A New General Method for the Asymmetric Synthesis of 4-Alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines

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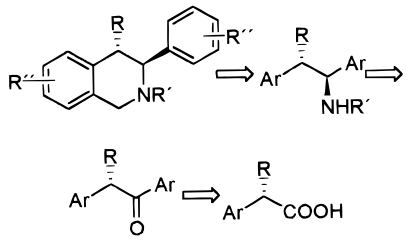
A highly enantioselective method for the synthesis of 4-alkyl substituted 1,2,3,4-tetrahydroisoquinolines is reported. The key step relies on the asymmetric synthesis of α-alkylarylacetic acids by alkylation of their corresponding amides employing *(S,S)*-(+)-pseudoephedrine as chiral inductor. Subsequent Friedel−Crafts acylation, stereocontrolled reductive amination and Pictet−Spengler cyclization affords the title compounds in excellent yields and enantioselectivities.

Introduction

During the last few years the stereoselective synthesis of isoquinoline alkaloids has been a field of increasing interest in synthetic organic chemistry.[1] Many methods have been already published for highly stereoselective syntheses of 1-substituted tetrahydroisoquinolines[2] that are very useful intermediates for the preparation of a wide range of enantiopure alkaloids.[3] However, although chiral nonracemic 3- and/or 4-substituted tetrahydroisoquinoline derivatives are of considerable interest due to their biological activity and as naturally occurring alkaloids,[4] the research toward their stereoselective synthesis is not as extended as in the case of the 1-substituted tetrahydroisoquinolines. Some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears an hydroxy function,[5] but only few reports can be found when the substitution at this position is an alkyl chain,[6] and none can be found in which additionally the substitution at the 3-position is an aryl moiety, which is found in nature quite often, e.g. in the protoberberine alkaloids thalictrifoline and corydalin methyl ester.

Scheme 1



In this context, and in connection with our studies in the field of the asymmetric synthesis of isoquinoline alkaloids,[5,7] we have developed a suitable and general enantioselective synthetic method to obtain 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines starting from chiral 1,2-diarylethylamine precursors (Scheme 1) that were prepared from appropriately substituted chiral nonracemic aryl benzyl ketones more commonly referred to as deoxybenzoins. The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4-position of the isoquinoline core and the high degree of stereoselectivity in which all the chiral centers in the molecule are generated. This can lead to the synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.

Results and Discussion

The synthetic pathway designed for the synthesis of the precursor ketones **4** (Scheme 2) consists of the asymmetric alkylation of an arylacetic acid via its (*S,S*)-pseudoephedrine amide **1**.[8] Then, a sequence of trans-

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(1) For a review, see: Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903−931.

(2) For the asymmetric synthesis of 1-substituted tetrahydroisoquinolines see, for example: (a) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1985**, *23*, 395−398. (b) Chan, W.; Lee, A. W. M.; Jiang, L. *Tetrahedron Lett.* **1995**, *36*, 715−718. (c) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859−4863. (d) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 90−102. (e) Kang, J.; Kim, J. B.; Cho, K. H.; Cho, B. T. *Tetrahedron: Asymmetry* **1997**, *8*, 657−660. (f) Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607−4610. (g) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 6709−6712. (h) Ukaji, Y.; Kenmoku, Y.; Inomata, K. *Tetrahedron: Asymmetry* **1996**, *7*, 53−56. (i) Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1992**, *48*, 9385−9390. (j) Murahashi, S.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645−2648.

(3) See, for example: (a) Dyke, S. F.; Kinsman, R. G. Kametami, T. G.; Fukumato, K.; McDonald, E. Isoquinolines. In *Heterocyclic Compounds*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, pp 1−275. (b) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589−2612.

(4) (a) Kihara, M.; Kashimoto, M.; Kobayasi, S.; Ishida, Y.; Moritoki, H.; Taira, Z. *J. Med. Chem.* **1990**, *33*, 2283−2286. (b) Mondeshka, D. M.; Stensland, B.; Angelova, I.; Ivanov, C. B.; Atanasova, R. *Acta Chem. Scand.* **1994**, *48*, 689−698. (c) Aboul-Enein, H. Y.; Islam, M. R.; Bakr, S. A. *J. Liq. Chromatog.* **1988**, *11*, 1485−1493. (d) Rinehart, K. L.; Holt, T. G.; Frege, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512−4217. (e) Wright, A. E.; Forleo, P. A.; Gumahandana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508−4512. (f) Kobayashi, J.; Kondo, J.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *J. Org. Chem.* **1992**, *57*, 6680−6682. (g) Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721−3724.

(5) Carrillo, L.; Badía, D.; Domínguez, E.; Tellitu, I.; Vicario, J. L. *Tetrahedron: Asymmetry* **1998**, *9*, 1809−1816 and references therein.

(6) (a) Philippe, N.; Levacher, V.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1997**, *7*, 417−420. (b) Tietzle, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331−1336. (c) Coote, S. G.; Davies, S. G.; Mobbs, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2257−2261.

(7) Carrillo, L.; Badía, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716−6721.; Carrillo, L.; Badía, D.; Domínguez, E.; Ortega, F.; Tellitu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 151−155.

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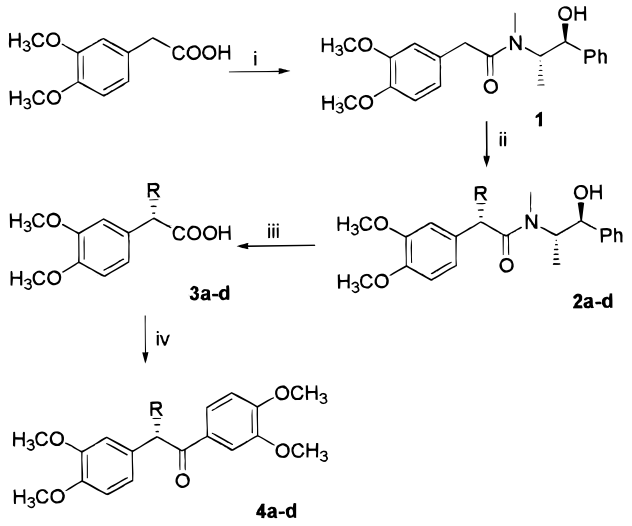
Scheme 2[a]

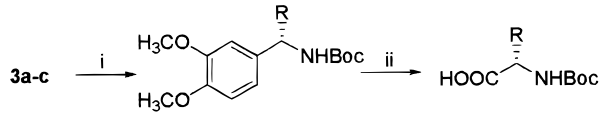


[a] Reagents and conditions: (i) (1) $SOCl_2$, toluene, reflux; (2) (+)-(*S*,*S*)-pseudoephedrine, Et_3N, THF, −20 °C. (ii) (1) LDA, LiCl, THF, −78 °C; (2) RI, THF, 0 °C. (iii) 4 M H_2SO_4/dioxane, reflux. (iv) (1) $SOCl_2$, toluene, reflux; (2) 1,2-dimethoxybenzene, $AlCl_3$, CH_2Cl_2, −20 °C.

formations (hydrolysis and Friedel−Crafts acylation) leads to the obtention of the chiral nonracemic ketones **4** with the appropriate substitution at the benzylic carbon atom.

The key step in the synthesis consists of the asymmetric alkylation of the (*S*,*S*)-pseudoephedrine amide **1** by kinetic deprotonation with LDA/LiCl in THF at −78 °C followed by electrophilic attack of the corresponding alkyl halide to the formed dianion. The ratio of the diastereomeric mixture of amides **2a**−**d** was determined by ^{1}H NMR spectroscopy and in all cases was found to be >95%. The stereochemistry of the final product was 1,4-syn, which was a posteriori confirmed on the arylacetic acids **3a**−**d**. The absolute configuration of the newly created chiral center was assigned as (*S*) by synthesizing the parent 2-phenylpropionic acid starting from the corresponding phenylacetic acid derived (+)-(*S*,*S*)-pseudoephedrine amide and comparing the obtained $[\alpha]^{20}_D$ value with data for commercially available (+)-(*S*)-2-phenylpropionic acid..[10] However a more rigorous absolute configuration assignment prompted us to correlate the structure of the arylacetic acids **3a**−**d** with other compounds of known stereochemistry. Therefore, the acids **3a**−**c** were subjected to a Curtius rearrangement, which is known to proceed with retention of configuration at the chiral center,[11] to afford *N*-Boc-2-alkylbenzylamines.[12] The crude carbamates yielded after exhaustive oxidation of the aryl ring[13] the desired *N*-Boc α-amino acids (Scheme 3), whose $[\alpha]^{20}_D$ values were correlated with data found in the literature for the same compounds, thus corroborating the assignment of

Scheme 3[a]



[a] Reagents and conditions: (i) (1) DPPA, Et_3N, benzene, reflux; (2) *t*-BuOH, TMSCl, CH_2Cl_2, rt. (ii) $NaIO_4$, $RuCl_3xH_2O$, rt.

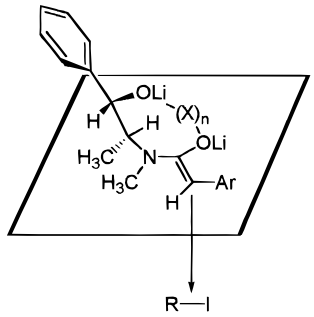


Figure 1. Proposed mechanism in the asymmetric alkylation of pseudophedrine-derived amide enolates. X denotes solvent or $(^iPr)_2NH$ molecules.

an (*S*) stereochemistry for the newly created chiral center in the diastereoselective alkylation of the amide **1**.

In a previously proposed mechanism,[14] the high diastereocontrol observed in the reported alkylation was attributed to the exclusive formation of the *Z* enolate (Ar cis to the oxygen) followed by the attack of the alkyl halide to yield a reactive open intermediate which remains in an opened staggered conformation (Figure 1). We believe that a more rigid structure for the reaction intermediate should be required in order to explain the high degree of stereoselection obtained and therefore there must be an interaction between the lithium ion on the enolate oxygen and the lithium alkoxide in the pseudoephedrine moiety that avoids the rotation around the C1−C2 axis in the pseudoephedrine moiety. This Li−X−Li interaction should be achieved through a bridging species present in the reaction media like the amine generated from the amide base after the deprotonation step, the solvent, or a chlorine anion from LiCl. When the alkylation is performed either in the absence of LiCl or when it is carried out in toluene as solvent, no variation is observed in the ee of the final product (ee >99%) and a very small decrease (ee 94−96%) is observed when switching to *n*-BuLi as base and THF as solvent. However, when both *n*-BuLi and toluene are employed, the enantioselectivity of the reaction suffers a significant lowering (ee 88%). This is indicating that the intermediate has a pronounced tendency to adopt the proposed staggered conformation by itself, but both the amine generated from the base after the deprotonation and the presence of a coordinating solvent have a significant contribution in the stereochemical outcome of the reaction, and therefore, it can be proposed that these two species are acting as a bridge between both metal ions on the intermediate, thus affording the required high level of rigidity for the reaction to proceed with such a high degree of stereoselection. The presence of LiCl in the reaction media does not exert any influence on the diastereoselectivity, but in its absence the rate of the

(9) Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M.-J. *Tetrahedron* **1994**, *50*, 2207−2218.

(10) The obtained 2-phenylpropionic acid showed $[\alpha]^{20}_D = +72.3$ (c = 1.6 $CHCl_3$), which was compared with the $[\alpha]^{20}_D$ value of commercially available (*S*)-(+)-2-phenylpropionic acid [$[\alpha]^{20}_D = +72°$ (c = 1.6 $CHCl_3$)].

(11) Fodor, G.; Csepreghy, G. *J. Chem. Soc.* **1961**, 3222−3224.

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(13) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

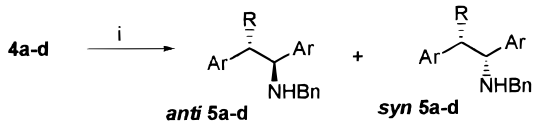
(14) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

Table 1. Yields and Stereoselectivities Obtained in the Asymmetric Synthesis of the Deoxybenzoins 4a−d

prod.	R	yield (%)	de (%)[a]	prod.	yield (%)	prod.	yield (%)	ee (%)[b]	t_R (min)[c]	t_R (min)[d]
2a	Me	89	>95	**3a**	98	**4a**	86	>99	16.6	19.3
2b	Et	84	>95	**3b**	96	**4b**	90	>99	16.9	18.3
2c	^{i}Pr	91	>95	**3c**	97	**4c**	86	>99	12.7	16.6
2d	Bn	89	>95	**3d**	98	**4d**	80	>99	12.9	21.3

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 93:7 as eluent, flow rate 1.0 mL/min.). [c] Retention time for the (*R*)-ketones **4a−d** observed in the analysis of the racemate synthesized by other methods.[9] [d] Retention time for the (*S*)-ketones **4a−d**.

Scheme 4[a]



[a] Reagents and conditions: (i) (1) $BnNH_2$, Et_3N, $TiCl_4$; THF, −20 °C; (2) $NaBH_4$, THF, −20 °C.

Table 2. Yields, Enantioselectivities, and Diastereomeric ratio of Products Obtained in the Reductive Amination of the Deoxybenzoins 4a−d

prod.	R	yield (%)[a]	anti/syn[b]	ee (%)[c]	t_R (min)[d]	t_R (min)[e]
5a	Me	91	78/22	>99	8.9	10.7
5b	Et	82	87/13	>99	8.6	11.0
5c	^{i}Pr	84	94/6	>99	7.7	10.3
5d	Bn	85	94/6	>99	8.5	9.9

[a] Global yield including both diastereoisomers. [b] Determined by ^{1}H NMR. [c] ee of the anti isomer determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 90:10 as eluent, flow rate 0.80 mL/min.). [d] Retention time for the (1*R*,2*R*)-amines ***anti*-5a−d** observed in the analysis of the racemate synthesized by other methods.[9] [e] Retention time for the (1*S*,2*S*)-amines ***anti*-5a−d**.

alkylation was dismished, that is, LiCl is acting most probably by modifiying the aggregation state of the enolate and thus enhancing its reactivity.[15]

The chiral inductor was cleanly removed by hydrolysis, thus providing, after typical acid−base workup, the α-alkylated arylacetic acids **3a−d** in excellent yield. From the extracts obtained from the aqueous basic layer it was possible to recover the chiral auxiliary (*S,S*)-(+)-pseudoephedrine in 88% yield after crystallization (hexanes/ethyl acetate 1:1) and without any racemization as the measurements of the $[\alpha]^{20}_D$ value indicated. Finally, the so obtained α-alkylated arylacetic acids were converted into the corresponding acid chloride derivative and subjected to Friedel−Crafts acylation with 1,2-dimethoxybenzene (veratrole) using $AlCl_3$ as Lewis acid, yielding the corresponding deoxybenzoins **4a−d** in good yields and with no loss of enantiomeric purity compared with the starting amides **2a−d** (Table 1).

Proceeding with the synthesis, the deoxybenzoins **4a−d** were submitted to reductive amination (Scheme 4). Thus the ketones **4a−d** were converted into *N*-benzylketimine intermediates which were reduced in situ with several reducing agents, yielding the wanted 1,2-diarylethylamines **5** as *N*-benzyl derivatives in good yield and with a variable diastereomeric ratio. Among all the hydride reagents employed, the most efficient one was proved to be $NaBH_4$ (Table 2). Bulkier metal hydride reagents such as sodium triacetoxyborohydride or lithium triethylborohydride were not able to react with the intermediate ketimines. The two obtained diastereoisomers were separated by flash column chromatography and it could be determined that the major product showed the relative stereochemistry of the two chiral groups to be *anti*[16] from the value of the coupling constant $J_{(H-H)}$ between the two benzylic protons of the 1,2-diarylethylamine moiety. This could be also proved a posteriori by the stereochemistry of the final tetrahydroisoquinoline derivatives employing NOE difference experiments. As the absolute configuration of the remaining chiral center at C-2 was already known and it remains unchanged, a (*1S,2S*) absolute configuration for the anti 1,2-diarylethylamines **5a−d** can also be proposed.

Table 3. Temperature in the Imine Formation Step and Obtained Enantioselectivities for the Reductive Amination of 4a

T (°C)	Yield (%)[a]	ee (%)[b]
reflux	89	0
r.t.	88	57
0	88	79
−20	91	>99

[a] Global yield including both diastereoisomers. [b] ee of ***anti*-5a** determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 90:10 as eluent, flow rate 0.80 mL/min.).

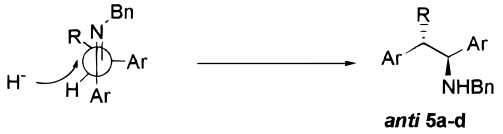


Figure 2.

The choice of temperature when forming the intermediate imine was found to have a critical effect on the ee of the final product. At high temperatures, the imine−enamine tautomerism takes place at a fast enough rate to allow notable racemization in the molecule, but upon lowering the temperature to −20 °C, no racemization occurred and the sought 1,2-diarylethylamines were obtained with no loss of enantiomeric purity compared to the starting ketones (Table 3).

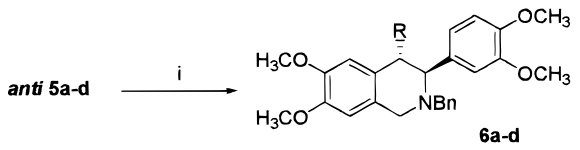
The diastereoselectivity in the metal hydride reduction of the C=N double bond becomes controlled by the configuration of the chiral center α to it, as should be expected by employing a $\sigma^*-\pi^*$ dominated Felkin−Ahn model[17] (Figure 2) in which the Ar group at the α-position to the imine double bond acts as the best σ-aceptor and therefore it should be aligned anti to the face undergoing

(15) For the influence of LiCl on the reactivity of metal enolates, see: (a) Miller, S. A.; Griffiths, S. L.; Seebach D. *Helv. Chim. Acta* **1993**, *76*, 563−571. (b) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124−1129.

(16) The anti/syn nomenclature used makes reference to the relative positions of both benzylic protons in the 1,2-diarylethylamine skeleton when the carbon chain is drawn in a way in which both aryl groups are placed with the less steric repulsions between each other. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem.* **1985**, *97*, 1−12.

(17) (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205−2208. (b) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (c) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361.

Scheme 5[a]



[a] Reagents and conditions: (i) aq HCHO, 1 M HCl, 60 °C, 24 h.

Table 4. Yields and Enantioselectivities in the Pictet−Spengler Cyclization of the Amines *anti*-5a−d

prod.	R	yield (%)	ee (%)[a]	t_R (min)[b]	t_R (min)[c]
6a	Me	83	>99	8.4	10.6
6b	Et	89	>99	8.3	10.2
6c	^{i}Pr	86	>99	7.9	10.0
6d	Bn	84	>99	8.9	11.1

[a] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 90:10 as eluent, flow rate 0.50 mL/min.). [b] Retention time for the (3*R*,4*R*)-tetrahydroisoquinolines **6a**−**d** observed in the analysis of the racemate synthesized by other methods.[9] [c] Retention time for the (3*S*,4*S*)-tetrahydroisoquinolines **6a**−**d**.

attack by the nucleophile. The steric bulk of the R alkyl chain in the 2-position of the deoxybenzoins **4a**−**d** will have a critical effect on the ratio of the diastereomeric amines **5a**−**d** obtained as the final products of the reaction and becomes increased when going from small alkyl groups to bigger ones (Table 2).

To complete the synthesis, the amines ***anti*-5a**−**d** were subjected to a standard Pictet−Spengler cyclization procedure[18] employing aqueous formaldehyde and 1 M HCl and stirring for 12 h at 60 °C, yielding the wanted 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines **6a**−**d** in excellent yield, with no racemization (Scheme 5). As shown in Table 4, the optical purity in all cases was shown to be higher than 99% by HPLC.

In summary, we have developed a short and efficient access to enantiomerically pure 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines starting form arylacetic acids in good yields and excellent enantioselectivities. Our approach was based on the asymmetric alkylation of the (+)-(*S*,*S*)-pseudoephedrine-derived amides of the corresponding acids followed by hydrolysis to remove the chiral appendage, yielding the wanted α-alkylated arylacetic acid which was subjected to Friedel−Crafts acylation and an stereocontrolled reductive amination step to yield the corresponding amines that, upon Pictet−Spengler cyclization, afforded the desired heterocycles.

Experimental Section

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20−25 °C, running at 250 MHz for ^{1}H and 62.8 MHz for ^{13}C in $CDCl_3$ solution, and resonances are reported in ppm relative to tetramethylsilane, unless otherwise stated. Assignment of individual ^{13}C resonances is supported by DEPT experiments. ^{1}H−{^{1}H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[19] Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[20] Flash column chromatography[21] on silica gel was performed with Merck Kiesegel 60 (230−400 mesh). Determination of enantiomeric excesses was performed by chiral HPLC analysis of noncrystallized samples using a Chiracel OD column with a UV detector and the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[22] *n*-BuLi was titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 °C) overnight and purged with argon.

Acylation of (+)-(*S*,*S*)-Pseudoephedrine. Synthesis of (+)-[1′*S*,2′*S*]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-*N*-methylacetamide (1). $SOCl_2$ (13.94 mL, 111.13 mmol) was carefully added over a cooled (0 °C) solution of (3,4-dimethoxyphenyl)acetic acid (15.00 g, 76.45 mmol) in dry toluene (200 mL). The reaction was refluxed for 3h, after which the volatiles were removed in vacuo. The resulting oil was dissolved in dry THF (150 mL) and was added dropwise within 45 min over a cooled (−10 °C) solution of (+)-(*S*,*S*)-pseudoephedrine (12.71 g, 76.45 mmol) and triethylamine (12.77 mL, 91.75 mmol) in dry THF (300 mL). The reaction was stirred for 1 h and quenched with saturated ammonium chloride (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, affording a yellowish oil which was purified by flash column chromatography (hexanes/ethyl acetate 2:8) to yield pure **1** as a sticky solid. An analytically pure sample was obtained by crystallization in toluene. Yield: 87%. Mp: 110−112 °C (toluene). $[\alpha]^{20}_D = +82.0$ (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks): 0.63* (d, 3H, J = 6.6); 0.88 (d, 3H, J = 6.6); 2.68 (s, 3H); 2.75* (s, 3H); 3.47 (s, 2H); 3.67* (s, 3H); 3.69 (s, 3H); 3.70 (s, 3H); 3.90 (m, 1H); 4.49 (bs, 1H); 4.53 (m, 1H); 6.53−6.74 (m, 3H); 7.21−7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 13.7, 14.7*, 26.7, 31.7*, 40.4*, 40.7, 55.3, 55.7*, 56.6*, 58.3, 74.6*, 75.3, 110.8, 111.5*, 111.6, 120.3*, 126.1, 126.3*, 126.8, 127.0*, 127.4, 127.6*, 127.7*, 127.9, 141.6, 141.8, 147.1, 147.2* 148.4*, 148.5, 172.0*, 172.5. IR (KBr): υ 3389, 1619 cm^{-1}. MS (EI) m/z (rel int): 343 (M^+, 1), 58 (100). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.98; H, 7.28; N, 4.00.

Typical Procedure for the Asymmetric Alkylation of the Pseudoephedrine Amide (1). Synthesis of (+)-[2*S*,1′*S*,2′*S*]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-*N*-methylpropionamide (2a). Over a cooled (−78 °C) suspension of LiCl (738 mg, 17.42 mmol) and LDA (5.90 mmol) in dry THF (20 mL) was slowly added a cooled solution (0 °C) of the amide **1** (1.00 g, 2.90 mmol) in dry THF (10 mL). The mixture was stirred for 1 h at −78 °C and 15 min at 0 °C, after which a solution of MeI (0.73 mL, 11.61 mmol) in dry THF (5 mL) was added at once. The reaction was stirred for 2−3 h at 0 °C and quenched with saturated Na_2CO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, affording crude **2a** which was purified by flash column chromatography (hexanes/ethyl acetate 2:8). Yield: 89% (oil). $[\alpha]^{20}_D = +90.0$ (c = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks): 0.45* (d, 3H, J = 6.7); 1.03 (d, 3H, J = 5.9); 1.35 (d, 3H, J = 6.5); 2.64 (s, 3H); 2.85* (s, 3H); 3.68 (q, 1H, J = 6.5); 3.76* (s, 3H); 3.77* (s, 3H); 3.79 (s, 3H); 3.80 (s, 3H); 4.05 (m, 1H); 4.43 (m, 1H); 4.47 (bs, 1H); 6.70−6.78 (m, 3H); 7.19−7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks): 13.8, 14.4*, 20.6, 27.1, 43.0*, 43.5, 55.6, 57.7, 75.0*,

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76.2, 109.8, 109.9*, 111.1, 119.0*, 119.3, 126.2, 126.6*, 127.3, 127.9, 128.1, 128.4*, 133.7, 134.8*, 141.5*, 142.0, 147.3*, 147.5, 148.9*, 149.0, 174.7*, 175.9. IR ($CHCl_3$): υ 3413, 1619 cm^{-1}. MS (EI) *m/z* (rel int): 357 (M^+, 1), 58 (100). Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.55; H, 7.62; N, 3.92. Found: C, 70.53; H, 7.60; N, 3.95.

(+)-[2*S*,1′*S*,2′*S*]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-*N*-methylbutanamide (2b). Yield: 84% (white solid). Mp: 58−60 °C (toluene). $[\alpha]^{20}_D = +124.0$ ($c = 0.3$, CH_2Cl_2). ^1H NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 0.47* (d, 3H, $J = 6.7$); 0.75 (t, 3H, $J = 7.4$); 1.03 (d, 3H, $J = 6.7$); 1.57 (m, 1H); 1.99 (m, 1H); 2.65 (s, 3H); 2.82* (s, 3H); 3.39 (t, 1H, $J = 7.4$); 3.65* (t, 1H, $J = 7.4$); 3.75* (s, 3H); 3.77* (s, 3H); 3.79 (s, 3H); 3.82 (s, 3H); 4.01 (m, 1H); 4.47 (bs, 1H); 4.51 (m, 1H); 6.68−6.74 (m, 3H); 7.17−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 11.9*, 13.6, 14.2, 26.9, 27.6*, 27.7, 50.1*, 50.8, 55.3, 57.2, 75.9*, 76.2, 109.9, 110.1*, 110.7, 119.6*, 119.8, 125.9, 126.3*, 126.9*, 127.6, 127.7*, 128.1, 131.7, 132.7*, 141.4*, 141.8, 147.1*, 147.4, 148.6*, 148.9, 173.8*, 175.1. IR (KBr): υ 3380, 1619 cm^{-1}. MS (EI) *m/z* (rel int): 371 (M^+, 1), 58 (100). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.12; H, 7.87; N, 3.77. Found: C, 71.22; H, 7.93; N, 3.70.

(+)-[2*S*,1′*S*,2′*S*]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-*N*,3-dimethylbutanamide (2c). Yield: 91% (oil). $[\alpha]^{20}_D = +88.2$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$) (4:1 rotamer ratio; *denotes minor rotamer peaks): 0.41* (d, 3H, $J = 6.7$); 0.53 (d, 3H, $J = 6.8$); 0.84 (d, 3H, $J = 6.3$); 0.95 (d, 3H, $J = 6.9$); 2.21 (m, 1H); 2.64 (s, 3H); 2.72* (s, 3H); 2.96 (d, 1H, $J = 10.0$); 3.30* (d, 1H, $J = 10$); 3.69* (s, 3H); 3.71 (s, 3H); 3.73 (s, 3H); 4.28 (m, 1H); 4.40 (m, 1H); 4.55 (bs, 1H); 6.60−6.74 (m, 3H); 7.09−7.27 (m, 5H). ^{13}C NMR ($CDCl_3$) (4:1 rotamer ratio; *denotes minor rotamer peaks): 13.4, 14.2*, 14.8, 21.5, 21.6*, 27.0, 31.4*, 31.5, 55.1*, 55.2, 55.8, 56.5*, 57.1, 74.7*, 75.3, 110.3*, 110.4, 120.3*, 120.7, 125.8, 126.3*, 126.8, 127.4*, 127.5, 128.0, 130.5, 131.6*, 141.7, 141.8*, 147.1*, 147.4, 148.4*, 148.6, 173.5*, 174.8. IR ($CHCl_3$): υ 3460, 1610 cm^{-1}. MS (EI) *m/z* (rel int): 385 (M^+,1), 58 (100). Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.65; H, 8.11; N, 3.63. Found: C, 71.58; H, 8.23; N, 3.73.

(+)-[2S,1′S,2′*S*]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-*N*-methyl-3-phenylpropionamide (2d). Yield: 89% (yellowish solid). Mp: 164−166 °C (hexanes/ethyl acetate 1:1). $[\alpha]^{20}_D = +168.0$ ($c = 0.3$, CH_2Cl_2). ^1H NMR ($CDCl_3$) (3:1 rotamer ratio; *denotes minor rotamer peaks): 0.53* (d, 3H, $J = 6.7$); 1.06 (d, 3H, $J = 6.7$); 2.60 (s, 3H); 2.87* (s, 3H); 2.92 (m, 1H); 3.42 (m, 1H); 3.52 (t, 1H, $J = 8.5$); 3.74* (s, 3H); 3.79 (s, 3H); 3.85 (s, 3H); 4.11 (m, 1H); 4.43 (bs, 1H); 4.53 (d, 1H, $J = 6.8$); 6.59−6.78 (m, 3H); 7.02−7.39 (m, 10H). ^{13}C NMR ($CDCl_3$) (3:1 rotamer ratio; *denotes minor rotamer peaks): 13.9, 14.4*, 27.4, 41.1, 50.8*, 51.6, 55.6*, 55.7, 57.6, 75.2*, 76.3, 110.5, 110.7*, 110.8*, 111.0, 120.0*, 120.1, 125.7*, 126.0, 126.2*, 126.6, 127.3*, 127.9, 128.0*, 128.1, 128.5, 129.1, 131.3, 131.9*, 139.8, 139.9*, 141.3*, 142.0, 147.6*, 147.8, 148.7*, 148.9, 173.7*, 174.8. IR (KBr): υ 3470, 1625 cm^{-1}. MS (EI) *m/z* (rel int): 433 (M^+,1), 415 (M^+ − 18, 6), 58 (100). Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.79; H, 7.21; N, 3.23. Found: C, 74.59; H, 7.33; N, 3.30.

General Procedure for the Hydrolysis of the Pseudoephedrine Amides. Synthesis of (*S*)-(+)-2-(3,4-Dimethoxyphenyl)propanoic Acid (3a). A solution of the amide (725 mg, 2.02 mmol) in dioxane (17 mL) was slowly added over a cooled (0 °C) 4 M H_2SO_4 solution (17 mL). When the addition was complete, the mixture was refluxed for 2 h. The reaction was quenched with water, carefully basified to pH = 12, and washed with EtOAc (3 × 20 mL). The aqueous layer was carefully driven to pH = 3 and extracted with CH_2Cl_2 (3 × 20 mL). After drying (Na_2SO_4), filtration, and removal of the solvent from the basic organic extracts, it was possible to recover, after crystallization (hexanes/EtOAc), pure (+)-(*S*,*S*)-pseudoephedrine in 83% yield. The collected organic acidic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo, yielding the arylacetic acid as a yellowish oil. Yield: 98%. $[\alpha]^{20}_D = +64.7$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.47 (d, 3H, $J = 7.1$); 3.65 (q, 1H, $J = 7.1$); 3.81 (s, 3H); 3.83 (s, 3H); 6.76−6.86 (m, 3H); 11.0−12.0 (bs, 1H). ^{13}C NMR ($CDCl_3$): 17.8, 44.6, 55.5, 110.5, 110.9, 119.4, 132.0, 148.0, 148.6, 180.6. IR ($CHCl_3$): υ 3123, 1707 cm^{-1}. MS (EI) *m/z* (rel int): 211 ($M^+ + 1$, 5), 210 (M^+, 37), 165 (100). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.95; H, 6.81.

(+)-(*S*)-2-(3,4-Dimethoxyphenyl)butanoic Acid (3b). Yield: 96% (oil). $[\alpha]^{20}_D = +73.5$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 0.90 (t, 3H, $J = 7.3$); 1.81 (m, 1H); 2.05 (m, 1H); 3.39 (t, 1H, $J = 7.7$); 3.82 (s, 3H); 3.84 (s, 3H); 6.77−6.86 (m, 3H); 10.9−11.2 (bs, 1H). ^{13}C NMR ($CDCl_3$): 11.9, 26.2, 52.8, 55.8, 110.9, 111.0, 120.2, 130.7, 148.2, 148.9, 180.5. IR ($CHCl_3$): υ 3412, 1701 cm^{-1}. MS (EI) *m/z* (rel int): 224 (M^+, 51), 179 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19. Found: C, 63.93; H, 7.11.

(+)-(*S*)-2-(3,4-Dimethoxyphenyl)-3-methylbutanoic Acid (3c). Yield: 97% (oil). $[\alpha]^{20}_D = +81.3$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 0.70 (d, 3H, $J = 6.6$); 1.06 (d, 3H, $J = 6.4$); 2.29 (m, 1H); 3.68 (d, 1H, $J = 10.7$); 3.84 (s, 3H); 3.85 (s, 3H); 6.75−6.89 (m, 3H); 9.5−10.2 (bs, 1H). ^{13}C NMR ($CDCl_3$): 20.0, 21.4, 31.6, 55.6, 59.5, 110.9, 111.2, 120.9, 130.2, 148.3, 148.8, 180.1. IR ($CHCl_3$): υ 3412, 1590 cm^{-1}. MS (EI) *m/z* (rel int): 239 ($M^+ + 1$, 8), 238 (M^+, 41), 195 (100). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.51; H, 7.62. Found: C, 65.41; H, 7.69.

(+)-(*S*)-2-(3,4-Dimethoxyphenyl)-3-phenylpropanoic Acid (3d). Yield: 98% (oil). $[\alpha]^{20}_D = +74.3$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 3.09 (dd, 1H, $J = 7.2, 13.7$); 3.45 (dd, 1H, $J = 7.2, 13.6$); 3.81 (t, 1H, $J = 7.2$); 3.88 (s, 3H); 3.90 (s, 3H); 6.75−7.07 (m, 3H); 7.17−7.40 (m, 5H); 10.0−11.0 (bs, 1H). ^{13}C NMR ($CDCl_3$): 39.1, 52.7, 55.6, 110.8, 110.9, 120.1, 126.2, 128.1, 128.7, 130.3, 130.6, 148.2, 148.6, 178.7. IR ($CHCl_3$): υ 2942, 1731 cm^{-1}. MS (EI) *m/z* (rel int): 287 ($M^+ + 1$, 4), 286 (M^+, 18), 195 (100). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.22; H, 6.39.

Absolute Configuration Determination of the 2-Alkyl-Substituted Arylacetic Acids 3a−d. Synthesis of *N*-Boc-alanine. Over a stirred solution of the starting arylacetic acid (50 mg, 0.24 mmol) in dried benzene was dropwise added diphenylphosphoryl azide (DPPA) (52 μL, 0.24 mmol) and triethylamine (33 μL, 0.24 mmol) at rt. The reaction was refluxed for 3 h, and the volatiles were removed in vacuo. The resulting oil was dissolved in CH_2Cl_2 (5 mL), *t*-BuOH (69 μL, 0.72 mmol) and TMSCl (91 μL, 0.72 mmol), and the resulting mixture was stirred for 18 h at rt. The reaction was then quenched with saturated $NaHCO_3$ (15 mL) and extracted with ether (3 × 10 mL), the combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The resulting oil was dissolved in dry CCl_4 (4 mL), acetonitrile (4 mL), and water (6 mL), to the resulting biphasic solution were added sodium periodate (1.03 g, 4.80 mmol) and $RuCl_3 \cdot xH_2O$ (21 mg, 0.1 mmol), and the mixture was stirred for 24 h at rt. The mixture was quenched with a 4 M NaOH solution (10 mL), the organic layer was discarded, and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), after which it was carefully driven to pH = 2−3 and extracted with Et_2O (3 × 10 mL). The combined ethereal fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, after which crystallization in hexane yielded pure (*S*)-(−)-*N*-(*tert*-butoxycarbonyl)alanine. (Yield: 59%. $[\alpha]^{20}_D = -24.9$ ($c = 2.0$, AcOH) (lit.[23] $[\alpha]^{20}_D$ −25.5, $c = 2.0$, AcOH). The other *N*-Boc α-amino acids were synthesized in an analogous way: (*S*)-(−)-2-[*N*-(*tert*-butoxycarbonyl)amino]butyric acid [Yield: 64%. $[\alpha]^{20}_D = -6.3$ ($c = 2.2$, CH_2Cl_2) (lit.[24] $[\alpha]^{20}_D$ −9.6, $c = 2.2$, CH_2Cl_2)], and (*S*)-(−)-*N*-(*tert*-butoxycarbonyl)valine [Yield: 48%. $[\alpha]^{20}_D = -5.9$ ($c = 1.0$, AcOH) (lit.[22] $[\alpha]^{20}_D$ −7.5, $c = 1.0$, AcOH)].

Typical Friedel−Crafts Acylation Procedure: Synthesis of (+)-(*S*)-1,2-Bis(3,4-dimethoxyphenyl)-1-propanone (4a). Over a cooled (0 °C) solution of the starting acid (235 mg, 1.11 mmol) in dry toluene (15 mL) was slowly added

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$SOCl_2$ (0.17 mL, 2.53 mmol). The mixture was stirred for 15 min at 0 °C and refluxed for 4 h. The volatiles were removed in vacuo, and the resulting red oil was dissolved in dry CH_2Cl_2 (10 mL) and was dropwise added within 40 min over a stirred suspension of $AlCl_3$ (358 mg, 2.46 mmol) and 1,2-dimethoxybenzene (0.16 mL, 1.21 mmol) in dry CH_2Cl_2 (20 mL) at −20 °C. The reaction was stirred at this temperature for 2 h and quenched with 4 M HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, yielding the pure ketone **4** after flash column chromatography purification (hexanes/ethyl acetate 1:1). An analytically pure sample was obtained by crystallization in MeOH. Yield: 86%. Mp: 62−64 °C (MeOH). $[\alpha]^{20}_D$ = +60.9 (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.44 (d, 3H, J = 6.9); 3.76 (s, 3H); 3.78 (s, 3H); 3.82 (s, 3H); 3.83 (s, 3H); 4.53 (q, 1H, J = 6.8); 6.70−6.79 (m, 4H); 7.47 (d, 1H, J = 2.0); 7.53 (dd, 1H, J = 2.0, 8.0). ^{13}C NMR ($CDCl_3$): 19.6, 46.9, 55.8, 55.9, 60.0, 109.9, 110.5, 111.0, 111.5, 119.9, 123.3, 129.6, 134.5, 147.9, 148.9, 149.3, 153.0, 199.0. IR (KBr): υ 1670 cm^{-1}. MS (EI) m/z (rel int): 330 (M^+, 4), 165 (100). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.18; H, 6.63.

(+)-(*S*)-1,2-Bis(3,4-dimethoxyphenyl)-1-butanone (4b). Yield: 90% (white solid). Mp: 76−78 °C (MeOH). $[\alpha]^{20}_D$ = +79.3 (c = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.88 (t, 3H, J = 7.3); 1.82 (m, 1H); 2.12 (m, 1H); 3.80 (s, 3H); 3.83 (s, 3H); 3.87 (s, 6H); 4.33 (t, 1H, J = 7.5); 6.74−6.84 (m, 4H); 7.53 (d, 1H, J = 1.9); 7.61 (dd, 1H, J = 1.9, 8.4). ^{13}C NMR ($CDCl_3$): 12.2, 21.7, 54.4, 55.7, 55.8, 55.9, 109.8, 110.7, 110.8, 111.2, 120.5, 123.1, 130.1, 132.6, 147.9, 148.8, 149.1, 152.9, 198.7. IR (KBr): υ 1663 cm^{-1}. MS (EI) m/z (rel int): 344 (M^+, 4), 165 (100). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.80; H, 7.10.

(+)-(*S*)-1,2-Bis(3,4-dimethoxyphenyl)-3-methyl-1-butanone (4c). Yield: 86% (white solid). $[\alpha]^{20}_D$ = +75.0 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.75 (d, 3H, J = 6.7); 0.98 (d, 3H, J = 6.4); 2.51 (m, 1H); 3.82 (s, 3H); 3.86 (s, 3H); 3.91 (s, 6H); 4.09 (d, 1H, J = 10.2); 6.74−6.96 (m, 4H); 7.54 (d, 1H, J = 1.0); 7.67 (dd, 1H, J = 1.0, 8.6). ^{13}C NMR ($CDCl_3$): 20.5, 21.9, 31.8, 56.1, 56.3, 60.2, 109.8, 110.6, 110.9, 121.2, 123.0, 124.2, 130.6, 131.5, 147.9, 148.9, 149.0, 153.0, 199.2. IR ($CHCl_3$): υ 1667 cm^{-1}. MS (EI) m/z (rel int): 358 (M^+, 4), 165 (100). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.62; H, 6.98.

(+)-(*S*)-1,2-Bis(3,4-dimethoxyphenyl)-3-phenyl-1-propanone (4d). Yield: 80% (white solid). $[\alpha]^{20}_D$ = + 103.5 (c = 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 3.01 (dd, 1H, J = 7.2, 13.5); 3.45 (dd, 1H, J = 7.2, 12.8); 3.71 (s, 3H); 3.72 (s, 3H); 3.74 (s, 3H); 3.76 (s, 3H); 4.68 (t, 1H, J = 7.1); 6.74−6.78 (m, 4H); 7.00−7.09 (m, 5H); 7.47 (d, 1H, J = 1.1); 7.57 (dd, 1H, J = 1.1, 8.7). ^{13}C NMR ($CDCl_3$): 39.8, 54.5, 55.3, 55.4, 55.6, 55.7, 109.4, 110.4, 110.5, 110.8, 120.1, 122.9, 125.7, 127.8, 128.8, 129.3, 131.7, 139.5, 147.6, 148.4, 148.7, 152.6, 197.4. IR ($CHCl_3$): υ 1666 cm^{-1}. MS (EI) m/z (rel int): 406 (M^+, 5), 165 (100). Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.62; H, 6.12.

Typical Reductive Amination Procedure. Synthesis of the 1,2-Diarylethylamines (*anti*-5) and (*syn*-5). To a stirred solution of the deoxybenzoin **4a** (1.65 g. 5.00 mmol), Et_3N (2.08 mL, 15.00 mmol), and benzylamine (0.60 mL, 5.50 mmol) in THF (30 mL) at −78 °C was slowly added a 1 M CH_2Cl_2 solution of $TiCl_4$ (5.00 mL, 5.00 mmol). The mixture was stirred for 5 min at −78 °C and for 1 h at −20 °C, after which a MeOH (20 mL) solution of $NaBH_4$ (851 mg, 22.5 mmol) was dropwise added within 30 min. The reaction was stirred for 2 h at −20 °C and quenched with saturated Na_2CO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, yielding the separated pure amines ***syn*-5** and ***anti*-5** after flash column chromatography purification (hexanes/ethyl acetate 1:1). An analytically pure sample of the ***anti*-5** amines was obtained by crystallization in MeOH.

(−)-(1*S*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-propylamine (*anti*-5a). Yield: 69% (white solid). Mp: 138−140 °C (MeOH). $[\alpha]^{20}_D$ = −38.6 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.92 (d, 3H, J = 7.0); 1.72 (bs, 1H); 2.79 (m, 1H); 3.27 (d, 1H, J = 13.7); 3.46 (d, 1H, J = 9.6); 3.56 (d, 1H, J = 13.6); 3.82 (s, 3H); 3.89 (s, 3H); 3.91 (s, 3H); 3.92 (s, 3H); 6.67 (d, 1H, J = 1.6); 6.77 (dd, 1H, J = 1.8, 8.6); 6.82 (s, 1H); 6.86 (s, 1H); 6.92−6.97 (m, 2H); 7.17−7.26 (m, 5H). ^{13}C NMR ($CDCl_3$): 19.1, 46.8, 50.8, 55.7, 55.8, 55.9, 67.2, 110.0, 110.4, 111.1, 119.7, 121.1, 121.2, 126.6, 128.0, 128.8, 134.8, 137.1, 140.2, 147.6, 148.0, 148.9, 149.0. IR (KBr): υ 3350 cm^{-1}. MS (EI) m/z (rel int): 421 (M^+, 1), 256 (100). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.07; H, 7.42; N, 3.32. Found: C, 74.15; H, 7.46; N, 3.41.

(+)-(1*R*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-propylamine (*syn*-5a). Yield: 19% (oil). $[\alpha]^{20}_D$ = +4.9 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.27 (d, 3H, J = 7.1); 1.67 (bs, 1H); 2.98 (m, 1H); 3.45 (d, 1H, J = 13.5); 3.66 (d, 1H, J = 13.5); 3.70 (d, 1H, J = 5.9); 3.73 (s, 3H); 3.77 (s, 3H); 3.84 (s, 3H); 3.86 (s, 3H); 6.48 (d, 1H, J = 1.6); 6.61 (dd, 1H, J = 1.8, 8.6); 6.63−6.83 (m, 4H); 7.14−7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): 16.5, 45.7, 51.4, 55.7, 55.8, 55.9, 67.5, 110.4, 110.6, 111.0, 111.7, 120.0, 120.4, 126.7, 127.9, 128.2, 134.2, 136.2, 140.6, 147.3, 147.7, 148.2, 148.4. IR ($CHCl_3$): υ 3350 cm^{-1}. MS (EI) m/z (rel int): 421 (M^+, 1), 256 (100). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.07; H, 7.42; N, 3.32. Found: C, 74.19; H, 7.41; N, 3.47.

(−)-(1*S*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-butylamine (*anti*-5b). Yield: 70% (white solid). Mp: 110−113 °C (MeOH). $[\alpha]^{20}_D$ = −40.2 (c = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.52 (t, 3H, J = 7.3); 1.28 (m, 2H); 1.80 (bs, 1H); 2.52 (dt, 1H, J = 4.7, 9.8); 3.24 (d, 1H, J = 13.9); 3.49 (d, 1H, J = 9.8); 3.56 (d, 1H, J = 13.9); 3.75 (s, 3H); 3.83 (s, 3H); 3.84 (s, 3H); 3.85 (s, 3H); 6.61 (d, 1H, J = 1.8); 6.77 (dd, 1H, J = 1.8, 8.2); 6.81−6.96 (m, 4H); 7.18−7.26 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.0, 26.0, 50.6, 54.7, 55.7, 55.8, 55.9, 66.4, 110.5, 111.1, 111.6, 119.9, 121.2, 121.3, 126.6, 128.0, 128.1, 134.7, 134.8, 140.0, 147.7, 148.1, 149.0, 149.1. IR (KBr): υ 3352 cm^{-1}. MS (EI) m/z (rel int): 435 (M^+, 1), 256 (100). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.42; H, 7.64; N, 3.22. Found: C, 74.55; H, 7.61; N, 3.30.

(−)-(1*R*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-butylamine (*syn*-5b). Yield: 9% (oil). $[\alpha]^{20}_D$ = −4.3 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.76 (t, 3H, J = 7.2); 1.57 (m, 1H); 1.71 (bs, 1H); 1.89 (m, 1H); 2.75 (m, 1H); 3.48 (d, 1H, J = 13.4); 3.65 (d, 1H, J = 13.4); 3.71 (s, 3H); 3.74 (s, 3H); 3.76 (d, 1H, J = 5.2); 3.83 (s, 3H); 3.85 (s, 3H); 6.39 (d, 1H, J = 1.8); 6.53 (s, 1H); 6.58 (dd, 1H, J = 1.8, 8.2); 6.68−6.74 (m, 3H); 7.19−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 24.2, 51.4, 54.0, 55.6, 55.7, 55.8, 66.8, 110.2, 110.4, 111.2, 112.3, 120.6, 121.2, 126.7, 128.0, 128.2, 133.9, 134.1, 140.7, 147.3, 147.6, 148.1, 148.2. IR ($CHCl_3$): υ 3350 cm^{-1}. MS (EI) m/z (rel int): 435 (M^+, 1), 256 (100). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.42; H, 7.64; N, 3.22. Found: C, 74.51; H, 7.68; N, 3.32.

(−)-(1*S*,2*S*)-*N*-benzyl-1,2-bis(3,4-dimethoxyphenyl)-3-methylbutylamine (*anti*-5c). Yield: 77% (oil). $[\alpha]^{20}_D$ = −64.3 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.42 (d, 3H, J = 7.1); 1.02 (d, 3H, J = 7.1); 1.68 (m, 1H); 1.80 (bs, 1H); 2.48 (dd, 1H, J = 4.6, 9.7); 3.22 (d, 1H, J = 13.9); 3.56 (d, 1H, J = 9.8); 3.66 (d, 1H, J = 13.9); 3.78 (s, 3H); 3.82 (s, 3H); 3.89 (s, 3H); 3.92 (s, 3H); 6.63 (d, 1H, J = 1.7); 6.75 (dd, 1H, J = 1.7, 8.4); 6.79−6.91 (m, 4H); 7.12−7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.0, 14.5, 26.5, 52.1, 56.2, 55.6, 55.9, 56.1, 65.4, 110.4, 110.9, 111.7, 119.2, 120.2, 121.4, 126.9, 128.5, 128.9, 134.7, 134.9, 140.6, 146.9, 147.8, 149.2, 149.3. IR ($CHCl_3$): υ 3354 cm^{-1}. MS (EI) m/z (rel int): 449 (M^+, 1), 434 (M^+ − 15, 3), 256 (100). Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.83; H, 7.78; N, 3.16.

(−)-(1*R*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-3-methylbutylamine (*syn*-5c). Yield: 5% (oil). $[\alpha]^{20}_D$ = −6.7 (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.63 (d, 3H, J = 7.1); 1.32 (d, 3H, J = 7.1); 1.73 (bs, 1H); 1.88 (m, 1H); 2.15 (m, 1H); 2.85 (m, 1H,); 3.58 (d, 1H, J = 13.2); 3.65 (d, 1H, J = 13.3); 3.70 (s, 3H); 3.73 (s, 3H); 3.79 (d, 1H, J = 5.2); 3.84 (s, 3H); 3.86 (s, 3H); 6.35 (d, 1H, J = 1.8); 6.49 (s, 1H); 6.60 (dd, 1H, J = 1.8, 8.2); 6.68−6.77 (m, 3H); 7.22−7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 16.5, 24.6, 52.4, 55.3, 55.7, 55.8, 55.9, 65.3, 110.4, 110.5, 111.9, 112.6, 121.9, 121.6, 127.2, 128.0, 128.5,

134.3, 134.8, 140.3, 147.6, 147.9, 148.5, 148.9. IR ($CHCl_3$): υ 3353 cm^{-1}. MS (EI) *m/z* (rel int): 449 (M^+, 1), 434 ($M^+ - 15$, 2), 256 (100). Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.81; H, 7.82; N, 3.19.

(−)-(1*S*,2*S*)-*N*-benzyl-1,2-bis(3,4-dimethoxyphenyl)-3-phenylpropylamine (*anti*-5d). Yield: 79% (oil). $[\alpha]^{20}_D = -157.1$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.84 (bs, 1H); 2.05 (dd, 1H, $J = 1.1, 11.1$); 2.69 (dd, 1H, $J = 3.2, 11.1$); 2.75 (dt, 1H, $J = 3.1, 10.3$); 3.29 (d, 1H, $J = 13.6$); 3.55 (d, 1H, $J = 13.6$); 3.59 (d, 1H, $J = 10.3$); 3.83 (s, 3H); 3.89 (s, 3H); 3.91 (s, 3H); 3.93 (s, 3H); 6.59 (d, 1H, $J = 1.4$); 6.74 (dd, 1H, $J = 1.4, 8.1$); 6.78−6.95 (m, 4H); 7.22−7.32 (m, 10H). ^{13}C NMR ($CDCl_3$): 39.9, 50.6, 55.1, 55.7, 55.8, 55.9, 65.3, 110.3, 110.4, 110.6, 110.8, 120.7, 121.2, 125.3, 126.6, 127.6, 127.9, 128.2, 128.6, 133.6, 134.6, 140.1, 140.3, 147.4, 148.0, 148.4, 149.0. IR ($CHCl_3$): υ 3348 cm^{-1}. MS (EI) *m/z* (rel int): 497 (M^+, 1), 91 (100). Anal. Calcd for $C_{32}H_{35}NO_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 77.22; H, 7.11; N, 2.90.

(−)-(1*R*,2*S*)-*N*-Benzyl-1,2-bis(3,4-dimethoxyphenyl)-3-phenylpropylamine (*syn*-5d). Yield: 4% (oil). $[\alpha]^{20}_D = -20.3$ ($c = 0.1$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.75 (bs, 1H); 2.33 (m, 1H); 2.45 (m, 1H); 2.93 (m, 1H); 3.43 (d, 1H, $J = 13.4$); 3.63 (d, 1H, $J = 13.4$); 3.74 (s, 3H); 3.77 (s, 3H); 3.84 (d, 1H, $J = 5.8$); 3.95 (s, 3H); 4.01 (s, 3H); 6.31 (d, 1H, $J = 1.8$); 6.51 (dd, 1H, $J = 1.8, 8.1$); 6.79−6.88 (m, 4H); 7.12−7.29 (m, 10H). ^{13}C NMR ($CDCl_3$): 34.3, 51.2, 55.3, 55.7, 55.8, 56.3, 56.5, 63.8, 110.1, 110.4, 110.6, 110.9, 120.3, 121.6, 125.1, 127.2, 127.9, 128.1, 128.2, 128.7, 133.1, 134.5, 140.1, 140.6, 147.2, 148.5, 148.9, 149.3. IR ($CHCl_3$): υ 3348 cm^{-1}. MS (EI) *m/z* (rel int): 497 (M^+, 1), 91 (100). Anal. Calcd for $C_{32}H_{35}NO_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 77.29; H, 7.01; N, 2.89.

Pictet−Spengler Cyclization. Synthesis of (+)-(3*S*,4*S*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-methyl-1,2,3,4-tetrahydroisoquinoline (6a). A solution of the amine ***anti*-5a** (100 mg, 0.24 mmol) and formaldehyde (0.12 mL, 1.42 mmol) in 1 M HCl (10 mL) was stirred for 16 h at 60 °C. Saturated Na_2CO_3 (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, yielding the pure heterocycle **6a** after flash column chromatography purification (hexanes/ethyl acetate 1:1). An analytically pure sample was obtained by crystallization in MeOH. Yield: 83%. Mp: 145−148 °C (MeOH). $[\alpha]^{20}_D = +18.3$ ($c = 0.2$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.30 (d, 3H, $J = 6.9$); 3.10 (m, 1H); 3.17 (d, 1H, $J = 13.3$); 3.30 (d, 1H, $J = 6.6$); 3.45 (d, 1H, $J = 14.9$); 3.36 (d, 1H, $J = 14.9$); 3.72 (d, 1H, $J = 13.3$); 3.80 (s, 3H); 3.82 (s, 3H); 3.87 (s, 3H); 3.88 (s, 3H); 6.47 (s, 1H); 6.75 (s, 1H); 6.82−6.90 (m, 3H); 7.23−7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): 20.9, 39.8, 53.6, 55.7, 55.8, 55.9, 59.6, 70.9, 108.8, 110.3, 110.5, 111.0, 121.2, 126.8, 128.1, 128.6, 126.3, 131.3, 133.9, 139.4, 147.1, 147.7, 148.1, 148.9. MS (EI) *m/z* (rel int): 433 (M^+, 4), 418 ($M^+ - 15$, 2), 178 (100). Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.87; H, 7.09; N, 3.30.

(+)-(3*S*,4*S*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-ethyl-1,2,3,4-tetrahydroisoquinoline (6b). Yield: 89% (white solid). Mp: 112−114 °C (MeOH). $[\alpha]^{20}_D = +66.8$ ($c = 0.1$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 0.92 (t, 3H, $J = 7.4$); 1.68 (m, 1H); 1.97 (m, 1H); 2.85 (m, 1H); 3.17 (d, 1H, $J = 13.2$); 3.25 (d, 1H, $J = 14.9$); 3.36 (d, 1H, $J = 14.9$); 3.62 (d, 1H, $J = 13.2$); 3.71 (s, 3H); 3.73 (d, $J = 4.5$); 3.81 (s, 3H); 3.85 (s, 3H); 3.87 (s, 3H); 6.50 (s, 1H); 6.61−6.82 (m, 4H); 7.24−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.4, 26.8, 46.1, 51.7, 55.5, 55.6, 55.7, 55.9, 59.4, 64.2, 108.7, 110.4, 111.1, 111.4, 120.9, 126.8, 128.1, 128.6, 127.0, 130.3, 132.7, 139.3, 147.0, 147.5, 147.9, 148.5. MS (EI) *m/z* (rel int): 447 (M^+, 5), 192 (100). Anal. Calcd for $C_{28}H_{33}NO_4$: C, 75.14; H, 7.43; N, 3.13. Found: C, 75.08; H, 7.40; N, 3.19.

(+)-(3*S*,4*S*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-(2-methylethyl)-1,2,3,4-tetrahydroisoquinoline (6c). Yield: 86% (white solid). Mp: 120−122 °C (MeOH). $[\alpha]^{20}_D = +77.5$ ($c = 0.1$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 0.92 (d, 3H, $J = 7.6$); 1.06 (d, 3H, $J = 7.6$); 1.96 (m, 1H); 2.87 (m, 1H); 3.12 (d, 1H, $J = 13.1$); 3.31 (d, 1H, $J = 14.7$); 3.42 (d, 1H, $J = 14.6$); 3.65 (d, 1H, $J = 13.2$); 3.72 (s, 3H); 3.75 (d, $J = 5.1$); 3.83 (s, 3H); 3.85 (s, 3H); 3.87 (s, 3H); 6.54 (s, 1H); 6.63−6.85 (m, 4H); 7.22−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.4, 12.1, 26.9, 45.8, 52.1, 55.5, 55.6, 55.7, 60.1, 66.3, 108.6, 110.5, 111.0, 111.6, 121.2, 126.8, 128.3, 128.7, 127.2, 130.5, 132.6, 139.2, 147.1, 147.8, 148.3, 148.6. MS (EI) *m/z* (rel int): 461 (M^+, 6), 192 (100). Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.03. Found: C, 75.48; H, 7.60; N, 3.11.

(+)-(3*S*,4*S*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-benzyl-1,2,3,4-tetrahydroisoquinoline (6d). Yield: 84% (white solid). Mp: (as HCl salt) 130−136 °C (MeOH). $[\alpha]^{20}_D = +85.7$ ($c = 0.1$, CH_2Cl_2). ^1H NMR ($CDCl_3$): 3.02−3.36 (m, 5H); 3.36 (d, 1H, $J = 14.5$); 3.54 (d, 1H, $J = 14.5$); 3.63 (s, 3H); 3.65 (s, 3H); 3.71 (d, $J = 2.8$); 3.82 (s, 3H); 3.84 (s, 3H); 6.33 (s, 1H); 6.51−6.77 (m, 4H); 7.23−7.68 (m, 10H). ^{13}C NMR ($CDCl_3$): 40.0, 46.4, 50.5, 55.4, 55.5, 56.7, 59.3, 63.9, 108.4, 110.3, 111.6, 111.7, 121.0, 125.8, 126.9, 128.1, 128.6, 128.8, 129.5, 130.0, 131.2, 136.5, 139.3, 140.8, 147.0, 147.1, 147.9, 148.2. MS (EI) *m/z* (rel int): 509 (M^+, 6), 91 (100). Anal. Calcd for $C_{33}H_{35}NO_4$: C, 77.77; H, 6.92; N, 2.75. Found: C, 77.72; H, 6.98; N, 2.77.

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