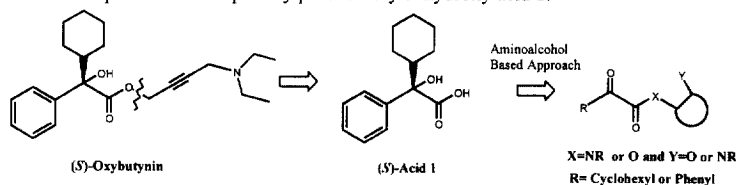


Rigid Aminoalcohol Backbone as a Highly Defined Chiral Template for the Preparation of Optically Active Tertiary α -Hydroxyl Acids

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Received 29 September 1998; revised 20 November 1998; accepted 23 November 1998

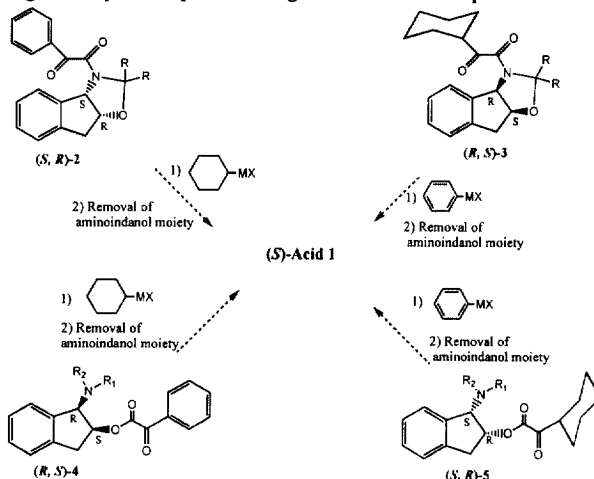
Abstract: Constrained aminoalcohol derived-ketoester or amides have provided a new entry for the production of enantiopure acid 1 for (*S*)-oxybutynin. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Tertiary hydroxy esters are highly important intermediates in the asymmetric synthesis of a variety of medicinal agents¹ and natural products.² For example, racemic oxybutynin (ditropan) a widely prescribed muscarinic receptor antagonist for the treatment of urinary incontinence contains a tertiary hydroxyl moiety. It has been documented that it exhibits classical antimuscarinic side effects such as dry mouth.³ However, preliminary biological results suggest that (*S*)-oxybutynin displays an improved therapeutic profile compared to its racemic counterpart, and is currently in clinical trials. Interestingly, most of the muscarinic receptor antagonists comprise of tertiary α -hydroxy acid as a key component.^{1,4} It has been revealed in the literature that the organometallic addition to cyclohexane based auxiliaries of ketoesters serve as the method of choice for the preparation of such optically enriched tertiary α -hydroxy acids.⁵ An enormous number of alcohol based auxiliaries have been examined in this context; however, most of the auxiliaries are not general, not readily accessible and are often inefficient or lack diastereo-control.⁶ Therefore, creating a tertiary alcohol center in which the absolute stereochemistry can be controlled by a defined chiral environment in the addition of organometallic reagents to ketones still represents a significant challenge.⁷ We envisage that optically pure α -tertiary alcohol acids could be obtained from either ketoamide or ketoester-derived readily available constrained chiral aminoalcohols because they can serve as a highly organized chiral environment with certain organometallic reagents in the transition state for the alkyl- or aryl-addition process. Herein, we report on the C-1 amine or C-2 hydroxyl moiety of constrained *cis*-aminoalcohols as a highly defined chiral handle for the production of optically pure tertiary α -hydroxy acid 1.



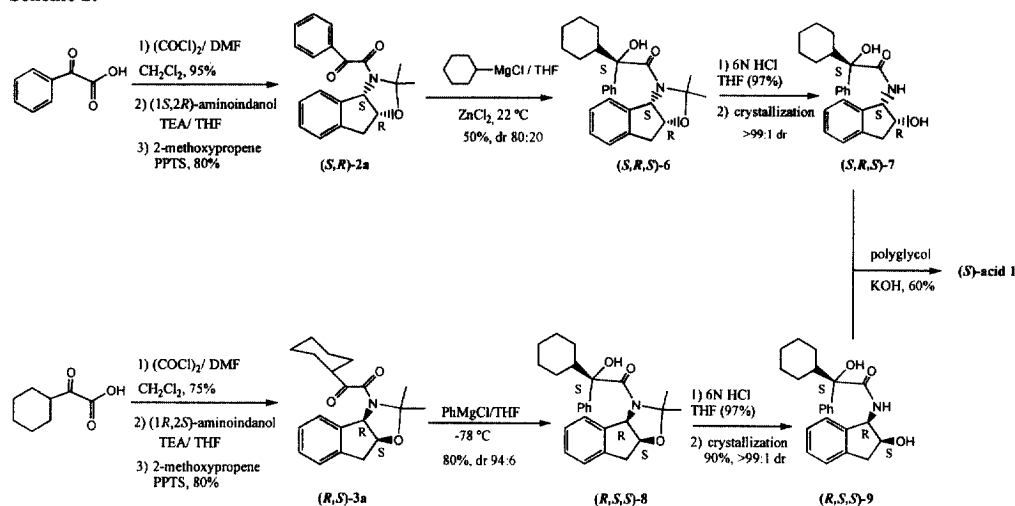
Recent reports indicate that the rigid benzocycloalk-1-ene-derived vicinal *cis*-aminoalcohol platform plays a crucial role in asymmetric synthesis.⁸ Interestingly, the generation of optically pure tertiary α -hydroxy acids have never utilized these inexpensive and valuable *cis*-aminoalcohols. As outlined in Figure 1, our plan was to take advantage of the C-1 amine or C-2 alcohol of *cis*-aminoindanol as a chiral handle and examine the diastereoselective cyclohexyl or phenyl Grignard addition process to the appropriate keto-moiety for generation of (*S*)-acid 1.

Figure 1: Synthetic plan for the generation of enantiopure α -tertiary alcohol acid 1



When the C-1 amine is utilized as a chiral handle, rigid tricyclic aminoindanol acetamide ketoamide (*S,R*)-**2a** and (*R,S*)-**3a** (where R= Me) were selected for the examination of diastereofacial Grignard addition process.⁹ Substrates (*S,R*)-**2a** and (*R,S*)-**3a** were prepared as depicted in Scheme 2 in high overall yields.¹⁰ First phenyl ketoamide (*S,R*)-**2a** was investigated in the presence of a variety of conditions with or without additives such as Zn²⁺, Ti⁴⁺, Mg²⁺, CuBr.Me₂S and CeCl₃. It is interesting to note that the addition of cyclohexyl Grignard with ZnCl₂ at room temperature provides the highest selectivity as 80:20 with a moderate yield (50%).¹¹ Without ZnCl₂, a complex mixture of products was observed. At low temperatures with or without ZnCl₂, the reactions proceeded extremely slowly. After mild acidic hydrolysis of the crude acetamide (*S,R,S*)-**6** to the corresponding diastereomeric amidoalcohols followed by crystallization provided >99:1, dr of the desired diastereomer as (*S,R,S*)-**7** (Scheme 2). On the other hand, we are gratified to disclose that when the cyclohexyl ketoamide (*R,S*)-**3a** was subjected to phenylmagnesium chloride in THF at -78 °C, high diastereoselectivity (>94:6, dr) with high yields resulted. The most favorable diastereoselective/temperature profile was found to be at -78 °C (-50 °C, 90:10, dr; 0 °C, 85:15, dr). Simple acidic hydrolysis followed by crystallization from EtOAc/ hexanes provided diastereomerically pure amidoalcohol (*R,S,S*)-**9** in >85% yield. (Scheme 2). However, attempts to hydrolyze the sensitive and hindered **6**, **7**, **8** or **9** with known conditions resulted in either decomposition or very low yield.¹² Fortunately, exposure of sterically congested compound (*R,S,S*)-**9** to polyglycol (ethylene glycol, diglyme or triglyme etc.) in the presence of KOH or NaOH at 130-140 °C provided ~60% yield with > 99% ee of (*S*)-acid **1**.¹³ The recovery of *cis*-aminoindanol was >85% by assay.

Scheme 2:



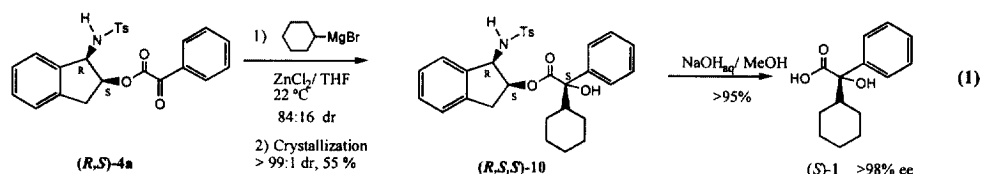
Since the hydrolysis of sterically congested compound (*S,R,S*)-**7** or (*R,S,S*)-**9** provided moderate yields of (*S*)-acid **1**, our attention was then focused on easily hydrolyzable C-2 hydroxyl derived esters. It was anticipated that the Grignard addition process might give high selectivities, because the rigid aminoindanol backbone has a highly defined chiral environment. Recently, Ghosh and co-workers have exemplified this phenomena by demonstrating that N-tosylate derived aminoindanol esters undergo several excellent diastereoselective processes⁸ for example, *syn* and *anti*-aldol,^{14a} and reduction of ketoesters.^{14b} As noted in Table 1, our focus was aimed at studying the role of C-1 amine ketoester derivatives (*R,S*)-**4** (Figure 1) in the Grignard addition process. When cyclohexyl Grignard addition to ketoester (*R,S*)-**4** was conducted without ZnCl₂ or CeCl₃ with ketoesters, diminished selectivities and yields were observed.

Table 1: Diastereoselective Cyclohexyl Grignard addition process with ketoester 4

Substrate	R ₁	R ₂	Cyclohexyl Grignard (Equiv.)	Additives (Equiv.)	dr (¹ H-NMR r)	Yield (%)
4a	Ts	H	2.5	-----	67:33	65
4a	Ts	H	2.5	ZnCl ₂ (0.3)	67:33	80
4a	Ts	H	2.5	ZnCl ₂ (1.0)	68:32	75
4a	Ts	H	2.5	ZnCl ₂ (2.5)	84:16	75
4a	Ts	H	2.5	ZnCl ₂ (5)	84:16	85
4a	Ts	H	3.0	CeCl ₃ (3)	80:20	70
4b	Ts	Me	1.5	ZnCl ₂ (2.5)	83:17	80
4c	Me	Me	1.5	ZnCl ₂ (2.5)	88:12	80

All reactions were conducted at 22 °C in THF.

Interestingly, in the presence of ZnCl₂ at ambient temperature, *N*-tosylate amino **4a**, *N*-methyl-*N*-tosylate amino **4b** or *N,N*-dimethylamino **4c** provided highly comparable asymmetric inductions with good yields. It is important to note that tosylate-derived ketoesters (*R,S*)-**4** are much more stable than the *N,N*-dimethyl counterpart. The ketoester (*R,S*)-**4b** with cyclohexyl Grignard addition provided crude addition products as an oily mixture and required further purification by chromatography. On the other hand, *N*-tosyl ketoester **4a** was crystalline, easy to prepare and the addition product was crystalline. Therefore, the (*R,S*)-**4a** was nominated as the ligand of choice for the optimization process in the preparation of (*S*)-acid **1**. Crude (*R,S,S*)-**10** from the reaction mixture can be crystallized with EtOAc/Hexane to provide >99% de with an overall yield of 55% from (*R,S*)-**4a** (equation 1). The hydrolysis of diastereopure (*R,S,S*)-**10** with NaOH/ MeOH/ H₂O provided enantiopure acid (*S*)-**1** with a recovery of the auxiliary.

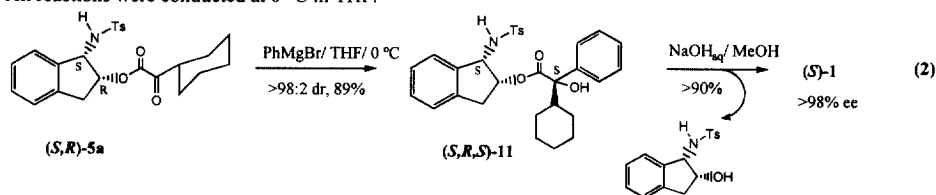


The salient feature of C-1 amine-derived ketoamide **2a** and **3a** with the Grignard addition process was that cyclohexyl-derived ketoamide **2a** required magnesium coordination, and for phenyl derivative **3a**, a zinc coordinated transition state was essential in order to obtain maximum selectivities. Since tosylate derived C-2 phenyl ketoester **4a** behaves in a similar fashion to C-1 phenyl ketoamide **2a**, then verification of the similarities of Grignard addition process to C-1 and C-2 cyclohexyl derivatives required the preparation of cyclohexyl derived-ketoester (*S,R*)-**5a**. As depicted in Table 2, surprisingly comparable additive effects with phenyl Grignard addition for cyclohexyl C-1 amide and C-2 ketoesters were observed. Compound **5a** with phenyl magnesium bromide at 0 °C provided excellent diastereofacialselectivity (>98:2, dr) of (*S,R,S*)-**11** with an 89% yield. In the presence of ZnCl₂, either phenyl lithium or phenyl magnesium bromide gave an essentially non-diastereoselective process. Mild basic hydrolysis of crude (*S,R,S*)-**11** (>98:2, dr) provided >98% ee of (*S*)-acid **1** (equation 2).

Table 2: Diastereoselective Cyclohexyl Grignard addition process with ketoester **5a**

Phenyl M (Equiv.)	Additives (Equiv.)	dr (¹ H-NMR ratios)	Yield %
MgBr (2.5)	ZnCl ₂ (5)	52:48	85
MgBr (2.5)	ZnCl ₂ (2.5)	50:50	85
MgBr (2.5)	---	>98:2	89
Li (2.5)	----	55:45	75
Li (2.5)	ZnCl ₂ (5)	not determine	< 10

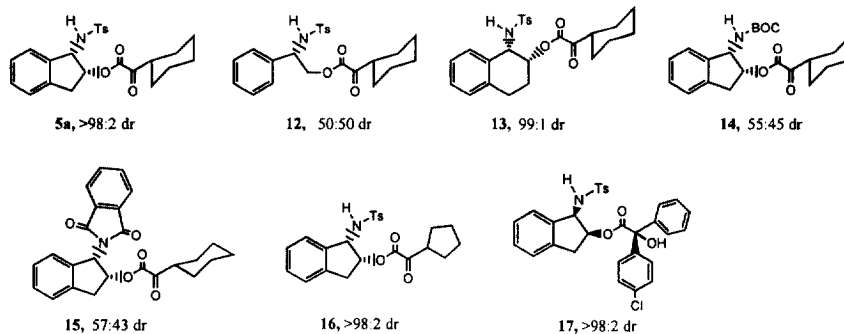
All reactions were conducted at 0 °C in THF.



Encouraged by the outstanding stereocontrolled outcome of the indane-derived tosylate ketoester **5a**, the following conformationally related ketoesters **12** and **13** were prepared. Phenyl glycinol derivative **12** with PhMgBr/THF at 0 °C provided no-selectivity. On the other hand, homologous six-membered analogue **13** gave comparable results (99:1, dr) to the indane system. Surprisingly, substitution of *N*-tosyl group with *N*-BOC (**14**), or phthalimido moiety (**15**) provides essentially no-induction with PhMgBr in THF at 0 °C.

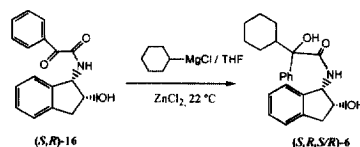
The viability of the high diastereoselective Grignard addition process was extended to other *N*-tosyl ketoesters and Grignards. When cyclopentyl ketoester **16** was exposed to PhMgBr/THF at 0 °C >98:2 diastereoselectivity of the corresponding tertiary hydroxyl ester (>85% yield) was obtained. Ketoester (*R,S*)-**4a** upon treatment with *p*-chlorophenyl magnesium bromide in the presence of ZnCl₂ at 22 °C provided excellent selectivity (>98:2 dr) of **17** in an 87% yield.

In conclusion, we have shown that either C-1 amine or C-2 alcohols of *cis*-aminoindanol or related constrained aminoalcohols can be utilized as a highly defined chiral handle for the preparation of enantiopure tertiary α-hydroxy acids *via* appropriate metal coordinated 1,1-dicarbonyl systems in the Grignard addition process. In our study, *N*-Tosyl-derived ketoesters provides the most expedient avenue to the preparation of optically pure (*S*)-acid **1**. The scope and limitations of generating tertiary alcohol centers of medicinally valuable targets with rigid aminoalcohol derivatives are being explored.



References and Notes

- (1) (a) Carter, P. J. Blob, L.; Audia, V. A.; Dupont, A. C.; McPherson, D. W.; Natalie Jr, K. J.; Rzeszotarski, W. J.; Spagnuolo, C. J.; Waid, P. P.; Kaiser, C. *J. Med. Chem.* **1991**, *34*, 3065. (b) Tambute, A.; Collet, A. *Bull. De La Chim. Fr.* **1984**, 1-2, II-77 (c) Kiesewetter, D. O. *Tetrahedron: Asymmetry* **1993**, *4*, 2183. (d) McPherson, D. W.; Knapp, F. F. *J. Org. Chem.* **1996**, *61*, 8335.
- (2) (a) Caldwell, C. G.; Rupprecht, K. M.; Bondy, S. S.; Davia, A. A. *J. Org. Chem.* **1990**, *55*, 2355. (b) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.
- (3) Yarker, Y. E.; Goa, K. L.; Fitton, A. *Drug Aging* **1995**, *6*, 243.
- (4) (a) Bugno, C.; Colombani, S. M.; Dapporto, P.; Garelli, G.; Giorgi, P.; Subissi, A.; Turbanti, L. *Chirality* **1997**, 721. (b) Atkinson, E. R.; McRitchie, D. D.; Schoer, L. F. *J. Med. Chem.* **1997**, *20*, 1612.
- (5) Cyclohexane based auxiliaries: (a) Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585. (b) Esser, P.; Buschmann, H.; Stork, M.; Scharf, H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1190 and references therein.
- (6) (a) Tamai, Y.; Nakano, T.; Miyano, S. *Chemistry Letters* **1992**, 807. (b) Boireau, G.; Deberly, A.; Abenham, D. *Tetrahedron Lett.* **1988**, 2175. (c) Boireau, G.; Korenova, A.; Deberly, A.; Abenham, D. *Tetrahedron Lett.* **1985**, 4181. (d) Kawanami, Y.; Fujita, I.; Ogawa, S.; Katsuki, T. *Chemistry Letters* **1989**, 2066.
- (7) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.*, **1986**, *108*, 6071. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, S. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1998**, *119*, 7893. (c) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (d) Wood, J. L.; Stoltz, B. M.; Dietrich, H. J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641.
- (8) (a) Senanayake, C. H. *Aldrichimica Acta* **1998**, *31*, 3. (b) Ghosh, A.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937.
- (9) The addition of $C_6H_{11}MgBr$ with or without $ZnCl_2$ to amide (*S,R*)-**16** provided low de (<2%) of **6** Therefore, conformationally locked acetone ketoamide (*S,R*)-**2a** was considered (see reference 9b). (b) Askin, D.; Wallace, J. P.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.



- (10) Cyclohexyl keto acid was prepared by reacting cyclohexyl MgBr with diethyl oxalate to give 80-87% yield of ethyl cyclohexyl keto ester followed by basic hydrolysis. See reference: Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Syn. Comm.* **1981**, 943.
- (11) (a) The major by-products were reduced forms of **2a**, and the structures were established by $NaBH_4$ reduction of (*S,R*)-**2a**. Recently Corey reported that isopropyl MgBr instead of addition to carbonyl group reduction was observed. See Corey, E. J.; Li, W.; Nagamitsu. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1677. (b) THF was the solvent of choice. For example, toluene and dioxane provided 60:40 dr and 80:20 dr respectively.
- (12) (a) Zheng, N.; Armstrong, J. D.; McWilliams, C.; Volante, R.P. *Tetrahedron Lett.* **1997**, *38*, 2817. (b) Kress, H. M.; Yang, C.; Yasuda, N.; Grabowski, E. J. *J. Tetrahedron Lett.* **1997**, *38*, 2633.
- (13) (a) Absolute stereochemistry was predicated by comparison to known rotations^{13b} and enantiomeric excesses were determined by Chiralpak AS. (b) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. (C)*. **1968**, 1693. The rotation of (*S*)-**1** is Lit. $[\alpha]_D^{25} = +22.6^\circ$ (EtOH) and synthetic $[\alpha]_D^{25} = +25.8^\circ$ (EtOH, c=1).
- (14) (a) Ghosh, A.; Onishi, M. *J. Amer. Chem. Soc.* **1996**, *118*, 2527. (b) Ghosh, A.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 6811.