated by reduction of the nitro group to the amine and the stereocontrolled Pictet–Spengler cyclization to give enantiopure tetrahydro- β -carbolines. Furthermore, we have, based on the X-ray structure of the chiral bis-sulfonamides, proposed an intermediate for the reaction.

Experimental

General methods

The ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm relative to CHCl₃ (δ 7.26) for ¹H and relative to the central CDCl₃ resonance (δ 77.0) for ¹³C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotation was measured on a Perkin-Elmer 241 polarimeter. All diastereoselectivities were measured by ¹H NMR spectroscopy on crude reaction mixtures. The enantiomeric excess (ee) of the products was determined by chiral HPLC using Daicel Chiralpak or Daicel Chiralcel columns with hexane–2-propanol as eluent, as indicated in the respective entries.

Materials

β-Nitrosytrene **1a** and its derivatives **1b**–**f**, *N*-methyl indole **2a**, and indole **2b** were purchased commercially and used as received. Bis-sulfonamide catalysts¹⁰ **4a**–**e**, *N*-protected indoles¹⁹ **2c**–**f**, alkyl-substituted nitrostyrenes²⁰ **1g**,**h** were prepared according to literature procedures.

N-(1,2-Diphenyl-2-trifluoromethanesulfonylaminoethyl)-C,C,Ctrifluoromethanesulfonamide (4a). $[a]_{ID}^{T} = +5.2$ (c = 1.0 g per 100 mL, CHCl₃); ¹H NMR (CDCl₃) δ 7.21–7.18 (m, 6H), 6.92–6.90 (m, 4H), 4.71 (s, 2H); ¹³C NMR (CDCl₃) δ 135.1, 129.2, 129.0, 127.0, 63.7. C₁₆H₁₄F₆N₂O₄S₂, M = 476.42, crystallizes in the hexagonal space group *P*6₅22 with unit cell dimensions: a = b = 11.6353(10), c = 52.806(9) Å, V =6191.1(13) Å³ at T = 100 K, Z = 12, μ (MoK α) = 0.336 mm⁻¹. A total of 62 518 reflections were measured, averaging to 5037 independent, $R_{int} = 0.107$; 4303 reflections with $I > 3\sigma I$ were used in the refinements finishing at R = 0.064, $R_w = 0.081$. The absolute configuration was established by refinement according to Rogers²¹ using all 4303 significant reflections including 1598 Bijvoet pairs.

CCDC reference number 272816. See http://www.rsc.org/ suppdata/ob/b5/b505220c/ for crystallographic data in CIF or other electronic format.

N-(1-*tert*-Butyl-3,3-dimethyl-2-trifluoromethanesulfonylaminobutyl)-C,C,C-trifluoromethanesulfonamide (4b). $[a]_{D}^{n}$ = +31.6 (*c* = 0.7 g per 100 mL, MeOH); ¹H NMR (CDCl₃) δ 4.60 (s, br, 2H), 3.72 (d, *J* = 8.0 Hz, 2H), 1.04 (s, 18H); ¹³C NMR (CDCl₃) δ 61.2, 36.1, 26.6. C₁₂H₂₂F₆N₂O₄S₂, *M* = 436.46, crystallizes in the tetragonal space group *P*4₁22 with unit cell dimensions: *a* = *b* = 12.2564(3), *c* = 13.4713(6) Å, *V* = 2023.65(11) Å³ at *T* = 100 K, *Z* = 4, μ(MoKα) = 0.335 mm⁻¹. A total of 61 260 reflections were measured, averaging to 4269 independent, *R*_{int} = 0.954; 3636 reflections with *I* > 3σ*I* were used in the refinements finishing at *R* = 0.044, *R*_w = 0.093. The absolute configuration was established by refinement according to Rogers²¹ using all 3636 significant reflections including 1466 Bijvoet pairs.

CCDC reference number 270611. See http://www.rsc.org/ suppdata/ob/b5/b505220c/ for crystallographic data in CIF or other electronic format.

N-(1,2-Dicyclohexyl-2-trifluoromethanesulfonylaminoethyl)-C,C,C-trifluoromethanesulfonamide (4c). ¹H NMR (CDCl₃) δ 3.39 (s, 2H), 1.84–1.42 (m, 22H); ¹³C NMR (CDCl₃) δ 61.1, 40.1, 31.3, 27.1, 26.1, 26.0, 25.9. $C_{16}H_{26}F_6N_2O_4S_2$, M = 488.53, crystallizes in a layer structure with much disorder, twinning as well as diffuse streaks. The strong spots from one crystal were indexed on a monoclinic unit cell, space group C2/c with unit cell dimensions: a = 20.6214(6), b = 10.7987(7), c = 9.401(3) Å, $V = 2082.1(7) \text{ Å}^3$ at $T = 100 \text{ K}, Z = 4, \mu(\text{MoK}\alpha) = 0.335 \text{ mm}^{-1}$. A total of 33 027 reflections were measured, averaging to 4126 independent, $R_{int} = 0.109$; 2968 reflections with $I > 2\sigma I$ were used in the refinements finishing at R = 0.143, $R_w = 0.169$. The structure within one layer (and thereby of the molecule) is believed to be correct, but the stacking of layers varies within the crystal and from crystal to crystal. Another crystal had its strong reflections indexed on a triclinic cell with a = 9.432(2), b = 10.891(3), c = 11.339(3) Å, $a = 104.54, \beta = 109.09(2), \gamma =$ 90.05(2)°. The disorder-streaks had fewer well defined maxima. It solved in space group P1 to give the same structure within the layer but a different stacking of layers.

CCDC reference number 270612. See http://www.rsc.org/ suppdata/ob/b5/b505220c/ for crystallographic data in CIF or other electronic format.

C,C,C - Trifluoro - N - (2 - trifluoromethanesulonylaminocyclo hexyl)methanesufonamide (4d). $[a]_{D}^{rt} = +1.7 (c = 1.0 \text{ g per})$ 100 mL, MeOH); ¹H NMR (CDCl₃) δ 5.01 (s, 2H), 3.25 (s, 2H), 2.30 (d, J = 13.2 Hz, 2H), 1.84 (d, J = 7.6 Hz, 2H), 1.44–1.31 (m, 4H); ¹³C NMR (CDCl₃) δ 59.3, 34.2, 24.7. C₈H₁₂F₆N₂O₄S₂, M = 397.43, crystallizes in the trigonal space group $P3_221$ with unit cell dimensions: a = b = 14.3841(2), c = 13.9800(4)Å, V = 2504.97(9) Å³ at T = 100 K, Z = 6, μ (MoK α) = 0.398 mm⁻¹. A total of 24180 reflections were measured, averaging to 6270 independent, $R_{int} = 0.081$; 5312 reflections with $I > 2\sigma I$ were used in the refinements finishing at R =0.034, $R_{\rm w} = 0.036$. The structure contains large channels along the unique axis filled by solvent molecules (n-hexane). The solvent is completely disordered forming an infinite chain. The absolute configuration was established by refinement according to Rogers²¹ using all 5312 significant reflections including 2288 Bijvoet pairs.

CCDC reference number 270613. See http://www.rsc.org/ suppdata/ob/b5/b505220c/ for crystallographic data in CIF or other electronic format.

General procedure for the enantioselective Friedel–Crafts type addition to nitro-olefins

To a stirred solution of the nitro-olefin (0.625 mmol) and hydrogen-bonding catalyst (2 mol%) in the solvent (0.5 mL), indole (1.25 mmol) was added and stirred at ambient temperature for 60 h. The reaction mixture was purified by FC on silica gel (Et₂O-pentane) to give the corresponding Friedel–Crafts adduct.

1-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (3a). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 97 : 3, flow rate 1.0 mL min⁻¹, τ_{minor} = 15.1 min; τ_{major} = 17.4 min). $[a]_{D}^{n}$ = +3.1 (c = 1.4 g per 100 mL, CHCl₃, 50% ee); ¹H NMR (CDCl₃) δ 7.47 (d, J = 7.6 Hz, 1H), 7.38–7.23 (m, 7H), 7.10 (m, 1H), 6.88 (s, 1H), 5.21 (t, J = 8.0 Hz, 1H), 5.06 (dd, J = 12.4, 8.0 Hz, 1H), 4.95 (dd, J = 12.4, 8.0 Hz, 1H), 3.75 (s, 3H); ¹³C NMR (CDCl₃) δ 139.3, 137.2, 128.8 (2C), 127.7 (2C), 127.5, 126.5, 126.3, 122.2, 119.4, 118.9, 112.7, 109.5, 79.5, 41.5, 32.8.

3-[1-(4-Bromophenyl)-2-nitroethyl]-1-methyl-1H-indole (3b). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 80 : 20, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 18.6 \text{ min}; \tau_{\text{major}} = 22.5 \text{ min}). [a]_{D}^{\text{m}} = -1.9 (c = 1.4 \text{ g} \text{ per 100 mL}, \text{CHCl}_3, 45\% \text{ ee}); {}^{1}\text{H} \text{NMR} (\text{CDCl}_3) \delta 7.45 (m, 1\text{H}), 7.34–7.22 (m, 6\text{H}), 7.12 (m, 1\text{H}), 6.87 (s, 1\text{H}), 5.16 (t,$ *J*= 8.0 Hz, 1H), 5.03 (dd,*J*= 12.4, 8.0 Hz, 1H), 4.90 (dd,*J* $= 12.4, 8.0 \text{ Hz}, 1\text{H}), 3.75 (s, 3\text{H}); {}^{13}\text{C} \text{NMR} (\text{CDCl}_3) \delta 138.4, 137.2, 131.9 (2C), 129.4 (2C), 126.2 (2C), 122.2, 121.3, 119.5, 118.7, 112.0, 109.6, 79.1, 40.9, 32.8.$

1-Methyl-3-[2-nitro-1-(2-nitrophenyl)ethyl]-1H-indole (3c). The ee was determined by HPLC using a Daicel Chiralcel AD column (hexane–2-propanol = 90 : 10, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 34.8 \text{ min}; \tau_{\text{major}} = 37.8 \text{ min}. [a]_{\text{D}}^{\text{m}} = +74.6 (c = 1.0 \text{ g} \text{ per 100 mL}, \text{CHCl}_3, 40\% \text{ ee}); {}^{1}\text{H} \text{ NMR} (\text{CDCl}_3) \delta 7.86 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.48–7.17 (m, 6\text{H}), 7.00 (m, 1\text{H}), 6.97 (s, 1\text{H}), 5.84 (t, J = 8.0 \text{ Hz}, 1\text{H}), 5.04 (m, 2\text{H}), 3.71 (s, 3\text{H}); {}^{13}\text{C} \text{ NMR} (\text{CDCl}_3) \delta 149.5, 137.2, 133.9, 133.2, 129.8, 128.5, 126.6, 126.3, 125.0, 122.4, 119.7, 118.7, 111.0, 109.5, 78.1, 36.3, 32.9. \text{ HRMS} C_{17}\text{H}_{15}\text{N}_3\text{O}_4 [M + \text{Na}]^+ calculated 348.0960; found 348.0963.$

3-[1-(4-Methoxyphenyl)-2-nitroethyl]-1-methyl-1H-indole (3d). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 95 : 5, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 26.1 \text{ min}; \tau_{\text{major}} = 31.2 \text{ min}). [a]_{D}^{\text{m}} = +2.4 (c = 2.0 \text{ g} \text{ per 100 mL, CHCl}_{3}, 32\% \text{ ee}); ^{1}\text{H NMR (CDCl}_{3}) \delta 7.44 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.31–7.21 (m, 4\text{H}), 7.07 (t, J = 7.2 \text{ Hz}, 1\text{H}), 6.87–6.85 (m, 3\text{H}), 5.13 (t, J = 8.0 \text{ Hz}, 1\text{H}), 5.04 (dd, J = 12.4, 7.6 \text{ Hz}, 1\text{H}), 4.89 (dd, J = 12.0, 8.4 \text{ Hz}, 1\text{H}), 3.78 (s, 3\text{H}), 3.75$

(s, 3H); ¹³C NMR (CDCl₃) δ 158.8, 147.3, 131.3, 128.8 (2C), 126.5, 126.2, 122.2, 119.4, 119.0, 114.2 (2C), 113.1, 109.5, 79.7, 55.2, 40.8, 32.8.

3-(1-Furan-2-yl-2-nitroethyl)-1-methyl-1H-indole (3e). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 95 : 5, flow rate 1.0 mL min⁻¹, τ_{major} = 34.2 min; τ_{minor} = 38.6 min). [a]_Dⁿ = -16.8 (c = 2.0 g per 100 mL, CHCl₃, 40% ee); ¹H NMR (CDCl₃) δ 7.51 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.09 (td, J = 7.6, 0.8 Hz, 1H), 6.94 (s, 1H), 6.27 (dd, J = 3.2, 2.0 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 5.19 (t, J = 8.0 Hz, 1H), 5.00 (dd, J = 12.4, 8.4 Hz, 1H), 4.86 (dd, J = 12.8, 7.2 Hz, 1H), 3.71 (s, 3H); ¹³C NMR (CDCl₃) δ 152.3, 142.2, 137.1, 127.3, 126.1, 122.1, 119.5, 118.8, 110.4, 109.9, 109.6, 107.2, 77.9, 35.6, 32.8. HRMS C₁₅H₁₄N₂O₃ [M + Na]⁺ calculated 293.0902; found 293.0915.

1-Methyl-3-(2-nitro-1-thiophen-2-ylethyl)-1H-indole (3f). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 95 : 5, flow rate 1.0 mL min⁻¹, $\tau_{\text{major}} = 43.5 \text{ min}; \tau_{\text{minor}} = 51.2 \text{ min}). [a]_{\text{D}}^{\text{n}} = +5.2 (c = 1.8 \text{ g per 100 mL}, CHCl_3, 43\% ee); ¹H NMR (CDCl_3) <math>\delta$ 7.51 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.19 (dd, J = 4.8, 1.2 Hz, 1H), 7.10 (td, J = 4.0, 1.2 Hz, 1H), 6.99–6.93 (m, 3H), 5.44 (t, $J = 8.0 \text{ Hz}, 1\text{H}), 5.05–4.94 (m, 2H), 3.76 (s, 3H); ¹³C NMR (CDCl_3) <math>\delta$ 143.1, 139.2, 126.9, 126.6, 126.1, 125.1, 124.8, 122.3, 119.6, 118.9, 112.4, 109.6, 80.1, 36.9, 32.9. HRMS C₁₅H₁₄N₂O₂S [M + Na]⁺ calculated 309.0674; found 309.0684.

3-(1-Cyclohexyl-2-nitroethyl)-1-methyl-1H-indole (3g). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 99 : 1, flow rate 1.0 mL min⁻¹, τ_{major} = 32.6 min; τ_{minor} = 37.4 min). [a]ⁿ_D = -4.5 (c = 1.4 g per 100 mL, CHCl₃, 11% ee); ¹H NMR (CDCl₃) δ 7.61 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.86 (s, 1H), 4.81 (dd, J = 8.0, 6.4 Hz, 1H), 1.87–1.63 (m, 6H), 1.32–0.99 (m, 5H); ¹³C NMR (CDCl₃) δ 136.9, 127.3, 126.8, 121.7, 119.1, 119.0, 111.5, 109.4, 78.5, 41.7, 40.4, 32.7, 31.4, 30.3, 26.2, 26.1, 26.1. HRMS C₁₇H₂₂N₂O₂ [M + Na]⁺ calculated 309.1579; found 309.1585.

1-Methyl-3-(1-nitromethylhexyl)-1H-indole (3h). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 99 : 1, flow rate 1.0 mL min⁻¹, τ_{major} = 17.6 min; τ_{minor} = 19.8 min). $[a]_{12}^{rt}$ = -5.0 (c = 1.5 g per 100 mL, CHCl₃, 19% ee); ¹H NMR (CDCl₃) δ 7.53 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.59–4.49 (m, 2H), 3.72–3.62 (m, 1H), 3.65 (s, 3H), 1.80–1.63 (m, 2H), 1.18 (m, 5H), 0.78–0.73 (m, 4H); ¹³C NMR (CDCl₃) δ 136.9, 137.2, 126.5, 121.8, 119.1, 118.8, 112.4, 109.5, 80.7, 36.2, 32.7, 32.4, 31.6, 26.8, 22.4, 14.0. HRMS C₁₇H₂₂N₂O₂ [M + Na]⁺ calculated 297.1579; found 297.1583.

3-(2-Nitro-1-phenylethyl)-1H-indole (3i). The ee was determined by HPLC using a Daicel Chiralcel AD column (hexane-2-propanol = 90 : 10, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 23.4$ min; $\tau_{\text{major}} = 25.4$ min). $[a]_{\text{c}}^{\text{rt}} = +0.8$ (c = 2.0 g per 100 mL, CHCl₃, 11% ee); ¹H NMR (CDCl₃) δ 8.05 (s br, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.32–7.14 (m, 7H), 7.04 (td, J = 7.6, 1.2 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 5.15 (t, J = 8.0 Hz, 1H), 5.04 (dd, J = 12.4, 8.0 Hz, 1H), 4.90 (dd, J = 12.4, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 139.1, 136.4, 129.0, 128.9, 127.7, 127.5, 127.0, 126.1, 122.7, 121.6, 119.9, 118.9, 114.4, 111.4, 79.5, 41.5.

1-Allyl-3-(2-nitro-1-phenylethyl)-1H-indole (3j). The ee was determined by HPLC using a Daicel Chiralcel AD column (hexane-2-propanol = 95 : 5, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 9.3 \text{ min}; \tau_{\text{major}} = 11.8 \text{ min}). [a]_{\text{D}}^{\text{rt}} = +7.8 (c = 0.9 \text{ g per 100 mL}, \text{CHCl}_3, 36\% \text{ ee}); ^{1}\text{H NMR} (\text{CDCl}_3) \delta 7.46 (d, J = 8.4 \text{ Hz}, 1\text{H}),$

7.35–7.20 (m, 7H), 7.09 (td, J = 7.2, 1.2 Hz, 1H), 6.93 (s, 1H), 6.03–5.93 (m, 1H), 5.23–5.18 (m, 2H), 5.17–5.04 (m, 2H), 4.95 (dd, J = 12.4, 8.8 Hz, 1H), 4.70–4.68 (m, 2H); ¹³C NMR (CDCl₃) δ 139.2, 136.7, 133.1, 128.9 (2C), 127.7 (2C), 127.5, 126.7, 125.2, 122.2, 119.6, 119.1, 117.5, 113.1, 109.9, 79.5, 48.8, 41.5. HRMS C₁₉H₁₈N₂O₂ [M + Na]⁺ calculated 329.1266; found 329.1265.

1-Benzyl-3-(2-nitro-1-phenylethyl)-1H-indole (3k). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 95 : 5, flow rate 1.0 mL min⁻¹, $\tau_{minor} = 15.1 \text{ min}$; $\tau_{major} = 17.7 \text{ min}$). $[a]_D^{rt} = +4.9$ (c = 1.9 g per 100 mL, CHCl₃, 13% ee); ¹H NMR (CDCl₃) δ 7.47 (d, J = 7.6 Hz, 1H), 7.37–7.25 (m, 10H), 7.18 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 7.2 Hz, 2H), 6.99 (s, 1H), 5.29 (s, 2H), 5.22 (t, J = 8.0 Hz, 1H), 5.07 (dd, J = 12.4, 7.6 Hz, 1H), 4.95 (dd, J = 12.4, 8.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 139.2, 137.1, 136.8, 128.8 (2C), 128.7 (2C), 127.7 (2C), 127.6, 127.5, 126.7, 126.6 (2C), 125.6, 122.4, 119.6, 119.1, 113.4, 110.0, 79.5, 50.0, 41.5. HRMS C₂₃H₂₀N₂O₂ [M + Na]⁺ calculated 379.1422; found 379.1427.

5-Methoxy-1-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (31). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 99 : 1, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 63.7 \text{ min}; \tau_{\text{major}} = 68.8 \text{ min}). [a]_{\text{D}}^{\text{rt}} = -12.3 (c = 1.7 \text{ g per} 100 \text{ mL}, \text{CHCl}_3, 63\% \text{ ee}); ^1\text{H NMR (CDCl}_3) \delta 7.36–7.28 (m, 5H), 7.20 (d, <math>J = 8.8 \text{ Hz}, 1\text{H}), 6.93–6.89 (m, 2\text{H}), 6.85 (s, 1\text{H}), 5.16 (t, <math>J = 8.0 \text{ Hz}, 1\text{H}), 5.04 (dd, J = 12.4, 8.0 \text{ Hz}, 1\text{H}), 4.93 (dd, J = 12.4, 8.0 \text{ Hz}, 1\text{H}), 3.80 (s, 3\text{H}), 3.70 (s, 3\text{H}); ¹³C NMR (CDCl}_3) \delta 153.9, 139.3, 132.6, 128.9 (2C), 127.7 (2C), 127.5, 126.8 (2C), 112.2, 112.1, 110.3, 100.8, 79.4, 55.8, 41.4, 33.0.$

6-Chloro-1-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (3m). The ee was determined by HPLC using a Daicel Chiralcel AS column (hexane–2-propanol = 99 : 1, flow rate 1.0 mL min⁻¹, $\tau_{\text{minor}} = 77.6 \text{ min}; \tau_{\text{major}} = 82.8 \text{ min}). [a]_{\text{D}}^{\text{n}} = +2.5 (c = 1.0 \text{ g per} 100 \text{ mL}, \text{CHCl}_3, 40\% \text{ ee}); {}^{1}\text{H} \text{ NMR} (\text{CDCl}_3) \delta 7.35–7.26 (m, 7\text{H}), 7.02 (dd, <math>J = 8.4, 1.2 \text{ Hz}, 1\text{H}), 6.89 (s, 1\text{H}), 5.14 (t, <math>J = 8.0 \text{ Hz}, 1\text{H}), 5.01 (dd, J = 12.4, 8.0 \text{ Hz}, 1\text{H}), 4.91 (dd, J = 12.4, 8.0 \text{ Hz}, 1\text{H}), 3.71 (s, 3\text{H}); {}^{13}\text{C} \text{ NMR} (\text{CDCl}_3) \delta 139.0, 137.6, 129.0 (2C), 128.2, 127.6 (2C), 126.8, 125.1, 120.1, 119.9 (2C), 113.0, 109.5, 79.4, 41.3, 32.9.$

2-(1-Methyl-1H-indol-3-yl)-2-phenylethylamine (5a). 0.39 mmol of optically pure **3a** was dissolved in 10 mL MeOH then 148 mg NH₄CO₂H and 70 mg Pd/C was added and the mixture was stirred for 6 h at 60 °C. After filtered Pd/C, MeOH was removed *in vacuo* and **5a** was obtained without further purification. ¹H NMR (CDCl₃) δ 7.39 (d, J = 8.0 Hz, 1H), 7.27–7.10 (m, 7H), 7.10 (t, J = 7.6 Hz, 1H), 6.82 (s, 1H), 4.17 (t, J = 7.2 Hz, 1H), 3.68 (s, 3H), 3.34 (dd, J = 12.4, 7.2 Hz, 1H), 3.20 (dd, J = 12.4, 7.6 Hz, 1H), 1.50 (s, br, 2H); ¹³C NMR (CDCl₃) δ 143.1, 137.2, 128.5, 128.1, 127.4, 126.3, 126.0, 121.7, 119.4, 118.8, 116.1, 109.2, 47.4, 46.9, 32.7. HRMS C₁₇H₁₈N₂ [M + H]⁺ calculated 251.1548; found 251.1537.

[2-(1-Methyl-1H-indol-3-yl)-2-phenylethyl]carbamic acid methyl ester (6). Compound 5a was dissolved in a mixture of CH_2Cl_2 and saturated Na₂CO₃ solution (1 : 1, 10 mL) and 1.17 mmol methyl chlorofomate was added. The reaction mixture was stirred at room temperature for 24 h and extracted by CH₂Cl₂, dried by Na₂SO₄. The solvent was removed in vacuo. The residue was purified by FC (20% Et₂O-petane) to obtain 6 in 92% yield based on 3a. The ee of 6 was determined by HPLC using a Daicel Chiralcel AS column (hexane-2-propanol = 97 : 3, flow rate 1.0 mL min⁻¹, $\tau_{minor} = 27.4$ min; $\tau_{major} = 32.0$ min). $[a]_{D}^{rt} =$ $+11.0 (c = 1.0 \text{ g per } 100 \text{ mL}, \text{CHCl}_3, 96\% \text{ ee}); ^1\text{H NMR} (\text{CDCl}_3)$ δ 7.51 (d, J = 8.0 Hz, 1H), 7.35–7.21 (m, 7H), 7.06 (t, J = 8.0 Hz, 1H), 6.88 (s, 1H), 4.78 (s br, 1H), 4.44 (t, J = 8.0 Hz, 1H), 4.00 (m, 1H), 3.80–3.70 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H); ¹³C NMR (CDCl₃) & 156.9, 142.1, 137.2, 128.6 (2C), 128.0 (2C), 127.2, 126.7, 126.3, 121.8, 119.5, 119.0, 115.1, 109.2, 52.0, 45.7, 43.1,

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32.7. HRMS $C_{19}H_{20}N_2O_2\ [M+Na]^+$ calculated 331.1422; found 331.1418.

9-Methyl-1,4-diphenyl-1,3,4,9-tetrahydro-\beta-carboline-2carboxylic acid tert-butyl ester (8a). .59 mmol of optically pure **3a** was dissolved in 10 mL MeOH then 224 mg NH₄CO₂H and 80 mg Pd/C was added and the mixture was stirred for 6 h at 60 °C. After filtered Pd/C, MeOH was removed in vacuo. The residue was dissolved in 10 mL CH₂Cl₂ and 0.59 mmol benzaldehyde was added together with 0.5 g MgSO₄. The reaction mixture was stirred at room temperature for 24 h and the suspension was filtered and the solvent was removed in vacuo. The residue was dissolved in 10 mL CH₂Cl₂ and cooled to 0 °C and then 1.18 mmol TFA was added slowly. The reaction mixture was then warmed to room temperature. After being stirred for 40 h, saturated NaHCO3 was added and the mixture was extracted with EtOAc. The combined organic phase was washed by brine, dried with MgSO4 and concentrated. Most of the impurities were removed by FC $(10\% \text{ Et}_2\text{O}-\text{CH}_2\text{Cl}_2)$ to obtain 7 followed by the addition of 220 mg di-tert-butyldicarbonate in 5 mL MeOH. The solution was stirred at room temperature overnight and purified by FC (5% Et₂O-CH₂Cl₂). The ee of 8a was determined by HPLC using a Daicel Chiralcel OD column (hexane–2-propanol = 99: 1, flow rate 1.0 mL min⁻¹, $\tau_{minor} = 7.0$ min; $\tau_{major} = 9.3$ min). $[a]_{D}^{n} = +139.5 (c = 1.3 \text{ g per } 100 \text{ mL}, \text{CHCl}_{3}, 99\% \text{ ee}); ^{1}\text{H NMR}$ $(CDCl_3) \delta$ 7.33–7.09 (m, 13H), 7.02 (t, J = 8.0 Hz, 1H), 6.76 (s, 1H), 4.33 (d, J = 4.0 Hz, 1H), 4.13 (d, J = 13.6 Hz, 1H), 3.46 $(dd, J = 13.6, 4.0 Hz, 1H), 3.43 (s, 3H), 1.06 (s, 9H); {}^{13}C NMR$ $(CDCl_3) \delta$ 154.7, 143.4, 139.7, 137.5, 134.4, 128.6 (2C), 128.4 (2C), 128.1 (2C), 128.0, 128.0 (2C), 126.1, 126.0, 121.6, 119.2 118.8, 110.9, 108.9, 79.6, 52.4, 45.6, 38.8, 30.0, 27.8 (3C). HRMS $C_{29}H_{30}N_2O_2$ [M + Na]⁺ calculated 461.2205; found 461.2211.

(4-Chlorophenyl)-(9-methyl-1,4-diphenyl-1,3,4,9-tetrahydro- β -carbolin-2-yl)methanone (8b). The procedure above was followed to form compound 7 (0.14 mmol) which was dissolved in CH₂Cl₂ with the addition of *p*-chlorobenzoyl chloride (0.14 mmol) and pyridine (0.14 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was purified by FC and crystallized in Et₂O-hexane. ¹H NMR (CDCl₃) δ 7.36-7.34 (m, 7H), 7.26-7.21 (m, 5H), 7.05–6.94 (m, 5H), 6.33 (d, J = 8.0 Hz, 2H), 4.34 (d, J = 3.6 Hz, 1H), 3.76 (dd, J = 13.2, 4.8 Hz, 1H), 3.62 (d, J = 14.0, 4.0 Hz, 1H), 3.50 (s, 3H); $^{13}\mathrm{C}$ NMR (CDCl₃) δ 170.2, 142.0, 139.1, 137.8, 134.6, 134.0, 133.6, 128.9 (2C), 128.6 (4C), 128.5, 128.3 (2C), 128.1 (2C), 127.7 (2C), 126.8, 125.7, 121.9, 119.5, 118.9, 110.0, 109.1, 51.0, 48.7, 39.0, 30.1. C₃₁H₂₅Cl₁N₂O₁, M = 397.43, crystallizes in the trigonal space group $P3_1$ with the unit cell dimensions: a = b = 10.0175(8) Å, c = 21.2378(13)Å, $a = \beta = 90^{\circ}$, $\gamma = 120^{\circ}$, V = 1845.7(2) Å³ at T = 225 K, Z = 3, $\mu = 0.182$ mm⁻¹. A total of 10444 reflections were measured, reduced to 4167 unique reflections after merging with SORTAV^{22a} with an $R_{int} = 0.049$. The refinement of 316 parameters against all data resulted in an $R_w(F^2)$ of 0.09 and a goodness of fit of 0.96. The absolute configuration was established by anomalous dispersion methods and the Flack parameter^{22b} refined to be 0.03(6).

CCDC reference number 268882. See http://www.rsc.org/ suppdata/ob/b5/b505220c/ for crystallographic data in CIF or other electronic format.

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References and notes

- For a review of asymmetric Michael addition to nitroalkenes, see:
 O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877.
- 2 For a review of asymmetric Friedel–Crafts alkylation, see: M. Bandini, M. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, 43, 550.
- See, for example: K. Lee and D. Y. Oh, *Tetrahedron Lett.*, 1988, 29, 2977; T. Ohe and S. Uemura, *Tetrahedron Lett.*, 2002, 43, 1269; K. Manabe, N. Naoyama and S. Kobayashi, *Adv. Synth. Catal.*, 2001, 343, 174; J. S. Yadav, S. Abraham, B. V. S. Reddy and G. Sabitha, *Synthesis*, 2001, 2165; M. Bandini, P. Melchiorre, A. Melloni and A. Umani-Ronchi, *Synthesis*, 2002, 1110; H. Firouzabadi, N. Iranpour and N. Nowrouzi, *Chem. Commun.*, 2005, 789.
- 4 See, for example: M. Bandini, M. Fagioli and A. Umani-Ronchi, *Adv. Synth. Catal.*, 2004, **346**, 545; G. Dessole, R. P. Herrera and A. Ricci, *Synlett*, 2004, 2374.
- 5 For reviews, see, for example: P. M. Pihko, Angew. Chem., Int. Ed., 2004, 43, 2062; P. R. Schreiner, Chem. Soc. Rev., 2003, 32, 289; P. I. Dalko and L. Moisan, Angew. Chem., Int. Ed., 2004, 43, 5138.
- 6 J. M. Betancort and C. F. Barbas, III, Org. Lett., 2001, 3, 3737; A. Alexakis and O. Andrey, Org. Lett., 2002, 4, 3611; J. M. Betancort, K. Sakthivel, R. Thayumanavan and C. F. Barbas, III, Tetrahedron Lett., 2001, 42, 4441; A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, Chem. Commun., 2004, 1808; B. List, P. Pojarliev and H. Martin, Org. Lett., 2001, 3, 2423; D. Enders and A. Seki, Synlett, 2002, 26; W. Wang, J. Wang and H. Li, Angew. Chem., Int. Ed., 2005, 44, 1369.
- 7 T. Okino, Y. Hoashi and Y. Takemoto, J. Am. Chem. Soc., 2003, 125, 12672; Y. Hoashi, T. Yabuta and Y. Takemoto, *Tetrahedron Lett.*, 2004, 45, 9185.
- 8 H. Li, Y. Wang, L. Tang and L. Deng, J. Am. Chem. Soc., 2004, 126, 9906; H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, Angew. Chem., Int. Ed., 2005, 44, 105.
- 9 For a review, see, for example: D. Lucet, T. L. Gall and C. Mioskowski, Angew. Chem., Int. Ed., 1998, 37, 2581.
- 10 Synthesis of chiral diamines, see, for example: E. J. Corey, R. Imwinkelried, S. Pikul and Y. B. Xiang, J. Am. Chem. Soc., 1989, 111, 5493; E. J. Corey, D.-H. Lee and S. Sarshar, *Tetrahedron: Asymmetry*, 1995, 6, 3; S. Roland and P. Mangeney, *Eur. J. Org. Chem*, 2000, 611; S. Rolan and P. Mangeney, *Synthesis*, 1999, 228.
- 11 For review of Calabar alkaloids, see, for example: S. Takano and K. Ogasawara, *Alkaloids*, 1989, **36**, 225; B. Robinson, *Alkaloids*, 1971, **13**, 213.
- 12 For reviews of pharmacology, see: N. H. Greig, X. F. Pei, T. T. Soncrant, D. K. Ingram and A. Brossi, *Med. Res. Rev.*, 1995, 15, 3.
- 13 Other catalysts were also tested for the reaction of 1a with 2a. For example, 10 mol% (*R*)-BINOL at room temperature in CH₂Cl₂ gave no conversion.
- 14 The slightly lower enantiomeric excess after column chromatography is due to fact that some of the Friedel–Crafts reactions never proceed to completion and the remaining starting materials react during the chromatography procedure catalyzed by silica gel to give a racemic product, thereby lowering the enantiomeric excess.
- 15 Silica gel-catalyzed reaction, see, for example: H. Kotsuki, K. Hayashida, T. Shimanouchi and H. Nishizawa, J. Org. Chem., 1996, 61, 984.
- 16 E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797; M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10588 and refs. cited therein.
- 17 K. W. Bentley, Nat. Prod. Rep., 2004, 21, 395 and refs. cited therein.
- 18 For a recent structure of a benzaldehyde-chiral biaryl diol complex, see: A. K. Unni, N. Takenaka, H. Yamamoto and V. H. Rawal, J. Am. Chem. Soc., 2005, 127, 1336.
- 19 C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller and Q. Deng, *Terahedron*, 2001, **57**, 5199; P. J. Beswick, C. S. Greenwood, T. J. Mowlem, G. Nechvatal and D. A. Widdowson, *Terahedron*, 1988, **44**, 7235.
- 20 S. E. Denmark and L. Marcin, J. Org. Chem., 1995, 60, 3221; S. E. Denmark and L. Marcin, J. Org. Chem., 1993, 58, 3580.
- 21 D. Rogers, Acta Crystallogr., Sect. A, 1981, 37, 734.
- 22 (a) R. H. Blessing, J. Appl. Crystallogr., 1989, 22, 396; (b) H. D. Flack, Acta Crystallogr., Sect. A, 1983, 39, 876.