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Chiral 1,4-aminoalkylphenols for enantioselective diethylzinc addition to aldehydes

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Abstract: Starting from a chiral secondary alcohol, novel enantiopure 1,4-aminoalkylphenols (AAPs) were prepared by exploiting conventional organic transformations such as the Mitsunobu reaction, Eschweiler–Clarke *N*-methylation, and demethylation of anisoles. The catalytic activity of the 1,4-AAPs was investigated in enantioselective Et₂Zn addition to benzaldehyde. They were found to accelerate the Et₂Zn addition to benzaldehyde. High yields and enantioselectivities (e.g., 95% yield and 82% *ee*) were achieved.

Key words: Asymmetric catalysis, aminoalcohols, aminoalkylphenols, diethylzinc addition

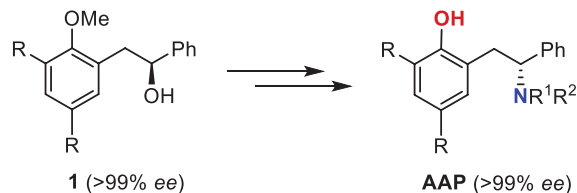
1. Introduction

In asymmetric catalysis, the design and synthesis of novel structural motifs are vitally important for the development of new chiral ligands or catalysts exhibiting high levels of activity and enantioselectivity.^{1,2} In this context, aminoalcohols constitute an important part of the field. In contrast, aminoalkylphenols (AAPs), the isosteres of aminoalcohols, have been rarely utilized as catalysts although some records have demonstrated that they are very promising for catalysis. For example, the Betti base^{3,4} and its derivatives are the traditional representatives of chiral AAPs and have been used as catalysts in the enantioselective addition reactions of diethylzinc (Et₂Zn)³ and as hydrogen-bond donor organocatalysts for hetero Diels–Alder reactions⁵ and the asymmetric acyl–Strecker reaction.⁶ Other well-known examples of this class are the demethylated derivatives of cinchona alkaloids that have been found to be useful in certain asymmetric reactions, such as [4+2] cycloaddition reactions,⁷ Morita–Baylis–Hillman (MBH) reactions,⁸ aza MBH reactions,⁹ conjugate additions to α,β -unsaturated systems,^{10–16} enantioselective addition to activated carbonyl compounds,^{17–19} enantioselective transamination,^{20,21} and some other asymmetric transformations as well.^{22,23} In addition, Maruoka et al. developed a binaphthyl-based axially chiral secondary amine/phenol bifunctional organocatalyst for the highly *anti*-diastereo- and enantioselective Mannich reaction.²⁴ A remarkable 7:1 *anti/syn* diastereomeric ratio and a 98% enantiomeric excess (*ee*) have been reported. Furthermore, Hirose et al. recently prepared some enantiopure 1,3-AAPs by resolution of their enantiomers via diastereomeric salt formation, and they exhibited high activity and selectivity in the asymmetric addition of Et₂Zn to benzaldehyde.^{25,26} It is also noteworthy that AAPs are models for proton-coupled electron transfer.²⁷

Recently, we developed the synthesis of chiral alcohols of type **1** in enantiomerically pure forms.^{28,29}

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We reasoned that these chiral alcohols could be suitable precursors for the synthesis of enantiopure 1,4-AAPs as potential catalysts (Scheme 1). Herein, we present the synthesis of novel chiral 1,4-AAPs as well as their catalytic performance in enantioselective Et_2Zn addition to benzaldehyde.



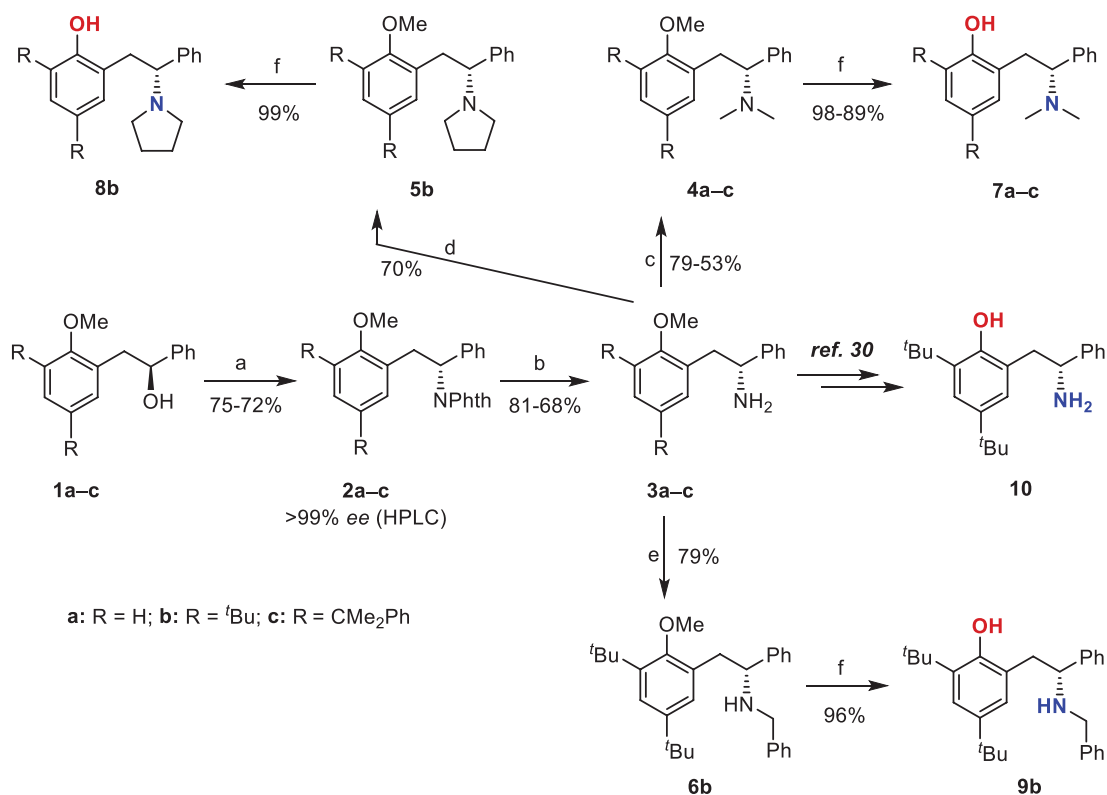
Scheme 1. Synthetic proposal for enantiopure 1,4-aminoalkylphenols (1,4-AAPs).

2. Results and discussion

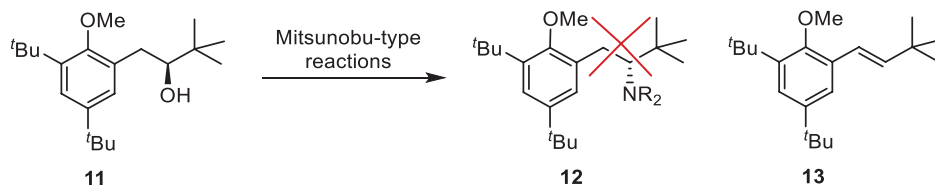
First, the enantiomerically pure secondary alcohols **1a–1c** were subjected to the Mitsunobu reaction by employing phthalimide as the nucleophilic partner (Scheme 2). Thus, the stereo-inversed phthalimide derivatives **2a–2c** were obtained in satisfactory yields (75%–72%). Their enantiomeric excesses were measured on a HPLC instrument equipped with a chiral column (Chiralpak AD-H) and determined to be >99%. Aminolysis of **2a–2c** with hydrazine hydrate provided the primary amines **3a–3c** in yields of 91%–68%. Tertiary amines **4a–4c** were prepared from the corresponding amines **3a–3c** by treating them with formic acid and aqueous formaldehyde under reflux. Similarly, **3b** was then treated with 1,4-diiodobutane as the alkylating agent. This provided us with the pyrrolidine derivative **5b** in 70% yield after column chromatography. The secondary amine **6b** was synthesized from **3b** in 76% overall yield, via a two-step reaction: **3b** was first treated with benzaldehyde to give the corresponding imine, which was then reduced to **6b** with sodium cyanoborohydride.

Next, we tried the well-established demethylation procedures in order to access 1,4-AAPs. Boron tribromide (BBr_3) was first employed using different solvents (e.g., toluene, THF, and DCM), by changing the reaction temperatures. However, formation of unknown side products was observed in most cases. On the other hand, ethanethiol-sodium *tert*-butoxide mixture in DMF turned out to be the most suitable for the demethylation of the aminoalkylanisoles (**4a–4c**, **5b**, **6b**), thus providing the corresponding 1,4-AAPs (**7a–7c**, **8b**, **9b**) in good yields (99%–89%). Synthesis of the 1,4-AAP **10** possessing a primary amine group was presented by us in a previous publication.³⁰ Thus, the synthesis of AAPs bearing primary, secondary, and tertiary amine groups was accomplished. The structures of all compounds were characterized by nuclear magnetic resonance spectroscopy. It should be mentioned that the compounds **2c**, **3c**, **4c**, and **7c** that carry 2,4-bis(1,1-dimethylbenzyl)-anisole or -phenol as the building unit feature remarkable patterns in their NMR spectra. Their 1,1-dimethyls, which are adjacent to the methoxyl or phenolic hydroxyl groups, resonate at different fields, i.e. their chemical shifts are different. That is, they are diastereotopic. Considering the presence of an asymmetric center in these molecules, this phenomenon must arise from the restricted or completely hindered rotation about the C(aryl)-C(benzyl) bond.

The secondary alcohol **11** was also considered as the precursor for the synthesis of further 1,4-AAPs bearing a *tert*-butyl group adjacent to the chiral center, which would make them sterically more demanding (Scheme 3). However, all attempts to convert **11** into **12** derivatives by employing the known modifications of the Mitsunobu reaction failed. In most cases, the elimination product **13** was detected as the sole product, instead of the expected product (**12**). This result can be apparently attributed to the very close presence of the bulky *tertiary* alkyl group to the reaction center as well as the conjugated position of the leaving group, which in turn accounts for the elimination.

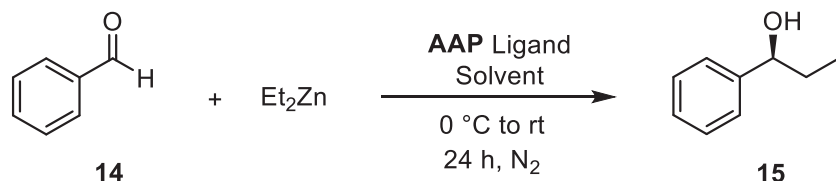


Scheme 2. Preparation of AAPs. NPhth = Phthalimido. Reagents and conditions: (a) Ph₃P (4.0 equiv.), HNPhth (3.0 equiv.), DIAD (4.0 equiv.), THF, 0 °C to rt, 12 h; (b) H₂NNH₂ • H₂O (10.0 equiv.), EtOH, reflux, 6 h; (c) HCOOH, HCHO (aq.), reflux, 12 h; (d) 1,4-diiodobutane, K₂CO₃, ACN, reflux, 12 h; (e) (1) PhCHO (1.0 equiv.), MgSO₄, DCM, rt, 16 h, (2) NaCNBH₃ (2.0 equiv.), AcOH (4.0 equiv.), MeCN, 0 °C to rt, 18 h; (f) NaO^tBu (ca. 3.0 equiv.), EtSH (ca. 8.0 equiv.), DMF, 120 °C, 2 h.



Scheme 3. Attempts at Mitsunobu-type reactions with sterically demanding alcohol **11**.

After the effective preparation of 1,4-AAPs, they were evaluated as catalysts in the Et₂Zn addition of benzaldehyde (**14**), a widely accepted test combination for evaluating the catalytic performance of new ligands in terms of both activity and enantiodiscrimination (Table).^{31–35} At this point, it should be mentioned that a number of 1,4-aminoalcohols were shown to accelerate this transformation with high levels of enantioselectivity.^{36–40} Initially, 10 mol% of **7b** was used as the catalyst in order to determine the general catalytic profile of the 1,4-AAPs (Table, entries 1–6). The combination of AAP **7b** with Ti(O^{*i*}Pr)₄ entirely removed the enantioselectivity (entry 1), while AAP **7b** performed the asymmetric Et₂Zn addition to benzaldehyde with 70% yield and 80% *ee* (entry 2). Significantly, changing the solvent from Et₂O to toluene hampered the catalytic activity of **7b** (entry 3). Of the various solvents tried (e.g., Et₂O, THF, DCM, hexane), hexane resulted in the highest enantioselectivity (82% *ee*, entries 2–6). Although **8b** is sterically more hindered

Table. Enantioselective diethylzinc addition to benzaldehyde (**14**) accelerated by 1,4-AAPs.^a

Entry	AAP	Solvent	Yield (%) ^b	ee (%) ^c
1	7b	Et ₂ O	73	Racemic ^d
2	7b	Et ₂ O	70	80 (<i>S</i>)
3	7b	Toluene	No reaction	–
4	7b	THF	75	16 (<i>S</i>)
5	7b	CH ₂ Cl ₂	68	76 (<i>S</i>)
6	7b	Hexane	80	82 (<i>S</i>)
7	8b	Et ₂ O	82	58 (<i>S</i>)
8	7c	Et ₂ O	83	65 (<i>S</i>)
9	10	Et ₂ O	77	36 (<i>S</i>)
10	10	Toluene	65	46 (<i>S</i>)
11	7a	Et ₂ O	76	74 (<i>R</i>)
12	9b	Et ₂ O	95	70 (<i>S</i>)

^a Reaction conditions: Reactions were run by employing **14** (0.5 mmol, 1.00 equiv.), Et₂Zn (1.80 equiv.), and AAP (10 mol%) in a solvent (2 mL).

^b Yield% of the NMR-pure product (**15**).

^c Determined by chiral GC (CP-Chirasil-Dex-CB).

^d Ti(O^{*i*}Pr)₄ was used.

around the nitrogen atom in comparison to **7b**, it catalyzed the Et₂Zn addition to benzaldehyde with a lower enantioselectivity (58% *ee* vs. 80% *ee*, entries 7 and 2). Similarly, increasing the steric hindrance around the phenolic hydroxyl group of the AAPs (**7c** vs. **7b**) resulted in a decrease in enantiomeric excess, 65% *ee* vs. 80% *ee*, respectively (entries 8 and 2). More interestingly, a reversal of enantioselectivity was observed when AAP **7a** was employed as the catalyst instead of **7b** (entries 11 and 2). This might be due to the preferential coordination of Et₂Zn to the oxygen atom of the zinc complex formed from **7a** and Et₂Zn. On the other hand, oxygen atoms of the zinc complexes expected to be formed in situ from Et₂Zn and the other AAPs should be more crowded, which can hinder coordination of Et₂Zn to the oxygen atoms of those zinc complexes. This result also hints that the reaction mechanism can be switched by changing the substituents adjacent to the phenolic hydroxyl group. AAP **10**, which bears a primary amine group, was also determined to be an effective catalyst. However, it afforded only 36% and 46% *ee* depending on the solvent used (entries 9 and 10). Among the AAPs tested so far, AAP **9b**, having a secondary amine moiety, appeared to be the most effective, thus providing addition product **15** in 95% yield albeit with 70% *ee* (entry 12). The highest activity of **9b** might be interpreted in different ways. However, there is likely an additional interaction between the zinc complex and benzaldehyde during the course of the reaction, e.g., $\pi \cdots \pi$ interaction between benzaldehyde and the benzyl group attached to the nitrogen atom. From the results of these catalytic studies, it is difficult to conclude that there is a correlation between the steric bulkiness of the AAPs and the enantioselectivity. It is generally accepted that the stereoselectivity of a catalytic system mainly depends on a subtle interplay between the catalyst and the reaction partners. The same seems to hold for our AAPs.

In summary, we prepared novel enantiopure 1,4-aminoalkylphenols by exploiting conventional organic transformations such as the Mitsunobu reaction, Eschweiler–Clarke *N*-methylation, and demethylation of

anisoles. Their catalytic activity in Et₂Zn addition to benzaldehyde was investigated. Thus, they were determined to be very promising catalysts for Et₂Zn addition to benzaldehyde, thereby affording high activity and enantioselectivity (up to 95% yield and 82% *ee*). We think that these AAPs will serve as catalysts in further asymmetric transformations.

3. Experimental

3.1. General

Dry nitrogen atmosphere was provided during the execution of the air-sensitive transformations. Gas-tight syringes were used for the addition of reagents and solvents under N₂. Thin-layer chromatography (TLC) sheets were made visual by staining with ethanolic phosphomolybdic acid (10%, w/v) and/or by UV light. Flash chromatography using silica gel (230–400 mesh) was applied for purification of the products. The melting point (mp) measurements were performed in a capillary tube and are uncorrected. A PerkinElmer Spectrum One FTIR spectrometer was used for recording the infrared (FTIR) spectra, $\tilde{\nu}_{max}$, in cm⁻¹. HR mass spectra were obtained in MeOH with the aid of electrospray ionization. A 500 MHz NMR spectrometer was utilized for recording the NMR spectra. Chemical shift values (δ) are given in ppm. The sample concentrations in the specific rotations ($[\alpha]$) were given in units of g/100 mL. Et₂O and THF were dried by refluxing with ketyl radicals generated from sodium/benzophenone and distilled under N₂. DMF and dichloromethane (DCM) were dried with CaH₂ and distilled under N₂.

3.2. General procedure I (Mitsunobu reaction of alcohols with phthalimide): (*R*)-2-(2-(2-methoxyphenyl)-1-phenylethyl)isoindoline-1,3-dione (**2a**)

(*S*)-2-(2-Methoxyphenyl)-1-phenylethanol (**1a**) (1.0 g, 4.4 mmol), PPh₃ (4.60 g, 17.6 mmol), and phthalimide (1.94 g, 13.2 mmol) were put into a Schlenk flask (250 mL). After evacuating and back-filling the flask with nitrogen, dry THF (180 mL) was added using a syringe. Then diisopropyl azodicarboxylate (DIAD) (3.50 mL, 3.56 g, 17.6 mmol) was dropwise transferred into the tube with the aid of a syringe, under cooling with an ice bath. The consumption of **1a** was followed by thin-layer chromatography (rt, 12 h). Then the THF was distilled under reduced pressure. Column chromatographic separation on silica gel furnished oily product **2a** (1.75 g, 3.3 mmol, 75%). TLC: $R_f = 0.52$ (silica gel; hexanes/EtOAc, 8:2). $[\alpha]_D^{22} = +96$ (c = 0.5, CHCl₃). HPLC: Daicel Chiralpak AD-H (4.60 mm ID × 250 mm column length); *n*-hexane/*i*PrOH (98:2), 0.5 mL/min; 254 nm (UV/Vis); $t_R = 11.7$ min (*ent*-**2a**), $t_R = 13.8$ min (**2a**). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.72$ – 7.78 (m, 2H), 7.60–7.68 (m, 4H), 7.34–7.41 (m, 2H), 7.28–7.33 (m, 1H), 7.15 (td, $J = 8.1, 1.7$ Hz, 1H), 7.09 (dd, $J = 7.4, 1.5$ Hz, 1H), 6.83 (d, $J = 8.1$ Hz, 1H), 6.74 (td, $J = 7.4, 0.9$ Hz, 1H), 5.85 (dd, $J = 10.9, 5.1$ Hz, 1H), 3.93 (dd, $J = 13.5, 10.9$ Hz, 1H), 3.84 (s, 3H), 3.61 (dd, $J = 13.5, 5.1$ Hz, 1H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 168.3$ (C), 157.8 (C), 139.9 (C), 133.8 (CH), 131.8 (C), 130.8 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.7 (C), 126.4 (C), 123.1 (CH), 120.3 (CH), 110.3 (CH), 55.3 (CH₃), 54.1 (CH), 32.4 (CH₂).

3.3. (*R*)-2-(2-(3,5-Di-*tert*-butyl-2-methoxyphenyl)-1-phenylethyl)isoindoline-1,3-dione (**2b**)

Following general procedure I as described above, **1b** (3.40 g, 10.0 mmol), PPh₃ (10.50 g, 40.0 mmol), DIAD (7.90 mL, 8.00 g, 40.0 mmol), phthalimide (4.40 g, 30.0 mmol), and 400 mL of THF were employed. After column chromatographic separation on silica gel, the title compound (**2b**) (3.5 g, 7.5 mmol, 75%) was obtained

as a colorless oil. TLC: $R_f = 0.25$ (silica gel; hexanes/EtOAc, 95:5). $[\alpha]_D^{22} = +140$ ($c = 0.5$, CHCl_3). HPLC: Daicel Chiralpak AD-H (4.60 mm ID \times 250 mm column length); n -hexane/ i PrOH (98:2), 0.5 mL/min; 254 nm (UV/Vis); $t_R = 17.1$ min (*ent*-**2b**), $t_R = 19.4$ min (**2b**). ^1H NMR (500 MHz, CDCl_3): $\delta = 7.69$ (dd, $J = 5.3, 3.1$ Hz, 2H), 7.64–7.56 (m, 4H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.28 (d, $J = 7.3$ Hz, 1H), 7.06 (d, $J = 2.1$ Hz, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 5.72 (dd, $J = 11.2, 4.8$ Hz, 1H), 3.98 (dd, $J = 13.8, 11.4$ Hz, 1H), 3.79 (s, 3H), 3.50 (dd, $J = 13.9, 4.8$ Hz, 1H), 1.26 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (APT, 125 MHz, CDCl_3): $\delta = 168.0$ (C), 156.3 (C), 145.5 (C), 142.0 (C), 139.7 (C), 133.6 (CH), 132.0 (C), 130.8 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 126.4 (CH), 122.9 (CH), 122.8 (CH), 61.8 (CH), 54.8 (CH_3), 35.2 (C), 34.2 (C), 32.8 (CH_2), 31.3 (CH_3), 31.0 (CH_3).

3.4. (*R*)-2-(2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-1-phenylethyl)isoindoline-1,3-dione (**2c**)

Following general procedure I as described above, **1c** (4.60 g, 10.0 mmol), PPh_3 (10.50 g, 40.0 mmol), DIAD (7.90 mL, 8.00 g, 40.0 mmol), phthalimide (4.40 g, 30.0 mmol), and 400 mL of THF were employed. After column chromatographic separation on silica gel, the title product (**2c**) (4.3 g, 7.2 mmol, 72%) was isolated as a colorless oil. TLC: $R_f = 0.29$ (silica gel; hexanes/EtOAc, 95:5). $[\alpha]_D^{22} = +118$ ($c = 0.5$, CHCl_3). HPLC: Daicel Chiralpak AD-H (4.60 mm ID \times 250 mm column length); n -hexane/ i PrOH (98:2), 0.5 mL/min; 254 nm (UV/Vis); $t_R = 16.2$ min (*ent*-**2c**), $t_R = 19.8$ min (**2c**). ^1H NMR (500 MHz, CDCl_3): $\delta = 7.1, 3.5$ Hz, 2H), 7.67–7.61 (m, 2H), 7.53 (d, $J = 7.4$ Hz, 2H), 7.30 (t, $J = 7.5$ Hz, 2H), 7.27–7.19 (m, 4H), 7.11 (ddd, $J = 14.9, 10.5, 3.9$ Hz, 5H), 7.05–7.00 (m, 3H), 6.93 (d, $J = 2.2$ Hz, 1H). 5.66 (dd, $J = 11.1, 5.0$ Hz, 1H), 3.81 (dd, $J = 13.8, 11.2$ Hz, 1H), 2.65 (s, 3H), 3.34 (dd, $J = 13.9, 5.0$ Hz, 1H), 1.46–1.53 (m, $J = 12.5$ Hz, 9H), 1.27 (s, 3H). ^{13}C NMR (APT, 125 MHz, CDCl_3): $\delta = 167.9$ (C), 155.7 (C), 151.9 (C), 150.80 (C), 145.0 (C), 142.4 (C), 139.5 (C), 133.6 (CH), 131.9 (C), 130.8 (C), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 126.6 (CH), 126.1 (CH), 125.4 (CH), 125.1 (CH), 124.5 (CH), 122.8 (CH), 59.6 (CH_3), 54.6 (CH), 42.6 (CH_2), 42.1 (C), 32.7 (C), 30.8 (CH_3), 30.7 (CH_3), 29.82 (CH_3), 29.80 (CH_3).

3.5. General procedure II (preparation of tertiary aminoalkylanisoles): (*R*)-2-(2-methoxyphenyl)-*N,N*-dimethyl-1-phenylethan-1-amine (**4a**)

First, **2a** (0.95 g, 2.7 mmol) was placed into a two-necked flask (100 mL). The flask was filled with dry N_2 . Ethanol (40 mL) and hydrazine hydrate (1.30 mL, 1.34 g, 27 mmol) were added consecutively. Refluxing was conducted for 6 h under N_2 . The consumption of **2a** was followed by TLC (6 h). For quenching the reaction, water (20 mL) was added. After the ethanol was distilled under reduced pressure, the organic components were separated from the aqueous residue by extraction with DCM (3 \times 60 mL). After the usual work-up procedures, including drying over Na_2SO_4 and filtration as well as concentration in vacuo, colorless solid product **3a** (500 mg, 2.2 mmol, 81%) was obtained. This product was directly used in the next step because it was determined not to be stable enough to isolate and store. Then **3a** (500 mg, 2.2 mmol) was put into a Schlenk tube (10 mL). After evacuating and back-filling the tube with nitrogen, formic acid (0.90 mL, 1.1 g, 24.0 mmol) and aqueous formaldehyde (37%, 360 μL , 391 mg, 4.8 mmol formaldehyde) were transferred into the tube successively. After the tube was equipped with a reflux condenser, refluxing was carried out for 12 h under N_2 . The consumption of **3a** was followed by TLC (12 h). Upon the completion of the conversion, the tube

was cooled down. The pH value was adjusted to 9–10 by adding saturated aqueous NaHCO₃. The organic components were separated from the aqueous residue by extraction with DCM (3 × 60 mL). After the additional work-up procedures, including drying over Na₂SO₄ and filtration as well as concentration in vacuo, column chromatographic separation on silica gel furnished colorless oily product **4a** (300 mg, 1.17 mmol, 53%). TLC: $R_f = 0.17$ (silica gel; hexanes/EtOAc/TEA, 9:1:0.5). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.20$ – 7.25 (m, 2H), 7.13–7.19 (m, 3H), 7.06–7.11 (m, 1H), 6.73–6.78 (m, 2H), 6.68 (td, $J = 7.4, 1.0$ Hz, 1H), 3.77 (s, 3H), 3.52 (dd, $J = 9.7, 4.8$ Hz, 1H), 3.44 (dd, $J = 13.0, 4.8$ Hz, 1H), 2.90 (dd, $J = 13.0, 9.7$ Hz, 1H), 2.29 (s, 6H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 157.4$ (C), 140.5 (C), 130.9 (CH), 128.7 (CH), 127.8 (C), 127.5 (CH), 126.9 (CH), 126.7 (CH), 119.9 (CH), 110.0 (CH), 70.8 (CH₃), 55.1 (CH), 43.1 (CH₃), 34.1 (CH₂).

3.6. (*R*)-2-(3,5-Di-*tert*-butyl-2-methoxyphenyl)-*N,N*-dimethyl-1-phenylethylamine (**4b**)

Following general procedure II as described above, **2b** (2.82 g, 6.0 mmol), 90 mL of ethanol, hydrazine hydrate (2.90 mL, 3.00 g, 60.0 mmol), formic acid (1.70 mL, 2.07 g, 45.0 mmol), and aqueous formaldehyde (37%, 672 μ L, 730 mg, 9.0 mmol formaldehyde) were employed. Column chromatographic separation on silica gel furnished the title compound (**4b**) (950 mg, 2.59 mmol, 64%) as a colorless oil. TLC: $R_f = 0.22$ (silica gel; hexanes/EtOAc/TEA, 9.5:0.25:0.25). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.12$ – 7.17 (m, 2H), 7.06–7.12 (m, 3H), 7.01 (d, $J = 2.5$ Hz, 1H), 6.56 (s, 1H), 3.79 (s, 3H), 3.51 (ddd, $J = 18.0, 11.6, 4.8$ Hz, 2H), 2.87 (dd, $J = 13.3, 9.9$ Hz, 1H), 2.30 (s, 6H), 1.34 (s, 9H), 1.08 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 155.9$ (C), 144.8 (C), 141.3 (CH), 140.7 (C), 131.7 (C), 128.6 (CH), 127.7 (CH), 126.8 (CH), 126.7 (CH), 121.8 (CH), 71.3 (CH₃), 61.6 (CH), 43.3 (CH₃), 35.4 (CH₂), 35.2 (s), 34.2 (C), 31.3 (CH₃), 31.1 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₂₅H₃₈NO: 368.2953; found: 368.2926.

3.7. (*R*)-2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-*N,N*-dimethyl-1-phenylethylamine (**4c**)

According to general procedure II as described above, **2c** (3.60 g, 6.00 mmol), 90 mL of ethanol, hydrazine hydrate (2.90 mL, 3.00 g, 60.0 mmol), formic acid (1.70 mL, 2.07 g, 45.0 mmol), and aqueous formaldehyde (37%, 672 μ L, 730 mg, 9.0 mmol formaldehyde) were employed. Column chromatographic separation on silica gel furnished the title compound (**4c**) (1.6 g, 3.24 mmol, 79%) as a colorless oil. TLC: $R_f = 0.2$ (silica gel; hexanes/EtOAc, 7:3). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.19$ – 7.13 (m, 4H), 7.12–7.00 (m, 7H), 6.98–6.90 (m, $J = 9.1, 4.4, 1.8$ Hz, 5H), 6.46 (d, $J = 2.4$ Hz, 1H), 3.40 (dd, $J = 10.4, 4.7$ Hz, 1H), 3.23 (dd, $J = 13.4, 4.8$ Hz, 1H), 2.69 (dd, $J = 13.3, 10.6$ Hz, 1H), 2.63 (s, 3H), 2.15 (s, 6H), 1.49 (s, 3H), 1.42 (d, $J = 7.7$ Hz, 6H), 1.36 (s, 3H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 155.26$ (C), 152.09 (C), 150.98 (C), 144.19 (C), 141.77 (C), 131.51 (C), 128.60 (CH), 127.81 (CH), 127.75 (CH), 127.66 (CH), 126.77 (CH), 126.67 (CH), 126.00 (CH), 125.30 (CH), 125.03 (CH), 123.42 (CH), 70.69 (CH₃), 59.40 (CH), 43.22 (CH₃), 42.45 (C), 42.10 (C), 35.31 (CH₂), 30.80 (CH₃), 30.70 (CH₃), 30.66 (CH₃), 29.44 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₃₅H₄₂NO: 492.3266; found: 492.3243.

3.8. (*R*)-1-(2-(3,5-Di-*tert*-butyl-2-methoxyphenyl)-1-phenylethyl)pyrrolidine (**5b**)

The amine **3b** (1.40 g, 4.1 mmol) and anhydrous K₂CO₃ (1.30 g, 9.4 mmol) were put into a two-necked flask (250 mL). The flask was filled with dry N₂. Dry acetonitrile (ACN, 25 mL) and 1,4-diiodobutane (540 μ L,

1.27 g, 4.1 mmol) were sequentially added to the flask. Then refluxing was conducted for 12 h under N₂. The resulting mixture was then stirred under reflux for 12 h under N₂. The consumption of **3b** was monitored by TLC. Upon completion of the conversion, the tube was cooled. For quenching the reaction, water (60 mL) was added. The organic components were separated from the aqueous residue by extraction with DCM (3 × 110 mL). After further work-up procedures, which included drying over Na₂SO₄ and filtration as well as concentration in vacuo, column chromatographic separation on silica gel furnished colorless oily product **5b** (1.13 g, 2.87 mmol, 70%). TLC: *R_f* = 0.24 (silica gel; hexanes/EtOAc/TEA, 9.5:0.25:0.25). ¹H NMR (500 MHz, CDCl₃): δ = 7.04–7.13 (m, 5H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 3.55 (dd, *J* = 13.2, 4.3 Hz, 1H), 3.41 (dd, *J* = 10.3, 4.3 Hz, 1H), 2.80 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.50 (dd, *J* = 9.7, 3.9 Hz, 2H), 1.78–1.81 (m, 4H), 1.34 (s, 9H), 1.07 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): δ = 156.0 (C), 144.7 (C), 143.0 (CH), 141.3 (C), 131.5 (C), 128.1 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH), 121.7 (CH), 71.6 (CH₃), 61.6 (CH), 53.0 (CH₂), 38.4 (CH₂), 35.1 (C), 34.1 (C), 31.3 (CH₃), 31.1 (CH₃), 23.4 (CH₂). HR MS (ESI): *m/z* [M+H]⁺ calcd for C₂₇H₄₀NO: 394.3110; found: 394.3132.

3.9. (*R*)-*N*-Benzyl-2-(3,5-di-*tert*-butyl-2-methoxyphenyl)-1-phenylethyl-amine (**6b**)

The amine **3b** (340.00 mg, 1.00 mmol) was put into a Schlenk tube (25 mL). Dry DCM (5 mL), MgSO₄ (240 mg, 2.00 mmol), and benzaldehyde (**14**, 102 μL, 106 mg, 1.0 mmol) were added to the tube sequentially. After magnetic stirring for 16 h at ambient temperatures, the reaction mixture was filtered and thus MgSO₄ was removed. DCM was distilled and the residue was transferred into another Schlenk tube (25 mL). It was flushed with dry nitrogen. Dry ACN (7 mL) was added. Under cooling of the resulting homogeneous mixture, sodium cyanoborohydride (105 μL, 126 mg, 2.0 mmol) was added and then it was stirred at 0 °C for 15 min. After the addition of glacial acetic acid (229 μL, 240 mg, 4.0 mmol), the resulting homogeneous mixture was further stirred at ambient temperature for 18 h. Upon completion of the reaction, the mixture was poured into a 100-mL beaker containing 2% methanolic (v/v) DCM (40 mL) and it was shaken with 1.0 N aqueous NaOH (3 × 30 mL). After filtration and drying over Na₂SO₄, the organic phase was concentrated. Column chromatographic purification on silica gel furnished colorless solid product **6b** (0.34 g, 0.79 mmol, 79%). Mp: 101–102 °C. TLC: *R_f* = 0.46 (silica gel; hexanes/EtOAc/TEA, 9:0.8:0.2). ¹H NMR (500 MHz, CDCl₃): δ = 7.46–7.41 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.32–7.18 (m, 5H), 7.11 (d, *J* = 6.9 Hz, 2H), 6.93 (d, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 8.6, 5.2 Hz, 1H), 3.79 (s, 3H), 3.70 (d, *J* = 13.7 Hz, 1H), 3.50 (d, *J* = 13.7 Hz, 1H), 3.09 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.97 (dd, *J* = 13.9, 5.2 Hz, 1H), 1.84 (s, 1H), 1.43 (s, 9H), 1.27 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): δ = 156.2 (C), 145.4 (C), 144.4 (C), 141.9 (C), 140.6 (C), 131.4 (C), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 126.2 (CH), 122.5 (CH), 62.7 (CH), 61.7 (CH₃), 51.4 (CH₂), 40.5 (C), 35.3 (C), 34.3 (CH₃), 31.5 (CH₃), 31.2 (CH₃). HR MS (ESI): *m/z* [M+H]⁺ calcd for C₃₀H₄₀NO: 430.3110; found: 430.3147.

3.9.1. General procedure III (demethylation of anisoles): (*R*)-2-(2-(dimethylamino)-2-phenylethyl)phenol (**7a**)

Dry DMF (10 mL) and ethanethiol (1.20 mL, 994 mg, 16.00 mmol) were put into a Schlenk tube (25 mL). The tube was flushed with dry N₂. To the ice-cooled tube was added NaO^{*t*}Bu (576 mg, 6.00 mmol). After the tube was stirred at 0 °C for 15 min, **4a** (510 mg, 2.00 mmol) was then added. The mixture was stirred at 120 °C

for 4 h. Upon completion of the conversion, the tube was cooled to 0 °C. The pH value was adjusted to 9–10 by adding 1.0 N HCl. The organic components were separated from the aqueous admixture by extraction with Et₂O (3 × 80 mL). After further work-up procedures, which included drying over Na₂SO₄ and filtration as well as concentration in vacuo, column chromatographic separation on silica gel furnished colorless solid product **7a** (430 mg, 1.78 mmol, 89%). Mp: 154–155 °C. **TLC**: $R_f = 0.56$ (silica gel; hexanes/EtOAc/TEA, 8:2:0.5). $[\alpha]_D^{23} = -164$ ($c = 0.5$, CHCl₃). FTIR (KBr): $\tilde{\nu}_{max}$ (cm⁻¹) = 3444 (w), 3041 (w), 2520 (w), 1770 (w), 1609 (w), 1582 (s), 1481 (s), 1420 (w), 1267 (s), 1152 (w), 1039 (w), 993 (w), 915 (w), 841 (w), 782 (s), 704 (s), 606 (s). ¹H NMR (500 MHz, CDCl₃): $\delta = 13.58$ (s, 1H), 7.44–7.32 (m, 3H), 7.25–7.19 (m, 2H), 7.18–7.12 (m, 1H), 6.93 (ddd, $J = 12.8, 7.7, 1.3$ Hz, 2H), 6.73 (td, $J = 7.4, 1.2$ Hz, 1H), 3.94 (d, $J = 10.6$ Hz, 1H), 3.71 (dd, $J = 15.0, 10.8$ Hz, 1H), 2.79 (d, $J = 15.0$ Hz, 1H), 2.29 (s, 6H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 157.7$ (C), 135.6 (C), 131.2 (CH), 129.0 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 126.7 (C), 118.7 (CH), 117.6 (CH), 69.8 (CH), 40.2 (CH₂), 37.5 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₀NO: 242.1545; found: 242.1532.

3.9.2. (*R*)-2,4-Di-*tert*-butyl-6-(2-(dimethylamino)-2-phenyl-ethyl)phenol (**7b**)

According to general procedure III as described above, **4b** (735 mg, 2.00 mmol), ethanethiol (1.20 mL, 994 mg, 16.00 mmol), NaO^{*t*}Bu (576 mg, 6.00 mmol), and 10 mL of dry DMF were employed. After column chromatographic separation on silica gel, the title compound (**7b**) (690 mg, 1.96 mmol, 98%) was obtained as a colorless solid. Mp: 146–147 °C. **TLC**: $R_f = 0.28$ (silica gel; hexanes/EtOAc, 7:3). $[\alpha]_D^{23} = -130$ ($c = 0.5$, CHCl₃). FTIR (KBr): $\tilde{\nu}_{max}$ (cm⁻¹) = 3415 (w), 3062 (m), 3029 (m), 2992 (s), 2961 (s), 2871 (s), 2794 (m), 2696 (m), 1960 (w), 1825 (w), 1597 (m), 1448 (s), 1391 (m), 1357 (s), 1294 (s), 1233 (s), 1116 (m), 1039 (m), 998 (m), 883 (m), 780 (m), 704 (s), 595 (m), 520 (w). ¹H NMR (500 MHz, CDCl₃): $\delta = 12.67$ (s, 1H), 7.33–7.41 (m, 3H), 7.20–7.24 (m, 3H), 6.82 (d, $J = 2.4$, 1H), 3.91 (d, $J = 10.4$, 1H), 3.69 (dd, $J = 10.5, 14.6$, 1H), 2.73 (d, $J = 14.6$, 1H), 2.26 (s, 6H), 1.46 (s, 9H), 1.25 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 153.9$ (C), 140.2 (C), 136.8 (C), 136.3 (C), 129.2 (CH), 128.1 (CH), 127.8 (CH), 127.4 (C), 126.0 (CH), 122.6 (CH), 70.5 (CH), 40.3 (CH₃), 38.1 (CH₂), 35.2 (C), 34.11 (C), 31.7 (CH₃), 29.8 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₂₄H₃₆NO: 354.2797; found: 354.2806.

3.9.3. (*R*)-2-(2-(Dimethylamino)-2-phenyl-ethyl)-4,6-bis(2-phenylpropan-2-yl)phenol (**7c**)

Following general procedure III as described above, **4c** (492 mg, 1.0 mmol, 1.00 equiv), ethanethiol (0.60 mL, 487 mg, 8.0 mmol), NaO^{*t*}Bu (288 mg, 3.0 mmol), and 5 mL of dry DMF were employed. After column chromatographic separation on silica gel, the title compound (**7c**) (430 mg, 0.9 mmol, 90%) was obtained as a colorless solid. Mp: 63–64 °C. **TLC**: $R_f = 0.44$ (silica gel; hexanes/EtOAc, 7:3). $[\alpha]_D^{23} = -106$ ($c = 0.5$, CHCl₃). FTIR (KBr): $\tilde{\nu}_{max}$ (cm⁻¹) = 3436 (w), 2964 (w), 1599 (w), 1493 (s), 1461 (m), 1442 (w), 1360 (w), 1283 (w), 1202 (w), 1030 (w), 764 (w), 699 (s). ¹H NMR (500 MHz, CDCl₃): $\delta = 12.06$ (s, 1H), 7.35–7.27 (m, 3H), 7.26–7.19 (m, 8H), 7.18–7.04 (m, 5H), 6.67 (d, $J = 2.4$ Hz, 1H), 3.68 (d, $J = 9.8$ Hz, 1H), 3.49 (dd, $J = 14.4, 10.2$ Hz, 1H), 2.61 (d, $J = 14.0$ Hz, 1H), 1.98 (s, 6H), 1.70 (s, 3H), 1.64 (d, $J = 2.0$ Hz, 6H), 1.63 (s, 3H). ¹³C NMR (APT, 125 MHz, CDCl₃): $\delta = 153.4$ (C), 152.1 (C), 151.4 (C), 139.6 (C), 136.5 (C), 136.5 (C), 128.9 (CH), 127.89 (CH), 127.82 (CH), 127.76 (CH), 127.67 (C), 127.60 (CH), 127.4 (CH), 126.7 (CH), 125.7 (CH),

125.2 (CH), 124.46 (CH), 124.42 (CH), 70.8 (CH), 42.3 (C), 40.4 (CH₃), 37.6 (CH₂), 31.1 (CH₃), 31.0 (CH₃), 30.6 (CH₃), 28.8 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₃₄H₄₀NO: 478.3110; found: 478.3109.

3.9.4. (*R*)-2,4-Di-*tert*-butyl-6-(2-phenyl-2-(pyrrolidin-1-yl)ethyl)phenol (**8b**)

According to general procedure III as described above, **5b** (760 mg, 2.00 mmol), ethanethiol (1.20 mL, 974 mg, 16.0 mmol), NaO^tBu (576 mg, 6.0 mmol), and 10 mL of dry DMF were employed. After column chromatographic separation on silica gel, the title compound (**8b**) (740 mg, 1.98 mmol, 99%) was obtained as a colorless solid. Mp: 116–117 °C. TLC: R_f = 0.26 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{23}$ = –42 (c = 0.5, CHCl₃). FTIR (KBr): $\tilde{\nu}_{max}$ (cm⁻¹) = 3430 (w), 3055 (m), 3032 (m), 2950 (s), 2910 (s), 2862 (s), 2482 (m), 2193 (m), 1815 (w), 1596 (m), 1452 (s), 1385 (m), 1358 (m), 1235 (s), 1200 (m), 1099 (m), 949 (m), 861 (m), 764 (m), 705 (s), 590 (m). ¹H NMR (500 MHz, CDCl₃): δ = 12.65 (s, 1H), 7.28–7.36 (m, 3H), 7.17–7.20 (m, 3H), 6.75 (d, J = 2.3, 1H), 4.09 (d, J = 9.9, 1H), 3.64 (m, 1H), 2.84 (d, J = 14.5, 1H), 2.78 (d, J = 8.4, 2H), 2.49 (d, J = 7.9, 2H), 1.73 (m, 4H), 1.45 (s, 9H), 1.23 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): δ = 153.9 (C), 140.2 (C), 137.5 (CH), 136.8 (C), 129.1 (CH), 128.0 (CH), 127.5 (CH), 127.3 (C), 126.1 (CH), 122.4 (CH), 67.0 (CH), 48.4 (CH₂), 39.1 (CH₂), 35.2 (C), 34.0 (C), 31.7 (CH₃), 29.8 (CH₃), 22.7 (CH₂). HR MS (ESI): m/z [M+H]⁺ calcd for C₂₆H₃₈NO: 380.2953; found: 380.2949.

3.9.5. (*R*)-2-(2-Benzylamino)-2-phenyl-ethyl-4,6-di-*tert*-butylphenol (**9b**)

Following general procedure III as described above, **6b** (860 mg, 2.0 mmol), ethanethiol (1.20 mL, 974 mg, 16.0 mmol), NaO^tBu (576 mg, 6.0 mmol), and 10 mL of dry DMF were employed. After column chromatographic separation on silica gel, the title compound (**9b**) (800 mg, 1.92 mmol, 96%) was obtained as a colorless solid. Mp: 136–137 °C. TLC: R_f = 0.6 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{23}$ = +38 (c = 0.5, CHCl₃). FTIR (KBr): $\tilde{\nu}_{max}$ (cm⁻¹) = 3433 (w), 3295 (s), 2905 (s), 2582 (w), 1598 (w), 1455 (s), 1439 (s), 1360 (s), 1300 (s), 1240 (s), 1201 (s), 1091 (s), 954 (w), 878 (w), 757 (s), 752 (s), 697 (s), 586 (w), 517 (w). ¹H NMR (500 MHz, CDCl₃): δ = 7.46 (t, J = 7.5 Hz, 2H), 7.26–7.41 (m, 9H), 6.85 (s, 1H), 3.89 (d, J = 9.5 Hz, 1H), 3.70 (s, 2H), 3.35 (dd, J = 14.6, 9.8 Hz, 1H), 2.88 (dd, J = 14.6, 1.0 Hz, 1H), 1.55 (s, 9H), 1.31 (s, 9H). ¹³C NMR (APT, 125 MHz, CDCl₃): δ = 153.2 (C), 140.7 (C), 137.0 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 126.2 (CH), 126.1 (CH), 122.7 (CH), 64.4 (CH), 51.8 (CH₂), 43.0 (CH₂), 35.2 (C), 34.1 (C), 31.7 (CH₃), 29.9 (CH₃). HR MS (ESI): m/z [M+H]⁺ calcd for C₂₉H₃₈NO: 416.2953; found: 416.2923.

3.9.6. Enantioselective diethylzinc addition of to benzaldehyde: (*S*)-(-)-1-phenylpropan-1-ol (**15**)

An AAP ligand (10 mol%) was placed in a 10-mL Schlenk tube. The tube was evacuated for 15 min and back-filled with dry N₂. Then an anhydrous solvent (2 mL) was added, which ensured dissolution of the ligand. After the solution was cooled to 0 °C, 0.9 mL of 1.0 M solution of Et₂Zn in hexanes (0.9 mmol, 1.80 equiv of Et₂Zn) was added dropwise and the mixture was stirred at 0 °C for a further 30 min. Then benzaldehyde (**14**) (51 μ L, 53 mg, 0.5 mmol, 1.00 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and then it was left to stir at ambient temperature for 16 h. Saturated aqueous NH₄Cl solution (2 mL) was added and the resulting slurry was extracted with EtOAc (2 \times 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Column chromatographic purification on silica gel

(hexanes/EtOAc, 9:1) afforded the title compound (**15**) as a colorless oil. $R_f = 0.18$ (silica gel; hexanes/EtOAc, 9:1). GC: CP-Chirasil-Dex CB, 25 m, 0.25 mm ID, 0.25 μm film thickness; 190 °C inlet (split mode); 195 °C detector (FID); He, 2.0 mL/min (constant flow mode); 80 °C (4 min), 10 °C/min, 110 °C (42 min), 10 °C/min, 180 °C (4 min); $t_R = 21.48$ min (*ent*-**15**), $t_R = 22.06$ min (**15**). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3368 (s), 2965 (s), 2933 (s), 2876 (s), 1948 (w), 1809 (w), 1603 (w), 1493 (s), 1453 (s), 1331 (w), 1201 (w), 1096 (w), 1014 (w), 974 (w), 763 (w), 700 (s), 545 (w). ^1H NMR (500 MHz, CDCl_3): $\delta = 7.36$ – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 4.55 (t, $J = 6.6$ Hz, 1H), 2.13 (s, 1H), 1.85 – 1.76 (m, 1H), 1.76 – 1.68 (m, 1H), 0.89 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (APT, 125 MHz, CDCl_3): $\delta = 144.6$ (C), 128.3 (CH), 127.4 (CH), 125.9 (CH), 75.9 (CH), 31.8 (CH_2), 10.1 (CH_3). GC MS: $t_R = 19.52$ min, m/z (%) = 136 ($[\text{M}]^+$, 14), 117 (7), 107 (100), 91 (7), 79 (71), 51 (10).

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