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A rapid and practical entry into *cis*-1,4-aminocyclohexanols

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ABSTRACT

A selective and practical approach for the formation of *cis*-1,4-aminocyclohexanol was developed. The key transformation involves a one-pot imine formation/ Lewis acid-directed imine reduction and results in a highly selective attack of the reducing agent. This simple and practical method is easily amenable to large-scale synthesis.

1. Introduction

The good understanding of the cyclohexane ring conformation and its easy amenability to Structure Activity Relationship has made this ring system an attractive scaffold for medicinal chemists for various applications such as, for example, antihelmintic agents,[1a] anti-inflammatory agents,[1b] Melanin-Concentrating Hormone Receptor antagonists,[1c] phosphodiesterase inhibitors,[1d] presynaptic silent antagonists,[1e] dopamine receptor antagonists,[1f–h] modulator of chemokine receptor activity,[1i] antibacterial agents,[1j] *N*-methyl-D-aspartate receptor antagonists,[1k] hypertensive agents,[1l] and chemokine receptor antagonists.[1m] The 1-substituted-4-aminocyclohexanol framework especially has in the last few years been extensively used by research chemists. It is generally synthesized in a non-stereoselective manner to give rise to both the cis and trans isomers. For the *cis* aminoalcohol isomer, the commonly used approach consists of an iminonitroso Diels–Alder sequence which upon reduction of the N–O bond gives rise to the desired aminocyclohexanol with a syn relationship of the amine and alcohol functionality.[2] An alternative often encountered is a non-stereoselective reductive amination of the corresponding cyclohexanone system, which induces at best a modest selectivity, and requires subsequent purification by column chromatography.[3] Both strategies suffer from poor practicality and ease of operations. The iminonitroso Diels–Alder approach also presents further drawbacks, for example, the cost inherent in the formation of the diene precursor and the safety limitations. We became interested in this specific problem and tried to design a system that could provide a selective entry into variously substituted *cis*-1,4-aminocyclohexanols in a practical, robust, and economical manner.

The numerous available methods of reductive amination prompted us to focus on this approach.[4] We were hoping that upon imine formation mediated by a suitable dehydrating agent, the latter could also serve as a Lewis acid to chelate the free hydroxyl group and the imine in a boat-like conformation, thus inducing the entry of the hydride from the opposite face (Scheme 1).[5]

Titanium-based reagents first appeared as suitable candidates to promote both the dehydration-imine formation and the chelation that would shield one face of the ring. An initial feasibility study showed that the reaction proceeded well with the mild Lewis acidic titanium tetraalkoxide (ethoxide or isopropoxide).[3d] We tested this reaction with compound **1**.[6] Encouraged by these results, we evaluated various entering amine group. An optimal ca 9:1 ratio of cis/trans isomer was obtained with benzylamine (Table 1).[7]

A subsequent screening of reducing agents showed that sodium borohydride was superior to other more complex boron or other hydride reagents or all other more expensive reagents (see Table 2, entries 1–5). The more reactive aluminum-based reducing agent was not assessed to guarantee high chemoselectivity and a larger compatibility with functional groups. No major counter-ion effect could be observed (entries 1 and 3). The aluminum-based hydride reagents especially led to much lower overall efficiency for both the yield and the selectivity. Solvent evaluation revealed that the selectivity was similar in various solvents and showed that alcohols were optimal (entries 6–8). We rationalize the marginal difference observed as a consequence of the addition of solid

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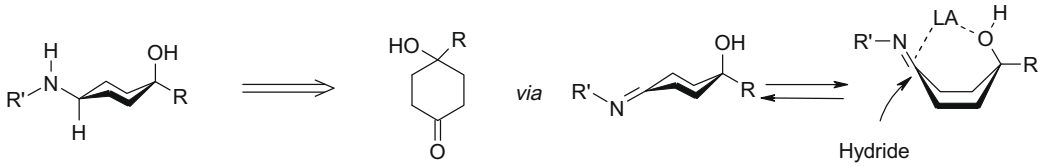
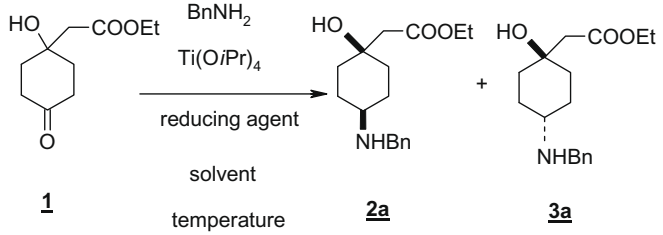


Scheme 1. Working hypothesis for the selective formation of *cis*-1,4-aminocyclohexanol.

Table 1
Optimization of reaction conditions for the synthesis of **2a**



Entry	Reducing agent	Solvent	Temperature	Yield	**2a**/**3a**(*)
1	$NaBH_4$	THF	−10 °C	66%	90:10
2	$NaBH_3CN$	THF	−10 °C	70%	80:20
3	$LiBH_4$	THF	−10 °C	69%	90:10
4	$NaBH(OAc)_3$	THF	−10 °C	63%	92:8
5	$NaBH(s\text{-}Bu)_3$	THF	−10 °C	Messy	—
6	$NaBH_4$	CH_2Cl_2	−10 °C	81%	95:5
7	$NaBH_4$	EtOH	−10 °C	76%	95:5
8	$NaBH_4$	*i*PrOH	−15 °C	82%	95:5
9	$NaBH_4$	EtOH	−60 °C	56%	96:4
10	$NaBH_4$	EtOH	−15 °C	75%	97:3
11	$NaBH_4$	EtOH	0–5 °C	75%	89:11
12	$NaBH_4$(**)	EtOH	−15 °C	80%	83:17

(*) Ratio determined by HPLC area% at 210 nm.
(**) From the imine generated under dehydrative conditions without $Ti(OiPr)_4$.

sodium borohydride which reacted rapidly with the imine without complexing the solvent. A final step of our optimization consisted in the identification of a practical and optimal temperature range. We herein found that selectivities >97:3 could be obtained at a temperature of ca. −15 °C which allowed a highly practical and economically attractive non-cryogenic process (entries 8–10). Interestingly, when the sodium borohydride was added directly to a solution of the imine preformed in the absence of a dehydrating agent but by azeotropic distillation, a ca 83:17 ratio of isomers was obtained (entry 12). The extent of the effectiveness of the chelation in a polar protic solvent as demonstrated, for example, by comparison of entries 10 and 12, is remarkable here.

We finally aimed at further enrichment of the isomeric ratio by salt formation. A rapid screening allowed us to identify methanesulfonic acid or the enantiopure mandelic acid as optimal acid partners for such systems that resulted, respectively, in excesses of 96:4 and 99:1 after crystallization from ethyl acetate at room temperature.

With an optimized process in hand, we turned our attention to the scope of the methodology (Table 2). Not surprisingly, ratio >97:3 could be observed for all substrates that displayed a conformational preference for an axial hydroxyl group (entries 2 to 4, R = *iso*-propyl, allyl, phenyl). In these cases, the ratio of isomers could be further enriched to >99:1 via salt formation as described

Table 2
Substrate scope

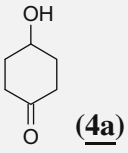
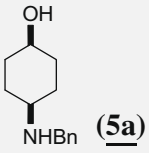
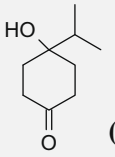
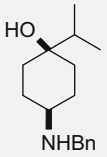
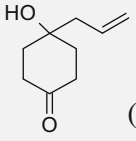
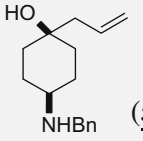
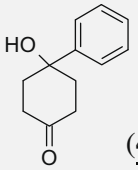
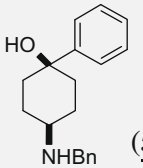
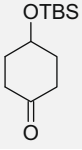
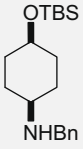
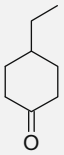
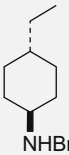
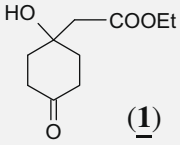
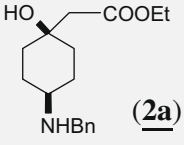
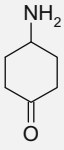
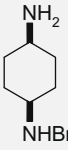
Entry	Ketone	Product Major isomer	Yield	Cis/trans Isomeric ratio(*)
1	 **(4a)**	 **(5a)**	57%	70/30
2	 **(4b)**	 **(5b)**	76%	98/2
3	 **(4c)**	 **(5c)**	79%	97/3
4	 **(4d)**	 **(5d)**	87%	98/2
5	 **(4e)**	 **(5e)**	>85%	80/20

Table 2 (*continued*)

Entry	Ketone	Product Major isomer	Yield	Cis/trans Isomeric ratio(*)
6	 (**4f**)	 (**5f**)	>95%	25/75
7	 (**1**)	 (**2a**)	94%	95/5
8	 (**4g**)	 (**5g**)	>95%	73/27

Reaction conditions: $BnNH_2$, $Ti(OiPr)_4$, EtOH, rt, 1 h then $NaBH_4$, −15 °C, 1 h.
(*) Ratio determined by HPLC area % at 210 nm.

above. Control experiments also showed the importance of the hydroxyl group to induce the hydride reduction from the opposite face. Protection of the latter by a non-coordinating group (OTBS entry 5) indeed showed a ca. 10% change in the selectivity. When the hydroxyl group was removed, the reductive amination even led to the formation of the trans isomer preferentially in a 75/25 ratio (entry 6).[4b] We finally showed that an amino group displayed the same directing effect as the hydroxyl group and confirmed the already described lack of selectivity (73/27 cis/trans isomeric ratio, entry 8).[3a,c]

In conclusion, we have designed practical and general reaction conditions that allow the selective formation of *cis*-1,4-aminocyclohexanols via a controlled reductive amination. The process is simple and directly amenable to large-scale synthesis. We are currently investigating extension to other well-defined ring systems and their use for the formation of chiral compounds.

2. Experimental section

General procedure: To a solution of ethyl 2-(1-hydroxy-4-oxocyclohexyl)acetate **1** (2.4 g, 12 mmol, 1.0 equiv) in anhydrous ethanol (12 mL) at room temperature were added titanium tetraisopropoxide (4.2 mL, 15 mmol, 1.25 equiv) and benzylamine (1.4 mL, 12 mmol, 1.0 equiv). The resulting mixture was stirred for 1 h, cooled to ca. −15 °C, and a freshly prepared solution of sodium borohydride (0.23 g, 6 mmol, 2 equiv) in anhydrous ethanol (2 mL) was added dropwise at a rate such that the temperature remained at ca. −15 °C. At completion, the mixture was quenched with water (excess), and ethyl acetate was added. Filtration through celite and extraction gave an organic extract that was washed with water once, and concentrated to give the crude reaction mixture.

Ethyl 2-((1S*, 4S*)-4-benzylamino)-1-hydroxycyclohexyl)acetate **2a** (major diastereoisomer) ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.10 (m, 5H), 4.22 (q, J = 7.7 Hz, 2H), 3.85 (s, 2H), 2.55–2.45 (m, 3H), 1.95–1.30 (m, 8H), 1.28 (t, J = 7.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 140.8, 129.0, 128.4, 126.8, 69.1, 60.6, 55.5, 50.9, 46.2, 35.8, 28.3, 14.2; HRMS calcd for $C_{17}H_{25}NO_3$ [M+] 291.18344; found 291.18171.

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1. (a) Chassaing, C. P. A.; Schroeder, J.; Ilg, T. S.; Uphoff, M.; Meyer, T. WO2009/077527.; (b) Ferrand, S.; Glickman, F.; Leblanc, C.; Ritchie, C.; Shaw, D.; Stiefl, N. J.; Furet, P.; Imbach, P.; Stauffer, F.; Capraro, H.-G.; Gessier, F.; Gaul, C.; Albaugh, P. A.; Chopiuk, G. WO2008/052734.; (c) Sekiguchi, Y.; Kanuma, K.; Omodera, K.; Sato, K.; Hayashi, M.; Yamamoto, S. WO2006/035967.; (d) Vergne, F.; Bernardelli, P.; Lorthiois, E.; Pham, N.; Proust, E.; Oliveira, C.; Mafroud, A.-K.; Ducrot, P.; Wrigglesworth, R.; Berlioz-Seux, F.; Coleon, F.; Chevalier, E.; Moreau, F.; Idrissi, M.; Tertre, A.; Descours, A.; Berna, P.; Li, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4615–4621; (e) Mattson, R. J.; Catt, J. D.; Sloan, C. P.; Gao, Q.; Carter, R. B.; Gentile, A.; Mahle, C. D.; Matos, F. F.; McGovern, R.; VanderMaelene, C. P.; Yocca, F. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 285–288; (f) Caprathe, B. W.; Jaen, J. C.; Smith, S. J.; Wise, L. D. US4957921.; (g) Urban, F. J.; Anderson, B. G.; Stewart, M. A.; Young, G. R. *Org. Process Res. Dev.* **1999**, *3*, 460–464; (h) Boy, K. M.; Dee, M.; Yevich, J.; Torrente, J.; Gao, Q.; Iben, L.; Stark, A.; Mattson, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4467–4470; (i) Xue, C.-B.; Metcalf, B.; Han, A. Q.; Robinson, D. J.; Zheng, C.; Wang, A.; Zhang, Y. WO2005/060665.; (j) Axten, J. M.; Daines, R. A.; Davies, D. T.; Gallagher, T. F.; Jones, G. E.; Miller, W. H.; Pearson, N. D.; Pendrak, I. WO2004/002992.; (k) Kawai, M.; Nakamura, H.; Sakurada, I.; Shimokawa, H.; Tanaka, H.; Matsumizu, M.; Ando, K.; Hattori, K.; Ohta, A.; Nukui, S.; Omura, A.; Kawamura, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5533–5536; (l) Xue, C.-B.; Zheng, C.; Cao, G.; Feng, H.; Xia, M.; Anand, R.; Glenn, J.; Metcalf, B. W. US2005/125647.; (m) Hersperger, R.; Janser, P.; Miltz, W. WO2008/101905.
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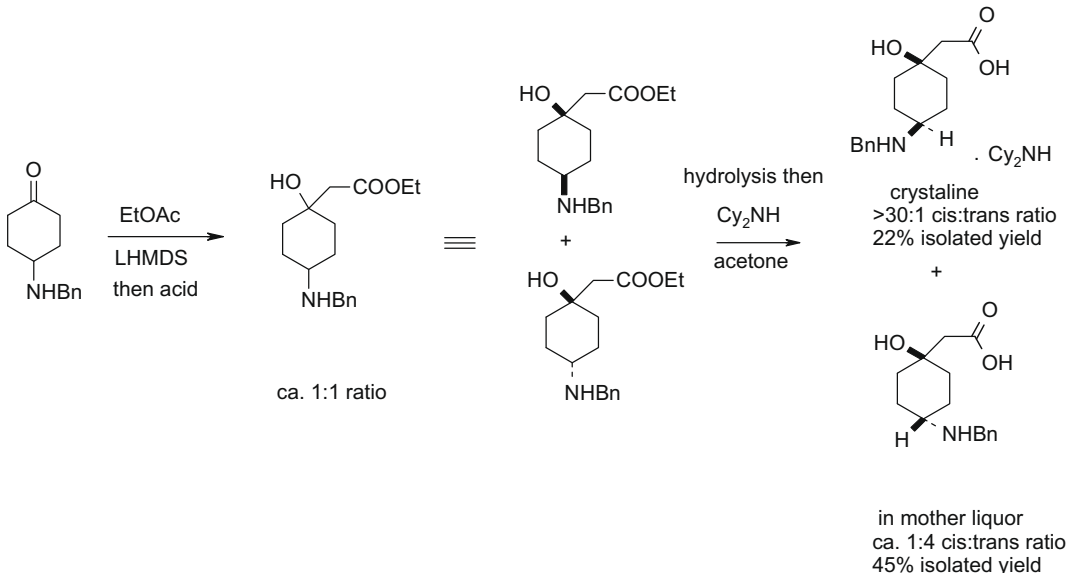
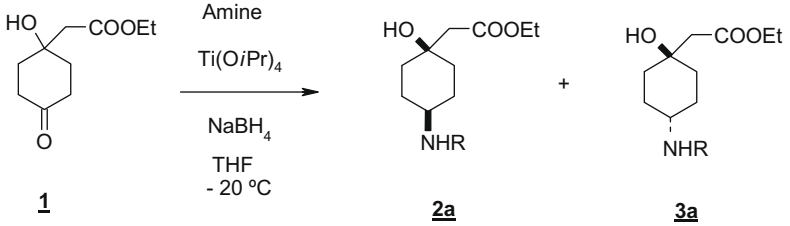
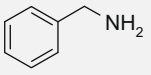
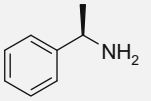
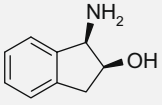
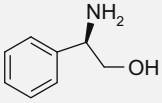
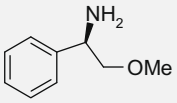
5. Reductive aminations of carbonyl compounds with borohydride and borane reducing agents, Baxter, E. W.; Reitz, A. B. In *Organic Reactions*; John Wiley & Sons: NewYork, 2002; pp 1–714.
6. Both the cis and trans isomers were prepared via the sequence showed below, purified as described, and the stereochemistry was unambiguously determined by extensive NMR study and subsequent derivatization to a known compound.



7. Only a marginal effect with an increase of the steric hindrance or additional electronic interaction was observed, when going from benzylamine to α-methylbenzylamine, to α-phenylglycinol, and to its *O*-methyl derivative. We rationalize these observations by the optimal chelation between the imine formed in situ and the Lewis acid brought in coordination sphere of the metal in a boat-like conformation with benzylamine. For all others, additional steric hindrance or competitive chelation of electrons with the Lewis acid reduced the extent of the selectivity.



1 **2a** **3a**

Entry	Amine	Yield	**2a**/**3a***
1		76%	90/10
2		81%	80/20
3		77%	88/12
4		73%	80/20
5		86%	89/11
6	NH3	51%	90/10

* Ratio determined by HPLC area % at 210 nm.