ORGANIC LETTERS

2004
Vol. 6, No. 13
2173−2176

Asymmetric Aminolysis of Aromatic Epoxides: A Facile Catalytic Enantioselective Synthesis of *anti*-β-Amino Alcohols

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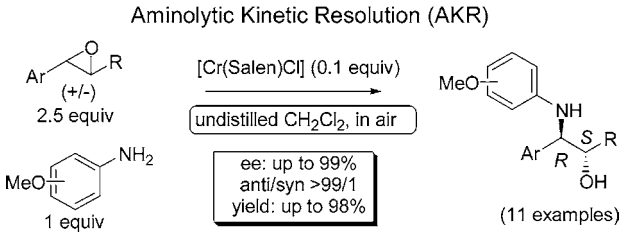
Received April 7, 2004

ABSTRACT



The first asymmetric aminolysis of *trans*-aromatic epoxides with anilines is described. The process affords enantioenriched *anti*-β-amino alcohols in up to 99% ee. The complete regio- and diastereoselectivity observed uses commercially available [Cr(Salen)Cl] as a Lewis acid catalyst and in combination with a very simple experimental procedure renders the present reaction a facile and practical tool for the synthesis of chiral nonracemic *anti*-β-amino alcohols.

Chiral β-amino alcohol units are found in many biologically active compounds and chiral auxiliaries/ligands that are used in asymmetric synthesis.[1] Several powerful methods exist for their catalytic enantioselective syntheses, the foremost of which are the Sharpless' osmium-catalyzed amino-hydroxylation (AA) of olefins[2] and the direct addition of α-hydroxy ketones to imines (Mannich-type reaction).[3] Currently these methods provide the most useful entry to highly enantioenriched *syn*-amino alcohols. By way of contrast, only two reports on the direct catalytic asymmetric synthesis of *anti*-β-amino alcohols have been published.[4] Both methods are based on the catalytic Mannich-type reaction and show excellent enantioselectivity. However, the particular nucleophiles used and the moderate diastereoselectivity observed, in some cases, impose some limitations on their synthetic utility.

A direct and practical approach to β-amino alcohols is the ring opening of 1,2-disubstituted epoxides using amines as the nucleophile.[5] Considering that this type of reaction is usually *anti*-stereospecific, a regio- and enantioselective aminolysis of *trans*-epoxides would constitute a useful

(1) For reviews on the asymmetric synthesis and use of vicinal amino alcohols, see: (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C. Eds.; Wiley-VCH: Weinheim, 1998; p 243.

(2) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Review: O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326.

(3) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338.

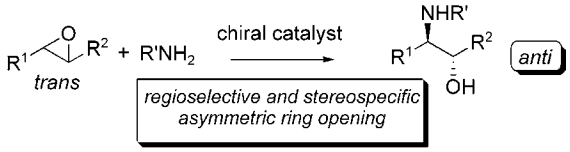
(4) (a) Kobayashi, S.; Hishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (b) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712.

(5) For examples about regioselective aminolysis of 1,2-disubstituted epoxides, see: (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1994**, *59*, 4131.

10.1021/ol049372t CCC: $27.50
Published on Web 05/22/2004

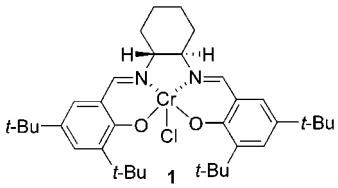
method for the catalytic asymmetric preparation of *anti*-β-amino alcohols with complete control of diastereoselectivity (Scheme 1). Notwithstanding this, no reports employing this

Scheme 1. Asymmetric Aminolysis of *trans*-1,2-Disubstituted Epoxides Providing *anti*-β-Amino Alcohols



strategy have appeared in the literature, probably as a consequence of difficulties in regiocontrol.[6,7]

Herein, we present the first highly regio-, diastereo-, and enantioselective aminolysis of racemic *trans*-1,2-disubstituted aromatic epoxides with anilines catalyzed by the commercially available [Cr(Salen)Cl] complex **1**. The method provides facile and practical access to chiral nonracemic *anti*-β-amino alcohols. The methodology is also effective for the desymmetrization of *meso*-epoxides to obtain highly enantioenriched *syn*-β-amino alcohols.



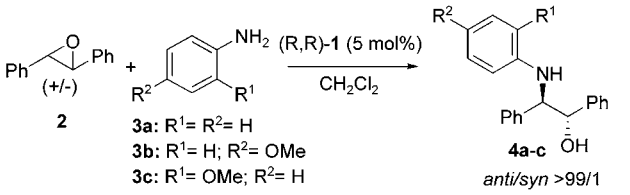
Considering the high selectivities observed in different asymmetric ring-opening reactions catalyzed by [Cr(Salen)Cl] complex **1**,[8] we initially tested the reaction of racemic *trans*-stilbene oxide **2** (2 equiv) with aniline **3a** (1 equiv) using catalyst **1** (0.1 equiv) in CH_2Cl_2 (Table 1). The reaction proceeded smoothly at room temperature, providing a high yield of the desired amino alcohol adduct **4a** with complete *anti*-selectivity and good enantiocontrol (86% ee, entry 1).[9]

Generally, the stereoselectivity of the kinetic resolution displays a strong temperature dependence.[10] Performing the reaction at −10 °C affords **4a** with excellent enantioselectivity (97% ee, entry 2). The reaction can also be performed under more user-friendly conditions by mixing the air-stable catalyst **1** and the reagents in undistilled CH_2Cl_2, without any precautions to exclude moisture. Under these conditions a slight decrease in catalytic activity is observed, but the amino alcohol **4a** is generated in enantiomerically pure form (s = selectivity factor = 268, ee > 99%, entry 3).[11] The optimal balance between reactivity and selectivity is achieved by carrying out the reaction at 0 °C in the open air using an excess of **2** (2.5 equiv, entry 4).

Another crucial requirement for a simple and synthetically useful preparation of chiral *anti*-β-amino alcohols is the use of an easily removable *N*-protecting group. Indeed, the use of *p*- and *o*-anisidine **3b** and **3c** provides the corresponding *N*-aryl amino alcohols **4b** and **4c**, respectively, which can be efficiently deprotected by oxidative dearylation without erosion of stereochemical integrity.[12] Although **3b** displayed a selectivity higher than that of **3c** in the room-temperature reaction (s = 33 to 26, respectively, entries 5 and 7), the high reactivity of *o*-anisidine **3c** allowed the aminolysis of *trans*-stilbene oxide **2** to be run at −10 °C. Under these conditions, the *anti*-β-amino alcohol **4c** was isolated in very high yield and enantioselectivity (entry 8).

The scope of the present asymmetric aminolytic kinetic resolution (AKR) was demonstrated by the reaction of

Table 1. Asymmetric Aminolysis of *trans*-Stilbene Oxide **2** with Anilines Catalyzed by [Cr(Salen)Cl] Complex 1[a,b]



entry	3	T[c] (°C)	t (h)	yield (%)[d]	ee of **4** (%)[e]	ee of **2** (%)[f]	s[g]
1	**a**	rt	18	91	86	80	28
2	**a**	−10	36	54	97	42	93
3[h]	**a**	−10	36	47	>99	30	268
4[h,i]	**a**	0	36	92	93	55	47
5[h]	**b**	rt	18	89	88	80	33
6[h,i]	**b**	0	24	60	93		37
7[h]	**c**	rt	12	98	83	81	26
8[h,i]	**c**	−10	24	93	94		57

[a] Experimental conditions (0.2 mmol scale): reactions run in 2 M CH_2Cl_2 under argon atmosphere using a 2:1 ratio of **2** to **3** and 5 mol % of catalyst **1** relative to racemic epoxide. [b] The complete *anti*-selectivity was determined by ^{1}H NMR analysis on the crude mixture. [c] rt = room temperature. [d] Yield of isolated product based on anilines **3**. [e] The ee values were determined by HPLC on a Chiralpak AD-H column. [f] The unreacted (*R*,*R*)-(+)-**2** was completely recovered after chromatography. [g] Selectivity factor; see ref 11 for details. [h] Performed under aerobic atmosphere in undistilled CH_2Cl_2. [i] 2.5 equiv of **2** was used.

(6) Moderate enantioselective ring opening with anilines has been reported only with *meso*-epoxides; see: (a) Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747. (b) Sekar, G.; Kamble, R. M.; Singh, V. K. *Tetrahedron: Asymmetry* **1999**, *10*, 3663.

(7) Highly enantioselective ring opening with azide has been reported only with *meso*- and terminal epoxides. *meso*-Epoxides, see: (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. Terminal epoxides, see: (c) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. Review: (d) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis I*−*III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 35.

(8) (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 84. For a review, see: (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. See also refs 7a and 7c.

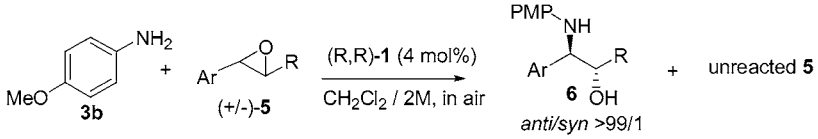
(9) The use of different chiral catalysts (e.g., Co(III)-(Salen) complexes) and aliphatic amines (e.g., pyrrolidine) resulted in no reaction.

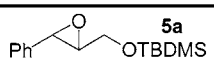
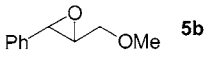
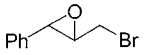
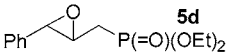
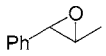
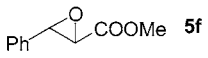
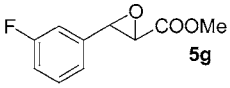
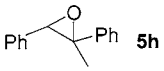
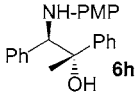
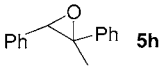
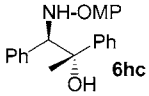
(10) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(11) The selectivity factors s were calculated using the equation $s = \ln[1 - c(1 + \text{ee})]/\ln[1 - c(1 - \text{ee})]$, where ee is the enantiomeric excess of the amino alcohol product and c is the conversion; see Supporting Information for details.

(12) (a) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131. (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

Table 2. Aminolytic Kinetic Resolution (AKR) of Aromatic *trans*-Epoxides[a,b]



entry	(+/-)-**5**	*T* (°C)	t (h)	product **6**	yield (%)[c]	ee of **6** (%)[d]	ee of **5** (%)[e]	*s*[f]
1	 **5a**	-20	48	**6a**	86	86	45	21
2	 **5b**	0	24	**6b**	93	82	48	16
3	 **5c**	0	24	**6c**	95	86	53	22
4	 **5d**	0	48	**6d**	90	77	-	12
5	 **5e**	0	48	**6e**	72	82	33	14
6	 **5f**	rt	24	**6f**	93	85	51	20
7	 **5g**	rt	36	**6g**	98	80	52	15
8	 **5h**	rt	144	 **6h**	44	81	16	11
9[g]	 **5h**	rt	72	 **6hc**	94	74	41	10

[a] Experimental conditions (0.2 mmol scale): open-air reactions run in undistilled CH_2Cl_2 (2 M) using a 2.5:1 ratio of **5** to **3b** and 4 mol % of catalyst **1** relative to racemic epoxides. [b] The complete regio- and *anti*-diastereoselectivity was determined by ^{1}H NMR analysis on the crude mixture; PMP = *p*-methoxy phenyl, OMP = *o*-methoxy phenyl. [c] Yield of isolated product based on **3b**. [d] The ee values were determined by HPLC on Chiralpak AD-H or AS-H columns. [e] The unreacted epoxides were completely recovered after chromatography. [f] Selectivity factor; see ref 11 for details. [g] Performed with *o*-anisidine **3c** to give product 1-(2-methoxy-phenylamino)-1,2-diphenyl-propan-2-ol **6hc**.

various aromatic epoxides (**5a**−**h**) with *p*-anisidine **3b**; the results are reported in Table 2. Although regiocontrol is generally difficult to achieve in the ring opening of 1,2-disubstituted oxiranes, the asymmetric aminolysis of aromatic epoxides with anilines catalyzed by **1** proceeds with complete regioselectivity for the benzylic carbon.[13] Racemic *trans*-1,2-disubstituted aromatic epoxides **5a**−**h** with different substituents in the 2-position or with a fluorine on the aromatic ring (entry 7), all undergo asymmetric aminolysis smoothly providing *anti*-amino alcohols **6** with complete regio- and diastereoselectivity[14] and in good ee (up to 86%).[15]

The presence of coordinating functional groups does not appear to affect the catalytic activity of the system. In particular, the tolerance of Lewis basic functionality such as a phosphonate group allowed the AKR of epoxide **5d** to obtain optically active *anti*-γ-amino-β-hydroxy phosphonate **6d** in high yield and good enantioselectivity (entry 4). Such molecules are of interest as potential phosphate mimics that are resistant to phosphatase hydrolysis.[16] Noteworthy also was the reaction of 1,2,2′-trisubstituted epoxide **5h**, which allowed a quaternary and a secondary carbon stereocenter to be set with complete *anti*-selectivity and good enantiomeric excess, although with a low reaction rate (entry 8). The use of *o*-anisidine **3c** ensured completion of the reaction after 72 h with a slight erosion of the enantioselectivity (entry 9).

The [Cr(Salen)Cl]-catalyzed asymmetric aminolysis was also effective for the desymmetrization of *meso*-stilbene oxide **7** with anilines **3a**−**c**, which afforded the corresponding *syn*-amino alcohols **8** with complete diastereocontrol and high enantioselectivity (Table 3).[17] Interestingly, the use of a catalytic amount of Et_3N as additive dramatically increased

(13) It has been shown that an aromatic substituent on the oxirane ring usually promotes the ring opening on the adjacent carbon: Jaime, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139. For a similar regioselectivity in [Cr(Salen)Cl]-catalyzed kinetic resolution of 1,2-disubstituted aromatic epoxides, see ref 8a.

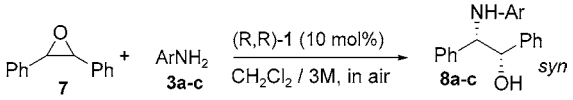
(14) In all cases, only the *anti*-diastereomer and a single regioisomer was detected by NMR and HPLC analysis. The relative stereochemistry was established through NOE studies on the corresponding cyclic carbamates; see Supporting Information for details.

(15) The absolute configuration of **4b** was established after conversion in the corresponding cyclic carbamate and subsequent CAN-promoted dearylation and by comparison of the optical rotation with an authentic sample. For products **6** the absolute configuration was assigned by analogy; see Supporting Information for details.

(16) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379 and references therein.

(17) The AKR of *cis*-1,2-disubstituted aromatic epoxides (i.e., naphthalene oxide and *cis*-β-methyl-styrene oxide) afforded the *syn*-β-amino alcohols with complete regio- and diastereocontrol but in low enantiomeric excess (less than 40% ee).

Table 3. Asymmetric Aminolysis of *meso*-Stilbene Oxide[a,b]



entry	**3**	additive	*t* (h)	yield (%)[c]	ee (%)[d]
1	**a**	none	20	95	76
2	**a**	Et_3N[e]	40	98	90[f]
3	**b**	Et_3N[e]	40	82	82
4	**c**	Et_3N[e]	36	91	80

[a] Experimental conditions (0.2 mmol scale): open-air reactions run at rt in undistilled CH_2Cl_2 (3 M) using a 1.2:1 ratio of **3** to **7** and 10 mol % of catalyst **1**. [b] The complete *syn*-selectivity was determined by ^1H NMR analysis on the crude mixture. [c] Yield of isolated product. [d] The ee values were determined by HPLC on Chiralpak AD-H or AS-H columns. [e] 11 mol % of Et_3N was added. [f] The (*S*,*S*) absolute configuration was established by comparison of the optical rotation with an authentic sample; see Supporting Information for details.

the enantioselectivity (from 76% to 90% ee, entries 1 and 2) but caused a moderate loss of reactivity.

Probing catalyst systems for a nonlinear relationship between product enantioselectivity and catalyst enantiopurity is now commonly being used as a mechanistic tool in asymmetric catalysis. A positive nonlinear effect [(+)-NLE] was found for the asymmetric aminolysis of *meso*-stilbene oxide **7** with aniline **3a**;[18] these results suggest that, probably, more than one molecule of the [Cr(Salen)Cl] catalyst **1** is involved in the transition state of the enantiodifferentiating step.[19] Further studies to elucidate the reaction mechanism and to expand the scope of the asymmetric AKR of epoxides are ongoing in our laboratories.

In summary, we have developed the first highly regio-, diastereo-, and enantioselective aminolysis of *trans*-1,2-disubstituted aromatic epoxides affording *anti*-β-amino alcohols (yield up to 98%, dr > 99/1, ee up to > 99%). The observed complete *anti*-selectivity, the commercial availability of the catalyst **1**, and the use of a removable *N*-protecting group in combination with a very simple procedure render the present reaction a facile and practical tool for the synthesis of enantioenriched *anti*-β-amino alcohols.

Acknowledgment. Work carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni" supported by MIUR, Rome, and FIRB National Project "Progettazione, preparazione e valutazione farmacologica di nuove molecole organiche quali potenziali farmaci innovativi".

Supporting Information Available: Experimental procedures and spectral data for all new amino alcohol compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049372T

(18) Plot of catalyst ee vs product ee is provided in Supporting Information.

(19) For similar observations about NLE in other [Cr(Salen)Cl]-catalyzed asymmetric ring opening of epoxides, see: (a) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924. For an excellent review about nonlinear effects, see: (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.