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Catalytic Lewis and Brønsted acid *syn*-diastereoselective benzylic substitutions of α-hydroxy-β-nitro- and α-hydroxy-β-azido-alkyl arenes

Raphaël Hensienne, Jean-Philippe Cusson, Étienne Chénard, and Stephen Hanessian

Abstract: A series of alkyl and alkenyl *p*-methoxy arenes containing α,β-disubstituted diamino and amino alcohol groups were synthesized from β-nitro and β-azido benzylic alcohols in the presence of $AuCl_3$ as catalyst. The formation of predominantly *syn*-disubstituted products were rationalized on the basis of mechanistic considerations and transition state models relying on $A^{1,3}$-allylic strain. The products could have utility in the design of medicinally relevant compounds and as chiral ligands for asymmetric catalysis. A new synthesis of (+)-sertraline (Zoloft) was achieved.

Key words: gold catalysis, benzylic sulfonamide, 1,1′-diaryl alkanes.

Résumé : Nous avons synthétisé une série de *p*-méthoxyarènes alkyliques ou alcényliques α,β-disubstitués par des groupes diamino ou aminoalcool à partir d'alcools β-nitrobenzyliques ou β-azidobenzyliques en présence d'$AuCl_3$ employé comme catalyseur. Pour expliquer la formation prédominante des produits disubstitués *syn*, nous avons fondé notre raisonnement sur des considérations mécanistiques et sur des modèles de l'état de transition reposant sur la tension allylique $A^{1,3}$. Les produits pourraient être utiles pour la conception de composés d'intérêt pharmacologique et comme ligands chiraux en catalyse asymétrique. Nous avons également réalisé une nouvelle synthèse de la (+)-sertraline (Zoloft). [Traduit par la Rédaction]

Mots-clés : catalyse par l'or, sulfonamide benzylique, 1,1′-diarylalkanes.

Introduction

The introduction of primary and secondary amino groups in aliphatic organic molecules has been an area of long-standing research activity.[1] Of particular interest is the inclusion of an amino group in the benzylic position of arenes especially in the context of pharmacologically important drugs exemplified by sertraline (Zoloft).[2] One of the simplest methods to achieve benzylic amination is through the application of the Ritter reaction to benzylic alcohols in the presence of catalytic amounts of protic acids in acetonitrile, which leads to benzylic acetamides.[3] Recent efforts to synthesize benzylic amines by catalytic enantioselective methods have been addressed in a number of creative ways particularly with regard to C–H activation.[4] The diastereoselective and asymmetric synthesis of vicinal α,β-disubstituted benzylic diamines and amino alcohols in acyclic organic compounds has been an area of interest for many years.[5] Other than applications to the synthesis of medicinally relevant compounds containing α- or β-aminoalkyl substituted arenes,[6] a great deal of progress has been made in the inventive use of vicinal diamines and amino alcohols as chiral non-racemic ligands for asymmetric catalysis.[7] For example, C_2-symmetric (*R*,*R*)- and (*S*,*S*)-1,2-diphenyl-diaminoethane[5a] or (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexane[7d] are among the most frequently used ligands for a multitude of catalytic and stoichiometric asymmetric reactions with great success. Ephedrine and pseudoephedrine are versatile chiral auxiliaries in enolate alkylation reactions.[8] They also represent examples of α-hydroxy-β-alkylamino arenes with pharmacological properties,[6b,6d,9] hence their regulated availability for research purposes. Thus, arenes with α,β-heteroatom substituted benzylic alkane appendages are interesting compounds to explore as novel pharmacophores, as well as ligands for asymmetric synthesis and catalysis.

There are numerous methods to access α,β-disubstituted benzylic diamines in a diastereoselective manner. Among the most frequently used methods are the direct S_N1 or S_N2 displacement of a suitable benzylic leaving group[5d] (Fig. 1, method A). By far the most popular method to access arenes with α,β-diaminoalkyl benzylic appendages has relied on the coupling of nitroalkanes with *N*-Boc aldimines derived mostly from aromatic aldehydes, also known as the nitro-Mannich or aza-Henry reaction[10] (Fig. 1, method B). A number of elegant catalytic enantioselective methods relying on C_2-symmetric ligands have been reported with simple nitroalkanes leading to *syn*- or *anti*- products as predominant if not exclusive diastereoisomers by Shibasaki[11] and Johnston,[12] respectively. Jacobsen has reported highly enantioselective *anti*-selective aza-Henry products from metal-free organocatalytic thiourea-mediated reactions.[13] There are a number of elegant methods for benzylic amination via C–H activation.[4b,4e–4h] However, the synthesis of α,β-diaminoalkyl arenes involving benzylic C–H activation and using a compatible source of a nitrogen-containing partner are scarce (Fig. 1, method C).

We have previously reported on the diastereoselective benzylic arylation of α-hydroxy-β-nitroalkyl arenes with electron rich aromatic compounds.[14] The major if not exclusive products in the presence of catalytic Au^{III} or Bi^{III} salts were the *syn*-diastereoisomers with regard to the incoming arenes and the β-nitro substituent on the alkyl chain. Inspired by the scholarly studies of Bach,[15a,15b] Olah,[15c,15d]

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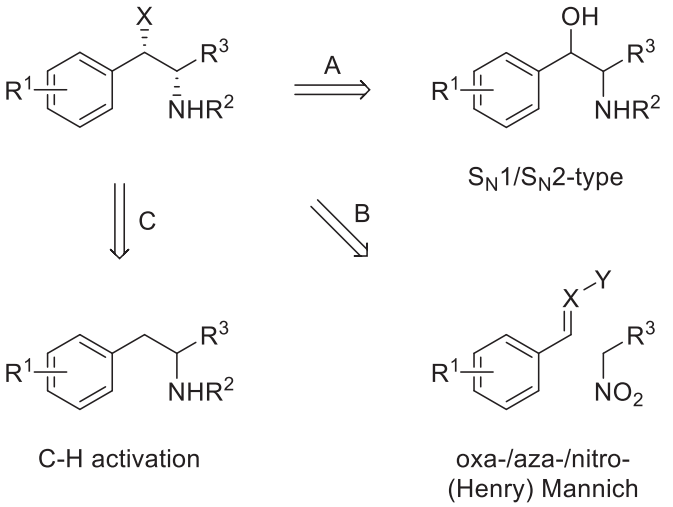
Fig. 1. Preferred methods toward benzylic substitution.



and Prakash,[15c,15d] we rationalized the predominance of *syn*-diastereoselectivity based on minimisation of $A^{1,3}$ strain in a putative quinonoid intermediate (Fig. 2). Furthermore, *syn*-nitro alcohols were much more reactive toward arenes in the presence of Bi^{III} salts compared with *anti*-nitro alcohols, resulting in an interesting kinetic diastereomer differentiation.[14]

Herein, we extended these studies to the introduction of amine and oxygen substitution at the benzylic position in the form of *N*-protected sulfonamides and *O*-benzyl and *O*-aryl ethers using racemic α-hydroxy-β-nitro- (or β-azido-) alkyl and α-hydroxy-β-nitro- (or β-azido-) allyl arenes in the presence of 10 mol% of $AuCl_3$ as catalyst. A new series of electron rich aromatic phenols led to the corresponding *syn*-*C*-aryl β-nitroalkyl arenes in the presence of $AuCl_3$ and to *syn*-*C*-aryl β-azidoalkyl arenes in the presence of catalytic *p*-toluenesulfonic acid monohydrate as major isomers.

Experimental

General

All reactions were performed in oven- or flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Dichloromethane, diethyl ether, and toluene were dried by passage through an activated alumina column under argon (Solvent drying system (SDS)). Reagents were purchased and used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) carried out on 0.25 mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate (Hanessian Stain), *p*-anisaldehyde, ninhydrin, and (or) potassium permanganate solution. Flash column chromatography were performed using silica (particle size 40–63 μm, 230–400 mesh) at increased pressure. FTIR spectra are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded at either 300, 400, or 500 MHz, and ^{13}C NMR spectra were recorded at either 75, 101, or 126 MHz. Chemical shifts for ^1H NMR spectra are recorded in parts per million relative to trimethylsilane (TMS, $\delta = 0.00$ ppm) with the solvent resonance as the internal standard ($CHCl_3$, $\delta = 7.26$ ppm; or CH_3OH, $\delta = 3.31$ ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), integration (xH). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ ($\delta = 77.16$ ppm) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm, using a 1 dm cell at ambient temperature and are reported in units of deg cm^3 g^{-1} dm^{-1}. High resolution mass spectra and analytical and preparative chiral HPLC were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Analytical chiral HPLC were performed with an Agilent 1100 Series HPLC, by chiralpak AD-H and chiralcel OD columns. All columns were 4.6 mm diameter × 250 mm height and were purchased from Daicel Chemical Industries Ltd. Chiral HPLC traces were obtained from a UV detector, with wavelength set at 254 and (or) 210 nm. The chiral HPLC separation conditions and results are described as follows: gradient, column, flow, column temperature, back pressure (BP, bar), retention time (RT), ratio.

Experimental procedures

General protocol for the synthesis of nitro alcohols[16]

To a mixture of *p*-anisaldehyde **1** (1.0 equiv.) and the nitro derivative **2** (5.0 equiv.) was added *N*,*N*-diisopropylethylamine (2.0 equiv.), followed by LiBr (0.20 equiv.). The reaction mixture was stirred at room temperature for 3 days. Ethyl acetate was added and the resulting mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (3×). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 9:1) to afford the corresponding nitro alcohol.

General protocol for the synthesis of bromoketones[17]

The starting ketone **12** (1.0 equiv.) was dissolved in diethyl ether (~1.5 mol L^{-1}). Bromine (1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature, and progress was monitored by TLC. After completion, a saturated aqueous solution of $Na_2S_2O_3$ was added at 0 °C. The resulting mixture was stirred at room temperature for 30 min, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the corresponding bromoketone.

General protocol for the synthesis of azidoketones

The starting bromoketone **13** (1.0 equiv.) was dissolved in dry *N*,*N*-dimethylformamide (~0.25 mol L^{-1}), NaN_3 (3.0 equiv.) was added, and the reaction mixture was stirred at room temperature for 2 h. Diethyl ether and brine were added, the organic layer was washed with brine (5×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 8:2) to afford the corresponding azidoketone.

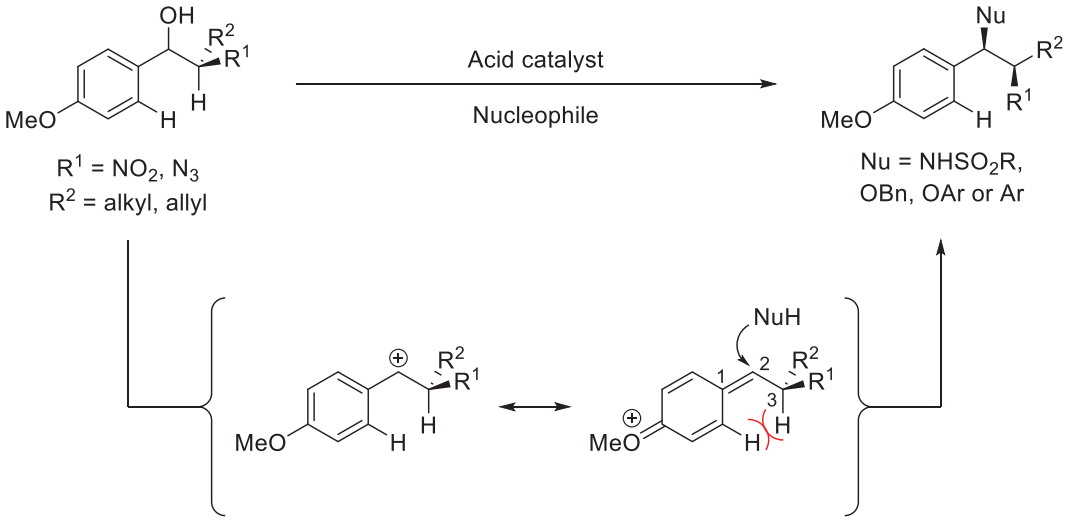
General protocol for the synthesis of azidoalcohols

The starting azidoketone **14** (1.0 equiv.) was dissolved in methanol (~0.25 mol L^{-1}). $NaBH_4$ (1.1 equiv.) was added, and the reaction mixture was stirred at room temperature for 1 h. Water was slowly added and the methanol was evaporated under reduced pressure. The resulting mixture was extracted with diethyl ether, the organic layer was washed with brine (2×), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was filtered on a short pad (silica gel, 5V diethyl ether) to afford the corresponding azidoalcohol.

General protocol for the acetylation of alcohols

The starting alcohol (1.0 equiv.) was dissolved in dichloromethane (~0.25 mol L^{-1}). Acetic anhydride (5.0 equiv.) was added, followed by triethylamine (2.0 equiv.) and 4-dimethylaminopyridine (0.10 equiv.). The reaction mixture was stirred at room temperature for 5 min, ethyl acetate was added, and the resulting mixture was washed with a saturated aqueous solution of $NaHCO_3$ (2×). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 9:1) to afford the corresponding acetate as a clear oil.

Fig. 2. Mechanistic rationale for *syn*-diastereoselectivity. [Colour online.]



General protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols and acetates[14]

The starting benzylic alcohol or acetate (1.0 equiv.) was dissolved in dichloromethane (~0.1 mol L^{-1}). The nucleophile (5.0 equiv.) was added, followed by the catalyst (10 mol%). The reaction mixture was stirred at room temperature and progress was monitored by TLC. After completion (usually overnight), the resulting mixture was diluted with dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 8:2) to afford the corresponding adduct.

(±)-(1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutan-1-ol (3a)

Following the general protocol for the synthesis of nitro alcohols and starting with 3.0 mL of *p*-anisaldehyde **1** and 11 mL of 1-nitropropane **2a**, nitro alcohol **3a** (2.9 g, 52%, dr 3–4.5:1) was obtained. R_f = 0.31 (hexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 6.96–6.85 (m, 2H), 5.09 (d, *J* = 5.4 Hz, 0.2H), 4.98 (d, *J* = 9.1 Hz, 0.8H), 4.63–4.51 (m, 1H), 3.82 (s, 2.3H), 3.80 (s, 0.6H), 2.57 (br s, 0.2H), 2.40 (br s, 0.8H), 2.14 (ddq, *J* = 14.6, 10.7, 7.3 Hz, 0.2H), 2.04–1.72 (m, 1H), 1.40 (dqd, *J* = 14.8, 7.5, 3.5 Hz, 0.84H), 0.94 (t, *J* = 7.4 Hz, 0.57H), 0.86 (t, *J* = 7.4 Hz, 2.43H); Major diastereomer (*syn*) ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 130.8, 128.3, 114.6, 95.5, 75.3, 55.5, 24.1, 10.2; Minor diastereomer (*anti*) ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 130.8, 127.7, 114.3, 94.9, 74.2, 55.4, 21.9, 10.5; IR (neat) 3456, 2981, 2947, 2848, 1615, 1552, 1517, 1464, 1376, 1308, 1251, 1180, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NNaO_4$ [M + Na]$^+$ 248.08933, found [M + Na]$^+$ 248.08874.

(±)-(1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitropent-4-en-1-ol (3b)

Following the general protocol for the synthesis of nitro alcohols and starting with 0.40 mL of *p*-anisaldehyde **1** and 1.0 g of 4-nitrobutene **2b**, nitro alcohol **3b** (0.48 g, 61%, dr 3:1) was obtained. R_f = 0.29 (hexane/ethyl acetate 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 6.95–6.89 (m, 2H), 5.70 (dddd, *J* = 16.9, 10.2, 7.9, 6.1 Hz, 0.28H), 5.65–5.55 (m, 0.73H), 5.19–4.97 (m, 3H), 4.77–4.63 (m, 1H), 3.82 (s, 2.14H), 3.81 (s, 0.74H), 2.88–2.81 (m, 0.28H), 2.70–2.62 (m, 0.28H), 2.56–2.46 (m, 1H), 2.38–2.36 (m, 0.71H), 2.20–2.13 (m, 0.76H); Major diastereomer ^{13}C NMR (126 MHz, CD_3NO_2) δ 161.6, 133.3, 132.5, 129.8, 119.7, 115.4, 95.0, 76.3, 56.1, 36.1; Minor diastereomer ^{13}C NMR (126 MHz, CD_3NO_2) δ 161.4, 134.0, 132.8, 129.3, 119.5, 115.1, 94.2, 75.3, 56.0, 34.9; IR (neat) 3445, 3013, 2962, 2942, 2851, 1615, 1550, 1517, 1374, 1308, 1251, 1179, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}N_2O_4$ [M + NH_4]$^+$ 255.13393, found [M + NH_4]$^+$ 255.13336 and calcd for $C_{12}H_{15}NNaO_4$ [M + Na]$^+$ 260.08933, found [M + Na]$^+$ 260.08859.

(±)-(1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl acetate (4a)

Following the general protocol for the acetylation of alcohols and starting with 250 mg of alcohol **3a**, acetate **4a** (249 mg, 84%, dr 17.5:1) was obtained. R_f = 0.49 (hexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.23 (m, 2H), 6.95–6.84 (m, 2H), 6.07 (d, *J* = 7.4 Hz, 0.14H), 6.01 (d, *J* = 10.2 Hz, 0.86H), 4.76 (td, *J* = 10.4, 3.4 Hz, 1H), 3.81 (s, 2.56H), 3.79 (s, 0.40H), 2.10 (s, 0.40H), 1.99 (s, 2.56H), 1.80 (ddq, *J* = 14.5, 10.6, 7.3 Hz, 1H), 1.44 (dddt, *J* = 14.7, 10.8, 7.5, 3.4 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 0.46H), 0.88 (t, *J* = 7.4 Hz, 2.64H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 160.5, 129.1, 127.3, 114.6, 92.5, 75.9, 55.5, 24.0, 21.0, 10.1; IR (neat) 2962, 1750, 1609, 1554, 1514, 1372, 1257, 1223, 1176, 1084, 1015 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}NNaO_5$ [M + Na]$^+$ 290.09989, found [M + Na]$^+$ 290.09914.

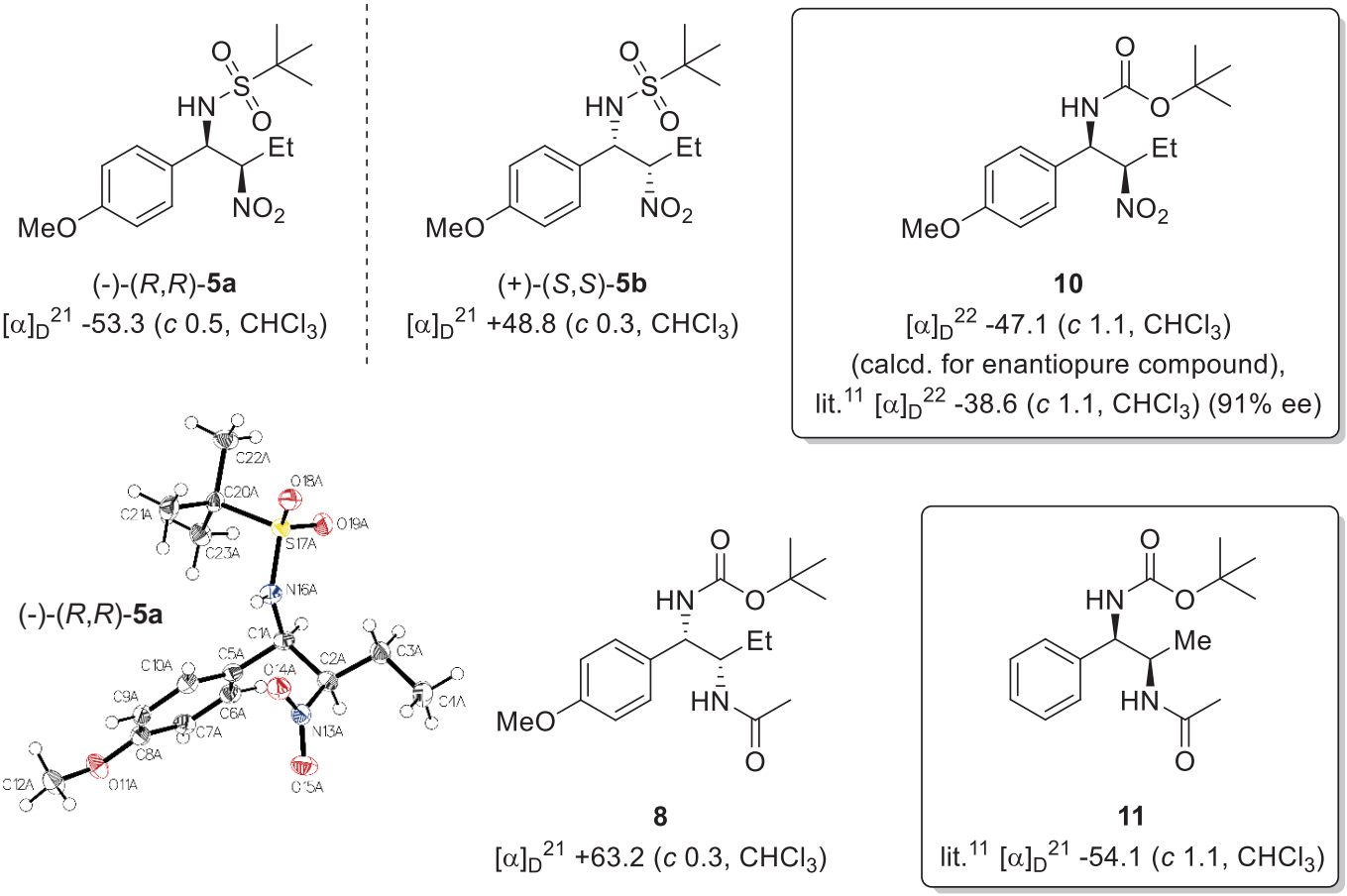
(±)-(1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitropent-4-en-1-yl acetate (4b)

Following the general protocol for the acetylation of alcohols and starting with 100 mg of alcohol **3b**, acetate **4b** (67 mg, 60%, dr 20:1) was obtained. R_f = 0.56 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2H), 6.95–6.88 (m, 2H), 6.02 (d, *J* = 10.2 Hz, 1H), 5.59 (dddd, *J* = 17.1, 10.2, 8.1, 5.9 Hz, 1H), 5.12–5.01 (m, 2H), 4.88 (td, *J* = 10.3, 3.5 Hz, 1H), 3.81 (s, 3H), 2.52–2.42 (m, 1H), 2.22–2.14 (m, 1H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 160.6, 130.3, 129.2, 126.9, 120.3, 114.6, 90.5, 75.6, 55.5, 34.8, 21.0; HRMS (ESI) calcd for $C_{14}H_{21}N_2O_5$ [M + NH_4]$^+$ 297.1445, found [M + NH_4]$^+$ 297.14532 and calcd for $C_{14}H_{17}NNaO_5$ [M + Na]$^+$ 302.09989, found [M + Na]$^+$ 302.10069.

(–)-*N*-((1*R*,2*R*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-2-methylpropane-2-sulfonamide (5a) and (+)-*N*-((1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-2-methylpropane-2-sulfonamide (5b)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **4a**, using *tert*-butylsulfonamide as the nucleophile and $AuCl_3$ as the catalyst, a mixture of sulfonamides **5a** and **5b** (26 mg, 82%, dr 20:1 *syn:anti*) was obtained as a white solid. R_f = 0.41 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.14 (m, 2H), 6.97–6.89 (m, 2H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.84 (dd, *J* = 10.0, 5.7 Hz, 1H), 4.62 (ddd, *J* = 10.1, 5.7, 4.1 Hz, 1H), 3.83 (s, 3H), 2.21 (ddq, *J* = 14.5, 10.4, 7.2 Hz, 1H), 1.95 (dqd, *J* = 15.0, 7.6, 4.0 Hz, 1H), 1.29 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 129.8, 127.9, 115.0, 95.2, 60.7, 59.5, 55.7, 25.7, 24.5, 10.7; IR (neat) 3231, 2895, 2877, 1632, 1522, 1489, 1453, 1378, 1300, 1156, 1034 cm^{-1};

Fig. 3. Absolute configurations and optical rotations of compounds (–)-(*R*,*R*)-**5a**, (+)-(*S*,*S*)-**5b**, (+)-**8**, **10**, and **11**. [Colour online.]



HRMS (ESI) calcd for $C_{15}H_{24}N_2NaO_5S$ [M + Na]$^+$ 401.1147, found [M + Na]$^+$ 401.1237. Preparative chiral HPLC was used to separate the enantiomers. Analytical separation conditions: 10% *i*PrOH/CO_2, chiralpak AD-H, 30 °C, BP = 150, RT: **5a** 4.15 min and **5b** 5.10 min, ratio 1:1.3 **5a–5b**; or 5% MeOH/CO_2, chiralpak AD-H, 30 °C, BP = 150, RT: **5a** 14.1 min and **5b** 16.7 min. For the *R*,*R*-enantiomer, **5a**: mp: 139.5–142.0 °C; $[\alpha]_D^{21}$ –53.3 (*c* 0.5, $CHCl_3$). For the *S*,*S*-enantiomer, **5b**: mp: 133.5–136.0 °C; $[\alpha]_D^{21}$ +48.8 (*c* 0.3, $CHCl_3$). Absolute configuration of the asymmetric centers for the *R*,*R*-enantiomer **5a** was determined by X-ray diffraction analysis (see Supplementary data for X-ray structural data); this result was confirmed by comparison with literature data after conversion to the *N*-Boc *N*-acetyl derivative **8** closely related to the reported compound **11**[11]: $[\alpha]_D^{21}$ –54.1 (*c* 1.1, $CHCl_3$) (see Results and discussion; Fig. 3).

(±)-*N*-((1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-2-(trimethylsilyl)ethane-1-sulfonamide (5c)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **4a**, using 2-(trimethylsilyl)ethane-1-sulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **5c** (30 mg, 86%, dr 20:1) was obtained as a white solid. R_f = 0.32 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 2H), 6.96–6.85 (m, 2H), 5.67 (d, *J* = 9.9 Hz, 1H), 4.78 (dd, *J* = 10.0, 8.2 Hz, 1H), 4.62 (ddd, *J* = 10.3, 8.2, 3.8 Hz, 1H), 3.79 (s, 3H), 2.71 (td, *J* = 14.1, 3.9 Hz, 1H), 2.58 (td, *J* = 14.1, 4.2 Hz, 1H), 1.97 (ddt, *J* = 14.5, 10.4, 7.3 Hz, 1H), 1.63 (dddd, *J* = 14.9, 11.3, 7.5, 3.9 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.82 (td, *J* = 13.7, 4.0 Hz, 1H), 0.70 (td, *J* = 13.7, 4.0 Hz, 1H), –0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 129.0, 128.1, 115.0, 94.0, 59.3, 55.5, 50.4, 25.2, 10.4, 10.3, –2.0; IR (neat) 3261, 2955, 1613, 1555, 1517, 1455, 1316, 1230, 1168, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{32}N_3O_5SSi$ [M + NH_4]$^+$ 406.18264, found [M + NH_4]$^+$ 406.18288 and calcd for $C_{16}H_{28}N_2NaO_5SSi$ [M + Na]$^+$ 411.13804, found [M + Na]$^+$ 411.13837.

(±)-*N*-((1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-4-methylbenzenesulfonamide (5d)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **4a**, using *p*-toluenesulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **5d** (21 mg, 59%, dr 18:1) was obtained as a white solid. R_f = 0.42 (hexane/ethyl acetate 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.91–6.86 (m, 2H), 6.71–6.67 (m, 2H), 5.62 (d, *J* = 9.3 Hz, 1H), 4.74 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.60–4.54 (m, 1H), 3.74 (s, 2.85H), 3.73 (s, 0.15H), 2.36 (s, 2.85H), 2.34 (s, 0.15H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 137.4, 129.5, 127.8, 127.1, 114.5, 94.2, 58.9, 55.4, 25.0, 21.6, 10.3; IR (neat) 3264, 2922, 2849, 1611, 1555, 1515, 1456, 1373, 1324, 1162, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_5S$ [M + Na]$^+$ 401.1147, found [M + Na]$^+$ 401.1237.

(±)-*N*-((1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitropent-4-en-1-yl)-2-(trimethylsilyl)ethane-1-sulfonamide (5e)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **4b**, using 2-(trimethylsilyl)ethane-1-sulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **5e** (24 mg, 68%, dr 20:1) was obtained as a white solid. R_f = 0.26 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 2H), 6.95–6.88 (m, 2H), 5.77–5.55 (m, 2H), 5.20–5.05 (m, 2H), 4.85–4.70 (m, 2H), 3.80 (s, 3H), 2.76–2.50 (m, 3H), 2.45–2.32 (m, 1H), 0.83 (td, *J* = 13.8, 4.1 Hz, 1H), 0.71 (td, *J* = 13.8, 4.1 Hz, 1H), –0.11 (s, 9H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 160.3, 130.5, 128.7, 128.2, 120.5, 115.0, 91.9, 59.2, 55.5, 50.4, 35.9, 10.3, –2.1; HRMS (ESI) calcd for $C_{17}H_{32}N_3O_5SSi$ [M + NH_4]$^+$ 418.18264, found [M + NH_4]$^+$ 418.18332 and calcd for $C_{17}H_{28}N_2NaO_5SSi$ [M + Na]$^+$ 423.13804, found [M + Na]$^+$ 423.13875.

(±)-*N*-((1*S*,2*S*)-2-Amino-1-(4-methoxyphenyl)butyl)-2-methylpropane-2-sulfonamide (6)

A mixture of the starting nitro derivatives **5a** and **5b** (30 mg, 0.086 mmol, 1 equiv.) was dissolved in methanol (0.8 mL). Trimethylsilyl chloride (0.30 mL, 2.6 mmol, 30 equiv.) was added, followed by zinc powder (112 mg, 1.7 mmol, 20 equiv.) slowly. The reaction mixture was stirred at room temperature for 5 min. A saturated aqueous solution of $NaHCO_3$ was added and the resulting mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, dichloromethane/methanol 100:0 to 97:3) to afford amine **6** (21 mg, 77%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 4.50 (d, *J* = 3.9 Hz, 1H), 3.80 (s, 3H), 3.15–3.09 (m, 1H), 1.75–1.66 (m, 1H), 1.54–1.44 (m, 1H), 1.21 (s, 9H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 133.1, 128.3, 114.3, 60.1, 59.7, 58.7, 55.4, 29.8, 24.3, 10.5; HRMS (ESI) calcd for $C_{15}H_{26}N_2NaO_3S$ [M + Na]$^+$ 337.1562, found [M + Na]$^+$ 337.1527.

***N*-((1*S*,2*S*)-1-((1,1-Dimethylethyl)sulfonamido)-1-(4-methoxyphenyl)butan-2-yl)acetamide (7)**

The starting nitro derivative **5b** (30 mg, 0.086 mmol, 1.0 equiv.) was dissolved in methanol (0.80 mL). Trimethylsilyl chloride (0.30 mL, 2.6 mmol, 30 equiv.) was added, followed by zinc powder (112 mg, 1.7 mmol, 20 equiv.) slowly. The reaction mixture was stirred at room temperature for 5 min. A saturated aqueous solution of $NaHCO_3$ was added and the resulting mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude amine (*S*,*S*)-**6** was dissolved in methanol (1.0 mL). Acetic anhydride (20 μL, 0.20 mmol, 2.3 equiv.) was added. The reaction mixture was stirred overnight at room temperature. A saturated aqueous solution of $NaHCO_3$ was added and the resulting mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 4:6) to afford amide **7** (25 mg, 82% over 2 steps) as a colorless oil. R_f = 0.24 (hexane/ethyl acetate 4:6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.66–6.54 (m, 0.65H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.28 (t, *J* = 8.8 Hz, 1H), 4.17–4.01 (m, 1H), 3.80 (s, 3H), 2.11 (s, 3H), 1.49–1.42 (m, 2H), 1.18 (s, 9H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.3, 133.7, 132.4, 128.6, 114.9, 114.3, 63.0, 59.4, 57.0, 55.4, 25.0, 24.2, 24.1, 23.2, 10.6; IR (neat) 3223, 2906, 2864, 2877, 1632, 1510, 1440, 1379, 1301, 1174, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{28}N_2NaO_4S$ [M + Na]$^+$ 379.1668, found [M + Na]$^+$ 379.1642.

***tert*-Butyl (+)-((1*S*,2*S*)-2-acetamido-1-(4-methoxyphenyl)butyl)carbamate (8)**

The starting sulfonamide **7** (47 mg, 0.13 mmol, 1.0 equiv.) was dissolved in dichloromethane (4 mL). A solution of triflic acid (70 μL, 0.79 mmol, 6.0 equiv.) in dichloromethane (4 mL) was added slowly at –20 °C. The reaction mixture was stirred at –20 °C for 30 min. A 10% aqueous NaOH solution (10 mL) was added and the resulting mixture was extracted with dichloromethane (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude amine was dissolved in dichloromethane (1.3 mL). Di-*tert*-butyl dicarbonate (43 mg, 0.20 mmol, 1.5 equiv.) was added. The reaction mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 8:2) to afford **8** (32 mg, 79% over two steps) as a colorless oil. $[\alpha]_D^{21}$ +63.2 (*c* 0.3, $CHCl_3$), lit. for analog (–)-(1*R*,2*R*)-**11**[11] $[\alpha]_D^{21}$ –54.1 (*c* 1.1, $CHCl_3$); R_f = 0.35 (hexane/ethyl acetate 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 4.2 Hz, 2H), 6.89–6.84 (m, 2H), 5.67 (d, *J* = 6.7 Hz, 1H), 4.47 (d, *J* = 9.8 Hz, 1H), 3.93–3.84 (m, 1H), 3.79 (s, 3H), 2.07 (s, 3H), 1.49 (d, *J* = 5.3 Hz, 1H), 1.40 (s, 9H), 1.34–1.30 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 159.6, 155.9, 130.2, 128.5, 114.0, 79.3, 56.1, 55.4, 28.5, 25.0, 21.3, 10.3; HRMS (ESI) calcd for $C_{17}H_{28}N_2NaO_4$ [M + Na]$^+$ 359.1947, found [M + Na]$^+$ 359.1889. Alternatively, compounds (+)-(*S*,*S*)-**8** and *ent*-**8** could be obtained by preparative chiral HPLC from a racemic mixture prepared from **5a,5b**; analytical separation conditions: 10% MeOH/CO_2, WHELK-01, 30 °C, BP = 150, RT: 2.60 min and 6.89 min, ratio 1:1.3. See Fig. 3.

(±)-(4*R*,5*R*)-4-Ethyl-5-(4-methoxyphenyl)imidazolidin-2-one (9)

The starting racemic amine **6** (13 mg), obtained by reduction of **5a** and **5b**, was dissolved in a mixture of dichloromethane (0.10 mL) and a saturated aqueous solution of $NaHCO_3$ (0.20 mL). Triphosgene (4.1 mg) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Ethyl acetate was added and the resulting mixture was washed rapidly with water (pH 3). The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed rapidly with a saturated aqueous solution of $NaHCO_3$, followed by brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the isocyanate intermediate (16 mg) as a dark oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.98 (s, 1H), 4.94 (d, *J* = 2.9 Hz, 1H), 3.81 (s, 3H), 3.51 (td, *J* = 6.3, 3.1 Hz, 1H), 1.75–1.66 (m, 2H), 1.22 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H).

The crude isocyanate (16 mg) was dissolved in dichloromethane (0.20 mL). $AlCl_3$ (16 mg, 0.12 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 40 min. Water (5 mL) was added and the resulting mixture was extracted with dichloromethane (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 9:1) to afford urea **9** (6 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.98 (s, 1H), 4.85 (s, 1H), 4.35 (d, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 3.46 (dd, *J* = 12.3, 7.0 Hz, 1H), 1.74–1.52 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 159.8, 133.4, 127.9, 114.4, 63.7, 62.2, 55.5, 27.8, 10.1; IR (neat) 3234, 2960, 2924, 2851, 1701, 1610, 1512, 1459, 1373, 1247, 1176, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}N_2NaO_2$ [M + H]$^+$ 221.1290, found [M + H]$^+$ 221.1317.

(±)-2-Bromo-1-(4-methoxyphenyl)propan-1-one (13a)[17,18]

Following the general protocol for the synthesis of bromoketones and starting with 3.0 g of 1-(4-methoxyphenyl)propan-1-one **12a**, bromoketone **13a** (4.6 g, quantitative) was obtained. R_f = 0.42 (hexane/dichloromethane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2H), 6.99–6.91 (m, 2H), 5.26 (q, *J* = 6.6 Hz, 1H), 3.88 (s, 3H), 1.89 (d, *J* = 6.6 Hz, 3H); analytical data are in accordance with literature data.[17,18]

(±)-2-Bromo-1-(4-methoxyphenyl)-3-methylbutan-1-one (13b)[17]

Following the general protocol for the synthesis of bromoketones and starting with 0.88 g of 1-(4-methoxyphenyl)-3-methylbutan-1-one **12b**, bromoketone **13b** (1.1 g, 89%) was obtained. R_f = 0.29 (hexane/dichloromethane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.95 (m, 2H), 6.99–6.91 (m, 2H), 4.90 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 3H), 2.54–2.39 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 164.1, 131.3, 128.0, 114.1, 55.9, 55.7, 31.3, 21.0, 20.6; IR (neat) 3018, 2965, 2929, 2875, 2836, 1670, 1599, 1452, 1367, 1312, 1266, 1235, 1164, 1020, 1016 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}{}^{79}BrO_2$ [M + H]$^+$ 271.03282, found [M + H]$^+$ 271.03179; analytical data are in accordance with literature data.[17]

(±)-2-Azido-1-(4-methoxyphenyl)propan-1-one (14a)[17]

Following the general protocol for the synthesis of azidoketones and starting with 2.0 g of bromoketone **13a**, azidoketone **14a** (1.5 g, 89%) was obtained. R_f = 0.43 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.87 (m, 2H), 7.03–6.91 (m, 2H), 4.65 (q, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H); IR (neat) 2982, 2841, 2093, 1679, 1595, 1573, 1255, 1221, 1171, 1029 cm^{-1}; analytical data are in accordance with literature data.[17]

(±)-2-Azido-1-(4-methoxyphenyl)-3-methylbutan-1-one (14b)

Following the general protocol for the synthesis of azidoketones and starting with 0.88 g of bromoketone **13b**, azidoketone **14b** (0.58 g, 76%) was obtained. R_f = 0.42 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.89 (m, 2H), 6.98–6.93 (m, 2H), 4.33 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 2.37–2.26 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 164.2, 131.1, 128.5, 114.2, 68.8, 55.7, 31.1, 20.0, 18.4; IR (neat) 2957, 2928, 2861, 2849, 2098, 1676, 1600, 1578, 1514, 1472, 1265, 1220, 1173, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}N_3O_2$ [M + H]$^+$ 234.1237, found [M + H]$^+$ 234.122797 and calcd for $C_{12}H_{15}N_3NaO_2$ [M + Na]$^+$ 256.10565, found [M + Na]$^+$ 256.10577.

(±)-2-Azido-1-(4-methoxyphenyl)-3,3-dimethylbutan-1-one (14c)

Following the general protocol for the synthesis of azidoketones and starting with 2.4 g of bromoketone **13c**, azidoketone **14c** (1.4 g, 69%) was obtained. R_f = 0.40 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H), 6.97–6.93 (m, 2H), 5.10 (s, 1H), 3.88 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 164.0, 131.1, 129.1, 114.1, 57.8, 55.7, 35.3, 27.6; IR (neat) 2957, 2932, 2868, 2100, 1671, 1597, 1509, 1365, 1307, 1171, 1089 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}N_3NaO_2$ [M + Na]$^+$ 270.1219, found [M + Na]$^+$ 270.1311.

(±)-(1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propan-1-ol (15a)

Following the general protocol for the synthesis of azidoalcohols and starting with 1.5 g of azidoketone **14a**, azidoalcohol **15a** (1.5 g, quantitative, dr 2:1) was obtained. R_f = 0.5 (hexane/ethyl acetate 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 2H), 6.93–6.85 (m, 2H), 4.71–4.62 (m, 0.36H), 4.40 (dd, *J* = 7.6, 2.9 Hz, 0.64H), 3.80 (s, 3H), 3.74–3.57 (m, 1H), 2.42 (d, *J* = 2.9 Hz, 0.61H), 2.10 (d, *J* = 3.3 Hz, 0.34H), 1.18 (d, *J* = 6.7 Hz, 1.05H), 1.08 (d, *J* = 6.7 Hz, 1.95H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.6, 132.5, 132.4, 128.1, 127.9, 114.1, 114.0, 77.9, 76.3, 63.8, 62.6, 55.4, 16.1, 14.0; IR (neat) 3409, 2963, 2935, 2902, 2839, 2101, 1611, 1586, 1552, 1512, 1463, 1443, 1246, 1175, 1032; HRMS (ESI) calcd for $C_{10}H_{13}N_3NaO_2$ [M + Na]$^+$ 230.09000, found [M + Na]$^+$ 230.09088.

(±)-(1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)-3-methylbutan-1-ol (15b)

Following the general protocol for the synthesis of azidoalcohols and starting with 0.20 g of azidoketone **14b**, azidoalcohol **15b** (0.19 g, 92%, dr 3:1) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 1.5H), 7.30–7.24 (m, 0.5H), 6.95–6.84 (m, 2H), 4.68–4.61 (m, 1H), 3.81 (s, 2.21H), 3.81 (s, 0.7H), 3.41 (dd, *J* = 7.3, 4.9 Hz, 0.74H), 3.33 (dd, *J* = 7.3, 4.2 Hz, 0.23H), 2.31 (s, 0.2H), 2.09–1.93 (m, 1.46H), 1.68–1.57 (m, 0.5H), 1.05 (d, *J* = 6.8 Hz, 2.29H), 0.99 (d, *J* = 6.8 Hz, 0.73H), 0.96 (d, *J* = 6.7 Hz, 0.23H), 0.91 (d, *J* = 6.7 Hz, 0.7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 159.7, 133.4, 133.3, 128.5, 127.9, 114.24, 114.15, 75.19, 75.16, 74.4, 74.1, 55.4, 29.4, 29.2, 21.1, 20.8, 17.0, 16.8; IR (neat) 3418, 2982, 2964, 2937, 2104, 1615, 1589, 1517, 1389, 1370, 1342, 1302, 1249, 1178, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_3NaO_2$ [M + Na]$^+$ 258.1213, found [M + Na]$^+$ 258.12067.

(±)-(1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)-3,3-dimethylbutan-1-ol (15c)

Following the general protocol for the synthesis of azidoalcohols and starting with 0.29 g of azidoketone **14c**, azidoalcohol **15c** (0.28 g, 95%, dr 6:1) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.34 (m, 2H), 6.92–6.88 (m, 2H), 4.90 (dd, *J* = 7.4, 2.9 Hz, 0.16H), 4.78 (dd, *J* = 5.9, 3.2 Hz, 0.84H), 3.82 (s, 2.5H), 3.80 (s, 0.5H), 3.46 (d, *J* = 5.9 Hz, 1H), 0.97 (s, 1.5H), 0.93 (s, 7.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 134.1, 129.2, 127.2, 127.1, 114.2, 114.0, 114.0, 77.4, 77.3, 75.1, 55.4, 35.4, 30.3, 27.5, 27.4; IR (neat) 3417, 2956, 2866, 2839, 2107, 1677, 1598, 1574, 1509, 1462, 1419, 1395, 1313, 1171, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_3NaO_2$ [M + Na]$^+$ 272.1375, found [M + Na]$^+$ 272.1504.

(±)-(1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propyl acetate (16)

Following the general protocol for the acetylation of alcohols and starting with 100 mg of alcohol **15a**, acetate **16** (115 mg, 96%, dr 2:1) was obtained. R_f = 0.58 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 2H), 6.94–6.83 (m, 2H), 5.70 (d, *J* = 5.0 Hz, 0.36H), 5.59 (d, *J* = 7.8 Hz, 0.63H), 3.85–3.73 (m, 4H), 2.12 (s, 1.07H), 2.11 (s, 1.91H), 1.20 (d, *J* = 6.7 Hz, 1.07H), 1.06 (d, *J* = 6.7 Hz, 1.94H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.9, 160.0, 159.9, 129.4, 128.7, 128.6, 128.5, 114.2, 114.0, 78.8, 77.5, 60.9, 60.5, 55.4, 21.2, 16.3, 15.3; IR (neat) 2986, 2972, 2956, 2843, 2838, 2114, 1741, 1613, 1515, 1232, 1177, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}N_3NaO_2$ [M + Na]$^+$ 272.10056, found [M + Na]$^+$ 272.10087.

(±)-*N*-((1*S*,2*S*)-2-Azido–1-(4-methoxyphenyl)propyl)-2-methylpropane-2-sulfonamide (17a)

Method A, from the alcohol

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 25 mg of alcohol **15a**, using *tert*-butylsulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17a** (24–27 mg, 61%–66%, dr 4.5–7:1) was obtained overnight as a white solid.

Method B, from the acetate

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 50 mg of acetate **16**, using *tert*-butylsulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17a** (36 mg, 55%, dr 2:1) was obtained overnight as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2H), 6.92–6.88 (m, 2H), 4.84 (d, *J* = 9.5 Hz, 0.05H), 4.66 (d, *J* = 9.2 Hz, 0.95H), 4.44 (dd, *J* = 9.2, 3.6 Hz, 0.95H), 4.38 (dd, *J* = 9.7, 4.4 Hz, 0.05H), 3.81 (s, 3H), 3.78 (dd, *J* = 6.6, 3.6 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 132.2, 129.2, 128.0, 114.3, 114.1, 63.7, 61.3, 60.1, 55.4, 24.3, 17.6; IR (neat) 3231, 2895, 2877, 2111, 1632, 1522, 1489, 1453, 1378, 1300, 1156, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_3S$ [M + Na]$^+$ 349.1311, found [M + Na]$^+$ 349.1341.

(±)-*N*-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propyl)-2-(trimethylsilyl)ethane-1-sulfonamide (17b)

Method A, from the alcohol

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 25 mg of alcohol **15a**, using 2-(trimethylsilyl)ethane-1-sulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17b** (30–35 mg, 67%–78%, dr 6:1) was obtained overnight as a white solid.

Method B, from the acetate

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **16**, using 2-(trimethylsilyl)ethane-1-sulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17b** (34 mg, 91%, dr 6:1) was obtained overnight as a white solid. R_f = 0.31 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 2H), 6.93–6.87 (m, 2H), 5.25 (d, *J* = 9.1 Hz, 0.14H), 5.11 (d, *J* = 7.2 Hz, 0.83H), 4.33 (dd, *J* = 9.1, 4.8 Hz, 0.15H), 4.27 (dd, *J* = 7.2, 5.9 Hz, 0.84H), 4.00–3.94 (m, 0.16H), 3.80 (s, 3H), 3.73 (p, *J* = 6.4 Hz, 0.84H), 2.61 (td, *J* = 14.1, 3.9 Hz, 1H), 2.46 (td, *J* = 14.1, 4.3 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 2.58H), 1.18 (d, *J* = 6.7 Hz, 0.50H), 0.91–0.80 (m, 1H), 0.74 (td, *J* = 13.9, 4.2 Hz, 0.85H), 0.65 (td, *J* = 14.1, 4.1 Hz, 0.18H), −0.14 (s, 7.30H), −0.16 (s, 1.50H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 130.9, 128.6, 114.5, 62.1, 61.4, 55.5, 50.2, 17.1, 10.4, −2.0; HRMS (ESI) calcd for $C_{15}H_{30}N_5O_3SSi$ [M + NH_4]$^+$ 388.18331, found [M + NH_4]$^+$

388.18305 and calcd for $C_{15}H_{26}N_4NaO_3SSi$ $[M + Na]^+$ 393.13871, found $[M + Na]^+$ 393.13842.

(±)-*N*-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propyl)-4-methylbenzenesulfonamide (17c)

Method A, from the alcohol

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 25 mg of alcohol **15a**, using *p*-toluenesulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17c** (29–37 mg, 68%–83%, dr 4:1) was obtained overnight as a white solid.

Method B, from the acetate

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic acetates, starting with 25 mg of acetate **16**, using *p*-toluenesulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17c** (23 mg, 63%, dr 1.5:1) was obtained overnight as a white solid. mp: 98–100 °C; R_f = 0.35 (hexane/ethyl acetate 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.44 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.99–6.89 (m, 2H), 6.71–6.63 (m, 2H), 5.53 (d, *J* = 8.4 Hz, 0.18H), 5.46 (d, *J* = 6.8 Hz, 0.81H), 4.23 (dd, *J* = 8.4, 4.8 Hz, 0.18H), 4.16 (dd, *J* = 6.3 Hz, 0.82H), 3.79–3.56 (m, 4H), 2.34 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 2.5H), 1.10 (d, *J* = 6.7 Hz, 0.59H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.41, 159.36, 143.24, 143.18, 137.44, 137.42, 129.9, 129.8, 129.43, 129.37, 129.0, 128.4, 128.1, 127.2, 127.1, 113.9, 113.8, 62.1, 61.5, 61.2, 60.9, 55.4, 21.6, 16.7, 16.1; IR (neat) 3282, 2928, 2859, 2113, 1616, 1517, 1444, 1326, 1253, 1161, 1094, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_4NaO_3S$ $[M + Na]^+$ 383.11483, found $[M + Na]^+$ 383.11623.

(±)-*N*-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl) propyl)benzenesulfonamide (17d)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15a**, using benzenesulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17d** (49 mg, 59%, dr 5:1) was obtained overnight as a colorless oil. R_f = 0.10 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 6.96–6.91 (m, 2H), 6.68–6.64 (m, 2H), 5.47 (d, *J* = 8.6 Hz, 0.15H), 5.41 (d, *J* = 6.9 Hz, 0.85H), 4.27 (dd, *J* = 8.6, 4.7 Hz, 0.15H), 4.22–4.18 (m, 0.85H), 3.89–3.85 (m, 0.15H), 3.74 (s, 3H), 3.67 (m, 0.85H), 1.21 (d, *J* = 6.6 Hz, 2.5H), 1.11 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 140.5, 132.4, 129.7, 129.0, 128.9, 128.8, 128.4, 127.13, 127.06, 114.0, 113.9, 62.1, 61.6, 61.3, 60.9, 55.4, 16.8, 16.1; IR (neat) 3275, 3063, 2930, 2837, 2106, 1611, 1585, 1513, 1446, 1380, 1322, 1249, 1178, 1159, 1091, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_4NaO_3S$ $[M + Na]^+$ 369.0998, found $[M + Na]^+$ 369.0944.

(±)-*N*-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propyl)-4-chlorobenzenesulfonamide (17e)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15a**, using *p*-chlorobenzenesulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamide **17e** (70 mg, 77%, dr 6:1) was obtained overnight as a colorless oil. R_f = 0.15 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2H), 7.27–7.23 (m, *J* = 8.7, 2.2 Hz, 2H), 6.95–6.91 (m, 2H), 6.70–6.67 (m, 2H), 5.76 (d, *J* = 8.7 Hz, 0.15H), 5.67 (d, *J* = 6.1 Hz, 0.85H), 4.30 (dd, *J* = 7.9, 4.6 Hz, 0.15H), 4.22 (t, *J* = 5.7 Hz, 0.85H), 3.93–3.89 (m, 0.15H), 3.77 (s, 3H), 3.69 (m, 0.85H), 1.24 (d, *J* = 6.6 Hz, 2.5H), 1.14 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 159.5, 139.1, 139.0, 138.80, 138.76, 129.3, 129.1, 129.0, 128.9, 128.6, 128.52, 128.46, 127.5, 114.0, 113.8, 62.0, 61.8, 61.1, 61.0, 55.4, 16.8, 16.1; IR (neat) 3271, 2932, 2837, 2108, 1610, 1585, 1439, 1250, 1161, 1089, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}ClN_4NaO_3S$ $[M + Na]^+$ 403.0608, found $[M + Na]^+$ 403.0529.

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (19a)[19] and (1*S*,4*R*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (19b)

A solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 mol/L in toluene, 200 μL, 200 μmol, 0.06 equiv.) was prepared in toluene (10 mL). *N*,*N*-diethylaniline borane (1.2 mL, 6.8 mmol, 2.0 equiv.) was added. A solution of 4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one **18** (1.0 g, 3.4 mmol, 1.0 equiv.) in toluene (12.5 mL) was slowly added via a syringe pump over 5 h. The reaction mixture was stirred at room temperature for 10.5 h. Methanol (2.5 mL) and 1 N HCl (2.5 mL) were carefully added and the resulting mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 5:1) to afford isolated alcohols **19a** (470 mg, 47%) and **19b** (498 mg, 50%) as colorless oils. **19a**: $[\alpha]_D^{25}$ +53.9 (*c* 0.5, $CHCl_3$), lit.[19] $[\alpha]_D^{25}$ +50.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.29–7.24 (m, 2H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 6.98 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 4.87 (t, *J* = 4.4 Hz, 1H), 3.99 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.13–1.97 (m, 4H), 1.81 (s, 1H); analytical data are in accordance with literature data.[19] **19b**: R_f = 0.28 (hexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.90–6.81 (m, 2H), 4.89 (t, *J* = 5.7 Hz, 1H), 4.14 (t, *J* = 6.4 Hz, 1H), 2.41–2.30 (m, 1H), 2.17–2.06 (m, 1H), 1.90–1.73 (m, 3H); IR (neat) 3327, 3022, 2936, 2862, 1558, 1468, 1396, 1265, 1131, 1030, 764 cm^{-1}.

***N*-((1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(trimethylsilyl)ethane-1-sulfonamide (20a) and *N*-((1*R*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(trimethylsilyl)ethane-1-sulfonamide (20b)**

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 79 mg of alcohol **19a**, using 2-(trimethylsilyl)ethane-1-sulfonamide as the nucleophile and $AuCl_3$ as the catalyst, sulfonamides **20a** (74 mg, 60%) and **20b** (26 mg, 21%) were obtained overnight and isolated after flash column chromatography. For **20a**: $[\alpha]_D^{25}$ +23.5 (*c* 0.4, $CHCl_3$); R_f = 0.52 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.17 (td, *J* = 7.5, 1.4 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.83 (d, *J* = 7.9 Hz, 1H), 4.68 (dt, *J* = 8.1, 4.8 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.12–2.94 (m, 2H), 2.19–2.09 (m, 1H), 2.06–1.93 (m, 3H), 1.11–0.97 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 138.7, 136.5, 132.7, 130.72, 130.65, 130.61, 130.3, 129.4, 128.5, 128.3, 127.6, 52.1, 50.6, 44.7, 29.3, 28.9, 11.0, –1.8; IR (neat) 3264, 2961, 1467, 1322, 1139, 757 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}Cl_2NNaO_2SSi$ $[M + Na]^+$ 478.08010, found $[M + Na]^+$ 478.08026 and calcd for $C_{21}H_{27}Cl_2KNO_2SSi$ $[M + K]^+$ 494.05404, found $[M + K]^+$ 494.05412. For **20b**: $[\alpha]_D^{25}$ +34.7 (*c* 0.6, $CHCl_3$); R_f = 0.34 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 4.79–4.71 (m, 1H), 4.39 (d, *J* = 8.6 Hz, 1H), 4.15–4.10 (m, 1H), 3.14–2.97 (m, 2H), 2.33–2.16 (m, 2H), 1.91–1.81 (m, 2H), 1.17–1.04 (m, 2H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 138.6, 136.9, 132.6, 130.7, 130.57, 130.55, 130.4, 128.6, 128.3, 128.1, 127.6, 52.5, 50.7, 44.4, 29.89, 29.85, 11.0, –1.8; IR (neat) 3247, 2924, 2856, 1468, 1310, 1144, 757 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{31}Cl_2N_2O_2SSi$ $[M + NH_4]^+$ 473.12471, found $[M + NH_4]^+$ 473.12461 and calcd for $C_{21}H_{27}Cl_2KNO_2SSi$ $[M + K]^+$ 494.05404, found $[M + K]^+$ 494.05435.

***N*-((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methyl-2-(trimethylsilyl)ethane-1-sulfonamide (21)**

The starting sulfonamide **20a** (57 mg, 0.13 mmol, 1.0 equiv.) was dissolved in *N*,*N*-dimethylformamide (1.7 mL). NaH (60% in min-

eral oil, 11 mg, 0.27 mmol, 2.1 equiv.) was added. The reaction mixture was stirred at room temperature for 2.5 h. Methyl iodide (20 μL, 0.32 mmol, 2.5 equiv.) was added. The reaction mixture was stirred at room temperature for 19 h. Water (2.5 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/ethyl acetate 10:0 to 9:1) to afford *N*-methyl sulfonamide **21** (61 mg, quantitative) as a white solid. $[\alpha]_D^{25}$ +44.5 (*c* 0.2, $CHCl_3$); R_f = 0.65 (hexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.33 (td, *J* = 7.7, 1.5 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.2 Hz, 1H), 5.16 (dd, *J* = 10.9, 6.3 Hz, 1H), 4.20 (dd, *J* = 5.6, 2.7 Hz, 1H), 3.10–2.92 (m, 2H), 2.70 (s, 3H), 2.30 (tdd, *J* = 13.1, 5.6, 3.1 Hz, 1H), 2.04 (ddt, *J* = 13.2, 5.2, 2.7 Hz, 1H), 1.88 (tdd, *J* = 13.3, 11.0, 2.9 Hz, 1H), 1.83–1.71 (m, 1H), 1.17–0.99 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 138.4, 135.5, 132.5, 130.9, 130.7, 130.34, 130.25, 128.1, 127.97, 127.95, 127.92, 56.7, 49.0, 43.0, 30.2, 29.9, 22.4, 10.8, –1.8; IR (neat) 2925, 2855, 1467, 1451, 1329, 1130, 756 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{29}Cl_2NNaO_2SSi$ $[M + Na]^+$ 492.09575, found $[M + Na]^+$ 492.09602 and calcd for $C_{22}H_{29}Cl_2KNO_2SSi$ $[M + K]^+$ 508.06969, found $[M + K]^+$ 508.07034.

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (22)[19]

The starting *N*-methyl sulfonamide **21** (52 mg, 0.11 mmol, 1.0 equiv.) was dissolved in *N*,*N*-dimethylformamide (1.0 mL). CsF (58 mg, 0.38 mmol, 3.4 equiv.) was added. The reaction mixture was stirred at 95 °C for 20 h. Methanol (0.5 mL) was added, the resulting mixture was concentrated under reduced pressure, and residual *N*,*N*-dimethylformamide was removed under high vacuum. Diethyl ether (5 mL) was added, the resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, dichloromethane/methanol 10:1) to afford amine **22** (22 mg, 65%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.21 (t, *J* = 7.1 Hz, 1H), 7.13 (td, *J* = 7.5, 1.5 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 3.99 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.85 (t, *J* = 4.4 Hz, 1H), 2.55 (s, 3H), 2.16–1.98 (m, 3H), 1.95–1.83 (m, 1H); analytical data are in accordance with literature data.[19]

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride, (+)-sertraline-HCl (23)[19,20]

Amine **22** (22 mg, 0.73 mmol, 1.0 equiv.) was dissolved in 4.0 mol/L HCl in dioxane (2.2 mL). The reaction mixture was stirred at room temperature. The resulting mixture was concentrated under reduced pressure and dried under high vacuum. The crude product was washed with diethyl ether and dried under high vacuum to afford amine hydrochloride **23** (18 mg, 71%) as a white solid. $[\alpha]_D^{25}$ +31.1 (*c* 0.4, CH_3OH), lit.[19] $[\alpha]_D^{25}$ +32.5 (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, *J* = 7.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.40–7.30 (m, 2H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 4.50 (t, *J* = 4.6 Hz, 1H), 4.19 (dd, *J* = 9.9, 5.5 Hz, 1H), 2.85 (s, 3H), 2.35–2.15 (m, 3H), 2.06–1.95 (m, 1H); analytical data are in accordance with literature data.[19,20]

(±)-1-Methoxy-4-((1*S*,2*S*)-1-(4-methoxyphenoxy)-2-nitrobutyl)benzene (24a)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 48 mg of alcohol **3a**, using 4-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, ether **24a** (41 mg, 58%, dr 7:1) was obtained after 2 h as a light yellow oil. R_f = 0.40 (hexane/ethyl acetate 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H), 6.95–6.87 (m, 2H), 6.75–6.64 (m, 4H), 5.25 (d, *J* = 9.6 Hz, 1H), 4.76 (td, *J* = 11.0, 3.3 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 1.83 (ddq, *J* = 14.4, 11.1, 7.2 Hz, 1H), 1.42 (dqd, *J* = 14.9, 7.5, 3.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 154.9, 151.3, 128.9, 128.2, 118.5, 114.6, 114.5, 94.4, 82.9, 55.7, 55.4, 23.8, 10.3; IR (neat) 3041, 2997, 2931, 2837, 1611, 1551, 1504, 1461, 1250, 1213, 1175, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NNaO_5$ $[M + Na]^+$ 354.13119, found $[M + Na]^+$ 354.13118.

(±)-1-(Benzyloxy)-4-((1*S*,2*S*)-1-(4-methoxyphenyl)-2-nitrobutoxy)benzene (24b)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 48 mg of alcohol **3a**, using *p*-(benzyloxy)phenol as the nucleophile and $AuCl_3$ as the catalyst, ether **24b** (24 mg, 67%, dr 20:1) was obtained after 2 h as a colorless oil. R_f = 0.20 (hexane/diethyl ether 17:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.27 (m, 7H), 6.96–6.86 (m, 2H), 6.80–6.65 (m, 4H), 5.26 (d, *J* = 9.7 Hz, 1H), 4.93 (s, 2H), 4.76 (ddd, *J* = 11.1, 9.8, 3.4 Hz, 1H), 3.80 (s, 3H), 1.83 (ddq, *J* = 14.6, 11.3, 7.4 Hz, 1H), 1.42 (dqd, *J* = 14.9, 7.6, 3.3 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 153.8, 151.2, 136.7, 128.6, 128.4, 127.9, 127.7, 127.3, 118.1, 115.3, 114.3, 94.1, 82.5, 70.3, 55.2, 23.5, 10.0; IR (neat) 3039, 3015, 2977, 2946, 2845, 1615, 1555, 1506, 1459, 1254, 1232, 1178, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_5$ $[M + NH_4]^+$ 425.2071, found $[M + NH_4]^+$ 425.20603 and calcd for $C_{24}H_{25}NNaO_5$ $[M + Na]^+$ 430.16249, found $[M + Na]^+$ 430.16158.

(±)-1-Methoxy-4-((1*S*,2*S*)-2-nitro-1-(*p*-tolyloxy)butyl)benzene (24c)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 48 mg of alcohol **3a**, using *p*-cresol as the nucleophile and $AuCl_3$ as the catalyst, ether **24c** (16 mg, 57%, dr 20:1) was obtained after 4 h as a colorless oil. R_f = 0.52 (hexane/diethyl ether 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 6.97–6.92 (m, 2H), 6.92–6.87 (m, 2H), 6.75–6.61 (m, 2H), 5.34 (d, *J* = 9.6 Hz, 1H), 4.76 (ddd, *J* = 11.1, 9.6, 3.4 Hz, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 1.85 (ddq, *J* = 14.4, 11.0, 7.2 Hz, 1H), 1.43 (dqd, *J* = 14.7, 7.4, 3.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 155.1, 131.4, 129.9, 128.8, 128.1, 116.8, 114.6, 94.4, 81.7, 55.4, 23.8, 20.6, 10.3; IR (neat) 2980, 2932, 2846, 1615, 1556, 1513, 1255, 1232, 1178, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_4$ $[M + NH_4]^+$ 333.18088, found $[M + NH_4]^+$ 333.18044 and calcd for $C_{18}H_{21}NNaO_4$ $[M + Na]^+$ 338.13628, found $[M + Na]^+$ 338.13592.

(±)-1-Methoxy-4-((1*S*,2*S*)-2-nitro-1-(*p*-tolyloxy)pent-4-en-1-yl)benzene (24d)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3b**, using *p*-cresol as the nucleophile and $AuCl_3$ as the catalyst, ether **24d** (34 mg, 49%, dr 20:1) was obtained overnight as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 5.62 (dddd, *J* = 16.5, 10.3, 8.2, 5.8 Hz, 1H), 5.42 (d, *J* = 7.2 Hz, 0.02H), 5.37 (d, *J* = 9.5 Hz, 0.98H), 5.12–5.04 (m, 2H), 4.89 (ddd, *J* = 10.7, 9.6, 3.5 Hz, 1H), 3.80 (s, 2.88H), 3.78 (s, 0.12H), 2.52 (ddd, *J* = 14.8, 10.7, 8.3 Hz, 1H), 2.23–2.15 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 155.1, 131.5, 130.8, 129.9, 128.9, 127.8, 120.0, 116.8, 114.7, 92.3, 81.4, 55.4, 34.7, 20.6; IR (neat) 2902, 2825, 1651, 1611, 1513, 1327, 1250, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_4$ $[M + Na]^+$ 350.1369, found $[M + Na]^+$ 350.1417.

(±)-1-Methoxy-4-((1*S*,2*S*)-1-(4-methoxyphenoxy)-2-nitropent-4-en-1-yl)benzene (24e)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3b**, using 4-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, ether **24e** (52 mg, 72%, dr 4:1) was obtained overnight as a light yellow oil. R_f = 0.36 (hexane/ethyl acetate 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 2H), 6.93–6.89 (m, 1.6H),

6.89–6.85 (m, 0.4H), 6.75–6.65 (m, *J* = 9.4, 6.7, 4.5 Hz, 4H), 5.76 (dddd, *J* = 16.2, 10.2, 8.2, 5.8 Hz, 0.2H), 5.61 (dddd, *J* = 16.2, 10.2, 8.2, 5.8 Hz, 0.8H), 5.35 (d, *J* = 7.2 Hz, 0.2H), 5.27 (d, *J* = 9.6 Hz, 0.8H), 5.20–5.12 (m, 0.4H), 5.07 (dd, *J* = 20.4, 5.0 Hz, 1.6H), 4.92–4.85 (m, 0.8H), 4.81 (ddd, *J* = 10.3, 7.2, 3.4 Hz, 0.2H), 3.80 (s, 2.4H), 3.78 (s, 0.6H), 3.71 (s, 0.6H), 3.69 (s, 2.4H), 2.55–2.45 (m, 1H), 2.20–2.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 155.0, 151.3, 131.7, 130.8, 129.0, 128.4, 128.2, 127.8, 120.0, 119.7, 118.5, 117.6, 114.7, 114.7, 114.6, 114.5, 92.4, 82.6, 80.8, 55.7, 55.7, 55.4, 55.4, 34.7, 33.9; IR (neat) 2901, 2850, 1681, 1600, 1572, 1510, 1421, 1312, 1118 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_5$ [M + Na]$^+$ 366.1318, found [M + Na]$^+$ 366.1375.

(±)-1-((1*S*,2*S*)-1-(Benzyloxy)-2-nitropent-4-en-1-yl)-4-methoxybenzene (24f)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3b**, using benzyl alcohol as the nucleophile and $AuCl_3$ as the catalyst, ether **24f** (52 mg, 76%, dr 20:1) was obtained overnight as a light yellow oil. R_f = 0.39 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 7.18–7.15 (m, 2H), 6.97–6.94 (m, 2H), 5.56 (dddd, *J* = 16.8, 10.2, 8.2, 5.8 Hz, 1H), 5.07–4.98 (m, 2H), 4.74 (ddd, *J* = 10.8, 9.7, 3.3 Hz, 1H), 4.66 (d, *J* = 9.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.85 (s, 3H), 2.41 (ddd, *J* = 14.9, 10.8, 8.3 Hz, 1H), 2.04 (dddd, *J* = 14.9, 7.2, 3.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 137.2, 131.0, 129.3, 128.5, 128.0, 127.8, 119.7, 114.7, 92.5, 81.2, 70.5, 55.5, 34.8, 29.9; IR (neat) 2923, 2852, 1609, 1555, 1512, 1455, 1250, 1174 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_4$ [M + Na]$^+$ 350.1369, found [M + Na]$^+$ 350.1296.

(±)-1-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenyl)propoxy)-4-methylbenzene (24g)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15a**, using *p*-cresol as the nucleophile and $AuCl_3$ as the catalyst, ether **24g** (43 mg, 61%, dr 5:1) was obtained overnight as a light yellow oil. R_f = 0.23 (hexane/diethyl ether 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.29 (m, 0.33H), 7.24–7.19 (m, 1.67H), 7.06–7.01 (m, 1H), 6.95–6.90 (m, 1H), 6.88–6.81 (m, 2.5H), 6.74 (d, *J* = 2.1 Hz, 0.3H), 6.69 (d, *J* = 8.1 Hz, 0.85H), 6.61 (d, *J* = 8.1 Hz, 0.15H), 5.43 (s, 1H), 4.40–4.28 (m, 1H), 4.18 (d, *J* = 9.1 Hz, 0.15H), 4.12 (d, *J* = 9.1 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.28 (s, 2.5H), 2.25 (s, 0.5H), 1.31 (dd, *J* = 6.4, 4.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 153.4, 151.5, 150.9, 133.3, 133.1, 130.4, 130.2, 130.1, 129.8, 129.6, 129.5, 128.7, 128.6, 128.4, 127.6, 116.9, 116.2, 115.2, 114.2, 114.0, 60.6, 60.2, 55.4, 51.3, 50.3, 20.9, 20.6, 18.8, 18.5; IR (neat) 2914, 2858, 2100, 1615, 1542, 1504, 1437, 1241, 1188, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_3NaO_3$ [M + Na]$^+$ 320.1375, found [M + Na]$^+$ 320.1321.

(±)-1-((1*S*,2*S*)-2-Azido-1-(4-methoxyphenoxy)propyl)-4-methoxybenzene (24h)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15a**, using 4-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, ether **24h** (50 mg, 67%, dr 5:1) was obtained overnight as a colorless oil. R_f = 0.21 (hexane/diethyl ether 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.28 (m, 0.4H), 7.22–7.18 (m, 1.6H), 6.86–6.81 (m, 3H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.33–4.25 (m, 1H), 4.19 (d, *J* = 8.8 Hz, 0.15H), 4.12 (d, *J* = 9.2 Hz, 0.85H), 3.78 (s, 0.5H), 3.77 (s, 2.5H), 3.75 (s, 2.5H), 3.73 (s, 0.5H), 1.32 (d, *J* = 6.4 Hz, 0.5H), 1.30 (d, *J* = 6.4 Hz, 2.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 154.0, 153.9, 147.7, 147.2, 132.8, 132.7, 129.8, 129.5, 129.4, 117.7, 116.9, 116.2, 115.7, 115.4, 115.0, 114.2, 114.1, 112.5, 112.1, 60.8, 60.1, 55.8, 55.4, 51.0, 50.2, 29.8, 18.8, 18.5; IR (neat) 2928, 2835, 2102, 1608, 1554, 1508, 1431, 1246, 1178, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_3NaO_3$ [M + Na]$^+$ 336.1324, found [M + Na]$^+$ 336.1273.

(±)-1-((1*S*,2*S*)-2-azido-1-(4-methoxyphenoxy)-3,3-dimethylbutyl)-4-methoxybenzene (24i)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 30 mg of alcohol **15c**, using 4-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, ether **24i** (28 mg, 65%, dr 4:1) was obtained overnight as a colorless oil. R_f = 0.20 (hexane/diethyl ether 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.38 (m, 0.4H), 7.35–7.32 (m, 1.6H), 6.94–6.90 (m, 1.6H), 6.89–6.86 (m, 0.4H), 6.79–6.73 (m, 4H), 5.30 (d, *J* = 2.7 Hz, 0.8H), 5.07 (d, *J* = 6.7 Hz, 0.2H), 3.82 (s, 2.4H), 3.82 (s, 0.6H), 3.73 (s, 2.4H), 3.73 (s, 0.6H), 3.59 (d, *J* = 6.7 Hz, 0.2H), 3.20 (d, *J* = 2.7 Hz, 0.8H), 1.10 (s, 7.2H), 1.02 (s, 1.8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 159.5, 154.1, 151.6, 131.9, 131.0, 130.7, 129.4, 127.8, 117.1, 116.6, 114.69, 114.66, 114.3, 114.02, 114.00, 80.6, 79.6, 77.6, 55.8, 55.4, 55.3, 42.5, 36.6, 35.6, 29.8, 29.0, 27.9, 27.5, 26.6; IR (neat) 2998, 2922, 2113, 1638, 1610, 1584, 1440, 1300, 1109, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}N_3NaO_3$ [M + Na]$^+$ 378.1794, found [M + Na]$^+$ 378.1752.

(±)-2,6-Di-*tert*-butyl-4-((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitrobutyl)phenol (25a)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3a**, using 2,6-di-*tert*-butylphenol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25a** (52 mg, 62%, dr 20:1) was obtained overnight as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 7.06 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.12 (td, *J* = 11.0, 3.0 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 0.16H), 3.77 (s, 2.84H), 1.86 (m, 1H), 1.67 (m, 1H), 1.41 (s, 0.7H), 1.39 (s, 17.3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 153.0, 136.0, 132.7, 130.7, 129.1, 124.0, 114.5, 94.1, 55.4, 54.9, 34.5, 30.4, 26.7, 10.6; IR (neat) 3406, 2854, 2832, 2814, 1638, 1610, 1580, 1454, 1357, 1225, 1124 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{35}NNaO_4$ [M + Na]$^+$ 436.2464, found [M + Na]$^+$ 436.2479.

(±)-4-((1*R*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-2,6-dimethylphenol (25b)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3a**, using 2,6-dimethylphenol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25b** (67 mg, 92%, dr 20:1) was obtained overnight as a yellow oil. R_f = 0.36 (hexane/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.91 (s, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.14 (ddd, *J* = 11.5, 10.5, 3.2 Hz, 1H), 4.60 (s, 1H), 4.25 (d, *J* = 11.6 Hz, 1H), 3.77 (s, 3H), 2.16 (s, 6H), 1.89 (tdd, *J* = 14.6, 7.3, 2.4 Hz, 1H), 1.77–1.65 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 151.5, 132.4, 131.8, 129.0, 127.5, 123.4, 114.6, 93.9, 55.4, 54.1, 26.6, 16.1, 10.5; HRMS (ESI) calcd for $C_{19}H_{27}N_2O_4$ [M + NH_4]$^+$ 347.19653, found [M + NH_4]$^+$ 347.19541 and calcd for $C_{19}H_{23}NNaO_4$ [M + Na]$^+$ 352.15193, found [M + Na]$^+$ 352.1511.

(±)-4-((1*R*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-2-methylphenol (25c)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3a**, using *o*-cresol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25c** (55 mg, 72%, dr 12:1) was obtained overnight as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.21 (m, 0.05H), 7.20–7.16 (m, 1.95H), 7.04–7.00 (m, 2H), 6.88–6.84 (m, 1.93H), 6.83–6.79 (m, 0.07H), 6.67 (d, *J* = 8.2 Hz, 0.06H), 6.61 (t, *J* = 5.3 Hz, 0.94H), 5.13 (td, *J* = 10.8, 3.1 Hz, 1H), 5.00 (s, 1H), 4.41 (d, *J* = 11.6 Hz, 0.01H), 4.28 (d, *J* = 11.5 Hz, 0.99H), 3.77 (s, 2.9H), 3.74 (s, 0.1H), 2.21 (s, 0.1H), 2.16 (s, 2.9H), 1.93–1.81 (m, 1H), 1.78–1.68 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 0.03H), 0.93 (t, *J* = 7.4 Hz, 2.97H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 153.2, 132.2, 132.2, 130.3, 129.0, 125.7, 124.4, 115.3, 114.6, 94.0, 55.4, 54.1, 26.5, 16.0, 10.5; IR (neat) 3433, 2972, 2934, 2879, 2837, 1608, 1584, 1545, 1508, 1249, 1178, 1030 cm^{-1}; HRMS (ESI)

calcd for $C_{18}H_{21}NNaO_4$ [M + Na]$^+$ 338.1369, found [M + Na]$^+$ 338.1395.

(±)-2-((1*R*,2*S*)-1-(4-Methoxyphenyl)-2-nitrobutyl)-5-methylphenol (25d)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 40 mg of alcohol **3a**, using *m*-cresol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25d** (42 mg, 71%, dr 20:1) was obtained after 5 h as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.63 (dd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 5.14 (td, J = 11.0, 3.0 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.76 (s, 2.9H), 3.73 (s, 0.1H), 2.32 (s, 0.1H), 2.25 (s, 2.9H), 1.87 (ddq, J = 14.5, 10.5, 7.3 Hz, 1H), 1.69 (dqd, J = 14.8, 7.4, 3.1 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 154.5, 138.2, 131.1, 130.7, 129.7, 126.3, 118.1, 114.5, 113.1, 93.4, 55.4, 49.3, 26.8, 19.9, 10.5; IR (neat) 3405, 2975, 2944, 2861, 1635, 1540, 1456, 1249, 1216, 1136, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_4$ [M + NH_4]$^+$ 333.1809, found [M + NH_4]$^+$ 333.1783 and calcd for $C_{18}H_{21}NNaO_4$ [M + Na]$^+$ 338.13628, found [M + Na]$^+$ 338.13654.

(±)-2,6-Dimethoxy-3-((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitrobutyl)phenol (25e)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **3a**, using 2,6-dimethoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25e** (51 mg, 64%, dr 20:1) was obtained overnight as a white oil. R_f = 0.16 (hexane/ethyl acetate 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.18 (m, 2H), 6.92 (d, J = 8.6 Hz, 1H), 6.85–6.77 (m, 2H), 6.60 (d, J = 8.6 Hz, 1H), 5.45 (s, 0.8H), 5.19 (ddd, J = 11.7, 10.6, 3.1 Hz, 1H), 4.79 (d, J = 11.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 1.89 (ddq, J = 14.5, 10.4, 7.2 Hz, 1H), 1.73 (dqd, J = 14.9, 7.5, 3.2 Hz, 1H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 147.1, 145.0, 139.0, 131.9, 129.6, 126.8, 116.3, 114.4, 106.2, 92.8, 60.5, 56.2, 55.4, 47.3, 26.7, 10.6; IR (neat) 3491, 2936, 2838, 1609, 1548, 1511, 1496, 1319, 1247, 1088 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_6$ [M + H]$^+$ 362.15981, found [M + H]$^+$ 362.16152 and calcd for $C_{19}H_{27}N_2O_6$ [M + NH_4]$^+$ 379.18636, found [M + NH_4]$^+$ 379.18629.

(±)-2-Methoxy-5-((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitrobutyl)phenol (25f)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 30 mg of alcohol **3a**, using 2-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25f** (37 mg, 84%, dr 4:1) was obtained after 5 h as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.16 (m, 2H), 6.88–6.73 (m, 5H), 5.56 (s, 0.25H), 5.51 (s, 0.75H), 5.15–5.07 (m, 1H), 4.29 (dd, J = 16.4, 8.0 Hz, 1H), 3.84 (s, 2.4H), 3.81 (s, 0.6H), 3.77 (s, 2.4H), 3.76 (s, 0.6H), 1.94–1.81 (m, 1H), 1.72 (dqd, J = 14.9, 7.5, 3.0 Hz, 1H), 0.95–0.90 (m, J = 7.4, 2.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.9, 146.7, 145.88, 145.85, 145.0, 133.5, 132.2, 132.04, 131.98, 129.1, 128.5, 119.9, 118.9, 114.8, 114.6, 114.4, 113.8, 110.9, 110.4, 93.9, 93.8, 56.02, 55.97, 55.4, 54.5, 54.3, 26.6, 26.5, 10.5; IR (neat) 3421, 2929, 2905, 1618, 1571, 1499, 1456, 1417, 1314, 1129, 1102, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ [M + H]$^+$ 332.1498, found [M + H]$^+$ 332.1466.

(±)-5-Methoxy-2-((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitrobutyl)phenol (25g)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 30 mg of alcohol **3a**, using 3-methoxyphenol as the nucleophile and $AuCl_3$ as the catalyst, diaryl **25g** (37 mg, 76%, dr 20:1) was obtained after 5 h as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.17 (m, 3H), 6.85–6.76 (m, 2H), 6.46–6.21 (m, 2H), 5.30 (ddd, J = 24.7, 12.4, 2.7 Hz, 1H), 4.70 (dd, J = 11.6, 3.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 1.5H), 3.67 (s, 1.5H), 1.87 (dtt, J = 21.4, 14.5, 7.3 Hz, 1H), 1.78–1.65 (m, 1H), 0.92 (q, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.8, 158.6, 158.1, 156.1, 154.1, 149.0, 132.0, 131.8, 129.60, 129.57, 129.0, 128.3, 127.8, 124.4, 121.0, 119.6, 114.4, 114.2, 114.2, 107.2, 106.5, 106.4, 102.9, 102.8, 99.9, 93.6, 92.66, 92.64, 55.7, 55.38, 55.36, 55.3, 48.0, 47.9, 31.7, 30.2, 29.8, 26.7, 26.3, 14.3, 10.59, 10.54; IR (neat) 3428, 2924, 2918, 1637, 1611, 1559, 1495, 1457, 1374, 1305, 1157, 1117, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ [M + H]$^+$ 332.1498, found [M + H]$^+$ 332.1425.

(±)-2-((1*R*,2*S*)-2-Azido-1-(4-methoxyphenyl)propyl)-4,6-dimethylphenol (25h)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15a**, using 2,4-dimethylphenol as the nucleophile and *p*-toluenesulfonic acid monohydrate as the catalyst, diaryl **25h** (43 mg, 58%, dr 6:1) was obtained overnight as a colorless oil. R_f = 0.12 (hexane/ethyl acetate 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 0.33H), 7.23–7.17 (m, 1.67H), 6.90 (d, J = 1.6 Hz, 0.85H), 6.88–6.80 (m, 3.15H), 5.25 (s, 0.8H), 4.35–4.26 (m, 1H), 4.18 (d, J = 8.8 Hz, 0.15H), 4.12 (d, J = 9.1 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.25 (s, 2.5H), 2.23 (s, 0.5H), 2.19 (s, 2.5H), 2.17 (s, 0.5H), 1.32–1.28 (m, J = 9.5, 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 149.9, 133.1, 130.3, 123.0, 129.8, 129.6, 129.5, 127.6, 127.4, 127.1, 124.6, 114.2, 114.1, 60.7, 60.2, 55.3, 51.1, 50.3, 20.9, 18.8, 18.6, 16.3, 16.1; IR (neat) 3423, 2925, 2100, 1685, 1607, 1582, 1509, 1482, 1454, 1377, 1301, 1245, 1178, 1123, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}N_3NaO_2$ [M + Na]$^+$ 334.1532, found [M + Na]$^+$ 334.1689.

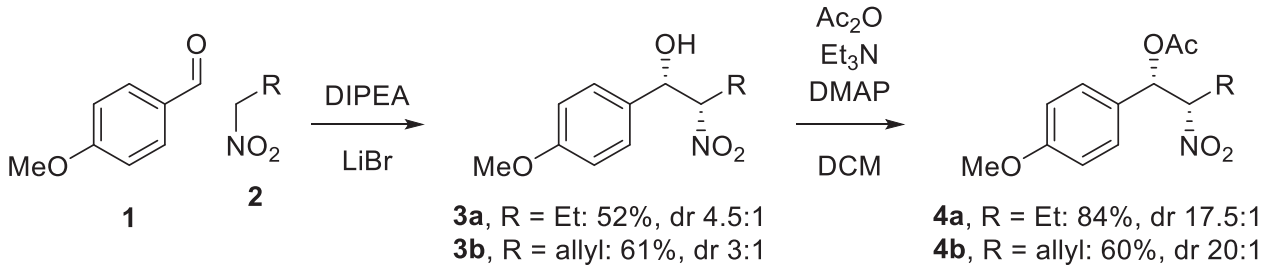
(±)-2-((1*R*,2*S*)-2-Azido-1-(4-methoxyphenyl)-3-methylbutyl)-4-methylphenol (25i)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15b**, using *p*-cresol as the nucleophile and *p*-toluenesulfonic acid monohydrate as the catalyst, diaryl **25i** (52 mg, 76%, dr 7:1) was obtained overnight as a white solid. mp: 112–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.37 (m, 3H), 7.26–7.22 (m, 1.7H), 7.09 (d, J = 1.8 Hz, 0.85H), 7.01 (d, J = 1.9 Hz, 0.15H), 6.91 (dd, J = 8.1, 2.1 Hz, 0.85H), 6.87–6.83 (m, 2.15H), 6.70 (d, J = 8.1 Hz, 0.85H), 6.58 (d, J = 8.1 Hz, 0.15H), 5.66 (s, 0.6H), 4.37 (dd, J = 9.7, 4.0 Hz, 1H), 4.09 (dd, J = 9.9, 3.7 Hz, 0.15H), 3.98 (dd, J = 9.4, 4.6 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.27 (s, 2.5H), 2.26 (s, 0.5H), 1.89–1.83 (m, 0.15H), 1.83–1.72 (m, 0.85H), 1.08–1.02 (m, 3H), 0.98 (d, J = 6.7 Hz, 2.5H), 0.91 (d, J = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 151.5, 150.6, 133.9, 133.2, 130.4, 130.3, 129.9, 129.7, 129.5, 128.7, 128.5, 128.2, 127.6, 116.9, 116.0, 114.3, 114.1, 73.0, 72.0, 66.0, 55.4, 48.1, 47.5, 30.9, 30.7, 29.8, 21.3, 21.1, 20.9, 16.6, 16.0, 15.4; IR (neat) 3402, 2963, 2930, 2873, 2096, 1670, 1573, 1541, 1462, 1482, 1454, 1357, 1388, 1225, 1141, 1135, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_3NaO_2$ [M + Na]$^+$ 348.1688, found [M + Na]$^+$ 348.1651.

(±)-2-((1*R*,2*S*)-2-Azido-1-(4-methoxyphenyl)-3-methylbutyl)-4-methoxyphenol (25j)

Following the general protocol for the acid catalyzed nucleophilic substitution of benzylic alcohols, starting with 50 mg of alcohol **15b**, using 4-methoxyphenol as the nucleophile and *p*-toluenesulfonic acid monohydrate as the catalyst, diaryl **25j** (60 mg, 84%, dr 5:1) was obtained overnight as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.38 (m, 0.33H), 7.24 (dd, J = 6.8, 5.0 Hz, 1.67H), 6.90 (d, J = 2.7 Hz, 0.8H), 6.87–6.83 (m, 2H), 6.80 (d, J = 2.4 Hz, 0.2H), 6.75 (s, 0.3H), 6.73 (s, 0.5H), 6.67 (d, J = 3.0 Hz, 0.5H), 6.66 (d, J = 3.0 Hz, 0.3H), 5.59 (s, 0.8H), 4.40 (d, J = 9.7 Hz, 1H), 4.05 (dd, J = 9.7, 3.8 Hz, 0.2H), 3.97 (dd, J = 9.6, 4.1 Hz, 0.8H), 3.77 (s, 2.5H), 3.76 (s, 0.5H), 3.75 (s, 2.5H), 3.74 (s, 0.5H), 1.91–1.76 (m, 1H), 1.07–1.03 (m, 3H), 0.97 (d, J = 6.7 Hz, 2.5H), 0.93 (d, J = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 153.9, 147.7, 147.0, 133.5, 132.9, 130.0, 129.9, 129.5, 129.5, 117.7, 116.6, 116.2, 115.6, 115.0, 114.3, 114.1, 112.7, 111.9, 73.1, 72.0, 66.0, 56.2, 55.3, 47.5, 47.3, 30.9, 30.7, 21.3, 21.1, 16.3, 16.1, 15.3; IR (neat) 3418, 2895, 2807, 2102, 1673, 1640, 1587, 1499,

Scheme 1. Synthesis of racemic α-hydroxy- and α-acetoxy-β-nitroalkyl (or β-nitroallyl) arenes.



1 **2**

3a, R = Et: 52%, dr 4.5:1
3b, R = allyl: 61%, dr 3:1

4a, R = Et: 84%, dr 17.5:1
4b, R = allyl: 60%, dr 20:1

1482, 1454, 1357, 1318, 1267, 1178, 1124, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_3NaO_3$ [M + Na]$^+$ 364.1637, found [M + Na]$^+$ 364.1704.

Results and discussion

We chose to use racemic α-hydroxy-β-nitroalkyl arenes to establish conditions for catalytic benzylic substitutions being cognizant that access to enantiopure nitroaldol products remains to be a challenge.[21] In fact, enantiopure or highly enriched *syn*- or *anti*-selective Henry reactions with aromatic aldehydes and nitroalkanes higher than nitromethane have been seldom achieved.[22] Therefore, rather than using enantioenriched nitroaldol products or trying to adapt the singularly successful enantioselective Henry reaction[23] to *p*-anisaldehyde and 1-nitropropane (or 4-nitrobutene) for the purposes of this study, we opted for racemic partners. However, we were pleased that enantiomeric *N*-sulfonamides could be separated by chiral HPLC (vide infra) and obtained as enantiopure *syn*-diastereomers.

The synthesis of racemic α-hydroxy- and α-acetoxy-β-nitroalkyl (or β-nitroallyl) arenes is shown in Scheme 1. Due to the acidity of the β-H, competing elimination occurred during the acetylation of alcohols **3a** and **3b**, presumably from the *anti*-isomer. As a result, the acetylated nitro alcohols **4a** and **4b** were highly enriched favoring the *syn*-isomer. In the course of our previous studies, we indeed observed a kinetic differentiation in the reactivity of *syn*- and *anti*-diastereoisomers of nitroalcohols.[14]

Treatment of a diastereomeric mixture of α-acetoxy-β-nitro arylalkanes[14] with *tert*-butylsulfonamide ($BusNH_2$),[24] 2-(trimethylsilyl) ethane-1-sulfonamide ($SESNH_2$),[25] and *p*-toluenesulfonamide in the presence of 10 mol% $AuCl_3$ in dichloromethane afforded the corresponding *syn*-oriented products as predominant diastereomers (Table 1, entries 1–3). The mixture of racemic *tert*-butylsulfonamides **5a** and **5b** could be separated by preparative chiral HPLC affording (–)-(*R*,*R*)-**5a** and (+)-(*S*,*S*)-**5b** as enantiomers. X-ray crystallographic analysis was performed on the (–)-(*R*,*R*)-**5a** enantiomer, allowing for the determination of the absolute configuration and *syn*-diastereoselectivity.

We had anticipated that the Bus and SES groups could be easily cleaved under acidic[24] or fluoride-mediated[26] conditions. However, **5a** or **5b** could not be converted to the free amine as the *tert*-butylsulfonamide moiety remained unreactive in mildly acidic media. Harsher conditions led to extensive decomposition through benzylic cleavage followed by retro-aldolization. Removal of the SES group in product **5c**, using various fluoride sources (such as CsF,[26a] tetra-*n*-butylammonium fluoride,[26b] tetra-*n*-butylammonium fluoride/acetic acid,[26c] triethylamine trihydrofluoride) under either basic or acidic conditions, failed in a similar fashion. Nonetheless, the nitro group in (+)-(*S*,*S*)-**5b** could be selectively reduced to the corresponding amine in the presence of zinc and trimethylsilyl chloride in methanol,[27] then *N*-acetylated to give compound **7** (Scheme 2). Treatment with triflic acid in dichloromethane at –20 °C, followed by protection of the resulting benzylic amine gave the enantiopure *N*-Boc derivative (+)-(*S*,*S*)-**8** in excellent overall yield. Additionally, we were pleased that chiral HPLC could also provide enantiopure (+)-(*S*,*S*)-**8** and *ent*-**8** from a racemic mixture.

Achieving predominantly *syn*- or *anti*-enantioselectivity in the aza-Henry reactions with nitroalkanes has been a challenge.[10] Although highly *anti*-enantioselective aza-Henry reactions have been reported by Johnston[12] and Jacobsen,[13] to the best of our knowledge, high *syn*-selectivity was reported for the first time by Shibasaki.[11] For example, reaction of *p*-anisaldehyde *N*-Boc aldimine with 1-nitropropane in the presence of a heterobimetallic Cu-Sm Schiff base complex derived from (1*R*,2*R*)-diaminocyclohexane, led to the coupled product (*R*,*R*)-**10** in 64% yield and 20:1 *syn*-selectivity (91% ee)[11] (Fig. 3). Comparison between the signs of optical rotations of compounds **5a**, **5b** and **10** on one hand, and **8** and **11** on the other led to a conclusion consistent with the result previously obtained from the X-ray diffraction analysis (Fig. 3) and consolidated our assignments of the absolute configurations of (–)-(*R*,*R*)-**5a**, (+)-(*S*,*S*)-**5b**, and (+)-(*S*,*S*)-**8** (Fig. 3).

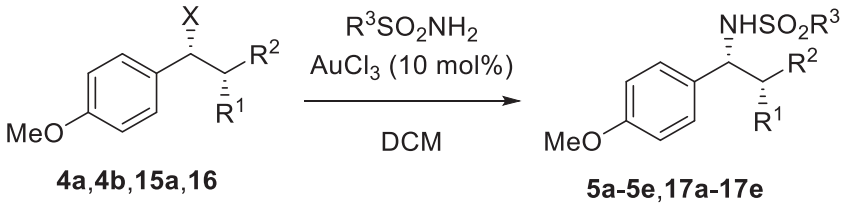
Reduction of a racemic mixture of **5a** and **5b** led to **6**, which was treated with triphosgene followed by $AlCl_3$ in dichloromethane, to afford racemic cyclic urea **9** with no erosion of *syn*-selectivity according to NMR spectroscopy.

The synthesis of racemic α-hydroxy- and α-acetoxy-β-azidoalkyl arenes is shown in Scheme 3. Benzylic sulfonamidation in this series could be achieved with the benzylic alcohol **15a** (Method A) or the corresponding acetate **16** (Method B) depending on the sulfonamide (Table 1, entries 5–12). Although the yields were generally acceptable in favor of the *syn*-isomers, they varied with the nature of the sulfonamide. Comparison between alcohol **15a** and acetate **16** (Table 1, entries 5–7 vs. 10–12) shows that the better the leaving group, the lesser the diastereoselectivity. Furthermore, the use of $TsNH_2$ led to diastereomeric ratios somewhat lower than those obtained with $BusNH_2$ and $SESNH_2$, as was also the case in the nitro series.

Attempts to cleave the Bus group in **17a** under acidic conditions led to degradation as was observed in the nitro series with compounds **5a** and **5b**. However, contrary to the nitro series with compound **5c**, treatment of the SES derivative **17b** with CsF[26a] afforded the corresponding amine that could be converted to the crystalline *N*-tosylamide **17c**. Presumably, this is due to the lower acidity of the β-H in **17b** compared to **5c**. X-ray crystal structures of several derivatives confirmed the *syn*-selectivity of the major products, although the ratios were diminished compared with their nitro analogues possibly due to the smaller size of the azido group.

To demonstrate the utility of the benzylic sulfonamidation, we report an expedient route to (+)-sertraline (Zoloft), one of the most frequently prescribed antidepressant drugs[2,28] (Scheme 4). Thus, reduction of the tetralone **18** with the CBS reagent[29] as described by Jung et al.[19] gave the alcohol **19** as a 1:1 mixture of diastereomers, which could be separated by column chromatography to give **19a** and **19b**. Treatment of **19a** with $SESNH_2$ in the presence of 10 mol% $AuCl_3$ afforded the sulfonamide **20** in 81% yield as a mixture of diastereomers (dr 3:1 in favor of the desired product), which could also be separated by column chromatography to give **20a** (major isomer) and **20b** (minor isomer). Methylation of **20a** and treatment with CsF in DMF at 95 °C afforded (+)-sertraline **23**

Table 1. Benzylic sulfonamidation.

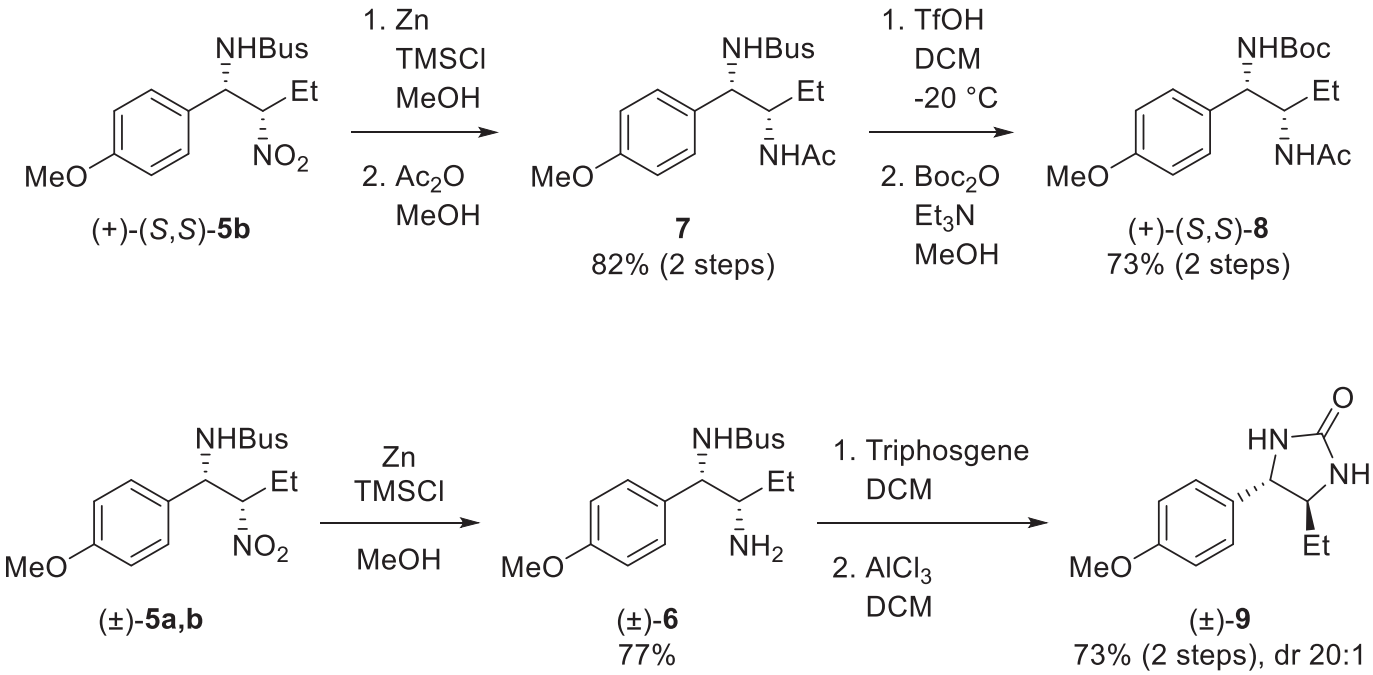


4a,**4b**,**15a**,**16** **5a-5e**,**17a-17e**

Entry	Substrate	R^1	R^2	X	R^3	Product[a]	Yield (dr[b])
1	**4a**	NO_2	Et	OAc	*t*Bu	**5a**[c], **5b**	82% (20:1)
2	**4a**	NO_2	Et	OAc	$Me_3Si(CH_2)_2$	**5c**	86% (20:1)
3	**4a**	NO_2	Et	OAc	*p*-MeC_6H_4	**5d**	59% (18:1)
4	**4b**	NO_2	Allyl	OAc	$Me_3Si(CH_2)_2$	**5e**	68% (20:1)
5	**15a**	N_3	Me	OH	*t*Bu	**17a**[c]	61%–66% (4.5–7:1)
6	**15a**	N_3	Me	OH	$Me_3Si(CH_2)_2$	**17b**	67%–78% (6:1)
7	**15a**	N_3	Me	OH	*p*-MeC_6H_4	**17c**[c]	68%–83% (4:1)
8	**15a**	N_3	Me	OH	C_6H_5	**17d**[c]	59% (5:1)
9	**15a**	N_3	Me	OH	*p*-ClC_6H_4	**17e**[c]	77% (6:1)
10	**16**	N_3	Me	OAc	*t*Bu	**17a**[c]	55% (2:1)
11	**16**	N_3	Me	OAc	$Me_3Si(CH_2)_2$	**17b**	91% (6:1)
12	**16**	N_3	Me	OAc	*p*-MeC_6H_4	**17c**[c]	63% (1.5:1)

[a]Racemic mixture.
[b]Ratios determined by ^1H NMR at 300, 400, or 500 MHz.
[c]X-ray structural data available (see Supplementary data).

Scheme 2. Functionalization of the diamine.

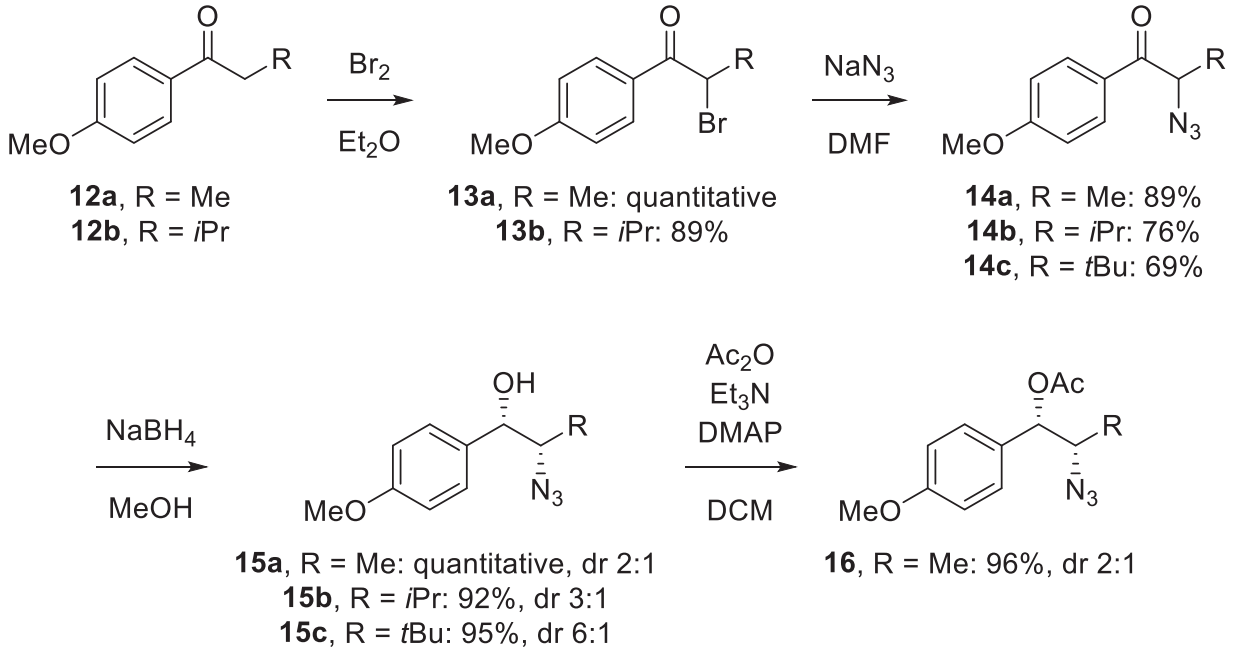


as the hydrochloride salt. The ketone **18** has been previously resolved into the desired (*S*)-isomer by a continuous chromatography protocol as part of the commercial process for the production of sertraline.[30] A new chemoenzymatic synthesis of sertraline was recently reported.[31]

The facile benzylic functionalization from the corresponding alcohols or acetates with sulfonamides led us to explore the corresponding ether formation, especially with *p*-substituted phenols, to provide α-phenoxy-β-nitro- (or β-azido-) alkyl arenes **24a–24i** (Table 2).[32] Using α-hydroxy-β-nitro- (or β-azido-) alkyl arenes **3** or **15** and 10 mol% $AuCl_3$, a variety of phenols led to the corresponding *syn*-substituted products **24a–24i** in acceptable yields and mostly excellent diastereoselectivities (Table 2). In general, selectivities were higher in the case of β-nitroalkanes compared with β-azidoalkanes. Benzyloxylation was also highly stereoselective (Table 2, entry 6).

Extending the benzylic phenoxylation to highly electron rich mono- and di-substituted phenols led as expected to the corresponding benzylic *C*-arylation products **25a–25j** (Table 3).[33] Highest arylation selectivities were obtained with phenols containing a para- or combined ortho- and para- donating groups (Table 3, entries 1, 2, 4, 5, and 7). In this series, it was also possible to achieve *C*-arylations using 10% *p*-toluenesulfonic acid (Table 3, entries 8–10). The major products were *syn*-selective, especially in the β-nitro series, as evidenced from X-ray crystallography. The products are examples of 1,1′-diarylmethanes with β-nitro and β-azido groups, which can be further functionalized and exploited in the context of medicinally important compounds.[34]

Scheme 3. Synthesis of racemic α-hydroxy- and α-acetoxy-β-azidoalkyl arenes.



12a, R = Me
12b, R = *i*Pr

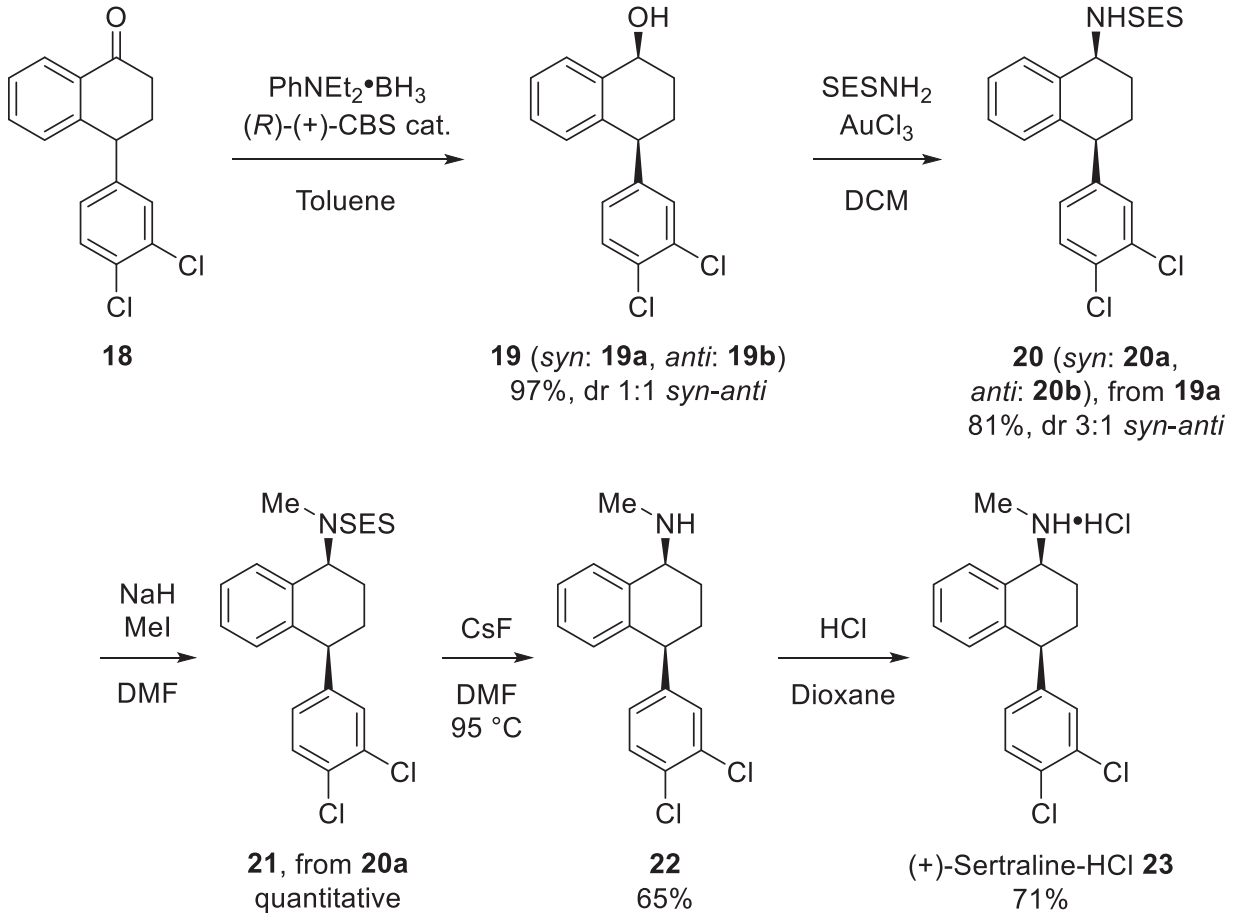
13a, R = Me: quantitative
13b, R = *i*Pr: 89%

14a, R = Me: 89%
14b, R = *i*Pr: 76%
14c, R = *t*Bu: 69%

15a, R = Me: quantitative, dr 2:1
15b, R = *i*Pr: 92%, dr 3:1
15c, R = *t*Bu: 95%, dr 6:1

16, R = Me: 96%, dr 2:1

Scheme 4. Synthesis of (+)-sertraline.



18

19 (*syn*: **19a**, *anti*: **19b**)
97%, dr 1:1 *syn*-*anti*

20 (*syn*: **20a**,
anti: **20b**), from **19a**
81%, dr 3:1 *syn*-*anti*

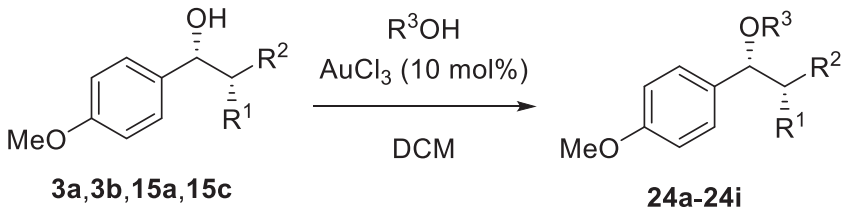
21, from **20a**
quantitative

22
65%

(+)-Sertraline-HCl **23**
71%

In conclusion, we have shown that α-acetoxy-β-nitro- (or α-hydroxy-β-azido-) alkyl arenes can be efficiently converted to the corresponding α-sulfonamido-, α-phenoxy- (or α-benzyloxy-), and α-aryl products with good to excellent *syn*-diastereoselectivity. The successful amino-functionalization of benzylic carbon atoms in the presence of β-nitroalkyl (or β-azidoalkyl) groups including an allylic chain provides possibilities for further individual manipulations of these functional groups possibly with orthogonal

Table 2. Benzylic phenoxylation and benzyloxylation.

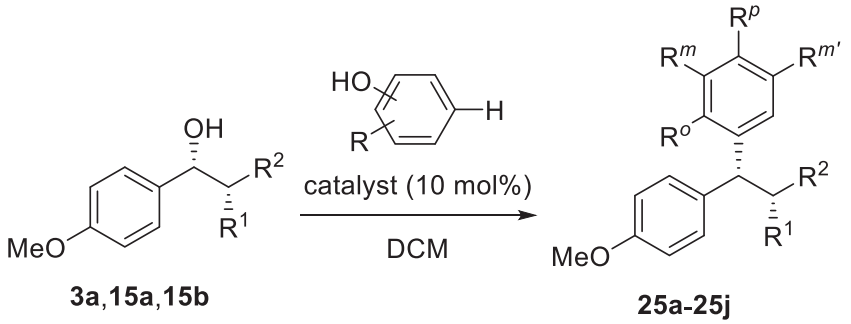


3a,3b,15a,15c **24a-24i**

Entry	Substrate	R^1	R^2	R^3	Product[a]	Yield (dr[b])
1	**3a**	NO_2	Et	*p*-$MeOC_6H_4$	**24a**	58% (7:1)
2	**3a**	NO_2	Et	*p*-$BnOC_6H_4$	**24b**	67% (20:1)
3	**3a**	NO_2	Et	*p*-MeC_6H_4	**24c**	57% (20:1)
4	**3b**	NO_2	Allyl	*p*-MeC_6H_4	**24d**	49% (20:1)
5	**3b**	NO_2	Allyl	*p*-$MeOC_6H_4$	**24e**	72% (4:1)
6	**3b**	NO_2	Allyl	Bn	**24f**	76% (20:1)
7	**15a**	N_3	Me	*p*-MeC_6H_4	**24g**	61% (5:1)
8	**15a**	N_3	Me	*p*-$MeOC_6H_4$	**24h**	67% (5:1)
9	**15c**	N_3	*t*Bu	*p*-$MeOC_6H_4$	**24i**	65% (4:1)

[a]Racemic mixture.
[b]Ratios determined by ^1H NMR at 300, 400, or 500 MHz.

Table 3. Benzylic *C*-arylation.



3a,15a,15b **25a-25j**

Entry	Substrate	R^1	R^2	R^o	R^m	$R^{m'}$	R^p	Catalyst	Product[a]	Yield (dr[b])
1	**3a**	NO_2	Et	H	*t*Bu	*t*Bu	OH	$AuCl_3$	**25a**	62% (20:1)
2	**3a**	NO_2	Et	H	Me	Me	OH	$AuCl_3$	**25b**	92% (20:1)
3	**3a**	NO_2	Et	H	Me	H	OH	$AuCl_3$	**25c**	72% (12:1)
4	**3a**	NO_2	Et	OH	H	H	Me	$AuCl_3$	**25d**	71% (20:1)
5	**3a**	NO_2	Et	OMe	OH	H	OMe	$AuCl_3$	**25e**	64% (20:1)
6	**3a**	NO_2	Et	H	OH	H	OMe	$AuCl_3$	**25f**	84% (4:1)
7	**3a**	NO_2	Et	OH	H	H	OMe	$AuCl_3$	**25g**	76% (20:1)
8	**15a**	N_3	Me	OH	Me	Me	H	*p*-TsOH·H_2O	**25h**[c]	58% (6:1)
9	**15b**	N_3	*i*Pr	OH	H	Me	H	*p*-TsOH·H_2O	**25i**[c]	76% (7:1)
10	**15b**	N_3	*i*Pr	OH	H	OMe	H	*p*-TsOH·H_2O	**25j**	84% (5:1)

[a]Racemic mixture.
[b]Ratios determined by ^1H NMR at 300, 400, or 500 MHz.
[c]X-ray structural data available (see Supplementary data).

reactivities toward more complex compounds. Extension of these methods to enantiopure (or enantioenriched) substrates, available via asymmetric nitro-aldol reactions[22] or starting from chiral, non-racemic compounds,[35] can provide access to alkyl arenes harboring vicinally substituted diamines or aminoalcohols as versatile ligands for asymmetric catalysis and for compounds of medicinal interest.[6a]

Supplementary data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2020-0016.

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