Diastereoselective Friedel-Crafts Alkylation of Indoles with Chiral α-Phenyl Benzylic Cations. Asymmetric Synthesis of *Anti*-1,1,2-Triarylalkanes

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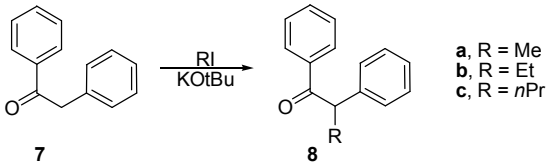
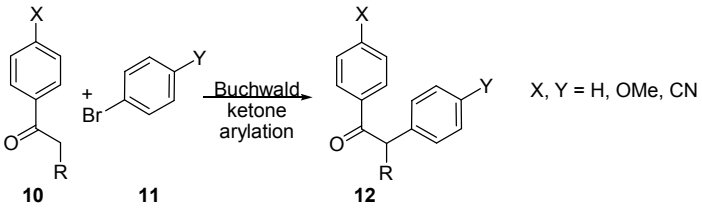
1. General synthetic methods of ketones 8 and 12

A. Method 1. Alkylation



To a solution of deoxybenzoin (**7**) (4 g, 20 mmol) in THF (40 mL) was added potassium *tert*-butoxide (1 M in THF, 22 mmol) (22 mL, 22 mmol) at 0 ºC over the course of 20 minutes. Iodomethane (22 mmol), iodoethane (22 mmol) or 1-iodopropane (22 mmol) was slowly added as to keep the internal temperature < 3 °C. The reaction was then allowed to warm up to room temperature. After aging for 2 hours at room temperature, the reaction mixture was slowly quenched with 2 N HCl (100 mL) and diluted with 200 mL ethyl acetate. The aqueous layer was removed and the organic layer was washed with water (50 mL) and brine (50 mL). The crude ketone was purified by flash chromatography using ethyl acetate/hexanes, MTBE/hexanes or DCM/hexanes.

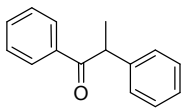
B. Method 2. Ketone Arylation



A mixture of $Pd(OAc)_2$ (0.052 mmol), ligand 2-(dicyclohexylphosphino)-2'-methylbiphenyl (0.098 mmol) or tol-BINAP (0.055 mmol) or dpePhos (0.055 mmol), sodium bis(trimethylsilyl)amide (3.67 mmol) or sodium *tert*-butoxide (5.14 mmol), and the respective phenone **10** (3.67 mmol) were dissolved in toluene (10 mL) or THF (10 mL). The dark solution obtained was degassed via vacuum and N_2 cycles and aged at room temperature for 0.5 h. After this time, a solution of bromobenzene **11** (3.67 mmol) in 3 mL was added. The new mixture was then heated to 60-80 °C for 4-15 h and then room temperature overnight. The slurry obtained was quenched with 10 mL pH 7 buffer solution and extracted with 40 mL ethyl Acetate, washed with water (10 mL) and brine (10 mL). The organic layer was then concentrated to an oil, which was purified via flash chromatography (eluent for aryl nitriles 10% EtOAc in hexanes; for methoxy aryl compounds 40% DCM in hexanes).

2. Spectral and analytical data for 8a-c, 12d-g

1,2-diphenylpropan-1-one (8a)



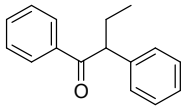
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.49 (m, 1H), 7.39 (m, 2H), 7.32-7.28 (m, 4H), 7.22 (m, 1H), 4.70 (q, *J* = 6.9 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 141.7, 136.8, 133.0, 129.2, 129.0, 128.7, 128.0, 127.1, 48.1, 19.7.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.63, H, 6.88.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; deoxybenzoin, RT = 0.67 min; product, RT = 0.9 min.

1,2-diphenylbutan-1-one (8b)



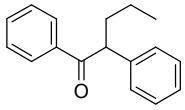
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.49 (m, 1H), 7.40 (m, 2H), 7.33-7.28 (m, 4H), 7.21 (m, 1H), 4.46 (t, *J* = 7.3 Hz, 1H), 2.22 (m, 1H), 1.88 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 139.9, 137.3, 133.0, 129.1, 128.9, 128.7, 128.5, 127.2, 55.7, 27.3, 12.5.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.65, H, 7.48.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; deoxybenzoin, RT = 0.67 min; product, RT = 1.02 min.

1,2-diphenylpentan-1-one (8c)



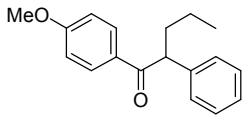
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.49 (m, 1H), 7.40 (m, 2H), 7.35-7.28 (m, 4H), 7.21 (m, 1H), 4.58 (t, *J* = 7.1 Hz, 1H), 2.18 (m, 1H), 1.85 (m, 1H), 1.42-1.22 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 140.1, 137.3, 133.0 129.0, 128.8, 128.7, 128.5, 127.1, 53.6, 36.4, 21.1, 14.3.

Anal. Calcd for $C_{17}H_{18}O \cdot 0.1\ H_2O$: C, 85.03; H, 7.64. Found: C, 85.22, H, 7.63.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; deoxybenzoin, RT = 0.74 min; product, RT = 1.2 min.

1-(4-methoxyphenyl)-2-phenylpentan-1-one (12d)



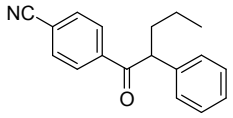
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 7.98 (m, 2H), 7.34-7.26 (m, 4H), 7.20 (m, 1H), 6.87 (m, 2H), 4.53 (t, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 2.17 (m, 1H), 1.82 (m, 1H), 1.40-1.20 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 163.4, 140.5, 131.1, 130.2, 129.0, 128.4, 127.0, 113.9, 55.6, 53.2, 36.4, 21.1, 14.3.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.76; H, 7.51. Found: C, 80.76; H, 7.63.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; 1-(4-methoxy-phenyl)-pentan-1-one, RT = 0.76 min; product, RT = 1.12 min.

4-(2-phenylpentanoyl)benzonitrile (12e)



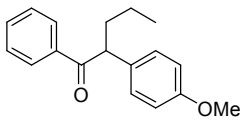
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.68 (m, 2H), 7.35-7.20 (m, 5H), 4.48, (t, *J* = 7.2 Hz, 1H), 2.16 (m, 1H), 1.83 (m, 1H), 1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 140.3, 139.0, 132.6, 129.3, 129.2, 128.4, 127.6, 118.1, 116.2, 54.3, 36.0, 20.9, 14.2.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.02; H, 6.42; N, 5.35.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; 1-(4-cyano-phenyl)-pentan-1-one, RT = 0.66 min; product, RT = 1.09 min.

2-(4-methoxyphenyl)-1-phenylpentan-1-one (12f)



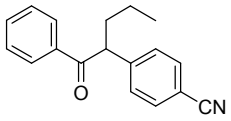
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.48 (m, 1H), 7.40 (m, 2H), 7.24 (m, 2H), 6.85 (m, 2H), 4.53 (t, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 2.15 (m, 1H), 1.82 (m, 1H), 1.40-1.22 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 158.7, 137.3, 132.9, 132.0, 129.4, 128.8, 128.7, 114.5, 55.4, 52.7, 36.3, 21.0, 14.3.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.24; H, 7.64.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *p*-bromoanisole, RT = 0.71 min; valerophenone, RT = 0.58; product, RT = 1.2 min.

4-(1-benzoylbutyl)benzonitrile (12g)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.59 (m, 2H), 7.53 (m, 1H), 7.47-7.39 (m, 4H), 4.66 (t, *J* = 7.3 Hz, 1H), 2.18 (m, 1H), 1.82 (m, 1H), 1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H);

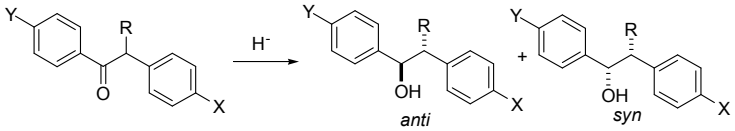
^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 145.1, 136.5, 133.3, 132.6, 129.1, 128.8, 128.5, 118.7, 111.0, 53.2, 36.1, 20.8, 14.0.

Anal. Calcd for $C_{18}H_{17}NO \cdot 0.1\ H_2O$: C, 81.54; H, 6.54; N, 5.28. Found: C, 81.26; H, 6.56; N, 5.21.

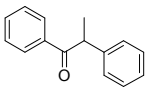
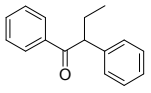
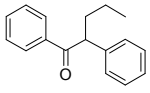
HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *p*-bromobenzonitrile, RT = 0.57 min; valerophenone, RT = 0.58; product, RT = 0.93 min.

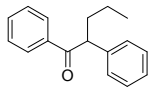
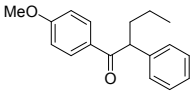
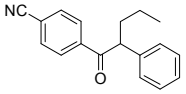
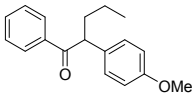
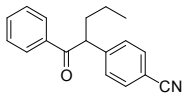
3. General synthetic procedures of alcohols 9a-c, 13d-g

The ketones were reduced under a variety of conditions outlined in the following table. The racemic benzyl alcohols were obtained via reduction of the ketones using either DIBAL-H/THF, $NaBH_4$/MeOH, or $NaBH_4$/IPA under the specified temperatures. Optically active benzyl alcohol was obtained through asymmetric hydrogenation via dynamic kinetic resolution (DKR).



8a-c, **12d-g** **9a-c**, **13d-g**

starting ketone	reduction conditions	*anti:syn*	*yield*
 **8a**	DIBAL-H/THF 0 – 5 ^oC	90:10	85
 **8b**	DIBAL-H/THF 0 – 5 ^oC	98.5:2.5	75
 **8c**	$NaBH_4$/IPA/ 80 ^oC	73:27	80

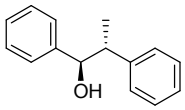
 **8c**	DKR	>99.5:<0.5	85
 **12d**	DIBAL-H/THF 0 – 5 °C	94:6	83
 **12e**	$NaBH_4$/MeOH 0 – 5 °C	95:5	75
 **12f**	DIBAL-H/THF 0 – 5 °C	90:10	85
 **12g**	$NaBH_4$/MeOH 0 – 5 °C	87:13	90

Preparation of Optically Active *Anti* Alcohol **9c** via DKR Reduction

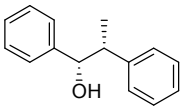
In a glove box, combined $RuCl_2$[(S)-xyl-SEGPHOS] [(S)-DAIPEN] (0.025 g, 0.021 mmol), potassium *tert*-butoxide (0.512 ml, 4.20 mmol) and 2-propanol (5 mL) in a flask and stirred at rt for 2 h. The resulting activated yellow catalyst solution was charged into a hydrogenation vessel and added a solution of 1,2-diphenylpentan-1-one (**8c**) (5.0 g, 20.98 mmol) in 2-propanol (25 ml). Caped the vessel, and submitted to hydrogenation at 100 psi hydrogen for 16 h at 25 ºC. The reaction mixture (~36 mL) was treated with 0.5 g Darco KB and stirred at rt for 40 min. The mixture was filtered through Solka-Floc and washed with 10 mL 2-propanol. The volume of 2-propanol in the filtrate was adjusted to about 40 mL. HPLC analysis indicated >99% conversion, >99% de, and 98% ee. To this solution was slowly added 80 mL H_2O over 45 min to crystallize the product. The resulting slurry was filtered and washed with 1:2 2-propanol/H_2O (40 mL). The wet cake was dried in vacuum oven (40 ºC/20 mmHg) over 24 h to afford 4.3 g (85%) *anti*-**9c** as a white solid. Chiral LC: 99.2% ee. Mother liquor contained 0.65g (13%) product (85% ee) by LC assay.

4. Spectral and analytical data of 9a-c, 13d-g

Syn- and *Anti*-1,2-diphenylpropan-1-ol (9a)



Anti



Syn

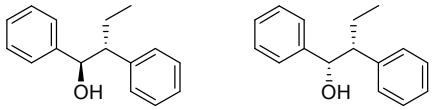
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ 7.41-7.28 (m, 10H), 4.68 (d, *J* = 8.6 Hz, 1H), 3.05 (dq, *J* = 8.6, 7.0 Hz, 1H), 1.91 (bs, -OH), 1.11 (d, *J* = 7.0 Hz, 3H); *syn* diastereomer, δ 7.28-7.15 (m, 10H), 4.82 (d, *J* = 5.8 Hz, 1H), 3.13 (apparent quintet, *J* = 6.8 Hz, 1H), 1.93 (bs, -OH), 1.34 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ 143.6, 142.8, 128.9, 128.5, 128.4, 128.3, 128.0, 127.2, 127.1, 79.9, 48.3, 18.5; *syn* diastereomer, δ 143.8, 143.1, 128.9, 128.4, 128.2, 127.4, 126.6, 126.5, 78.9, 47.4, 15.2.

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.50, H, 7.79.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; methyl ketone, RT = 0.9; *anti* diastereomer, RT = 0.68 min; *syn* diastereomer, RT = 0.64 min.

Syn- and *Anti*-1,2-diphenylbutan-1-ol (9b)



Anti *Syn*

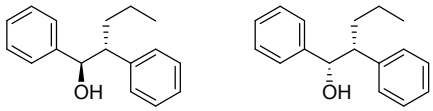
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ 7.40-7.32 (m, 6H), 7.32-7.25 (m, 4H), 4.74 (d, *J* = 8.6 Hz, 1H), 2.76 (ddd, *J* = 10.8, 8.6, 4.3 Hz, 1H), 1.80 (bs, -OH), 1.55 (m, 1H), 1.46 (m, 1H), 0.65 (t, *J* = 7.4 Hz, 3H); *syn* diastereomer (partial), δ 7.25-7.14 (m, 8H), 7.07 (m, 2H), 4.81 (d, *J* = 6.2 Hz, 1H), 2.85 (m, 1H), 0.76 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ 143.0, 141.4, 129.1, 128.8, 128.5, 127.9, 127.2, 127.1, 78.9, 56.5, 25.2, 12.2.

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.68, H, 8.12.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; ethyl ketone, RT = 1.02 min; *anti* diastereomer, RT = 0.82 min; *syn* diastereomer, RT = 0.72 min.

(1*R*,2*R*)- and (1*S*,2*R*)-1,2-diphenylpentan-1-ol (9c)



Anti *Syn*

^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ 7.40-7.25 (m, 10H), 4.73 (dd, *J* = 8.4, 2.7 Hz, 1H), 2.88 (ddd, *J* = 11.2, 8.4, 4.0 Hz, 1H), 1.81 (d, *J* = 2.7 Hz, -OH), 1.53 (m, 1H), 1.32 (m, 1H), 1.01 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer, δ 7.25-7.14 (m, 8H), 7.07 (d, *J* =7.3 Hz, 2H), 4.81 (dd, *J* = 6.1, 2.5 Hz, 1H), 2.97 (m, 1H), 1.97 (d, *J* = 2.8 Hz, -OH), 1.91 (m, 1H), 1.78 (m, 1H), 1.20 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

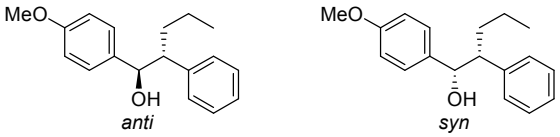
^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ 143.0, 142.7, 129.0, 128.8, 128.5, 127.9, 127.2, 127.1, 79.1, 54.4, 34.4, 20.6, 14.1; *syn* diastereomer, δ 143.2, 141.8, 129.0, 128.3, 128.1, 127.4, 126.7, 126.5, 78.8, 53.7, 32.2, 20.8, 14.3.

Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.93, H, 8.49.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *syn* diastereomer, RT = 0.96 min; *anti* diatereomer, RT=1.08 min.

Chiral HPLC. Analytical SFC Method: Chiralcel OJ-H (250 x4.6mm, 5μm) isocratic 20% MeOH/CO_2, 1.5 mL/min, 210 nm, 200 bar, 35ºC for 8 minutes: *(S,S)*-diastereomer, RT = 4.47 min; *(R,R)*-diastereomer, RT = 4.95 min.

Syn- and *Anti*-1-(4-methoxyphenyl)-2-phenylpentan-1-ol (13d)



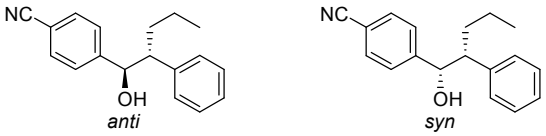
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 7.37 (m, 2H), 7.28 (m, 5H), 6.91 (m, 2H), 4.68 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.84 (s, 3H), 2.85 (ddd, *J* = 11.8, 8.8, 3.9 Hz, 1H), 1.82 (d, *J* = 2.4 Hz, -OH), 1.55 (m, 1H), 1.36 (m, 1H), 1.13-0.96 (m, 2H), 0.75 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial), δ: 7.21 (m, 2H), 7.17 (m, 1H), 7.04 (m, 4H), 6.77 (m, 2H), 4.74 (dd, *J* = 6.6, 3.5 Hz, 1H), 3.77 (s, 3H), 2.93 (m, 1H), 2.00 (d, *J* = 3.5 Hz, -OH), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 159.4, 141.9, 135.2, 129.0, 128.8, 128.3, 127.0, 113.9, 78.6, 55.4, 54.4, 34.4, 20.6, 14.1; *syn* diastereomer (partial) δ: 135.4, 129.1, 128.2 127.8, 126.4, 113.4, 78.3, 53.7, 53.6, 32.6, 20.8, 14.3.

Anal. Calcd for $C_{18}H_{22}O_2 \cdot 0.1\ H_2O$: C, 79.43; H, 8.22. Found: C, 79.42; H, 7.99.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; Ketone, RT = 1.12 min; *anti* diastereomer, RT = 0.91 min; *syn* diastereomer, RT = 0.80 min.

Syn- and *Anti*-4-[1-hydroxy-2-phenylpentyl]benzonitrile (13e)



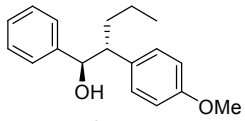
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 7.62 (m, 2H), 7.39 (m, 2H), 7.37-7.31 (m, 2H), 7.30-7.26 (m, 1H), 7.18 (m, 2H), 4.79 (dd, *J* = 7.7, 2.8 Hz, 1H), 2.81 (ddd, *J* = 11.5, 7.7, 4.3 Hz, 1H), 1.94 (bd, *J* = 2.8 Hz, -OH), 1.62 (m, 1H), 1.37 (m, 1H), 1.16-0.98 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 7.50 (m, 2H), 7.24-7.21 (m, 4H), 7.01 (m, 2H), 4.80 (m, 1H), 2.89 (m, 1H), 2.16 (bs, -OH), 0.83 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 148.4, 140.2, 132.2, 129.0, 128.9, 127.8, 127.5, 119.0, 111.6, 78.1, 54.3, 34.1, 20.6, 14.1; *syn* diastereomer (partial): 131.9, 128.8, 128.6, 127.4, 77.43, 20.7.

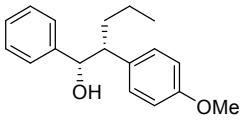
Anal. Calcd for $C_{18}H_{19}NO \cdot 0.2\ H_2O$: C, 80.38; H, 7.27; N, 5.21. Found: C, 80.42; H, 7.30; N, 5.14.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; ketone, RT = 1.09 min; *anti* diastereomer, RT = 0.79 min; *syn* diastereomer, RT = 0.74 min.

Syn- and *Anti*-2-(4-methoxyphenyl)-1-phenylpentan-1-ol (13f)



anti



syn

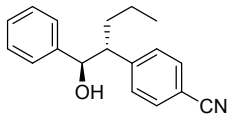
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 7.39-7.30 (m, 5H), 7.17 (m, 2H), 6.91 (m, 2H), 4.67 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 2.82 (m, 1H), 1.86 (bs, -OH), 1.52 (m, 1H), 1.34 (m, 1H), 1.13-0.95 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial) 6.96, (m, 2H), 6.77 (m, 2H), 4.75 (d, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 2.91 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 158.5, 142.9, 133.1, 129.7, 128.3, 127.7, 127.0, 114.0, 78.9, 55.2, 53.3, 34.2, 20.4, 13.9.

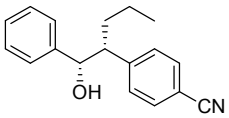
Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.91; H, 8.39.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; Ketone, RT = 1.12 min; *anti* diastereomer, RT = 0.91 min; *syn* diastereomer, RT = 0.78 min.

Syn- and *Anti*-4-{1-[hydroxy(phenyl)methyl]butyl}benzonitrile (13g)



anti



syn

^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 7.57 (m, 2H), 7.35-7.25(m, 5H), 7.22 (m, 2H), 4.80 (dd, *J* = 7.3, 2.6 Hz, 1H), 2.94 (ddd, *J* = 11.2, 7.3, 4.4 Hz, 1H), 1.97 (d, *J* = 2.9 Hz, -OH), 1.61 (m, 1H), 1.49 (m, 1H), 1.11-1.00 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 7.45 (m, 2H), 7.11 (m, 2H), 7.07 (m, 2H), 4.74 (dd, *J* = 7.3, 3.1 Hz, 1H), 3.00 (ddd, *J* = 11.0, 6.9, 3.9 Hz, 1H), 2.20 (d, *J* = 3.3 Hz, -OH), 2.00 (m, 1H), 1.72 (m, 1H), 1.16-1.05 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 147.8, 142.8, 132.1, 129.9, 128.5, 128.1, 126.7, 119.2, 110.4, 78.2, 54.0, 34.2, 20.6, 14.0; *syn* diastereomer: δ 147.7, 142.5, 131.9, 129.8, 128.3, 127.8, 126.6, 119.1, 110.2, 78.3, 53.9, 32.5, 20.7, 14.2.

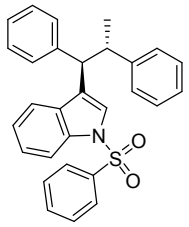
Anal. Calcd for $C_{18}H_{19}NO \cdot 0.1\ H_2O$: C, 80.93; H, 7.24; N, 5.24. Found: C, 80.67; H, 7.30; N, 5.10.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; Ketone, RT = 0.93; *anti* diastereomer, RT = 0.77 min; *syn* diastereomer, RT = 0.69 min.

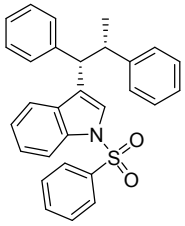
5. General Procedure for Friedel-Crafts Reactions

The benzyl alcohol (1.05 mmol) and the arene nucleophile (1.0 mmol) were combined with either dichloromethane (5 mL) and $BF_3{\cdot}OEt_2$ (3 mmol) (Method A), or TFA (5 mL) (Method B) and aged at 22 ºC for 1-20 h. The mixture was diluted with isopropyl acetate and analyzed by HPLC to determine the ratio of two product diastereomers and the combined yield. The isopropyl acetate solution was washed with saturated $NaHCO_3$ solution and 10% NaCl solution, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography using either ethyl acetate/hexanes, methyl t-butyl ether/hexanes, or dichloromethane/hexanes as eluents. Compounds were characterized by spectroscopic methods and elemental analyses. The purified materials were used as standards for determination of HPLC yields.

Syn- and *Anti*-3-(1,2-diphenylpropyl)-1-(phenylsulfonyl)-1*H*-indole (15a) & (16a)



anti



syn

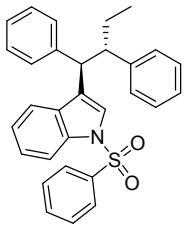
^{1}H NMR (500 MHz, $CDCl_3$) *anti* diastereomer (partial): δ 4.40 (d, *J* = 11.1 Hz, 1H), 3.59 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H); *syn* diastereomer (partial): δ 4.33 (d, *J* = 10.3 Hz, 1H), 3.61 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) *anti* diastereomer: δ 146.7, 142.4, 137.9, 135.1, 133.4, 131.2, 129.1, 128.8, 128.74, 128.72, 127.3, 127.1, 126.7, 126.6, 126.3, 124.6, 124.4, 123.2, 120.0, 113.5, 48.9, 44.9, 23.0; *syn* diastereomer: δ 145.0, 142.2, 138.2, 135.5, 133.8, 131.3, 129.4, 128.5, 128.2, 128.0, 127.8, 126.7, 125.0, 124.8, 123.6, 123.5, 123.3, 121.6, 120.1, 113.5, 50.3, 44.8, 21.2.

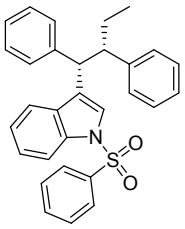
HRMS m/z $[M + NH_4]^+$ calcd for $C_{29}H_{29}N_2O_2S$ 469.1950, found 469.1948.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; N-benzenesulfonyl indole, RT = 0.72 min; *anti* diastereomer, RT = 4.68 min; *syn* diastereomer, RT = 4.58 min.

Syn- and *Anti*-3-(1,2-diphenylbutyl)-1-(phenylsulfonyl)-1*H*-indole (15b) & (16b)



anti



syn

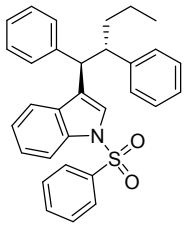
^{1}H NMR (500 MHz, $CDCl_3$) *anti* diastereomer: δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.44-7.14 (m, 17H), 7.12 (m, 1H), 7.05 (m, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 3.27 (ddd, *J* = 14.3, 10.8, 3.4 Hz, 1H), 1.59 (m 1H), 1.40 (m, 1H), 0.64 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 7.60 (s, 1H), 7.50 (m, 1H), 7.01 (m, 2H), 4.30 (d, *J* = 10.6 Hz, 1H), 3.26 (m, 1H), 1.88 (m, 1H), 1.60 (m, 1H), 0.73 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) *anti* diastereomer: δ 144.3, 142.7, 138.0, 135.1, 133.4, 131.3, 129.2, 128.78, 128.75, 128.6, 128.4, 126.9, 126.6, 126.2, 125.6, 124.6, 124.5, 121. 5, 120.0, 113.6, 52.0, 48.2, 28.4, 11.9.

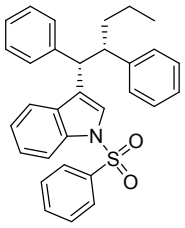
HRMS m/z $[M + Ag]^+$ calcd for $C_{30}H_{27}AgNO_2S$ 572.0814, found 572.0825.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; N-benzenesulfonyl, RT = 0.72 min; *anti* diastereomer, RT = 2.43 min; *syn* diastereomer, RT = 2.32 min.

Syn- and *Anti*-3-(1,2-diphenylpentyl)-1-(phenylsulfonyl)-1*H*-indole (15c) & (16c)



anti



syn

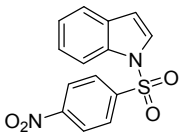
^{1}H NMR (500 MHz, $CDCl_3$) *anti* diastereomer (partial): δ 7.74, (d, *J* = 8.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 3.37 (ddd, *J* = 14.4, 10.7, 3.6 Hz, 1H), 1.48 (m, 1H), 1.82 (m, 1H), 1.10-0.95 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 4.28 (d, *J* = 10.7 Hz, 1H), 3,36 (m, 1H), 1.80 (m, 1H), 1.61 (m, 1H), 1.17-1.10 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$) *anti* diastereomer: δ 144.7, 142.6, 135.1, 133.4, 131.3, 129.2, 128.8, 128.7, 128.5, 128.3, 126.8, 126.6, 126.1, 125.6, 124.6, 124.4, 123.2, 121.4, 120.0, 113.6, 50.1, 48.5, 37.7, 20.4, 14.1.

HRMS m/z $[M + Ag]^+$ calcd for $C_{31}H_{29}AgNO_2S$ 586.0970, found 586.0979.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^{o}C column temperature; N-benzenesulfonyl indole, RT = 0.72 min; *syn* diastereomer, RT = 2.72 min; *anti* diastereomer, RT = 2.80 min.

1-[(4-nitrophenyl)sulfonyl]-1*H*-indole (17d)



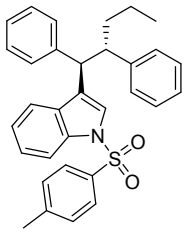
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (m, 2H), 8.05 (m, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.57-7.53 (m, 2H), 7.36 (m, 1H), 7.28 (m, 1H), 6.73 (d, *J* = 3.7 Hz, 1H).

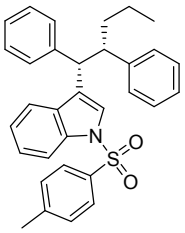
^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 143.5, 134.9, 131.0, 128.2, 126.1, 125.4, 126.6, 124.2, 121.9, 113.5, 110.8.

Anal. Calcd for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27; S, 10.61. Found: C, 55.43; H, 3.28; N, 9.21; S, 10.59.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; product RT = 0.82 min.

***Syn*- and *Anti*-3-(1,2-diphenylpentyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indole (18a) & (19a)**





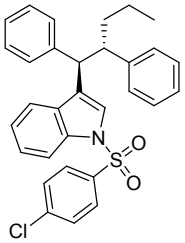
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.40-7.35 (m, 3H), 7.32-7.17 (m, 10H), 7.11 (m, 1H), 7.07-7.00 (m, 4H), 4.36 (d, *J* = 11.3 Hz, 1H), 3.36 (ddd, *J* = 14.7, 10.7, 3.9 Hz, 1H), 2.30 (s, 3H), 152-1.35 (m, 2H), 1.1-0.95 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 4.27 (d, *J* = 10.6 Hz, 1H), 2.34 (s, 3H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 144.6, 144.3, 142.5, 135.0, 134.9, 131.1, 129.8, 129.6, 128.64, 128.56, 128.4, 128.2, 126.7, 126.5, 125.9, 125.2, 124.31, 124.30, 122.9, 113.5, 50.0, 48.4, 37.5, 21.6, 20.3. 14.0; *syn* diastereomer (partial): δ 144.8, 142.9, 142.1, 135.5, 135.5, 131.3, 129.9, 128.5, 128.0, 127.9, 126.7, 126.2, 126.0, 124.8, 123.1, 114.0, 50.8, 49.3, 36.9, 20.9, 14.1.

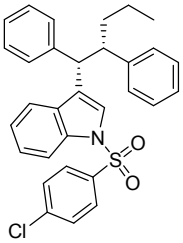
HRMS m/z $[M + Ag]^+$ calcd for $C_{32}H_{35}AgN_2O_2S$: 600.1127, found 600.1125.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; N-tosyl indole, RT = 0.92 min; *anti* diastereomer, RT = 3.23 min; *syn* diastereomer, RT = 3.17 min.

***Syn*- and *Anti*-1-[(4-chlorophenyl)sulfonyl]-3-(1,2-diphenylpentyl)-1*H*-indole (18b) & (19b)**



anti



syn

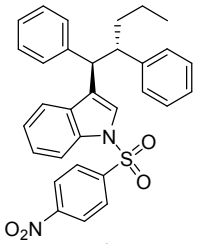
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer (partial): δ 7.78 (d, *J* = 7.9 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 3.42 (ddd, *J* = 14.0, 10.9, 3.4 Hz, 1H), 1.60-1.40 (m, 2H), 1.15-1.00 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 4.35 (d, *J* = 10.3 Hz, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 1.24-1.10 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 144.8, 142.9, 140.0, 136.3, 135.0, 131.3, 129.5, 128.74, 128.72, 128.6, 128.3, 128.0, 126.9, 126.2, 126.1, 124.8, 124.3, 123.5, 120.2, 113.6, 50.1, 48.4, 37.8, 20.4, 14.1; *syn* diastereomer (partial): δ 142.9, 142.0, 140.6, 136.6, 135.6, 131.5, 127.7, 125.3, 123.8, 122.9, 120.2, 114.1, 50.7, 49.4, 37.0, 21.0, 14.3.

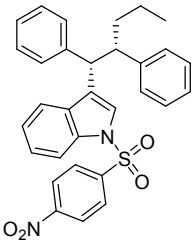
HRMS m/z $[M + Ag]^+$ calcd for $C_{31}H_{28}AgClNO_2S$ 620.0580, found 620.0578.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; N-(4-chlorophenylsulfonyl) indole, RT = 0.72 min; *anti* diastereomer, RT = 3.77 min; *syn* diastereomer, RT = 3.66 min.

Syn- and *Anti*-3-(1,2-diphenylpentyl)-1-[(4-nitrophenyl)sulfonyl]-1*H*-indole (18c) & (19c)



anti



syn

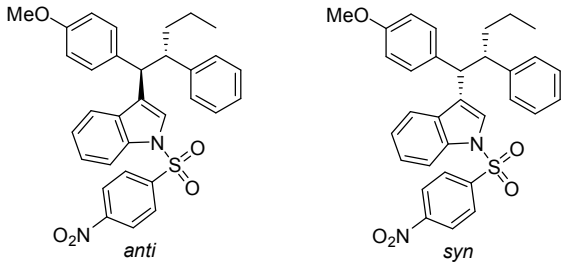
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 8.03 (m, 2H), 7.74 (m, 1H), 7.44-7.35 (m, 5H), 7.35-7.25 (m, 8H), 7.22 (m, 1H), 7.17 (m, 1H), 7.10 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 3.38 (dt, *J* = 10.8, 3.6 Hz, 1H), 1.45 (m, 1H), 1.39 (m, 1H), 1.10-0.90 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 8.21 (m, 2H), 7.97 (m, 2H), 4.29 (d, *J* = 10.8 Hz, 1H),), 3.38 (dt, *J* = 10.8, 3.6 Hz, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.20-1.09 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 150.3, 144.9, 143.0, 142.2, 135.0, 131.4, 128.9, 128.73, 128.69, 128.3, 127.8, 127.2, 127.1, 126.3, 125.2, 124.4, 124.1, 124.0, 120.4, 113.6, 50.0, 48.3, 37.9, 20.3, 14.1; *syn* diastereomer: δ 150.8, 143.4, 142.8, 141.9, 135.5, 131.7, 128.5, 128.4, 128.2, 128.14, 128.09, 126.4, 126.3, 125.7, 124.7, 124.6, 124.4, 122.7, 121.5, 114.1, 50.7, 49.4, 37.1, 21.0, 14.3.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *syn* diastereomer, RT = 2.79 min; *anti* diatereomer, RT = 2.98 min.

Chiral HPLC. Analytical SFC Tandem Column OJ-H 250 × 4.6mm 10um, OD-H 150 × 4.6 mm 10 μm, hold 4% MeOH for 4 min, ramp to 40% MeOH at 22min, hold 3min/CO_2, 3 mL/min, 200 bar, 210 nm for 15 min: *anti* diastereomers, RT = 10.51 (*1S, 2R*), 11.55 (*1R, 2S*) min; *syn* diastereomers, RT = 12.09 (*1S,2S*), 12.73 (*1R, 2R*) min; N-nosyl-indole, RT = 11.11 min.

Anti- and *Syn*-3-[1-(4-methoxyphenyl)-2-phenylpentyl]-1-[(4-nitrophenyl)sulfonyl]-1*H*-indole (20d) & (21d)

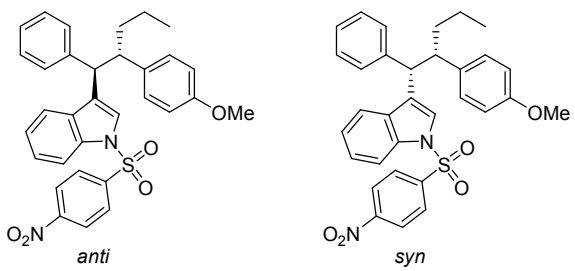


^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 8.03 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.39 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.33 (s, 1H), 7.31-7.23 (m, 7H), 7.17 (m, 1H), 7.10 (m, 1H), 6.84 (m, 2H), 4.32 (d, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 3.30 (ddd, *J* = 14.3, 10.9, 3.4 Hz, 1H), 1.49 (m, 1H), 1.39 (m, 1H), 1.02 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 8.21 (m, 2H), 7.98 (m, 2H), 7.51 (s, 1H), 7.50 (d, *J* = 8.0Hz, 1H), 6.89 (m, 2H), 6.55 (m, 2H), 4.24 (d, *J* = 10.4 Hz, 1H), 3.65 (s, 3H), 3.31 (m, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 0.89 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ: 158.6, 150.8, 145.0, 143.5, 135.0, 134.2, 131.5, 129.6, 128.7, 128.3, 127.8, 127.5, 126.2, 125.2, 124.6, 124.0, 123.9, 120.9, 114.2, 113.6, 55.4, 50.2, 47.4, 37.9, 20.4, 14.2; *syn* diastereomer (partial), δ: 158.0, 150.7, 143.3, 142.9, 135.6, 133.9, 131.7, 129.5, 128.6, 128.2, 128.1, 126.3, 125.7, 124.3, 122.5, 120.6, 114.1, 113.5, 55.3, 50.7, 48.5, 37.1, 20.9, 14.3.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *anti* diastereomer, RT = 2.74 min; *syn* diastereomer, RT = 2.64 min.

Anti- and *Syn*-3-[2-(4-methoxyphenyl)-1-phenylpentyl]-1-[(4-nitrophenyl)sulfonyl]-1*H*-indole (20f) & (21f)



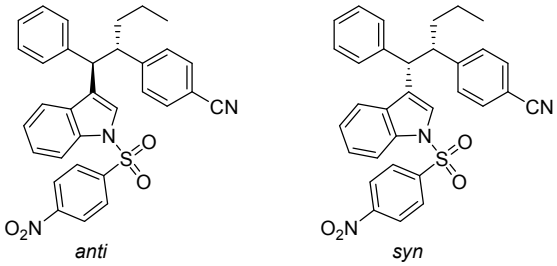
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 8.07 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.40-7.27 (m, 4H), 7.31 ("t", *J* = 7.6 Hz, 2H), 7.23-7.15 (m, 4H), 7.10 ("t", *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.32 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.32 (ddd, *J* = 14.3, 11.0, 3.3 Hz, 1H), 1.46 (m, 1H), 1.35 (m, 1H), 1.13-0.94 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ: 158.0, 150.5, 142.9, 142.3, 136.8, 135.0, 131.5, 129.1, 128.9, 128.7, 127.9, 127.2, 127.0, 125.2, 124.4, 124.1, 124.0, 120.4, 114.1, 113.6, 55.4, 49.2, 48.6, 38.0, 29.9, 20.4, 14.1.

HRMS m/z $[M + Ag]^+$ calcd for $C_{32}H_{30}AgN_2O_5S$ 661.0927, found 661.0944.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; N-nosyl indole, RT = 0.74 min; *anti* diastereomer, RT = 2.63 min; *syn* diastereomer, RT = 2.61 min.

Syn- and *Anti*-4-{1-[{1-[(4-nitrophenyl)sulfonyl]-1*H*-indol-3-yl}(phenyl)methyl]butyl}benzonitrile (20g) & (21g)



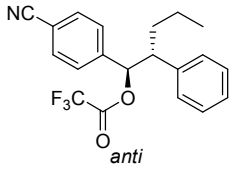
^{1}H NMR (500 MHz, $CDCl_3$) *major* diastereomer, δ: 8.15 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.40-7.31 (m, 6H), 7.30-7.20 (m, 4H), 7.13 (dd, *J* = 14.7, 7.3 Hz, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 3.44 (ddd, *J* = 14.0, 10.8, 3.2, 1H), 1.55 (m, 1H), 1.45 (m, 1H), 1.10-0.95 (m, 2H), 0.73 (t, *J* = 7.3 Hz, 3H); *minor* diastereomer (partial), δ: 8.22 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.03 (m, 2H), 6.99 (m, 2H), 4.24 (d, *J* = 11.0 Hz, 1H), 1.82 (m, 1H), 1.61 (m, 1H), 1.16-1.08 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H).

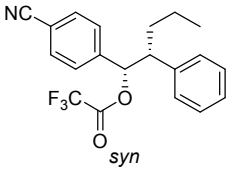
^{13}C NMR (100 MHz, $CDCl_3$) *major* diastereomer, δ: 150.7, 150.3, 143.0, 141.4, 135.0, 132.4, 130.9, 129.1, 129.0, 128.5, 127.8, 127.4, 126.8, 125.6, 124.5, 124.1, 123.4, 120.2, 118.7, 113.7, 110.4, 50.1, 48.0, 36.9, 20.0, 13.7; *minor* diastereomer (partial), δ: 143.2, 141.1, 135.5, 132.1, 129.3, 128.2, 128.1, 124.6, 51.1, 49.2, 36.9, 21.0, 14.2.

HRMS m/z $[M + Ag]^+$ calcd for $C_{32}H_{27}AgN_3O_4S$ 656.0773, found 656.0792.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; N-nosyl indole, RT = 0.74 min; *anti* diastereomer, RT = 2.01 min; *syn* diastereomer, RT = 1.94 min.

Syn- and *Anti*-1-(4-cyanophenyl)-2-phenylpentyl trifluoroacetate (22)





^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 7.65 (d, *J* = 8.3 Hz, 2H), 7.35-7.25 (m, 5H), 7.12 (m, 2H), 6.06 (d, *J* = 7.4 Hz, 1H), 3.11 (ddd, *J* = 11.3, 7.5, 4.3 Hz, 1H), 1.70 (m, 1H), 1.46 (m, 1H), 1.19 (m, 1H), 1.13 (m, 1H), 0.81 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial), δ: 7.52 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.22 (m, 2H), 6.96 (m, 2H), 5.96 (d, *J* = 8.6 Hz, 1H), 3.16 (ddd, *J* = 11.6, 8.9, 3.9 Hz, 1H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ: 156.5 (q, J_{CF} = 42.7 Hz), 142.3, 138.3, 132.6, 128.8, 128.7, 127.9, 127.7, 118.4, 114.5 (q, J_{CF} = 285.9 Hz), 113.1, 82.6, 51.2, 33.4, 20.4, 13.9; *syn* diastereomer (partial), δ: 138.2, 132.3, 112.7, 83.1, 51.4, 33.1, 29.9, 14.0.

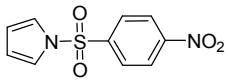
^{19}F NMR (376 MHz, $CDCl_3$) *anti* diastereomer, δ: -75.7; *syn* diastereomer, -75.5.

HRMS m/z $[M + NH_4]^+$ calcd for $C_{20}H_{22}F_3N_2O_2$ 379.1633, found 379.1631.

HRMS m/z $[M + Ag]^+$ calcd for $C_{20}H_{22}AgF_3N_2O_2$ 468.0341, found 468.0357.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; N-nosyl indole, RT = 0.74 min; *anti* diastereomer, RT = 1.71 min; *syn* diastereomer, RT = 1.70 min.

1-[(4-nitrophenyl)sulfonyl]-1*H*-pyrrole (24e)

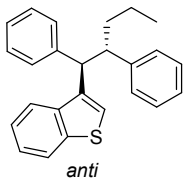


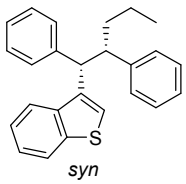
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (m, 2H), 8.02 (m, 2H), 7.17 ("t", *J* = 2.3 Hz, 2H), 6.37 ("t", *J* = 2.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 144.6, 128.3, 124.8, 121.2, 115.1.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; product, RT = 0.61 min.

Anti- and *Syn*-3-(1,2-diphenylpentyl)-1-benzothiophene (24b) & (25b)





^{1}H NMR (400 MHz, $CDCl_3$) *major* diastereomer, δ: 7.70 (m, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.30 ("d", *J* = 7.6 Hz, 2H), 7.27-7.12 (m, 7H), 7.08 (m, 2H), 4.61 (d, *J* = 10.8 Hz, 1H), 3.49 ("dt", *J* = 10.6, 3.7 Hz, 1H), 1.60-1.42 (m, 2H), 1.20-0.97 (m, 2H), 0.74 (t, *J* =

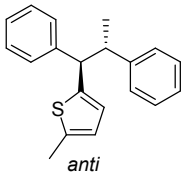
7.3 Hz, 3H); *minor* diastereomer (partial), δ: 7.86 (m, 2H), 4.53 (d, *J* = 10.9 Hz, 1H), 3.41 (m, 1H), 1.91 (m, 1H), 1.65 (m, 1H), 0.80 (t, *J* = 7.3 Hz, 3H).

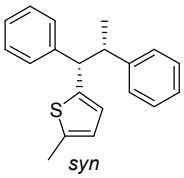
^{13}C NMR (100 MHz, $CDCl_3$) *major* diastereomer, δ: 144.3, 142.9, 140.2, 139.2, 138.3, 128.9, 128.6, 128.33, 128.27, 126.7, 126.1, 124.1, 123.8, 122.7, 122.4, 122.1, 51.1, 50.5, 37.4, 20.5, 14.2; *minor* diastereomer (partial), δ: 143.4, 138.9, 128.8, 128.1, 128.0, 126.0, 124.5, 124.2, 123.0, 122.2, 121.2, 52.0, 37.0, 21.0.

HRMS m/z $[M + Ag]^+$ calcd for $C_{25}H_{24}AgS$ 463.0650, found 463.0661.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *syn* diastereomer, RT = 3.09 min; *anti* diastereomer, RT = 2.87 min.

Anti- and *Syn*-2-(1,2-diphenylpropyl)-5-methylthiophene (24c) & (25c)



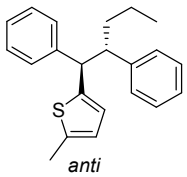


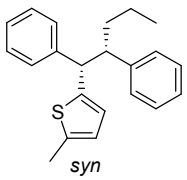
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer: δ 7.39 (m, 2H), 7.35 (m, 2H), 7.28-7.20 (m, 5H), 7.17 (m, 1H), 6.35 (d, *J* = 3.5 Hz, 1H), 6.33 ("dd", *J* =3.5, 0.9 Hz, 1H), 4.24 (d, *J* = 10.7 Hz, 1H), 3.46 (m, 1H), 2.29 (d, *J* = 0.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H); *syn* diastereomer: δ 7.16-7.12 (m, 4H), 7.11-7.05 (m, 4H), 7.04 (m, 1H), 7.01 (m, 1H), 6.79 (d, *J* = 3.4 Hz, 1H), 6.58 ("dd", *J* = 3.3, 1.0 Hz, 1H), 4.22 (d, *J* =10.9 Hz, 1H), 3.44 (m, 1H), 2.44 (d, *J* = 1.0 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100.5 MHz, $CDCl_3$) *anti* diastereomer: δ 146.1, 145.7, 143.9, 137.8, 128.7, 128.5, 128.2, 127.8, 126.8, 126.3, 124.5, 124.4, 54.9, 46.3, 21.9, 15.4; *syn* diastereomer: δ 145.9, 145.6, 143.8, 138.3, 128.4, 128.2 (two peaks), 127.8, 126.2, 126.0, 124.7, 124.4, 55.3, 46.5, 22.0, 15.6.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; *syn* diastereomer, RT = 2.09 min; *anti* diatereomer, RT = 1.88 min.

Anti- and *Syn*-2-(1,2-diphenylpentyl)-5-methylthiophene (24d) & (25d)





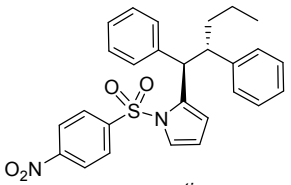
^{1}H NMR (500 MHz, $CDCl_3$) *anti* diastereomer: δ 7.38 (m, 2H), 7.35 (m, 2H), 7.26-7.20 (m, 4H), 7.17 (m, 2H), 6.30 (d, *J* = 3.6 Hz, 1H), 6.29 (m, 1H), 4.26 (d, *J* = 10.8 Hz, 1H), 3.28 (ddd, *J* = 14.4, 10.8, 3.6 Hz, 1H), 2.27 (s, 3H), 1.54-1.44 (m, 2H), 1.13 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer (partial): δ 7.11 (m, 2H), 7.05 (m, 2H), 6.78 (d, *J* = 3.4 Hz, 1H), 6.58 (m, 1H), 4.25 (d, *J* = 11.1 Hz, 1H), 3.26 (ddd, *J* = 13.3, 11.1, 3.2

Hz, 1H), 2.44 (d, *J* = 1.0 Hz, 3H), 1.81 (m, 1H), 1.58 (m, 1H), 1.10 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H).

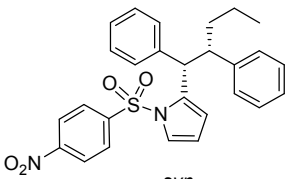
^{13}C NMR (125.7 MHz, $CDCl_3$) *anti* diastereomer: δ 145.9, 144.0, 143.9, 137.7, 128.8, 128.7, 128.5, 128.2, 126.7, 126.2, 124.5, 124.30, 54.4, 51.9, 36.9, 20.7, 15.4, 14.1; *syn* diastereomer: δ 146.1, 143.9, 143.6, 138.3, 128.7, 128.3, 128.2, 128.1, 126.01, 125.98, 124.7, 124.31, 54.6, 52.2, 37.2, 20.8, 15.6, 14.2.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; *syn* diastereomer, RT = 2.89 min; *anti* diastereomer, RT = 2.60 min.

***Anti*- and *Syn*-2-(1,2-diphenylpentyl)-1-[(4-nitrophenyl)sulfonyl]-1*H*-pyrrole (24e) & (25e)**



anti



syn

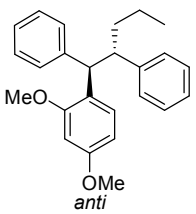
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 7.92 (m, 2H), 7.22 (m, 2H), 7.20-7.08 (m, 10H), 7.05 (dd, *J* = 3.4, 1.6 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.4 Hz, 1H), 6.21 ("t", *J* = 3.4 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 3.08 (dt, *J* = 10.8, 3.9 Hz, 1H), 1.40-12.0 (m, 2H), 1.03-0.80 (m, 2H), 0.64 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer: δ 7.91 (m, 2H), 7.36 (m, 2H), 7.10-7.00 (m, 4H), 6.89 (m, 2H), 6.83 (m, 1H), 6.78 (m, 2H), 6.65 (m, 2H), 6.55 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.46 ("t", J = 3.4 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 3.00 (ddd, *J* = 14.1, 11.3, 2.9 Hz, 1H), 1.78 (m, 1H), 1.57 (m, 1H), 1.12-0.98 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer: δ 150.0, 145.2, 144.1, 141.4, 138.5, 129.4, 128.35, 128.34, 127.3, 126.7, 126.2, 124.2, 123.13, 123.10, 115.1, 112.7, 51.4, 48.4, 37.2, 20.5, 14.0; *syn* diastereomer: δ 150.1, 144.8, 142.4, 140.9, 138.5, 129.1, 128.8, 128.1, 127.8, 127.6, 126.3, 126.0, 124.1, 123.2, 113.7, 112.9, 53.1, 49.3, 36.5, 21.0, 14.1.

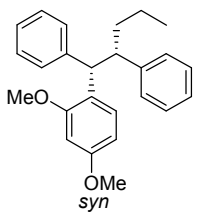
HRMS m/z $[M + Ag]^+$ calcd for $C_{27}H_{26}AgN_2O_4S$ 581.0664, found 581.0684.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 °C column temperature; *syn* diastereomer, RT = 2.39 min; *anti* diastereomer, RT = 2.57 min.

***Anti*- and *Syn*-1-(1,2-diphenylpentyl)-2,4-dimethoxybenzene (24g) & (25g)**



anti



syn

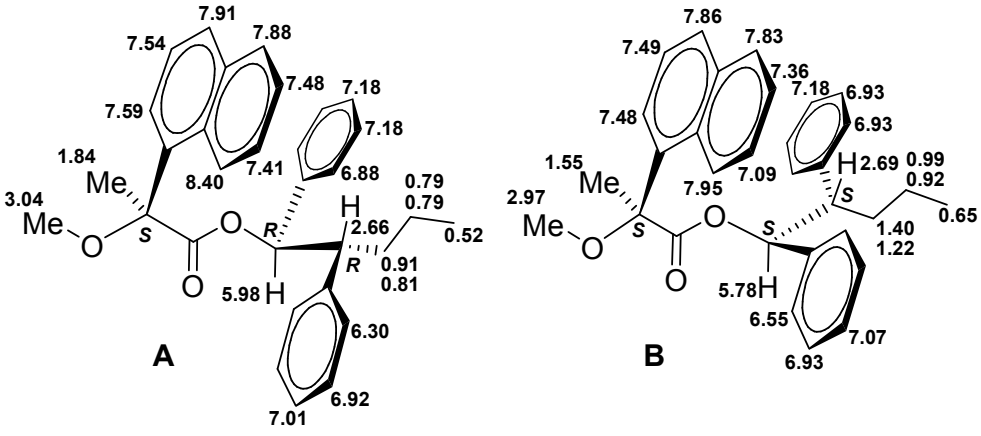
^{1}H NMR (400 MHz, $CDCl_3$) *anti* diastereomer, δ: 7.43 (m, 2H), 7.29 (m, 2H), 7.19-7.10 (m, 6H), 7.03 (m, 1H), 6.27 (dd, J = 8.5, 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.44 (ddd, *J* = 20.1, 11.7, 8.4 Hz, 1H), 1.75 (m, 1H), 1.45 (m, 1H), 1.14-0.98 (m, 2H), 0.73 (t, *J* = 7.3 Hz, 3H); *syn* diastereomer, δ: 7.37 (d, *J* = 8.5 Hz, 2H), 7.19-7.10 (m, 6H), 7.25 (m, 2H), 6.92 (m, 1H), 6.54 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.45 (ddd, *J* = 22.7, 11.3, 3.3 Hz, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.15-0.99 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H).

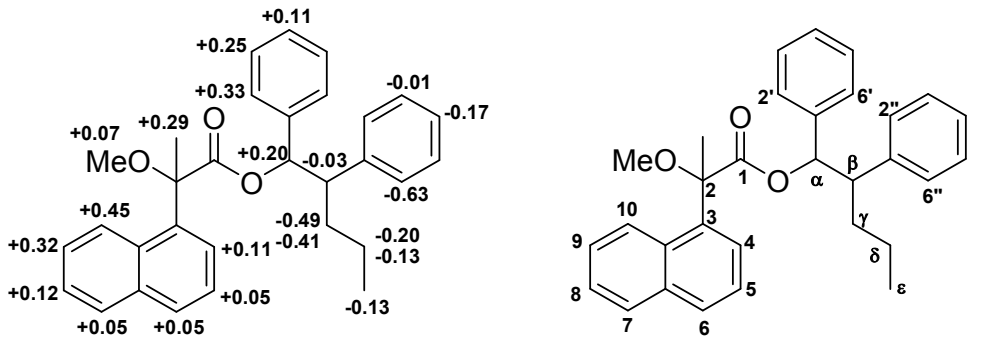
^{13}C NMR (100 MHz, $CDCl_3$) *anti* diastereomer, δ: 158.6, 157.7, 145.0, 144.4, 128.9, 128.7, 128.6, 128.5, 127.8, 125.9, 125.7, 125.6, 104.3, 98.6, 55.6, 55.3, 49.4, 48.8, 37.8, 20.7, 14.2; *syn* diastereomer, δ: 159.1, 158.5, 144.6, 144.5, 128.9, 128.8, 128.4, 128.0, 127.8, 125.7, 125.6, 125.3, 104.8, 99.0, 55.8, 55.2, 49.7, 49.3, 36.9, 20.8, 11.8.

HRMS m/z $[M + Ag]^+$ calcd for $C_{25}H_{29}AgO_2$ 467.1140, found, 467.1153.

HPLC conditions: Zorbax Eclipse Plus C18, 4.6 x 50 mm; A: 0.1% H_3PO_4 aqueous; B: acetonitrile; 75% to 95% B over 4 min, hold 1 min, post time 2 min. 1.5 mL/min, 3 μL, 210 nm, 22 ^oC column temperature; 1,3-dimethoxybenzene, RT = 0.59 min; *syn* diastereomer, RT = 2.60 min; *anti* diastereomer, RT = 2.73 min.

7. Assignments of Absolute Configuration of alcohol 9c via MαNP Esters A and B (Harada esters) ^{1}H NMR chemical shifts.





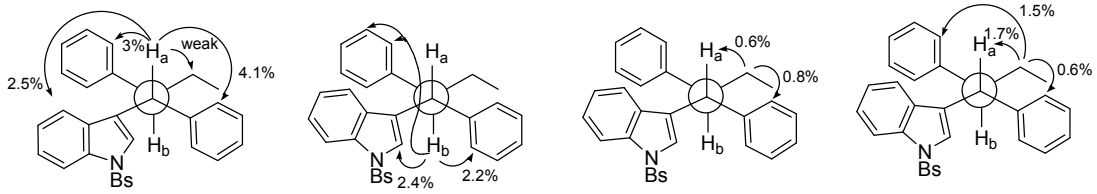
$\Delta\delta = \delta_A - \delta_B$

^{1}H chemical shifts (δ) for A and B.

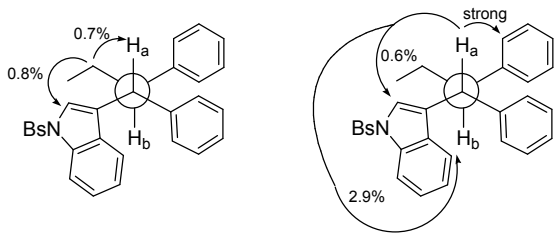
	α	β	γ	δ	ε	2-Me	2-OMe	4	5	6	7	8	9	2', 6'	3', 5'	4'	2", 6"	3", 5"	4"	10
A: ^{1}H chemical shifts δ (from (R,R)-**9c**)	5.98	2.66	0.91 0.81	0.79 0.79	0.52	1.84	3.04	7.59	7.54	7.91	7.88	7.48	7.41	6.88	7.18	7.18	6.30	6.92	7.01	8.40
B: ^{1}H chemical shifts δ (from (S,S)-**9c**)	5.78	2.69	1.40 1.22	0.99 0.92	0.65	1.55	2.94	7.48	7.49	7.86	7.83	7.36	7.09	6.55	6.93	7.07	6.93	6.93	7.18	7.95

8. NOE studies of 15b, 16b, 20a, 25b, 26b, 25c, 26c, 25d, 26d, 25g, 26g

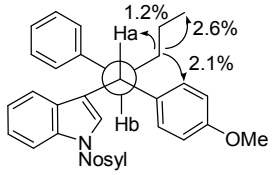
NOE observed for *anti*-15b



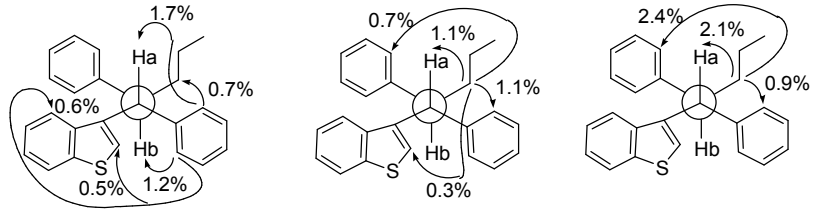
NOE observed for *syn*-16b



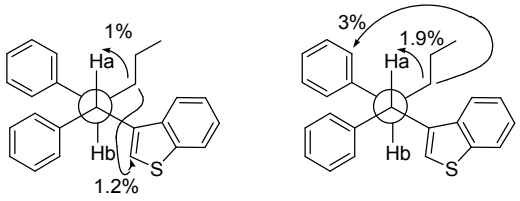
NOE observed for *anti*-20a



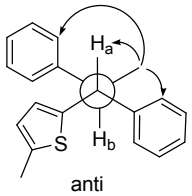
NOE observed for *anti*-25b



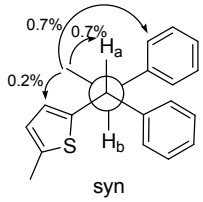
NOE observed for *syn*-26b



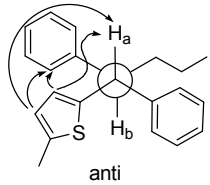
NOE observed for *anti*-25c



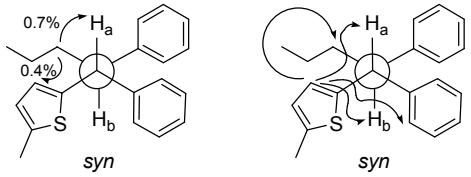
NOE observed for *syn*-26c



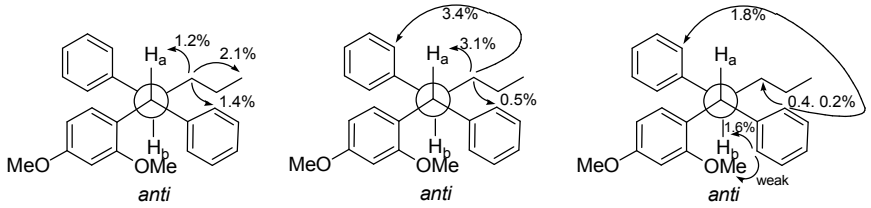
NOE observed for *anti*-25d



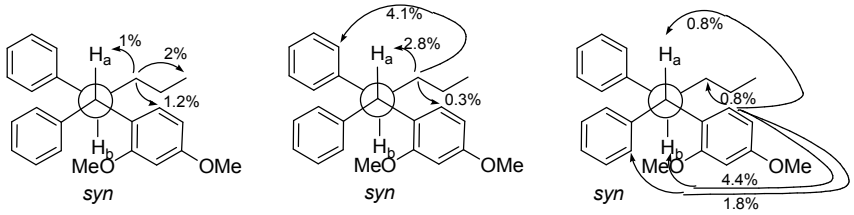
NOE observed for *syn*-26d



NOE observed for *anti*-25g

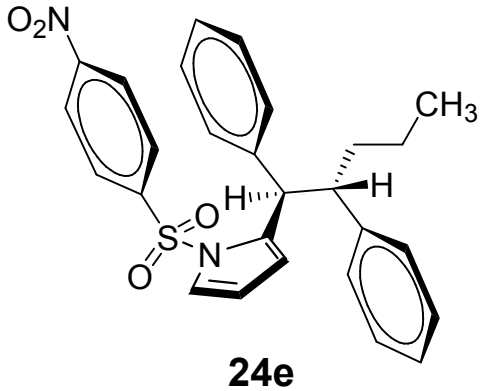


NOE observed for *syn*-26g

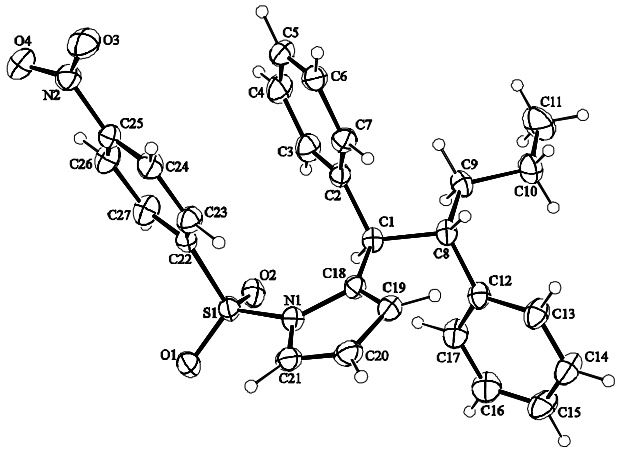


9. Single Crystal X-ray data of 24e

Compound $C_{27}H_{26}N_2O_4S$, M_r = 474.570, triclinic, $P\bar{1}$, a = 9.5409(14), b = 11.5565(17), c = 12.0312(17) Å, α = 64.324(2), β = 81.666(2), γ = 81.311(2)°, V = 1177.1(3) Å^3, Z = 2, D_x = 1.339 gcm^{-3}, monochromatized radiation λ(Mo) = 0.71073 Å, μ = 0.17 mm^{-1}, F(000) = 500, T = 100° K. Data were collected on a Bruker CCD diffractometer to a θ limit of 28.19° which yielded 16180 reflections. There are 5780 unique reflections with 4828 observed at the 2σ level. The structure was solved by direct methods (SHELXS-97, Sheldrick, G.M. *Acta Crystallogr.*, 1990, A46, 467-473) and refined using full-matrix least-squares on F^2 (SHELXL-97, Sheldrick, G.M. *SHELXL-97. Program for the Refinement of Crystal Structures.* Univ. of Göttingen, Germany). The final model was refined using 308 parameters and all 5780 data. All non-hydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics are: R = 0.038 (based on 4828 reflections with $I > 2\sigma(I)$), wR = 0.099, S = 1.03 with $(\Delta/\sigma)_{max} < 0.01$. The maximum peak height in a final difference Fourier map is 0.348 e Å^{-3} and this peak is without chemical significance. CCDC 677816 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

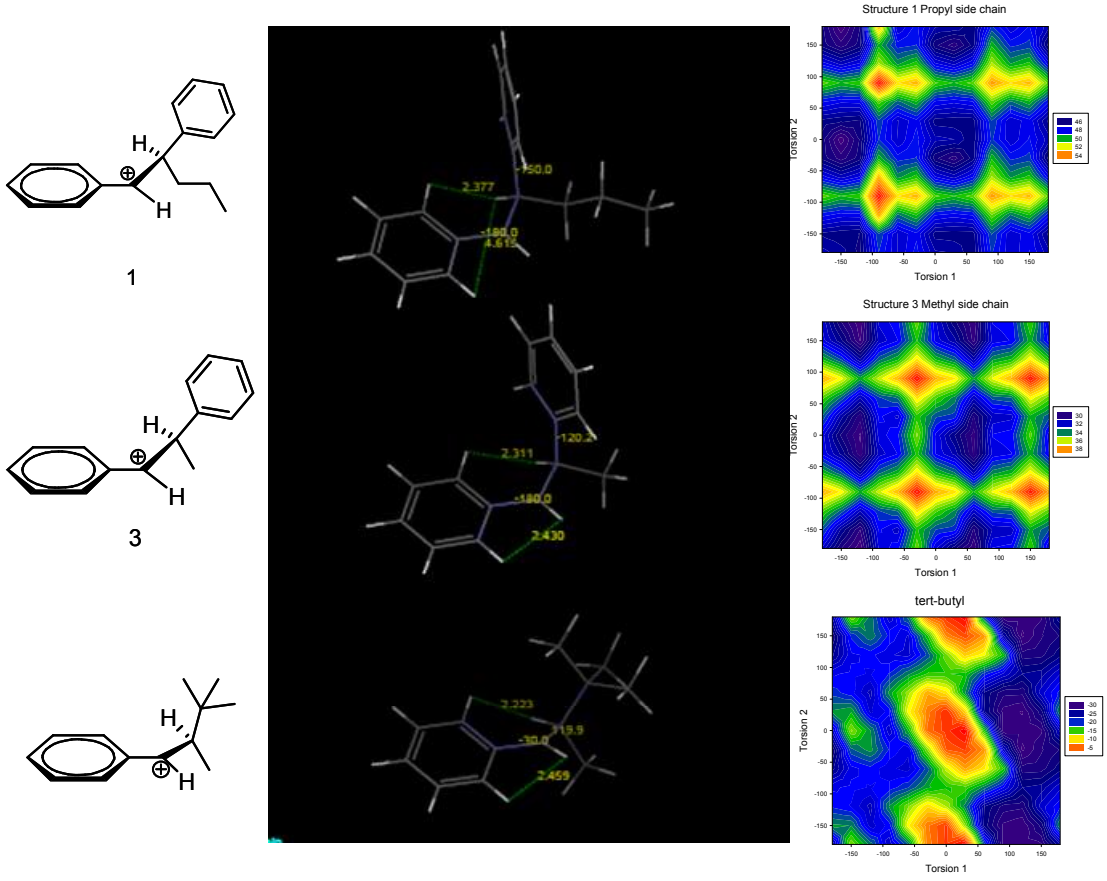


24e

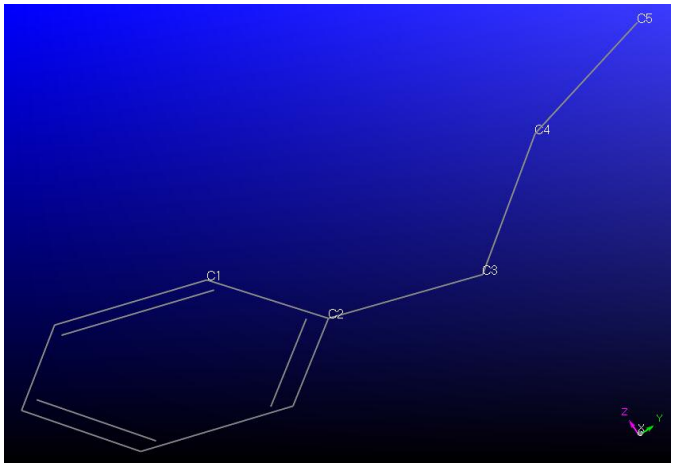


10. Molecular Modeling of Benzylic cations

All simulations were carried out using the Conformer Search module of CERIUS2. The DREIDING force field was used to describe the energetics. Partial atomic charges were assigned using the charge equilibration method. The molecular modeling calculations for the α-branched benzyl carbocations all showed that the α-hydrogens expected to be close enough to observed NOE with the phenyl group of the benzyl cation are indeed close "through space". In each case two torsion angles were simultaneously varied and the energy computed using molecular mechanics. An angle interval of 10° was chosen for the simulations. The energy vs angle plots are shown for comparison. The optimal torsion angles that result in the minimum energy conformation are picked out and the structure recorded as shown. The angles are indicated in the figure along with the inter-atomic distances between relevant H-atoms.



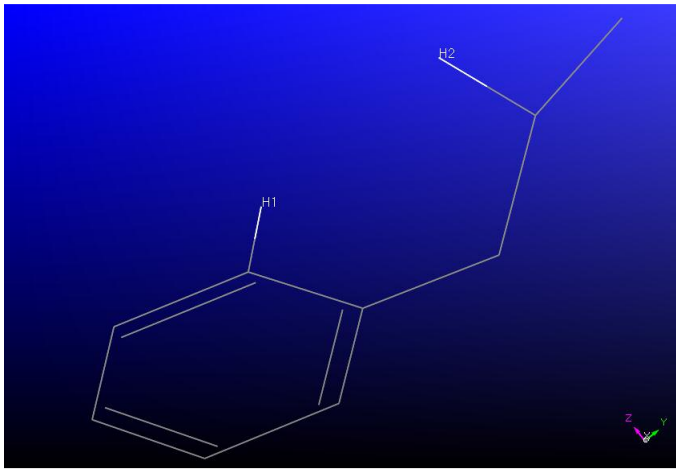
Torsional angle definitions



Torsion 1 = C1-C2-C3-C4
Torsion 2 = C2-C3-C4-C5

	Torsion 1	Torsion 2
tert-butyl	-30	120
Structure-3 Methyl side chain	-180	-150
Structure-1 Propyl side chain	-180	-120

Relevant α-hydrogens



	Distance between °-hydrogens (A)
tert-butyl	2.377
Structure-3 Methyl side chain	2.311
Structure-1 Propyl side chain	2.223