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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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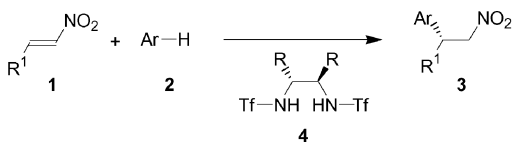
The enantioselective Friedel–Crafts addition of indoles to nitro-olefins using chiral hydrogen-bonding bis-sulfonamides as the catalysts has been developed. The reactions, in the presence of only 2 mol% catalyst, generally proceed in high yields and with enantioselectivities up to 64% ee, and the enantiomeric 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 nitro-olefins catalyzed, for example, by L-proline and its derivatives,[6] chiral urea[7] 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 diamines[10] and potentially activate the oxygen atoms of the nitro-olefin *via* a hydrogen-bonding 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)].

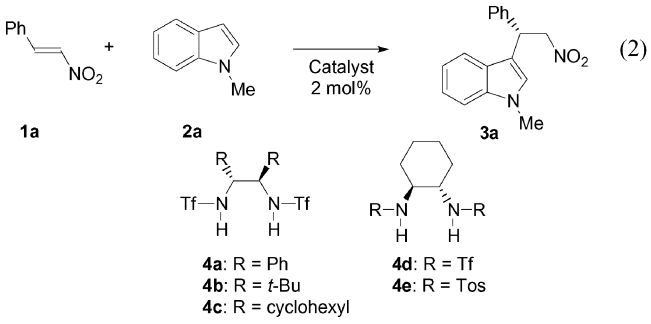


(1)

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]



(2)

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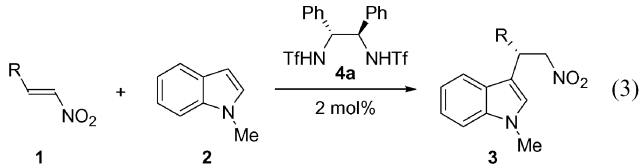
Table 1 Result for the enantioselective Friedel–Crafts reaction of β-nitrosytrene **1a** with *N*-methyl indole **2a** catalyzed by bis-sulfonamides **4** under various reaction conditions

Entry	Catalyst	Solvent	*T*/°C	Time/h	Conversion (%)[a]	Ee (%)[b]
1	—	CH_2Cl_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	**4e**	CH_2Cl_2	rt	16	0	—
7	**4a**	CH_2Cl_2	rt	18	100	21
8	**4a**	$ClCH_2CH_2Cl$	rt	18	98	26
9	**4a**	THF	rt	18	35	18
10	**4a**	Toluene	rt	18	95	27
11	**4a**	CH_2Cl_2	−24	40	85	43
12	**4a**	CH_2Cl_2	−40	40	65	43
13[c]	**4a**	Toluene	−24	60	90	46
14[d]	**4a**	$CHCl_3$	−24	96	83	47

[a] Determined by ^{1}H NMR. [b] Determined on crude samples by chiral stationary HPLC. [c] 1 mol% catalyst. [d] 0.5 mol% catalyst.

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.



(3)

a: R = Ph
b: R = *p*-Br-Ph
c: R = *o*-NO_2-Ph
d: R = *p*-OMe-Ph
e: R = 2-furanyl
f: R = 2-thiophenyl
g: R = cyclohexyl
h: R = *n*-pentyl

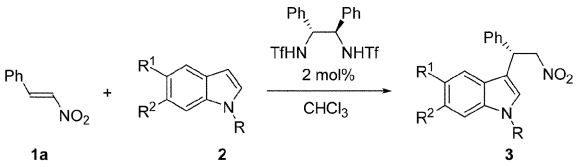
First, it is worthy to note that the reaction also proceeded well in the presence of 50 mg silica gel as a mild heterogeneous catalyst and that the corresponding product was isolated in 97% yield (Table 1, entry 1).[15] In toluene, nitrostyrene **1a** reacted with *N*-methyl indole **2a** to give 91% 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*/°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	**1h**	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 $CHCl_3$ [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-methoxyindole **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.



(4)

2b: R = R^1 = R^2 = H
2c: R = allyl, R^1 = H, R^2 = H
2d: R = Bn, R^1 = H, R^2 = H
2e: R = Me, R^1 = OMe, R^2 = H
2f: R = Me, R^1 = H, R^2 = Cl

3i: R = R^1 = R^2 = H
3j: R = allyl, R^1 = H, R^2 = H
3k: R = Bn, R^1 = H, R^2 = H
3l: R = Me, R^1 = OMe, R^2 = H
3m: R = Me, R^1 = H, R^2 = Cl

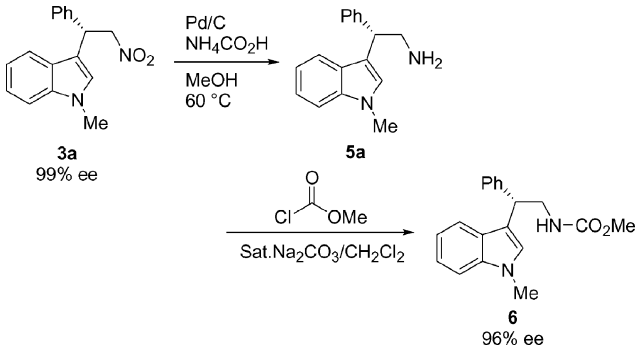
The Friedel–Crafts adducts obtained can be recrystallized in Et_2O/hexane giving these compounds as optically pure, as shown for **3a**. Furthermore, the nitro group in, for example, **3a** can easily be reduced by Pd/C in the presence of NH_4CO_2H, followed by reaction with methyl chloroformate to the 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

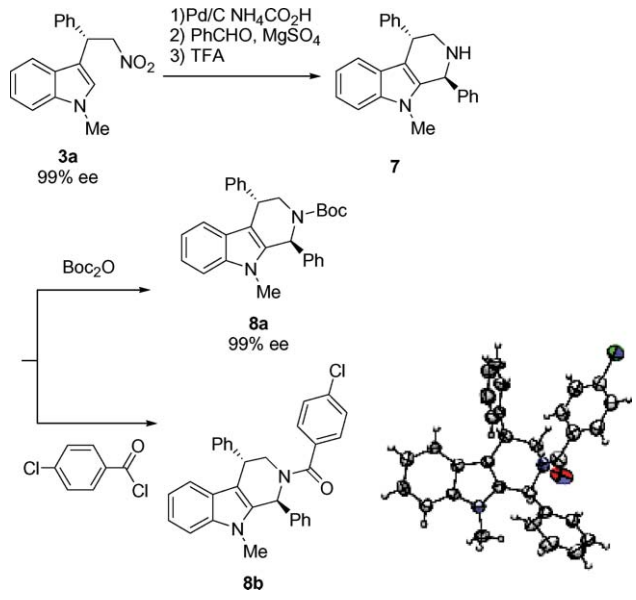
Entry	Substrate	*T*/°C	Yield[a] (%)	Ee[b,c] (%)
1	**2b**	−24	86 (**3i**)	15 (11)
2	**2c**	−24	20 (**3j**)	36 (35)
3	**2d**	−24	37 (**3k**)	13 (26)
4	**2e**	−40	87 (**3l**)	63 (64)
5	**2f**	−24	27 (**3m**)	40 (43)

[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.

cyclization[16] 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 NH_4CO_2H, 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

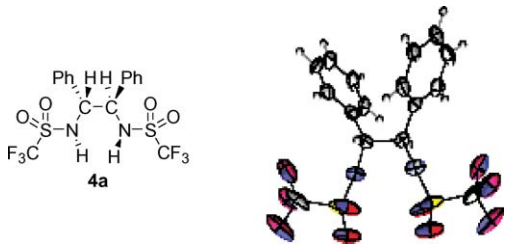


Fig. 1 X-Ray structure of the bis-sulfonamide catalyst **4a**.

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 bis-sulfonamide catalyst having a large N–C–C–N dihedral angle.

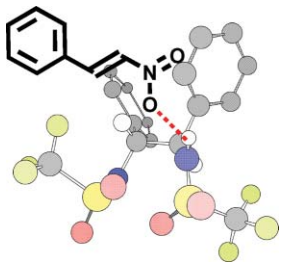


Fig. 2 Proposed interaction of nitrostyrene with one of the amino hydrogen atoms in bis-sulfonamide catalyst **4a** (the hydrogen atoms in the catalyst are omitted, with the exception of those at the chiral carbon atoms and the nitrogen atoms).

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 ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26) for ^{1}H and relative to the central $CDCl_3$ resonance (δ 77.0) for ^{13}C 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 ^{1}H 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 catalysts[10] **4a**–**e**, *N*-protected indoles[19] **2c**–**f**, alkyl-substituted nitrostyrenes[20] **1g**,**h** were prepared according to literature procedures.

***N*-(1,2-Diphenyl-2-trifluoromethanesulfonylaminoethyl)-C,C,C-trifluoromethanesulfonamide (4a).** $[a]_D^{rt} = +5.2$ ($c = 1.0$ g per 100 mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.21–7.18 (m, 6H), 6.92–6.90 (m, 4H), 4.71 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 135.1, 129.2, 129.0, 127.0, 63.7. $C_{16}H_{14}F_6N_2O_4S_2$, $M = 476.42$, crystallizes in the hexagonal space group $P6_522$ with unit cell dimensions: $a = b = 11.6353(10)$, $c = 52.806(9)$ Å, $V = 6191.1(13)$ Å^3 at $T = 100$ K, $Z = 12$, μ(MoKα) = 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 Rogers[21] 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-trifluoromethanesulfonyl-aminobutyl)-C,C,C-trifluoromethanesulfonamide (4b).** $[a]_D^{rt} = +31.6$ ($c = 0.7$ g per 100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.60 (s, br, 2H), 3.72 (d, $J = 8.0$ Hz, 2H), 1.04 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 61.2, 36.1, 26.6. $C_{12}H_{22}F_6N_2O_4S_2$, $M = 436.46$, crystallizes in the tetragonal space group $P4_122$ with unit cell dimensions: $a = b = 12.2564(3)$, $c = 13.4713(6)$ Å, $V = 2023.65(11)$ Å^3 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 $I > 3\sigma I$ were used in the refinements finishing at $R = 0.044$, $R_w = 0.093$. The absolute configuration was established by refinement according to Rogers[21] 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).** ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 2H), 1.84–1.42 (m, 22H); ^{13}C NMR ($CDCl_3$) 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, $V = 2082.1(7)$ Å^3 at $T = 100$ K, $Z = 4$, μ(MoKα) = 0.335 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, $\alpha = 104.54$, $\beta = 109.09(2)$, $\gamma = 90.05(2)°$. 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). $[a]_D^{rt} = +1.7$ ($c = 1.0$ g per 100 mL, MeOH); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 59.3, 34.2, 24.7. $C_8H_{12}F_6N_2O_4S_2$, $M = 397.43$, crystallizes in the trigonal space group $P3_221$ with unit cell dimensions: $a = b = 14.3841(2)$, $c = 13.9800(4)$ Å, $V = 2504.97(9)$ Å^3 at $T = 100$ K, $Z = 6$, μ(MoKα) = 0.398 mm^{-1}. A total of 24 180 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 $R = 0.034$, $R_w = 0.036$. 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 Rogers[21] 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 (Et_2O–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). $[a]_D^{rt} = +3.1$ ($c = 1.4$ g per 100 mL, $CHCl_3$, 50% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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}, τ_{minor} = 18.6 min; τ_{major} = 22.5 min). $[a]_D^{rt} = -1.9$ ($c = 1.4$ g per 100 mL, $CHCl_3$, 45% ee); ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 1H), 7.34–7.22 (m, 6H), 7.12 (m, 1H), 6.87 (s, 1H), 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 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 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}, τ_{minor} = 34.8 min; τ_{major} = 37.8 min). $[a]_D^{rt} = +74.6$ ($c = 1.0$ g per 100 mL, $CHCl_3$, 40% ee); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, $J = 8.4$ Hz, 1H), 7.48–7.17 (m, 6H), 7.00 (m, 1H), 6.97 (s, 1H), 5.84 (t, $J = 8.0$ Hz, 1H), 5.04 (m, 2H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 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. HRMS $C_{17}H_{15}N_3O_4$ [M + 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}, τ_{minor} = 26.1 min; τ_{major} = 31.2 min). $[a]_D^{rt} = +2.4$ ($c = 2.0$ g per 100 mL, $CHCl_3$, 32% ee); ^{1}H NMR ($CDCl_3$) δ 7.44 (d, $J = 8.4$ Hz, 1H), 7.31–7.21 (m, 4H), 7.07 (t, $J = 7.2$ Hz, 1H), 6.87–6.85 (m, 3H), 5.13 (t, $J = 8.0$ Hz, 1H), 5.04 (dd, $J = 12.4$, 7.6 Hz, 1H), 4.89 (dd, $J = 12.0$, 8.4 Hz, 1H), 3.78 (s, 3H), 3.75

(s, 3H); ^{13}C NMR ($CDCl_3$) 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). $[\alpha]_D^{rt} = -16.8$ (c = 2.0 g per 100 mL, $CHCl_3$, 40% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{15}H_{14}N_2O_3$ [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}, τ_{major} = 43.5 min; τ_{minor} = 51.2 min). $[\alpha]_D^{rt} = +5.2$ (c = 1.8 g per 100 mL, $CHCl_3$, 43% ee); ^{1}H NMR ($CDCl_3$) δ 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 Hz, 1H), 5.05–4.94 (m, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 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 $C_{15}H_{14}N_2O_2S$ [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). $[\alpha]_D^{rt} = -4.5$ (c = 1.4 g per 100 mL, $CHCl_3$, 11% ee); ^{1}H NMR ($CDCl_3$) 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), 4.72 (dd, J = 12.0, 9.6 Hz, 1H), 3.75 (s, 3H), 3.69 (m, 1H), 1.87–1.63 (m, 6H), 1.32–0.99 (m, 5H); ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{22}N_2O_2$ [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). $[\alpha]_D^{rt} = -5.0$ (c = 1.5 g per 100 mL, $CHCl_3$, 19% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{22}N_2O_2$ [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}, τ_{minor} = 23.4 min; τ_{major} = 25.4 min). $[\alpha]_D^{rt} = +0.8$ (c = 2.0 g per 100 mL, $CHCl_3$, 11% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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}, τ_{minor} = 9.3 min; τ_{major} = 11.8 min). $[\alpha]_D^{rt} = +7.8$ (c = 0.9 g per 100 mL, $CHCl_3$, 36% ee); ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 1H), 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); ^{13}C NMR ($CDCl_3$) 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 $C_{19}H_{18}N_2O_2$ [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}, τ_{minor} = 15.1 min; τ_{major} = 17.7 min). $[\alpha]_D^{rt} = +4.9$ (c = 1.9 g per 100 mL, $CHCl_3$, 13% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{23}H_{20}N_2O_2$ [M + Na]$^+$ calculated 379.1422; found 379.1427.

5-Methoxy-1-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (3l). 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_{minor} = 63.7 min; τ_{major} = 68.8 min). $[\alpha]_D^{rt} = -12.3$ (c = 1.7 g per 100 mL, $CHCl_3$, 63% ee); ^{1}H NMR ($CDCl_3$) δ 7.36–7.28 (m, 5H), 7.20 (d, J = 8.8 Hz, 1H), 6.93–6.89 (m, 2H), 6.85 (s, 1H), 5.16 (t, J = 8.0 Hz, 1H), 5.04 (dd, J = 12.4, 8.0 Hz, 1H), 4.93 (dd, J = 12.4, 8.0 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 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}, τ_{minor} = 77.6 min; τ_{major} = 82.8 min). $[\alpha]_D^{rt} = +2.5$ (c = 1.0 g per 100 mL, $CHCl_3$, 40% ee); ^{1}H NMR ($CDCl_3$) δ 7.35–7.26 (m, 7H), 7.02 (dd, J = 8.4, 1.2 Hz, 1H), 6.89 (s, 1H), 5.14 (t, J = 8.0 Hz, 1H), 5.01 (dd, J = 12.4, 8.0 Hz, 1H), 4.91 (dd, J = 12.4, 8.0 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 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 NH_4CO_2H 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. ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{18}N_2$ [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 Na_2CO_3 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 CH_2Cl_2, dried by Na_2SO_4. The solvent was removed *in vacuo*. The residue was purified by FC (20% Et_2O–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}, τ_{minor} = 27.4 min; τ_{major} = 32.0 min). $[\alpha]_D^{rt}$ = +11.0 (c = 1.0 g per 100 mL, $CHCl_3$, 96% ee); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 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,

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-β-carboline-2-carboxylic acid *tert*-butyl ester (8a). .59 mmol of optically pure **3a** was dissolved in 10 mL MeOH then 224 mg NH_4CO_2H 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 CH_2Cl_2 and 0.59 mmol benzaldehyde was added together with 0.5 g $MgSO_4$. 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 CH_2Cl_2 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 $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic phase was washed by brine, dried with $MgSO_4$ and concentrated. Most of the impurities were removed by FC (10% Et_2O–CH_2Cl_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% Et_2O–CH_2Cl_2). 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). $[a]_D^{rt} = +139.5$ ($c = 1.3$ g per 100 mL, $CHCl_3$, 99% ee); ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 CH_2Cl_2 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 Et_2O–hexane. ^{1}H NMR ($CDCl_3$) 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}C NMR ($CDCl_3$) 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. $C_{31}H_{25}Cl_1N_2O_1$, $M = 397.43$, crystallizes in the trigonal space group $P3_1$ with the unit cell dimensions: $a = b = 10.0175(8)$ Å, $c = 21.2378(13)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 1845.7(2)$ Å^3 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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