Tetrahedron 65 (2009) 3232–3238

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A process for the rapid removal of dialkylamino-substituents from aromatic rings. Application to the expedient synthesis of (*R*)-tolterodine

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ARTICLE INFO

Article history:
Received 25 September 2008
Received in revised form 3 December 2008
Accepted 5 December 2008
Available online 24 December 2008

Keywords:
Reductive deamination
Organocatalysis
Enantioselective
Tolterodine

ABSTRACT

A range of *N*,*N*-dialkylanilines have been successfully converted to the parent substituted benzenes by a novel two-step pathway. The products are obtained in good yields and optical purity of adjacent stereocenters is maintained. This technology has been applied toward the synthesis of (*R*)-tolterodine.

1. Introduction

Over the last 10 years, Friedel–Crafts alkylations,[1] hydroxyalkylations,[2a] and aminoalkylations[2b] have emerged as new strategies for the enantioselective, catalytic construction of medicinally[3] important benzylic stereocenters. While the scope of the electrophilic component in these catalytic coupling reactions has continued to grow, it is intriguing to consider that Friedel–Crafts nucleophiles are generally restricted to electron-rich or neutral aromatic systems (e.g., indoles, anisoles, pyrroles, furans). Recently, we hypothesized that the inherent value of enantioselective Friedel–Crafts chemistry might be expanded via the identification of an activation group that (i) would allow π-neutral or π-deficient substrates to function as suitable nucleophiles for a variety of asymmetric alkylation reactions yet (ii) be readily excised from the parent aromatic ring using operationally trivial conditions.

In this context, it has long been established that dialkylamines, particularly dimethyl and cyclically constrained amines, are among the most powerful[4] electron-donating substituents for the acceleration of electrophilic aromatic substitution reactions. However, the general use of dialkylamines as a removable activation handle for Friedel–Crafts alkylations has yet to be demonstrated,[5] presumably due to the lack of existing methods to readily cleave tertiary amines from aromatic or heteroaromatic rings. Herein, we describe a novel process for the scission of *N*,*N*-dialkyl substituted amines from aryl or heteroaryl rings via formation and reduction of the corresponding quaternary ammonium salt. This process represents a general and operationally trivial method for the cleavage of dialkylamine activation handles from the enantioenriched products of catalytic Friedel–Crafts alkylations. Most important, we anticipate that this deamination reaction will allow a wide variety of aromatic rings to become suitable substrates for enantioselective catalytic Friedel–Crafts chemistry (Fig. 1).

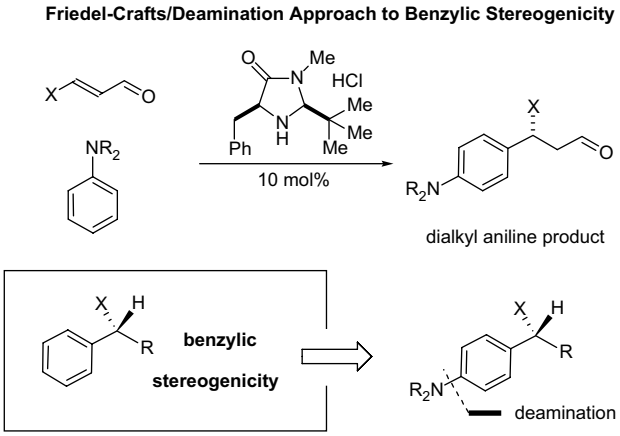

Figure 1. Organocatalytic access to benzylic stereocenters.

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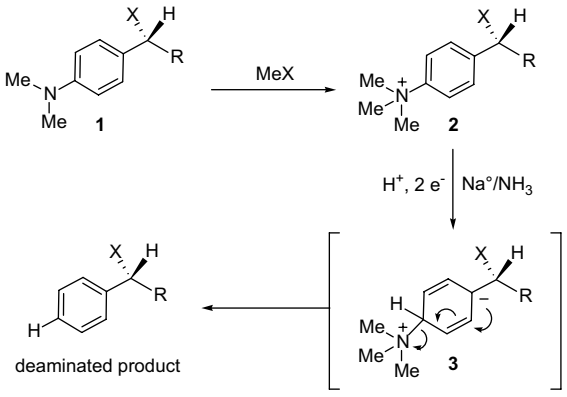
doi:10.1016/j.tet.2008.12.054

2. Results and discussion

2.1. Design plan

We hypothesized that treatment of a dialkylamino-substituted aryl ring **1** with methyl triflate or methyl iodide would rapidly generate the corresponding aryl-trialkylammonium adduct **2** (Scheme 1). Subsequent in situ exposure of this electron-deficient aromatic system to dissolving metal conditions was then expected to induce regioselective Birch reduction to form 3-ammonium-1,4-cyclohexadienyl intermediate **3**. At this stage we anticipated a vinylogous Hoffman elimination[6] would rapidly reconstitute the aromatic ring while ejecting the trialkyl amine substituent. As fundamental design features we assumed facile N-alkylation and a highly regioselective[7] *ipso-para*-reduction of the ammonium salt substituent.



Scheme 1. Proposed quaternization–reduction sequence.

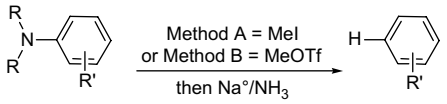
2.2. Deamination substrate scope

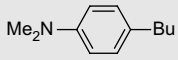
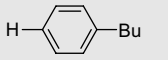
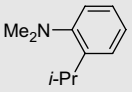
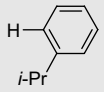
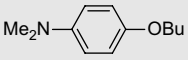
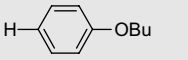
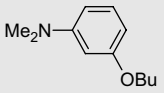
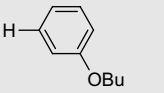
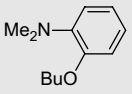
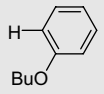
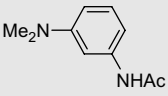
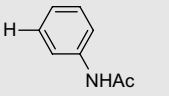
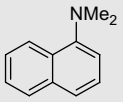
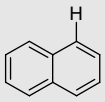
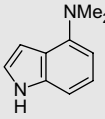
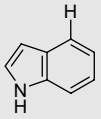
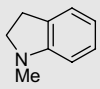
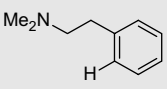
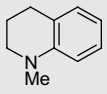
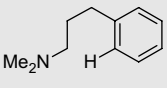
Our proposed trialkyl ammonium-Birch reduction strategy was first examined using *N*,*N*-dimethyl-4-butylaniline, methyl iodide, and dissolving metal conditions. As revealed in Table 1, entry 1, the corresponding quaternary ammonium iodide was formed in quantitative yield after 8 h. The resulting crystalline solid was then subjected to sodium in liquid ammonia to afford the parent butylbenzene ring in 83% yield over two steps. Having established the optimal oxidation conditions for dialkylamine removal, we next examined the scope of the arylamine component in this sequence. As shown in Table 1, a variety of aniline rings are compatible with this methodology. For example, the bulky isopropyl *ortho*-substituent did not impede the reduction–elimination sequence (2-*i*-Pr, 86% yield, entry 2), nor did electron-donating groups at any position on the benzene ring (entries 3–6). Dialkylamines could also be quaternized and reductively removed from indole and naphthalene rings (77–78% yield, entries 7 and 8) without reduction of the parent aromatic π-system. Notably, treatment of saturated cyclic amines allowed access to ring opened products with concomitant N-methylation (entries 9 and 10).

It is important to note that while the use of neat MeI was sufficient for quaternization of many aniline substrates, it was typically unsuitable for sterically demanding cases. In this scenario we found that the use of MeOTf in CH_2Cl_2 provided access to the requisite ammonium salt (entries 2, 5, and 8).

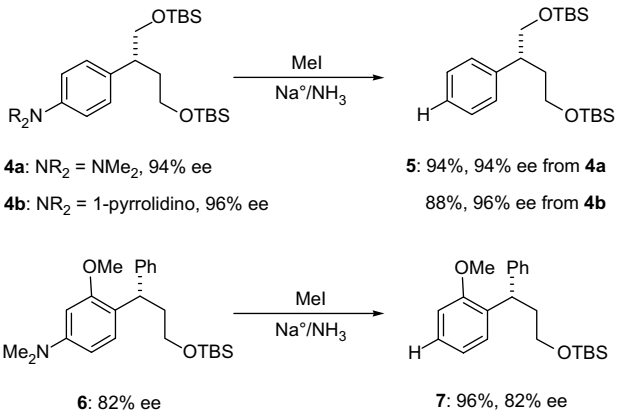
Having established the utility of this quaternization–reduction sequence with simple aromatic substrates we next examined the use of aniline systems that incorporate stereogenicity. As revealed in Scheme 2, dimethyl amine and pyrrolidine substituted rings **4a** and **4b**, respectively, could be quaternized and reduced in highly

Table 1
Reductive deamination of representative anilines



Entry	Aryl amine	Method	Product	% Yield[a]
1		A		83[b]
2		B		86[b]
3		A		89
4		A		90
5		B		90[b]
6		A		74
7		A		78
8		B		77[b]
9		A		61[c]
10		A		78[c]

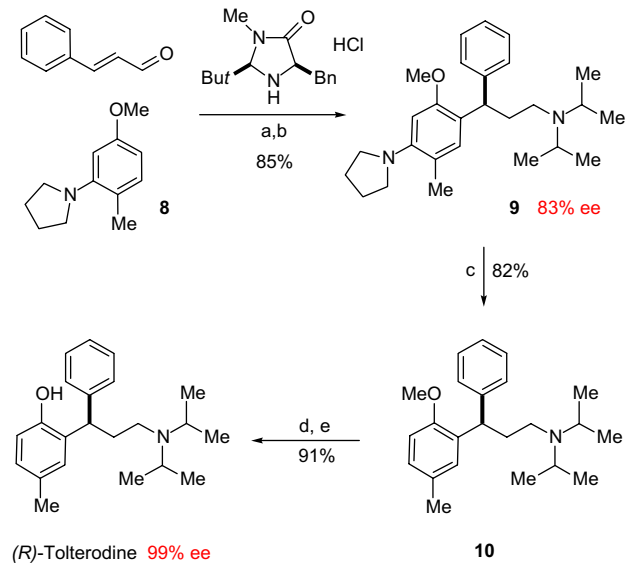
[a] Unless otherwise noted, yield from recrystallized quaternary ammonium as determined by GC analysis with internal standard.
[b] Overall yield of a two-step quaternization–reduction protocol without intervening purification.
[c] Isolated yield after the two-step protocol.



Scheme 2. Reductive deamination of enantioenriched dialkylanilines.

efficient fashion without change in the enantiopurity of the accompanying benzylic stereocenter. Moreover, the bis-benzylic carbon of *N*,*N*-dimethyl aniline **6** was tolerated without complication in this sequence to provide the corresponding deaminated product **7** in 96% overall yield with no side-products arising from reduction of the spectator benzene. It is important to note that we observed no erosion[8] of optical purity in all examples employing enantioenriched substrates (Scheme 2).

Given the potential to use our own asymmetric Friedel–Crafts-aniline additions in combination with this new aryl ammonium reduction strategy, we became interested in the application of this synthetic sequence toward production of the drug (*R*)-tolterodine.[9] Tolterodine (marketed[10] by Pfizer under the name Detrol™) is a potent muscarinic receptor antagonist that is used on a worldwide basis for the treatment of urge incontinence. Our strategy toward tolterodine (Scheme 3) hinged on an organocatalytic conjugate addition of an appropriately substituted anisidine to cinnamaldehyde followed by arene deamination of the resulting enantioenriched bis-aryl intermediate. Apart from demonstrating an economical route to enantiopure tolterodine, we hoped this synthetic sequence would serve as a test bed for the utility of our deamination methodology in the presence of other tertiary amines.



Scheme 3. Synthesis of (*R*)-tolterodine. Reagents and conditions: (a) 20 mol % (*R*,*R*)-*tert*-Bu,Bn-imidazolidanone·HCl, THF, 4 °C; (b) *i*-Pr_2NH, STAB, THF; (c) MeOTf, DCM, then Na^0/NH_3; (d) BBr_3, DCMl (e) tartaric acid, then MeOH/acetone.

Known 3-(1-pyrrolidino)-anisole **8** was prepared from commercially available 2-bromo-4-methyl-anisole and pyrrolidine. Alkylation of anisidine **8** with cinnamaldehyde proceeds smoothly at 4 °C in the presence of (*R*,*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one hydrochloride to afford the carbon core of tolterodine in good chemical yield and optical purity (88% yield, 83% ee). Direct conversion of the β-branched aldehyde to the diisopropylamine was accomplished by reductive amination using sodium triacetoxyborohydride to afford tertiary amine **9** in 97% yield (85% over two steps). Attempts to selectively methylate the aniline nitrogen of **9** in the presence of the tertiary amine, or salts thereof, proved unsuccessful. However, we were pleased to find that the exhaustively methylated derivative of **9** underwent direct conversion to *O*-methyl tolterodine **10** in 82% yield when subjected to dissolving metal reduction. Finally, deprotection of the phenol ether was effected by BBr_3 in good yield to afford (*R*)-tolterodine. Reverse phase chiral HPLC analysis revealed that the enantioselectivity obtained in the initial organocatalytic conjugate addition step had been preserved through the four-step sequence affording enantioenriched (*R*)-tolterodine in 64% overall yield from anisidine **8**. Salt formation and recrystallization from methanol/acetone following the established procedure provided the desired tolterodine hydrogen tartrate (Detrol™) in >99% ee.

In summary, this report describes a novel method for the cleavage of dialkylamines from arenes using inexpensive reagents. The method is compatible with a range of oxygen-, nitrogen-, and carbon-containing substituents. We believe this new transformation may serve to broaden the scope and selectivity of electrophilic aromatic substitution reactions in general. Furthermore, we have demonstrated the utility of this transformation in concert with an asymmetric organocatalytic Friedel–Crafts alkylation of activated benzenes via the asymmetric synthesis of the pharmaceutical agent (*R*)-tolterodine.

3. Experimental section

3.1. General

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[11] All non-aqueous solvents were purified according to the method of Grubbs[12] and were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Chromatographic purification of products was accomplished using force-flow chromatography on ICN 60 32–64 mesh silica gel according to the method of Still.[13] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, anisaldehyde, or $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz or 75 MHz) and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame-ionization detectors using Hewlett-Packard HP-1 (30 m×0.25 mm) columns. High performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 series HPLC UV detection monitored at 254 nm, using columns as noted.

3.2. General procedure

3.2.1. General deamination procedure A (using MeI)

To a 25 mL pear-shaped flask equipped with a magnetic stir bar was added arylamine (0.200 mmol, 1.00 equiv) and iodomethane (2.00 mmol, 10.0 equiv). The neat reaction mixture was stirred at ambient temperature for 8–12 h until the starting material was consumed as determined by TLC analysis. The iodomethane was removed in vacuo to furnish the quaternary ammonium iodide. The quaternary ammonium salt was then taken up/suspended in dry THF (~3 mL) and then added to a rapidly stirring solution of sodium metal (1.00 mmol, 5.00 equiv) in liquid ammonia (~20 mL) at −78 °C. After 5 min, the reaction mixture was quenched with benzylmethyl ether (0.2 mL) (the deep blue color was supplanted almost immediately by a bright orange). The mixture was then treated with isopropanol (2 mL) and stirred at −78 °C for another 5 min (by which time all color had dissipated). Diethyl ether (20 mL) and

saturated ammonium chloride (10 mL) were then added carefully and the reaction vessel was allowed to warm gradually to room temperature. The organic layer was then separated and combined with ether extracts (2×5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was then purified by column chromatography (solvents noted) to provide the title compounds (or was taken up in 5 mL of EtOH and charged with 1.00 equiv of tridecane as an analytical standard to obtain assay yield of previously known compounds via GC analysis).

3.2.2. General deamination procedure B (for hindered anilines, using MeOTf)

To a 25 mL flask equipped with a magnetic stir bar was added aryl amine (0.333 mmol, 1.00 equiv) and dry dichloromethane (3.33 mL). Methyl triflate (0.666 mmol, 2 equiv) was then added and the resulting mixture was stirred at ambient temperature for 8–12 h until the starting material was consumed as determined by TLC analysis. At this stage the volatiles were removed in vacuo to furnish the quaternary ammonium iodide. The quaternary ammonium salt was then taken up/suspended in dry THF (~5 mL) and added to a rapidly stirring solution of sodium metal (1.67 mmol, 5.00 equiv) in liquid ammonia (~35 mL) at −78 °C. After 5 min, the reaction mixture was treated with benzylmethyl ether (0.3 mL) (the deep blue color was supplanted almost immediately by a bright orange). The mixture was then treated with isopropanol (3 mL) and stirred at −78 °C for another 5 min (by which time all color had dissipated). Diethyl ether (20 mL) and saturated ammonium chloride (10 mL) were then added carefully and the reaction vessel was allowed to warm gradually to room temperature. The organic layer was then separated and combined with ether extracts (2×5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was then purified by column chromatography (solvents noted) to provide the title compounds (or taken up in 5 mL of EtOH and charged with 1.00 equiv of tridecane as an analytical standard to obtain assay yield of previously known compounds through GC analysis).

3.3. Synthesis and characterization

3.3.1. 1-Butylbenzene (Table 1, entry 1)

Prepared according to general procedure A from 4-butyl-*N*,*N*-dimethylbenzeneamine (16.9 g, 82.1 mmol) and methyl iodide (15.3 mL, 247 mmol) in dichloromethane (15 mL) at ambient temperature to afford a quantitative yield of the corresponding quaternary aniline (26.2 g, 82.1 mmol) after removal of volatiles. Without further purification, a portion of the quaternary aniline (0.106 g, 0.330 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 83% GC yield (tridecane standard) over two steps. Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[14]

3.3.2. Cumene (Table 1, entry 2)

Prepared according to general procedure B from 2-isopropyl-*N*,*N*-dimethylbenzeneamine (54.0 mg, 0.333 mmol) and methyl triflate (75.0 μL, 0.666 mmol) in dichloromethane (3.3 mL) at ambient temperature to afford a quantitative yield of the corresponding quaternary aniline (109 mg, 0.333 mmol) after removal of volatiles. Without further purification, the quaternary aniline was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 86% GC yield (tridecane standard) over two steps. Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[13]

3.3.3. 1-Butoxybenzene (Table 1, entries 3–5)

Prepared according to general procedure A from 4-butoxy-*N*,*N*-dimethylbenzeneamine (10.7 g, 55.5 mmol) and methyl iodide (17.3 mL, 278 mmol) in dry dichloromethane (20 mL) at ambient temperature to afford a 93% yield of the corresponding quaternary aniline (17.3 g, 51.6 mmol) after removal of volatiles and trituration with diethyl ether. A portion of the quaternary aniline (0.124 g, 0.370 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 89% GC yield (tridecane standard). Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[13]

Also prepared according to general procedure A from 3-butoxy-*N*,*N*-dimethylbenzeneamine (15.0 g, 77.7 mmol) and methyl iodide (24.1 mL, 388 mmol) in dry dichloromethane (25 mL) at ambient temperature to afford an 88% yield of the corresponding quaternary aniline (22.8 g, 68.1 mmol) after removal of volatiles and trituration with ethanol. A portion of the quaternary aniline (111 mg, 0.330 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 90% GC yield (tridecane standard).

Also prepared according to general procedure B from 2-butoxy-*N*,*N*-dimethylbenzeneamine (387 mg, 2.00 mmol) and methyl triflate (249 μL, 2.20 mmol) in dichloromethane (10 mL) at ambient temperature to afford quantitative yield of the corresponding quaternary aniline (709 mg, 2.00 mmol) after removal of volatiles. Without further purification, a portion of the quaternary aniline (119 mg, 0.333 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 90% GC yield (tridecane standard) over two steps.

3.3.4. N-Phenylacetamide (Table 1, entry 6)

Prepared according to general procedure A from *N*-(3-(dimethylamino)phenyl)acetamide (179 mg, 1.00 mmol) and methyl iodide (0.187 mL, 3.00 mmol) in dry dichloromethane (0.50 mL) at ambient temperature to afford 99% yield of corresponding quaternary aniline (320 mg, 0.990 mmol) after removal of volatiles. A portion of the quaternary aniline (107 mg, 0.333 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 74% GC yield (tridecane standard). Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[13]

3.3.5. Naphthalene (Table 1, entry 7)

Prepared according to general procedure A from *N*,*N*-dimethylnaphthalen-1-amine (4.00 mL, 24.3 mmol) and methyl iodide (4.54 mL, 78.9 mmol) in dry dichloromethane (10 mL) at ambient temperature to afford the corresponding quaternary aniline after removal of volatiles and trituration with diethyl ether. A portion of the quaternary aniline (104 mg, 0.333 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound in 78% GC yield (tridecane standard). Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[13]

3.3.6. 1H-Indole (Table 1, entry 8)

Prepared according to general procedure B from *N*,*N*-dimethyl-1-*H*-indol-4-amine (27.0 mg, 0.166 mmol) and methyl triflate (38.0 μL, 0.332 mmol) in dichloromethane (1.0 mL) at ambient temperature to afford a quantitative yield of the corresponding quaternary aniline (51.0 mg, 0.166 mmol) after removal of volatiles. Without further purification, the quaternary aniline was taken forward according to the general procedure in 10 mL of liquid ammonia to afford the title compound in 77% GC yield (tridecane

standard) over two steps. Material for characterization was obtained by filtration through a silica gel plug. Obtained spectral data were in agreement with previously reported values.[13]

3.3.7. N,N-Dimethyl-2-phenylethanamine (Table 1, entry 9)

Prepared according to general procedure A from 1-methylindoline (1.98 g, 15.0 mmol) and methyl iodide (4.67 mL, 75.0 mmol) in dry dichloromethane (5 mL) at ambient temperature to afford a 98% yield of the corresponding quaternary aniline (4.05 g, 14.7 mmol) after removal of volatiles and trituration with diethyl ether. A portion of the quaternary aniline (100 mg, 0.363 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound (33.0 mg, 0.221 mmol) in 61% isolated yield after silica gel chromatography (48:50:2 EtOAc/hexanes/Et_3N) over two steps. Obtained spectral data of isolated material were in agreement with previously reported values.[15]

3.3.8. N,N-Dimethyl-3-phenylpropan-1-amine (Table 1, entry 10)

Prepared according to general procedure A from 1,2,3,4-tetrahydro-1-methylquinoline (2.00 g, 13.6 mmol) and methyl iodide (4.23 mL, 67.9 mmol) in dry dichloromethane (5 mL) at ambient temperature to afford a 99% yield of corresponding quaternary aniline (3.95 g, 13.5 mmol) after removal of volatiles and trituration with diethyl ether. A portion of the quaternary aniline (96.0 mg, 0.333 mmol) was taken forward according to the general procedure in 20 mL of liquid ammonia to afford the title compound (43.0 mg, 0.259 mmol) in 78% isolated yield after silica gel chromatography (48:50:2 EtOAc/hexanes/Et_3N) over two steps. Obtained spectral data of isolated material were in agreement with previously reported values.[16]

3.3.9. (R)-3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol-tert-butyldimethylsilylether (**6**)

(*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol (0.250 g, 0.877 mmol, 1.0 equiv) was dissolved in dichloromethane (3.0 mL) and treated sequentially with triethylamine (0.148 mL, 1.05 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl chloride (0.159 g, 1.05 mmol, 1.20 equiv). The reaction mixture was stirred overnight and then loaded directly onto a column of silica gel for purification. Gradient elution with 10–20% EtOAc in hexanes afforded the product as a pale yellow oil in 75% yield (244 mg, 0.659 mmol). Obtained optical rotation, ^1H and ^{13}C NMR spectral data of isolated material were in agreement with previously reported values.[1c] ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H, Ar*H*), 7.20–7.13 (m, 2H, Ar*H*), 6.35 (dd, *J*=2.7, 8.8 Hz, 1H, Ar*H*), 6.29 (d, *J*=2.4 Hz, 1H, Ar*H*), 4.48 (t, *J*=8.2 Hz, 1H, ArC*H*), 3.81 (s, 3H, OCH_3), 3.63 (t, *J*=7.1 Hz, 2H, CH_2O), 2.97(s, 6H, N(CH_3)$_2$), 2.33–2.24 (m, 2H, CHCH_2), 0.95 (s, 9H, C(CH_3)$_3$), 0.06 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.5, 145.8, 128.3, 128.2, 125.7, 122.0, 105.1, 97.0, 62.1, 55.7, 41.2, 39.4, 38.5, 26.4, 18.8, −4.8; $[\alpha]_D$ −15.4 (*c* 0.82, $CHCl_3$).

3.3.10. (R)-1-Methoxy-2-(3-tert-butyldimethylsiloxy-1-phenyl-propyl)-benzene (**7**)

In a 25 mL pear-shaped flask equipped with a magnetic stir bar, **3** (244 mg, 0.659 mmol, 1.00 equiv) was dissolved in iodomethane (0.41 mL, 6.6 mmol, 10 equiv). The neat reaction mixture was stirred at ambient temperature for 8 h at which time TLC analysis showed the starting material to be completely consumed. The iodomethane was removed in vacuo to furnish the quaternary ammonium iodide quantitatively (335 mg, 0.659 mmol) without need for further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.52 (d, *J*=2.7 Hz, 1H, Ar*H*), 7.34 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.28–7.12 (m, 6H, ArH), 4.57 (t, *J*=7.7 Hz, 1H, ArC*H*), 4.05 (s, 3H, OCH_3), 3.99 (s, 9H, N(CH_3)$_3$), 3.55–3.49 (m, 2H, CH_2O), 2.20 (q, *J*=7.7 Hz, 2H, CHCH_2), 0.95 (s, 9H, C(CH_3)$_3$), 0.06 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 143.0, 137.0, 128.9, 128.6, 128.3, 126.6, 110.0, 103.8, 61.2, 58.5, 58.0, 39.7, 37.6, 26.2, 18.6, −5.0.

A portion of the quaternary ammonium salt (100 mg, 0.195 mmol, 1.00 equiv) was dissolved/suspended in tetrahydrofuran (3.0 mL) and added to a rapidly stirring solution of sodium (18.0 mg, 0.782 mmol, 4.00 equiv) in liquid ammonia (approx. 25 mL) at −78 °C. After 5 min, the cold reaction mixture was treated with benzylmethyl ether (0.2 mL) and the deep blue color was supplanted almost immediately by a bright orange. The mixture was then treated with isopropanol (2 mL) and stirred at −78 °C for another 5 min by which time all color had dissipated from the reaction. Diethyl ether (20 mL) and saturated aq ammonium chloride (10 mL) were added carefully and the reaction vessel was allowed to warm to room temperature. The organic phase was then dried over Na_2SO_4, concentrated, and the residue purified by silica gel chromatography. Gradient elution with 2–10% EtOAc in hexanes provided the deaminated product in 96% yield (61.2 mg, 0.187 mmol). IR (film) 3027, 2954, 2929, 2856, 1601, 1492, 1462, 1438, 1244, 1100, 1051, 945.9, 834.8, 775.2, 751.9, 698.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.12 (m, 7H, Ar*H*), 6.93 (dt, *J*=1.1, 7.7 Hz, 1H, Ar*H*), 6.84 (d, *J*=8.7 Hz, 1H, Ar*H*), 4.58 (t, *J*=7.7 Hz, 1H, ArC*H*), 3.78 (s, 3H, OCH_3), 3.58 (t, *J*=7.1 Hz, 1H, CH_2O), 2.27 (dq, *J*=0.9, 6.6 Hz, 2H, CHCH_2), 0.90 (s, 9H, C(CH_3)$_3$), 0.00 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 144.9, 142.0, 133.3, 128.7, 128.5, 128.4, 128.3, 127.9, 127.3, 16.1, 126.0, 61.8, 55.7, 39.8, 38.3, 38.2, 26.3, 18.7, −4.9; HRMS [CI] requires *m*/*z* 357.2250 for $[M+H]^+$, found *m*/*z* 357.2240; $[\alpha]_D$ −15.7 (*c* 0.977, $CHCl_3$).

3.3.11. 4-Methyl-3-(1-pyrrolidino)-anisole (**8**)

A solution of *n*-BuLi (2.5 M in hexanes, 30.0 mL, 75.0 mmol, 1.50 equiv) was added dropwise to a stirring solution of pyrrolidine (6.30 mL, 100 mmol, 2.00 equiv) in THF (75 mL) under argon at 0 °C. Thirty minutes after addition had begun, the ice-water bath was removed and the reaction mixture was allowed to warm to ambient temperature. One hour after the bath was removed, 2-bromo-4-methyl-anisole (10.0 g, 49.7 mmol, 1.00 equiv) was added very carefully. (Warning: rapid addition of aryl bromide can result in a violent exotherm after an induction period of 1–3 min.) The reaction mixture was stirred at ambient temperature for 24 h and then acidified slowly with concd aq HCl. The mixture was diluted with Et_2O and extracted twice with water. The aqueous layers were combined and treated with 4 N aq NaOH until pH of the solution exceeded 10. The resulting mixture was then extracted with three portions of CH_2Cl_2. This organic solution was dried over sodium sulfate, concentrated, and purified by silica gel chromatography. Gradient elution in 1–10% EtOAc in hexanes afforded the known product as a pale yellow oil in 37% yield (3.56 g, 18.6 mmol).[17]

3.3.12. (R)-Diisopropyl-[3-(2-methoxy-5-methyl-4-pyrrolidin-1-yl-phenyl)-3-phenyl]-amine (**9**)

A dry 2-dram vial equipped with a magnetic stir bar was charged with (2*R*,5*RS*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·hydrochloride (113 mg, 0.400 mmol, 0.200 equiv) and THF (2.0 mL). Cinnamaldehyde (0.756 mL, 6.00 mmol, 3.00 equiv) was added via syringe and the reaction vessel was cooled to 0 °C in an ice-water bath. Then, 4-methyl-3-(1-pyrrolidino)-anisole **8** (0.324 mL, 2.00 mmol, 1.00 equiv) was added slowly via syringe so as not to raise the internal temperature of the reaction. The reaction mixture was allowed to warm to +4 °C over the course of 8 h and then stirred for an additional 32 h. At that time, the reaction mixture was diluted with 50 mL of Et_2O and extracted twice with 50 mL 1 N aq HCl. The combined aqueous layers were washed with 2×50 mL Et_2O. The aqueous layer was then neutralized with 2 N aq NaOH (50 mL) and extracted with 2×150 CH_2Cl_2. These organic extracts were combined, dried over Na_2SO_4, and concentrated in

vacuo to give a red-orange oil. Purification of the crude residue by silica gel chromatography (gradient elution: 5–20% EtOAc in hexanes) afforded the product (*R*)-3-(2-methoxy-5-methyl-4-(1-pyrrolidino)-phenyl)-dihydrocinnamaldehyde as a colorless oil in 88% yield (571 mg, 1.77 mmol); 83% ee. IR (film) 2959, 2860, 2817, 1723, 1611, 1569, 1505, 1445, 1403, 1320, 1222, 1114, 1022, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, J=2.2 Hz, 1H, C*H*O), 7.28–7.32 (m, 4H, Ar*H*), 7.16–7.24 (m, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 6.44 (s, 1H, Ar*H*), 4.94 (t, J=8.0 Hz, 1H, Ar_2CH), 3.80 (s, 3H, OCH_3), 3.19–3.23 (m, 4H, $N(CH_2)_2$), 3.09 (dd, J=2.2, 8.2 Hz, 2H, CH_2CHO), 2.23 (s, 3H, $ArCH_3$), 1.90–2.00 (m, 2H, $CH_2(CH_2)_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 155.3, 149.0, 143.8, 1314, 128.6, 128.2, 126.4, 122.7, 120.2, 99.8, 55.8, 51.3, 49.0, 38.3, 25.4, 20.5; HRMS [EI$^+$] requires m/z 323.1885 for $[M]^+$, found m/z 323.1896; $[\alpha]_D$ +20.9 (c 0.95, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiralpak AD column (0.46×25 cm) and AD guard (0.46×5 cm) (5.0% isopropanol/hexanes, 1 mL/min); *S* isomer t_R=13.6 min, *R* isomer t_R=16.1 min.

In a dry 10 mL round-bottom flask equipped with a magnetic stir bar, a solution of (*R*)-3-(2-methoxy-5-methyl-4-(1-pyrrolidino)-phenyl)-dihydrocinnamaldehyde (571 mg, 1.77 mmol, 1.00 equiv) in THF (4.0 mL) was treated with diisopropylamine (0.722 mL, 3.54 mmol, 2.00 equiv) and sodium triacetoxyborohydride (0.746 g, 3.54 mmol, 2.00 equiv). The reaction mixture was stirred for 6 h at ambient temperature and then diluted with 50 mL of Et_2O. The suspension was then treated with 25 mL aq 2 N NaOH. The layers were separated and the aqueous phase was extracted with 2×20 mL Et_2O. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford the product as a colorless oil in 97% yield (702 mg, 1.71 mmol) without further purification. IR (film) 2964, 2871, 2806, 1611, 1502, 1458, 1440, 1354, 1317, 1220, 1114, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 4H, Ar*H*), 7.12 (tt, J=2.2, 7.1 Hz, 1H, Ar*H*), 6.99 (s, 1H, Ar*H*), 6.41 (s, 1H, Ar*H*), 4.24 (t, J=7.7 Hz, 1H, Ar_2CH), 3.74 (s, 3H, OCH_3), 3.10–3.22 (m, 4H, $N(CH_2)_2$), 2.98 (dt, J=6.6, 6.6 Hz, 2H, $CH_2N(i\text{-}Pr)_2$), 2.26–2.38 (m, 2H, $N(CH)_2$), 2.24 (s, 3H, $ArCH_3$), 1.90–2.00 (m, 2H, $CH_2(CH_2)_2CH_2$), 0.94 (d, J=6.5 Hz, 12H, $N(CH(CH_3)_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 148.1, 145.9, 130.8, 128.3, 128.2, 125.6, 125.3, 120.3, 100.1, 56.0, 51.3, 49.3, 44.8, 41.3, 37.6, 25.3, 21.0, 20.9, 20.3; HRMS [EI$^+$] requires m/z 408.3141 for $[M]^+$, found m/z 408.3148; $[\alpha]_D$ +1.20 (c 0.48, $CHCl_3$).

3.3.13. (R)-Diisopropyl-[3-(2-methoxy-5-methyl-phenyl)-3-phenyl]-amine (**10**)

In a dry 10 mL round-bottom flask equipped with a magnetic stir bar, methyl trifluoromethanesulfonate (0.600 mL, 5.30 mmol, 3.00 equiv) was added to a stirring solution of **9** (702 mg, 1.71 mmol, 1.00 equiv) in CH_2Cl_2 (8.8 mL). The resulting mixture was stirred at ambient temperature for 20 h. The volatiles were then evaporated to afford the corresponding ammonium salt quantitatively (1.25 g, 1.25 mmol), which was used without further purification. ^1H NMR (300 MHz, CD_3OD) δ 7.43 (s, 1H, Ar*H*), 7.19–7.39 (m, 5H, Ar*H*), 7.17 (s, 1H, Ar*H*), 4.46–4.55 (m, 2H, $ArN(CHH)_2$), 4.32 (dd, J=6.0, 9.3 Hz, 1H, Ar_2CH), 3.87–4.06 (m, 4H, $ArN(CHH)_2$, $CHCH_2CH_2$), 3.91 (s, 3H, $ArNCH_3$), 3.41 (s, 3H, OCH_3), 3.23–3.35 (m, 1H, $CHCH_2$), 3.02–3.14 (m, 1H, $CHCH_2$), 2.86 (s, 3H, $NCH_3(i\text{-}Pr)_2$), 2.63 (s, 3H, $ArCH_3$), 2.49–2.65 (m, 2H, $N(CH)_2$), 2.31–2.38 (m, 4H, $NCH_2(CH_2)_2$), 1.21–1.39 (m, 12H, $N(CH(CH_3)_2)_2$).

A solution of sodium (393 mg, 17.1 mmol, 10.0 equiv) in freshly condensed liquid ammonia (100 mL) was prepared in a three-neck round-bottomed flask equipped with a cold finger and a mechanical stirrer. The flask was maintained at −78 °C using a dry ice/acetone bath. To this stirring blue mixture, a homogeneous solution of previous salt (1.71 mmol, 1.00 equiv) in THF (12 mL) and DMF (0.6 mL) was added in one portion. After 10 min, the reaction mixture was quenched with saturated aq sodium bicarbonate. The mixture was diluted with diethyl ether and stirred at ambient temperature until most of the ammonia had evaporated. The resulting ether suspension was diluted with water and the phases were separated. The aqueous layer was extracted with ether (2×5 mL) and the combined organics were washed with brine (2×5 mL) and dried over sodium sulfate. Concentration and subsequent purification via silica gel chromatography (25% EtOAc/1% triethylamine/74% hexanes) afforded **10** in 82% yield (478 mg, 1.41 mmol). IR (film) 2963, 2867, 2834, 1494, 1456, 1381, 1360, 1241, 1162, 1115, 1036, 804, 735, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 4H, Ar*H*), 7.14 (tt, J=1.8, 6.9 Hz, 1H, Ar*H*), 7.08 (d, J=2.3 Hz, 1H, Ar*H*), 6.95 (dd, J=1.5, 8.5 Hz, 1H, Ar*H*), 6.72 (d, J=8.1 Hz, 1H, Ar*H*), 4.36 (t, J=7.7 Hz, 1H, Ar_2CH), 3.75 (s, 3H, OCH_3), 2.98 (dt, J=6.6, 6.6 Hz, 2H, $CH_2N(i\text{-}Pr)_2$), 2.23–2.38 (m, 2H, $N(CH)_2$), 2.27 (s, 3H, $ArCH_3$), 2.12–2.17 (m, 2H, $CH_2(CH_2)_2CH$), 0.94 (d, J=6.5 Hz, 12H, $N(CH(CH_3)_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 145.4, 133.7, 129.8, 128.6, 128.4, 128.3, 127.4, 125.9, 110.9, 55.8, 49.0, 44.4, 41.5, 37.3, 21.0, 20.8; HRMS [EI$^+$] requires m/z 339.2562 for $[M]^+$, found m/z 339.2564; $[\alpha]_D$ −6.14 (c 0.95, $CHCl_3$).

3.3.14. (R)-Tolterodine: (R)-diisopropyl-[3-(2-hydroxy-5-methyl-phenyl)-3-phenyl]-amine

In a dry 10 mL round-bottom flask equipped with a magnetic stir bar, a solution of **7** (478 mg, 1.41 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C. A solution of boron tribromide (1.00 M in CH_2Cl_2, 2.71 mL, 2.71 mmol, 1.91 equiv) was added dropwise over the course of 30 min. The resulting solution was stirred for an additional 30 min before the reaction vessel was transferred to an ice-water bath. The reaction mixture was maintained at 0 °C for 1 h then cooled to −78 °C, and quenched with methanol. The mixture was then allowed to warm to ambient temperature and neutralized with saturated aq $NaHCO_3$. The mixture was then diluted with 50 mL of CH_2Cl_2 and treated with 75 mL of saturated aq NH_4Cl. The layers were separated and the aqueous layer was extracted with 3×50 mL CH_2Cl_2. The organics were combined, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (25–50% *i*-PrOH/CH_2Cl_2) to afford (*R*)-tolterodine in 91% yield (418 mg) as a colorless oil, which solidified on standing; 81% ee. This material was spectroscopically identical to the literature compound in all respects. The enantiomeric ratio of the product was determined by HPLC ChromTech Chiral-AGP (0.2×10 cm) (isopropanol/0.01 M potassium phosphate buffer 0.22 mL/min); *S* isomer t_R=13.6 min, *R* isomer t_R=16.1 min. The tartrate salt was prepared and recrystallized to optical purity as previously described.[9]

Acknowledgements

Financial support was provided by the NIHGMS (R01 GM078201-01-01) and kind gifts from Amgen and Merck. This article is dedicated to Justin 'sweet hands' DuBois on the occasion of him winning the Tetrahedron Young Investigator Award.

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