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Highly Enantioselective Synthesis of β-Amino Alcohols: A Catalytic Version

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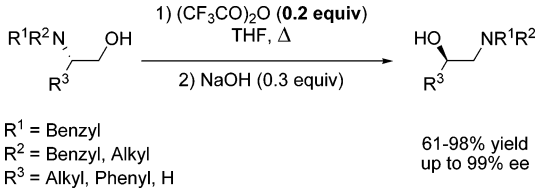

Highly enantioselective rearrangement of β-amino alcohols was realized by using a catalytic amount of trifluoroacetic anhydride.

Introduction

Amino alcohols are present in a large variety of naturally occurring and pharmacologically active molecules,[1] and the relative stereochemistry of the hydroxy and amino groups is highly important for the biological activity of these molecules. Amino alcohols have also been used extensively in asymmetric synthesis, both as chiral ligands and auxiliaries.[2]

Linear *N*,*N*-dialkyl-β-amino alcohols have been shown to rearrange, via an aziridinium ion, into β-halogeno-amines on treatment with $SOCl_2$,[3] $SOBr_2$,[4] MsCl,[5] TsCl,[5b] CBr_4/PPh_3,[6] Ph_3PCl_2,[7] Ph_3PBr_2,[7] DAST,[8] or Deoxofluor.[9] Transforming the alcohol moiety into a good leaving group (such as halides or sulfonates) has allowed the introduction of carbon,[10−12] nitrogen,[5a,c,11,12] oxygen,[5a,13,14] phosphorus,[5a,15] and sulfur[5a,12,16] nucleophiles with anchimeric participation of the neighboring nitrogen atom. As far as we know, these rearrangements always need stoechiometric quantities of the reagents.

Recently, we have reported that prolinols of type **A** can be rearranged stereoselectively to give optically active piperidin-3-ols of type **B** via an aziridinium intermediate by using $(CF_3CO)_2O$ (1,5 equiv) and Et_3N (3 equiv) followed by the addition of NaOH (8 equiv).[17,18] When these conditions were applied to linear optically active β-amino alcohols of type **C**, the latter were rearranged to give β-amino alcohols of type **D** in a very regio-, stereo-, and enantioselective process (Scheme 1).[19]

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(2) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.
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(5) (a) Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663−1671. (b) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647−649. (c) Frizzle, M. J.; Caille, S.; Marshall, T. L.; McRae, K.; Nadeau, K.; Guo, G.; Wu, S.; Martinelli, M. J.; Moniz, G. A. *Org. Proc. Res. Dev.* **2007**, *11*, 215−222.
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(8) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691−706.
(9) Ye, C.; Shreeve, J. M. *J. Fluorine Chem.* **2004**, *125*, 1869−1872.
(10) Schultz, E. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1948**, *70*, 48−52.
(11) Gmeiner, P.; Junge, D.; Kaertner, A. *J. Org. Chem.* **1994**, *59*, 6766−6776.
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(13) Bach, F. L.; Cohen, E. *Chem. Commun. (London)* **1968**, 415−416.
(14) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585−4586.
(15) Dahlenburg, L.; Goetz, R. *Eur. J. Inorg. Chem.* **2004**, 888−905.
(16) Jimeno, C.; Moyano, A.; Pericas, M. A.; Riera, A. *Synlett* **2001**, 1155−1157.
(17) For comprehensive reviews, see: (a) Cossy, J.; Gomez Pardo, D. *Chemtracts* **2002**, *15*, 579−605. (b) Cossy, J.; Gomez Pardo, D. *Targets Heterocycl. Syst.* **2002**, *6*, 1−26.
(18) (a) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693−1699. (b) Brandi, A.; Cicchi, S.; Paschetta, V.; Gomez Pardo, D.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357−9359. (c) Déchamps, I.; Gomez Pardo, D.; Karoyan, P.; Cossy, J. *Synlett* **2005**, 1170−1172. (d) Mena, M.; Bonjoch, J.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930−5935. (e) Roudeau, R.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2006**, *62*, 2388−2394 and references therein. (f) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Arkivoc* **2007**, *v*, 38−45.

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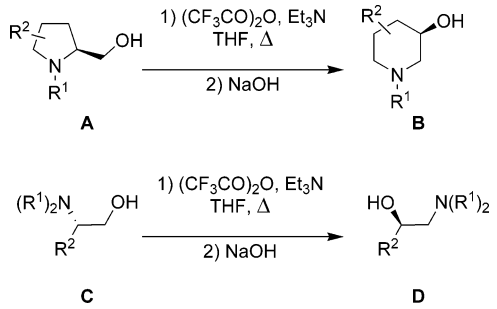
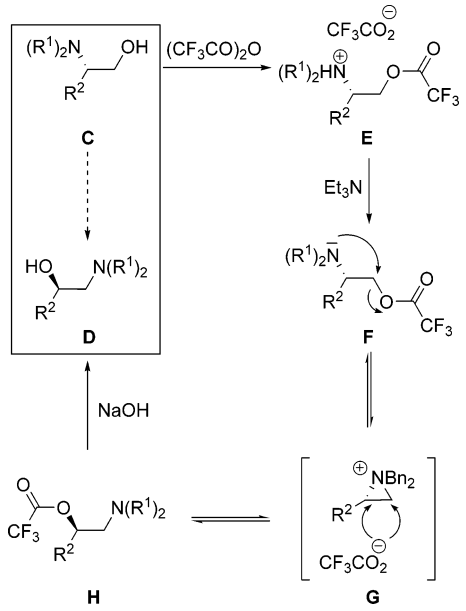
SCHEME 1. β-Amino Alcohol Rearrangement



SCHEME 2. Mechanism of Rearrangement



The mechanism that we have postulated for this rearrangement implies the formation of an aziridinium intermediate **G**, which is formed from the ammonium trifluoroacetate **E** via the aminoester **F** after treatment with Et_3N (Scheme 2). As a trifluoroacetate anion is liberated into the reaction media, this anion can attack the more substituted carbon atom of the aziridinium **G**, producing the aminoester **H**, which after saponification leads to the rearranged β-amino alcohol **D**.

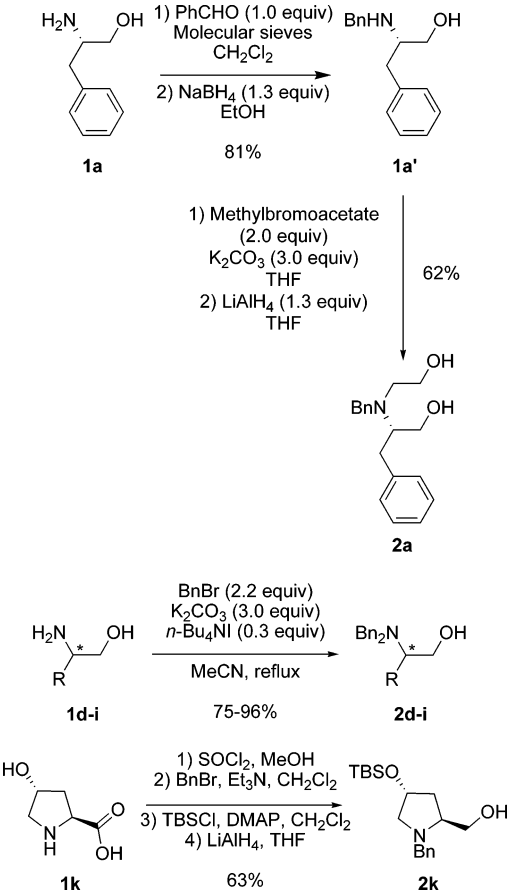
Results and Discussion

Here we report a catalytic version of this rearrangement by using only 0.2 equiv of $(CF_3CO)_2O$ followed by the addition of NaOH (0.3 equiv). We have to point out that when using $(CF_3CO)_2O$ in catalytic quantities, Et_3N is not necessary for the rearrangement to proceed.

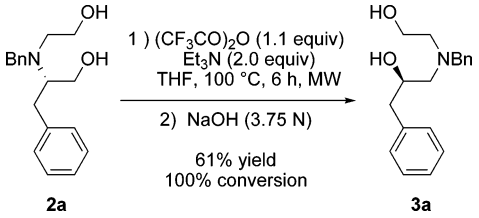
Amino diol **2a** was prepared from the commercially available amino alcohol **1a**, which after reductive amination with benzaldehyde led to the corresponding *N*-benzylamine **1a′** (PhCHO, CH_2Cl_2, molecular sieves 4 Å, then $NaBH_4$, 81% yield). After treatment with methylbromoacetate (2.0 equiv) in the presence of K_2CO_3 (3.0 equiv) in THF at room temperature for 48 h, the crude material was directly engaged in the reduction with $LiAlH_4$ (1.3 equiv, THF, 2 h, rt) to furnish **2a** (62% yield).

(19) Métro, T.-X.; Appenzeller, J.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509−3512.

SCHEME 3. Synthesis of Starting Amino Alcohols



SCHEME 4. Rearrangement of Amino Alcohol 2a

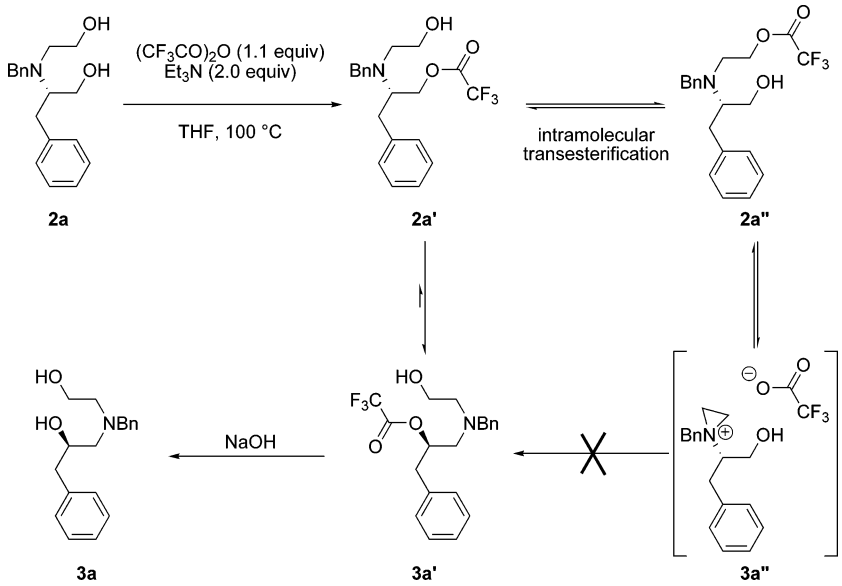


The synthesis of compounds **2d**, **2e**, and **2g**−**i** was achieved from the commercially available amino alcohols **1d**, **1e**, and **1g**−**i** by bis *N*-benzylation using benzyl bromide (2.2 equiv) in the presence of K_2CO_3 (3.0 equiv) and *n*-tetrabutylammonium iodide (0.3 equiv) in refluxing acetonitrile.[19] Compounds **2b**, **2c**, **2f**, and prolinol **2j** are commercially available and **2k** was prepared from *trans*-4-hydroxy-L-proline **1k** (Scheme 3).[18e]

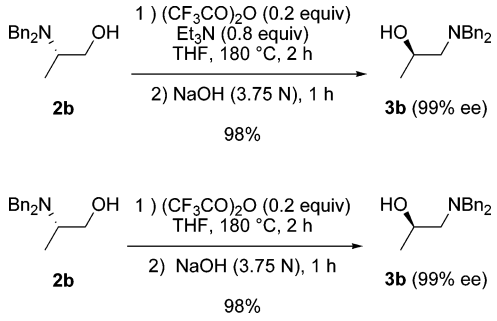
When compound **2a**, in a THF solution, was treated under the usual conditions, e.g., with 1.1 equiv of $(CF_3CO)_2O$ for 15 min, then with Et_3N (2.0 equiv) and heated at 100 °C under microwave irradiation (MW) for 6 h, followed by addition of NaOH (3.75 N), **3a** was obtained in 61% yield and the starting material was totally consumed (Scheme 4).

If the previously proposed mechanism intervened in the rearrangement, a mixture of the two trifluoroacetates **2a′** and **2a″** would be expected as a result of the two primary hydroxy groups esterification of compound **2a** with 1.1 equiv of $(CF_3CO)_2O$ (Scheme 5). Upon heating, trifluoroacetate **2a′** will rearrange into trifluoroacetate **3a′**, whereas trifluoroacetate **2a″** will form aziridinium **3a″**. Opening of this aziridinium **3a″** by a trifluoroacetate anion cannot lead directly to the rearranged

SCHEME 5. Proposed Mechanism for Rearrangement of Amino Alcohol 2a



SCHEME 6. Rearrangement of Amino Alcohol 2b under Catalytic Conditions



aminoester **3a′** but only to the starting aminoester **2a″**. As the starting amino alcohol **2a** is totally consumed during the reaction, it seems reasonable to have an equilibrium between **2a′** and **2a″** due to an intramolecular transesterification. The displacement of the equilibrium will be due to the formation of the more stable amino ester **3a′**, which will release the rearranged amino alcohol **3a** after saponification.

If an intermolecular transesterification can take place between the rearranged aminoester and the starting amino alcohol, the rearrangement could be induced by a catalytic amount of $(CF_3CO)_2O$ only. Thus, amino alcohol **2b** was treated with $(CF_3CO)_2O$ (0.2 equiv) and Et_3N (0.8 equiv) in THF at 180 °C for 2 h under microwave irradiation. After addition of an aqueous NaOH solution, **3b** was isolated in 98% yield with an enantiomeric excess of 99% (Scheme 6). It is worth noting that the yield in **3b** and its enantiomeric excess were very similar to those obtained by using 3 equiv of $(CF_3CO)_2O$ and 4 equiv of Et_3N (99% yield, 99% ee).[19] Furthermore, by using catalytic amounts of $(CF_3CO)_2O$ the presence of Et_3N in the reaction media is not necessary, as the treatment of **2b** with only 0.2 equiv of $(CF_3CO)_2O$ (THF, 180 °C, 2 h, MW) followed by saponification with NaOH led to **3b** with similar yield and enantiomeric excess (98%, 99% ee) (Scheme 6).

The reaction is general, and the results are reported in Table 1. For comparison, the results obtained under stoechiometric conditions have been indicated in brackets.[19] When compounds **2b**−**k** were submitted to the catalytic conditions [$(CF_3CO)_2O$ (0.2 equiv), THF, 180 °C, 2 h, MW then NaOH (3.75 N; 0.3 equiv), rt, 1 h], the yields and the enantiomeric excess for the rearranged *β*-amino alcohols were good to excellent. We have to point out that for compounds **2e**, **2h**, **2i**, and **2k** the rearrangement was performed at 100 °C for 18 h (50 h for compound **2k**) in order to prevent partial decomposition obtained at higher temperatures. In the case of the cyclic compounds **2j** and **2k**, the 3-hydroxypiperidines **3j** and **3k** were formed under the catalytic conditions in good to excellent yield and good enantiomeric excess.

The (*R*) absolute configuration was established for compounds **3b**,[20] **3c**[21] and **3f**[20] by comparison of the $[\alpha]_D$ reported in the literature. The (*S*) absolute configuration of **3h**[22] was determined by comparison of the $[\alpha]_D$ of the (*S*)-*N*,*N*-2-dibenzylamino-1-phenylethanol synthesized from the commercially available (*S*)-2-amino-1-phenylethanol by bis *N*-benzylation (BnBr, K_2CO_3, CH_3CN, reflux, 4 h), and the (*S*) absolute configuration of compound **3g** was established by application of the modified Mosher method.[23] The relative configuration of the two hydroxy groups in diol **3i** was determined by chemical correlation. The racemic allylic alcohol (±)-**4** was treated by TBHP (1.5 equiv) and $VO(acac)_2$ (0.3 equiv) in CH_2Cl_2 during 18 h at room temperature (Scheme 7), and a mixture of the two diastereoisomers (±)-**5** and (±)-**6** was isolated in 65% yield with a diastereomeric ratio of 5/1.[24] The two diastereoisomers (±)-**5** and (±)-**6** were then treated with dibenzylamine (3.0 equiv) in acetonitrile at 100 °C during 10 h under microwave irradiation and aminodiol (±)-**3i** was synthesized in 64% yield. As this latter aminodiol had ^1H and ^{13}C NMR spectra identical with those of the aminodiol obtained by rearrangement of compound **2i**, the *anti* configuration of the two hydroxy groups in **3i** has been confirmed.

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(21) Koppenhoefer, B.; Trettin, U.; Wächtler, A. *Synthesis* **1994**, *12*, 1141−1142.
(22) Shibata, T.; Takahashi, T.; Konishi, T.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2458−2460.
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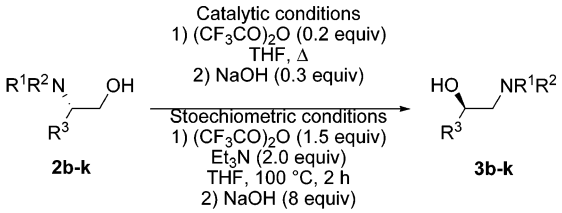
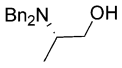
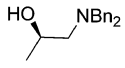
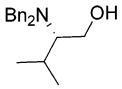
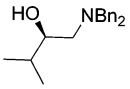
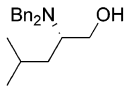
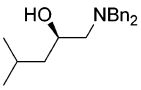
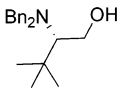
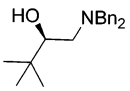
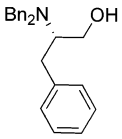
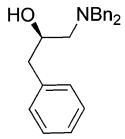
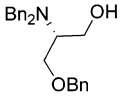
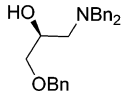
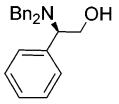
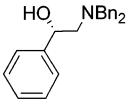
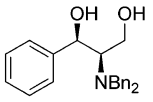
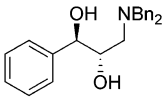
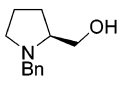
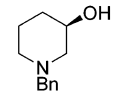
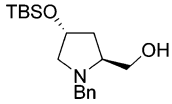
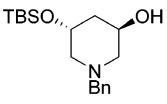
(24) Dittmer, D. C.; Zhang, Y.; Discordia, R. P. *J. Org. Chem.* **1994**, *59*, 1004−1010.

TABLE 1. Rearrangement under Catalytic versus Stoechiometric Conditions

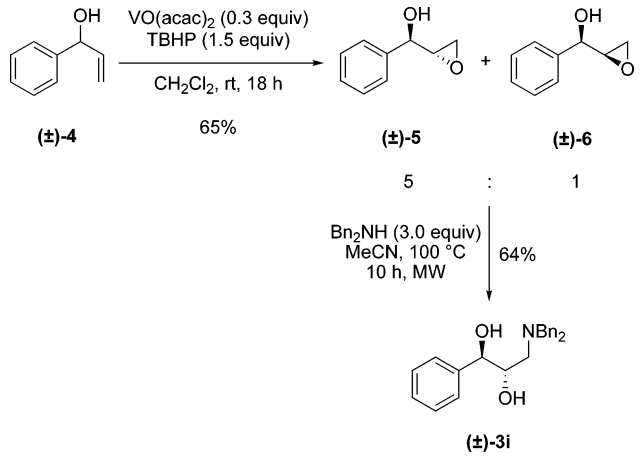


entry	substrates	products	catalytic conditions	yield(ee)[a] [yield(ee)][b]
1	 **2b**	 **3b**	180 °C, 2 h	98%(99%) [99%[c](99%)]
2	 **2c**	 **3c**	180 °C, 2 h	93%(99%) [88%(99%)]
3	 **2d**	 **3d**	180 °C, 2 h	89% [82%]
4	 **2e**	 **3e**	100 °C, 18 h	74%(99%) [99%(99%)]
5	 **2f**	 **3f**	180 °C, 2 h	87%(99%) [97%(99%)]
6	 **2g**	 **3g**	180 °C, 2 h	96%(99%) [76%(99%)]
7	 **2h**	 **3h**	100 °C, 18 h	78%(99%) [93%(99%)]
8	 **2i**	 **3i**	100 °C, 18 h	83%(99%) [66%[d](99%)]
9	 **2j**	 **3j**	180 °C, 2 h	87% [63%]
10	 **2k**	 **3k**	100 °C, 50 h	61% [82%]

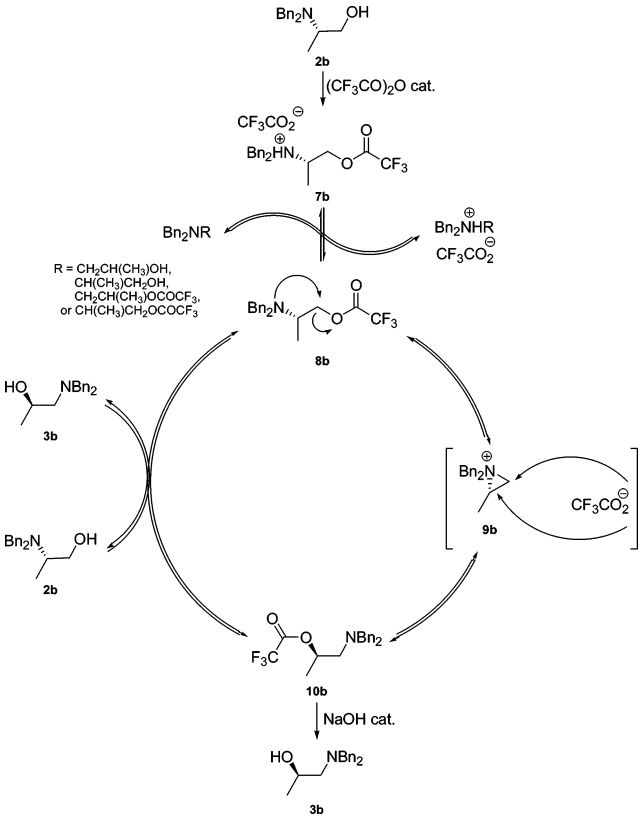
[a] Catalytic conditions. [b] Stoechiometric conditions. [c] $CF_3(CO)_2O$ (3.0 equiv), Et_3N (4.0 equiv), reflux, 37 h. [d] $CF_3(CO)_2O$ (1.1 equiv), Et_3N (2.0 equiv).

The formation of **3b** from **2b** under catalytic conditions without any Et_3N can be explained by the formation of a catalytic amount of the ammonium trifluoroacetate ester **7b**, which can be deprotonated by any amines of type Bn_2NR present in the reaction media (R being either -$CH(CH_3)CH_2$-OH, -$CH(CH_3)CH_2OCOCF_3$, -$CH_2CH(CH_3)OH$, or -CH_2CH-

SCHEME 7. Synthesis of (±)-3i



SCHEME 8. Supposed Mechanism for Rearrangement of β-Amino Alcohol 2b under Catalytic Conditions



$(CH_3)OCOCF_3$) (Scheme 8). An S_N2 intramolecular substitution by the *N*,*N*-dialkylamine functionnality of **8b** can form the aziridinium **9b**, liberating a trifluoroacetate anion in the reaction media. The latter anion could attack the more substituted carbon atom of the aziridinium **9b**, producing the amino ester **10b** according to a S_N2 substitution. An intermolecular transesterification between the amino alcohol **2b** and the amino ester **10b** can take place to form the β-amino alcohol **3b** and the amino ester **8b**, which will be again transformed into the aziridinium **9b**. By analogy with the work of Gmeiner,[11] we assume that compounds **8b** and **10b** are in equilibrium. Moreover, because the species **2b**, **3b**, **8b**, and **10b** engaged in the transesterification are also in equilibrium, we believe both the rearranged amino alcohol **3b** and the aminoester **10b** are the thermodynamic products. At the end of the reaction the resulting catalytic amount of **10b** will be saponified by NaOH to furnish the rearranged β-amino alcohol **3b**. Because of the high enantiomeric excess observed in the rearrangement, it is unlikely that the reaction proceeds via a planar carbocation intermediate.

Conclusion

We have shown that, when treated with a catalytic amount of $(CF_3CO)_2O$, linear *N*,*N*-dialkyl β-amino alcohols of type **C** and *N*-alkylated substituted prolinols of type **A** can be rearranged into β-amino alcohols of type **D** and 3-hydroxypiperidines of type **B,** respectively, with high yield and excellent enantiomeric excess. Further studies using the rearranged β-amino alcohols in the synthesis of pharmacologically active products are currently under investigation.

Experimental Section

General Method A. To a solution of the *N*,*N*-dibenzylamino alcohols **2a**−**k** (1 mmol, 1.0 equiv) in THF (2 mL) cooled at 0 °C was added dropwise trifluoroacetic anhydride (212 μL, 1.5 mmol, 1.5 equiv). After 20 min of stirring at room temperature, Et_3N (212 μL, 2 mmol, 2.0 equiv) was added. The reaction mixture was then heated at 100 °C during 2 h under microwave irradiation. After addition of an aqueous 3.75 M NaOH solution (2 mL), the mixture was stirred at room temperature for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, *n*-pentane/AcOEt) afforded the corresponding *N*,*N*-dibenzylamino alcohols **3a**−**k**.

General Method B. To a solution of the *N*,*N*-dibenzylamino alcohols **2b**−**k** (1 mmol, 1.0 equiv) in THF (1.5 mL) at room temperature was added trifluoroacetic anhydride (28 μL, 0.2 mmol, 0.2 equiv). The reaction mixture was then heated at 180 °C during 2 h under microwave irradiation or at 100 °C in a sealed tube placed in an oil bath until the reaction was finished. After addition of an aqueous 3.75 M NaOH solution (10 μL, 0.3 equiv), the mixture was stirred at room temperature for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, *n*-pentane/AcOEt) afforded the corresponding *N*,*N*-dibenzylamino alcohols **3b**−**k**.

(*R*)-1-[Benzyl-(2-hydroxyethyl)-amino]-3-phenylpropan-2-ol (3a). CH_2Cl_2/MeOH 90/10; 61% yield [Method A with $(CF_3CO)_2O$ (1.1 equiv), Et_3N (2.0 equiv), THF, 100 °C, 6 h, MW]; yellow oil; $C_{18}H_{23}NO_2$; MW = 285.38 g mol^{-1}; $[\alpha]^{20}_D = -59.9$ (*c* 1.0, $CHCl_3$); IR (neat) 3500−3100, 3026, 3000−2500, 1601, 1494, 1452, 1027, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.14 (10H), 3.88 (m, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.63−3.50 (3H), 2.94 (bs, 2H), 2.78−2.48 (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (s), 138.3 (s), 129.3 (d), 129.0 (d), 128.5 (d), 128.4 (d), 127.3 (d), 126.4 (d), 69.5 (d), 60.1 (t), 59.8 (t), 59.6 (t), 56.3 (t), 41.5 (t); HRMS (ESI) calcd for $C_{18}H_{24}NO_2$ (M + H$^+$) 286.1801, found 286.1804.

(*R*)-1-*N*,*N*-Dibenzylaminopropan-2-ol (3b).[20] Petroleum ether/AcOEt 95/5; 99% yield (method A), 98% yield (method B); yellow oil; $C_{17}H_{21}NO$; MW = 255.35 g mol^{-1}; $[\alpha]^{20}_D = -92.2$ (*c* 1, $CHCl_3$) [lit.[20] $[\alpha]^{20}_D = +99.4$ (*c* 2, $CHCl_3$) for *S* isomer]; IR (neat) 3433, 3027, 2967, 2931, 2801, 1494, 1452, 1372, 1248, 1056, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (10H), 3.89−3.80 (3H), 3.40 (d, *J* = 13.5 Hz, 2H), 3.24 (bs, 1H), 2.41 (d, *J* = 6.6 Hz, 2H), 1.05 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (s), 129.1 (d), 128.5 (d), 127.3 (d), 63.2 (d), 61.4 (t), 58.5 (t), 19.9 (q); MS-EI *m*/*z* (%) 255 (M$^{+\bullet}$, 1), 210 (83), 91 (100); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 5% MeOH, 8 mL/min, λ = 220 nm, t_R (major) = 1.5 min, t_R (minor) = 1.7 min).

(*R*)-1-(*N*,*N*-Dibenzylamino)-3-methyl-2-butanol (3c).[21] Hexane/AcOEt 90/10); 88% yield (method A), 93% yield (method B);

yellow oil; $C_{19}H_{25}NO$; MW = 283.41 g mol^{-1}; $[\alpha]^{20}_D = -26.6$ (*c* 0.5, MeOH) [lit.[21] $[\alpha]^{20}_D = +24.5$ (*c* 1, MeOH) for *S* isomer]; IR (neat) 3448, 3028, 2957, 2930, 2872, 2803, 1576, 1495, 1452, 1368, 1246, 1069, 967, 872, 746, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (10H), 3.88 (d, *J* = 13.4 Hz, 2H), 3.52 (bs, 1H), 3.43 (ddd, *J* = 10.8, 6.4, 4.4 Hz, 1H), 3.36 (d, *J* = 13.4 Hz, 2H), 2.46 (m, 2H), 1.51 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (s), 129.1 (d), 128.4 (d), 127.3 (d), 71.5 (d), 58.3 (t), 57.1 (t), 32.3 (d) 18.4 (q), 18.3 (q); MS-EI *m*/*z* (%) 283 ($M^{+\bullet}$, 0.4), 240 (3), 210 (100), 181 (8), 118 (3), 91 (99); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 5% MeOH, 8 mL/min, λ = 220 nm, t_R (major) = 1.2 min, t_R (minor) = 1.4 min).

(*R*)-1-(*N*,*N*-Dibenzylamino)-4-methylpentan-2-ol (3d). Hexane/AcOEt 95/5); 82% yield (method A), 89% yield (method B); colorless oil; $C_{20}H_{27}NO$; MW = 297.43 g mol^{-1}; $[\alpha]^{20}_D = -59.8$ (*c* 1, $CHCl_3$); IR (neat) 3400−3200, 3028, 2951, 2802, 1494, 1453, 1367, 1293, 1121, 1071, 1028, 975, 914, 882, 839, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.22 (10H), 3.85 (d, *J* = 13.4 Hz, 2H), 3.74 (m, 1H), 3.68 (d, *J* = 13.4 Hz, 2H), 3.27 (bs, 1H), 2.45−2.37 (2H), 1.77 (m, 1H), 1.27 (ddd, *J* = 13.9, 8.6, 5.6 Hz, 1H), 1.03 (ddd, *J* = 13.5, 8.6, 4.0 Hz, 1H), 0.89 (d, *J* = 5.2 Hz, 3H), 0.87 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (s), 129.1 (d), 128.5 (d), 127.3 (d), 65.0 (d), 60.4 (t), 58.6 (t), 43.9 (t), 24.7 (d), 23.5 (q), 22.3 (q); MS-EI *m*/*z* (%) 297 ($M^{+\bullet}$, 0.2), 210 (100), 181 (7), 118 (4), 91 (79). Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.64; H, 8.88; N, 4.65.

(*R*)-1-*N*,*N*-Dibenzylamino-3,3-dimethylbutan-2-ol (3e).[19] Hexane/AcOEt 80/20); 99% yield (method A), 74% yield (method B); yellow oil; $C_{20}H_{27}NO$; MW = 297.43 g mol^{-1}; $[\alpha]^{20}_D = -85.4$ (*c* 0.5, $CHCl_3$); IR (neat) 3440, 3027, 2954, 1574, 1450, 1365, 1241, 1086, 973, 747, 730, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (10H), 3.90 (d, *J* = 13.4 Hz, 2H), 3.40 (dd, *J* = 10.6, 3.3 Hz, 1H), 3.35 (d, *J* = 13.4 Hz, 2H), 2.46 (m, 2H), 0.80 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (s), 129.2 (d), 128.3 (d), 127.3 (d), 73.5 (d), 58.2 (t), 54.2 (t), 33.5 (s), 25.7 (q); MS-EI *m*/*z* (%) 297 ($M^{+\bullet}$, 0.3), 282 (1), 240 (5), 210 (100), 181 (8), 91 (94); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 2% MeOH, 2 mL/min, λ = 220 nm, t_R (major) = 9.6 min, t_R (minor) = 10.1 min); HRMS (CI^+, CH_4) calcd for $C_{20}H_{28}NO$ ($M + H^+$) 298.2171, found 298.2174.

(*R*)-1-*N*,*N*-Dibenzylamino-3-phenylpropan-2-ol (3f).[20] Hexane/AcOEt 98/2; 97% yield (method A), 87% yield (method B); colorless oil; $C_{23}H_{25}NO$; MW = 331.45 g mol^{-1}; $[\alpha]^{20}_D = -87.4$ (*c* 0.5, $CHCl_3$) [lit.[20] $[\alpha]^{20}_D = +26.1$ (*c* 1, $CHCl_3$) 50% ee for *S* isomer]; IR (neat) 3438, 3026, 2803, 1494, 1453, 1370, 1246, 1072, 1028, 735, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.15 (15H), 3.93 (m, 1H), 3.80 (d, *J* = 13.4 Hz, 2H), 3.39 (d, *J* = 13.5 Hz, 2H), 3.28 (bs, 1H), 2.72 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.58 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (s), 138.4 (s), 129.2 (d), 129.1 (d), 128.4 (d), 128.3 (d), 127.3 (d), 126.2 (d), 68.3 (d), 59.2 (t), 58.4 (t), 41.2 (t); MS-EI *m*/*z* (%) 331 ($M^{+\bullet}$, 0.5), 328 (5), 210 (75), 181 (5), 120 (5), 106 (5), 91 (100); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 10% MeOH, 8 mL/min, λ = 220 nm, t_R (major) = 2.0 min, t_R (minor) = 2.3 min). (*R*) isomer was determined by application of the modified Mosher method.[23]

(*S*)-1-*N*,*N*-Dibenzylamino-3-*O*-benzyl-2,3-propanediol (3g).[19] Hexane/AcOEt 95/5; 76% yield (method A), 96% yield (method B); yellow oil; $C_{24}H_{27}NO_2$; MW = 361.48 g mol^{-1}; $[\alpha]^{20}_D = -37.1$ (*c* 0.7, $CHCl_3$); IR (neat) 3429, 3027, 2854, 1494, 1452, 1365, 1250, 1100, 1027, 735, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (15H), 4.49 (s, 2H), 3.93 (m, 1H), 3.75 (d, *J* = 13.5 Hz, 2H), 3.49 (d, *J* = 13.5 Hz, 2H), 3.45 (dd, *J* = 9.9 Hz, *J* = 4.2 Hz, 1H), 3.38 (dd, *J* = 9.9 Hz, *J* = 5.9 Hz, 1H), 3.14 (bs, 1H), 2.59 (dd, *J* = 12.8 Hz, *J* = 8.6 Hz, 1H), 2.54 (dd, *J* = 12.8 Hz, *J* = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (s), 138.2 (s), 129.1 (d), 128.5 (d), 128.4 (d), 127.7 (d), 127.6 (d), 127.2 (d), 73.4 (t), 72.6 (t), 67.2 (d), 58.6 (t), 56.3 (t); MS-EI *m*/*z* (%) 361 ($M^{+\bullet}$, 0.1), 309 (1), 252 (1), 210 (81), 181 (5), 107 (12), 91 (100); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 20% MeOH, 8 mL/min, λ = 220 nm, t_R (major) = 1.46 min, t_R (minor) = 1.94 min). (*S*) isomer was determined by application of the modified Mosher method;[23] HRMS (CI^+, CH_4) calcd for $C_{24}H_{28}NO_2$ ($M + H^+$) 362.2120, found 362.2123.

(*S*)-2-*N*,*N*-Dibenzylamino-1-phenylethanol (3h).[22] Hexane/AcOEt 95/5); 93% yield (method A), 78% yield (method B); colorless oil; $C_{22}H_{23}NO$; MW = 317.42 g mol^{-1}; $[\alpha]^{20}_D = +138.2$ (*c* 0.95, $CHCl_3$); IR (neat) 3427, 3027, 2834, 1494, 1452, 1026, 746, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (15H), 4.71 (t, *J* = 6.9 Hz, 1H), 3.92 (d, *J* = 13.4 Hz, 2H), 3.79 (bs, 1H), 3.48 (d, *J* = 13.4 Hz, 2H), 2.64 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1 (s), 138.3 (s), 129.1 (d), 128.5 (d), 128.3 (d), 127.4 (d), 127.3 (d), 125.9 (d), 69.6 (d), 61.9 (t), 58.4 (t); MS-EI *m*/*z* (%) 299 ($M^{+\bullet} - H_2O$, 7), 210 (44), 106 (41), 91 (100), 77 (30); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 20% MeOH, 8 mL/min, λ = 220 nm, t_R (minor) = 1.5 min, t_R (major) = 2.1 min).

(1*R*,2*S*)-3-(*N*,*N*)-Dibenzylamino-1-phenyl-1,2-propanediol (3i).[19] CH_2Cl_2/MeOH 99/1); 66% yield (method A), 83% yield (method B); yellow oil; $C_{23}H_{25}NO_2$; MW = 347.45 g mol^{-1}; $[\alpha]^{20}_D = -84.0$ (*c* 0.3, $CHCl_3$); IR (neat) 3387, 3028, 2839, 1494, 1452, 1064, 1027, 733, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (15H), 4.62 (d, *J* = 5.6 Hz, 1H), 3.82−3.75 (2H), 3.61 (d, *J* = 13.2 Hz, 2H), 3.56 (d, *J* = 13.2 Hz, 2H), 2.73 (dd, *J* = 12.8 Hz, *J* = 8.0 Hz, 1H), 2.46 (dd, *J* = 12.9 Hz, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (s), 137.9 (s), 129.3 (d), 128.6 (d), 128.4 (d), 127.7 (d), 127.5 (d), 126.4 (d), 76.3 (d), 70.1 (d), 58.9 (t), 53.7 (t); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of CO_2, 20% MeOH, 5 mL/min, λ = 220 nm, t_R (major) = 2.7 min, t_R (minor) = 3.4 min); HRMS (CI^+, CH_4) calcd for $C_{23}H_{26}NO_2$ ($M + H^+$) 348.1964, found 348.1966.

(*R*)-1-Benzylpiperidin-3-ol (3j).[18a] *n*-Pentane/AcOEt 50/50; 63% yield (method A), 87% yield (method B); yellow oil; $C_{12}H_{17}NO$; MW = 191.27 g mol^{-1}; $[\alpha]^{20}_D = -12.8$ (*c* 1.0, MeOH); IR (neat) 3322, 2935, 2858, 2795, 1494, 1453, 1368, 1347, 1296, 1153, 1100, 1059, 1025, 972, 737, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.21 (5H), 3.80 (dddd, *J* = 4.3, 4.3, 4.3, 4.3 Hz, 1H), 3.50 (s, 2H), 2.66−2.38 (4H), 2.26 (m, 1H), 1.78 (m, 1H), 1.65−1.46 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (s), 129.1 (d), 128.3 (d), 127.1 (d), 66.3 (d), 63.0 (t), 60.3 (t), 53.5 (t), 31.8 (t), 21.7 (t); MS-EI *m*/*z* (%): 191 ($M^{+\bullet}$, 31), 190 (18), 146 (10), 134 (22), 114 (18), 100 (36), 92 (11), 91 (100), 65 (11).

(3*R*,5*R*)-1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-piperidin-3-ol (3k).[18e] CH_2Cl_2/MeOH 95/5; 82% yield (method A), 61% yield (method B); yellow oil; $C_{18}H_{31}NO_2Si$; MW = 321.53 g mol^{-1}; $[\alpha]^{20}_D = +24.6$ (*c* 0.5, EtOH) [lit.[18e] $[\alpha]^{20}_D = +25.3$ (*c* 1.75, EtOH)]; IR (neat) 3450, 1460, 1250, 1150, 1090, 840, 775, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (5H), 4.05 (h, *J* = 4.8 Hz, 1H), 3.96 (m, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 2.90 (m, 1H), 2.75 (m, 1H), 2.50 (bs, 1H), 2.19 (dd, *J* = 11.4, 1.8 Hz, 1H), 2.09 (m, 1H), 1.97 (dd, *J* = 10.1, 10.1 Hz, 1H), 1.38 (ddd, *J* = 13.0, 10.3, 2.6 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (s), 128.9 (d), 128.3 (d), 127.2 (d), 66.0 (d), 65.3 (d), 62.3 (t), 61.2 (t), 58.6 (t), 40.9 (t), 25.8 (q), 18.1 (s), −4.7 (q), −4.8 (q); MS-EI *m*/*z* (%) 321 ($M^{+\bullet}$, 5), 264 (39), 246 (7), 134 (23), 120 (10), 101 (10), 91 (100), 73 (11).

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Supporting Information Available: Experimental procedures and characterization of the products **1a′**, **2a**, **2d**, **2e**, **2g**, **2h**, **2i**, and the corresponding mandelic esters **11a**, **11b**, **12a**, and **12b** from amino alcohols **3f** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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