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Asymmetric Catalytic Synthesis of Enantiopure *N*-Protected 1,2-Amino Alcohols

Giuseppe Bartoli,* Marcella Bosco, Armando Carlone, Manuela Locatelli, Paolo Melchiorre,* and Letizia Sambri

Department of Organic Chemistry "A. Mangini", University of Bologna v.le Risorgimento 4, 40136 Bologna, Italy

giuseppe.bartoli@unibo.it; pm@ms.fci.unibo.it

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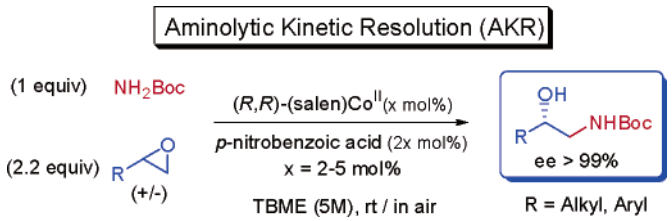
ABSTRACT



The asymmetric aminolytic kinetic resolution (AKR) of racemic terminal epoxides using carbamates as the nucleophile catalyzed by (salen)Co^{III} complex provides a practical and straightforward method for the synthesis of both aliphatic and aromatic *N*-Boc- or *N*-Cbz-protected 1,2-amino alcohols in almost enantiomerically pure form (ee ≥ 99%). The AKR uses an easily accessible catalyst and inexpensive starting materials, and the reactions are conveniently carried out at room temperature under an air atmosphere.

The biological importance of vicinal amino alcohols continues to stimulate the development of new effective methods for the synthesis of these compounds in enantiomerically pure form.[1] Among the catalytic asymmetric methods available,[2−4] the ring opening of racemic terminal epoxides catalyzed by chiral (salen)Cr-Cl complex **1** with $TMSN_3$ followed by reduction of the azido moiety constitutes an ingenious route to 1-amino-2-ols.[3]

An intriguing alternative approach lies in the development of an enantioselective kinetic resolution based on the use of carbamates as the nitrogen source. Such a strategy would constitute a highly practical and useful tool for the direct preparation of optically active 1,2-amino alcohols bearing easily removable *N*-protecting groups. This aim represents an ambitious challenge from a synthetical standpoint as, surprisingly, no effective methods to open epoxides with carbamates have been devised to date.[5]

We report here the first asymmetric aminolytic kinetic resolution (AKR) of racemic terminal epoxides using carbamates as the nucleophile catalyzed by chiral (salen)Co^{III} complexes to afford *N*-Cbz- or *N*-Boc-protected 1-amino-2-ols in almost enantiomerically pure form (ee ≥ 99%, Scheme 1). The presented AKR shows extraordinary enan-

(1) (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) While chiral 2-amino-1-ols are readily accessible by reduction of α-amino acids, asymmetric routes to 1,2-amino alcohols with a stereogenic hydroxy-substituted carbon center are relatively uncommon. For some leading references, see: (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (c) Effenberger, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1515. (d) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510. (e) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241.

(3) (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. Review: (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(4) For carbamate-based aminohydroxylation of olefins, see: Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813.

(5) During the manuscript preparation, an interesting opening of enantiopure terminal epoxides with *N*-Boc-2-nitrobenzenesulfonamide was reported: Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952.

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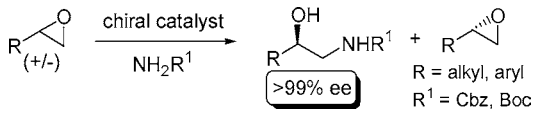
Scheme 1. Carbamate-Based Asymmetric AKR of Racemic Terminal Epoxides



tioselectivity even at room temperature (s = selectivity factor exceeding 3000 for some substrates), using a low loading (2−5 mol %) of a readily available catalyst, a minimum amount of solvent under an air atmosphere, and inexpensive, easily handled starting materials. Noteworthy, and at variance with analogous kinetic resolution procedures,[3] complete regioselectivity for the terminal position is achieved not only with aliphatic epoxides but also with aromatic derivatives.

Given the high selectivities obtained in the recently reported asymmetric aminolysis of *trans*-aromatic epoxides with anilines catalyzed by (salen)Cr-Cl complex **1**,[6] we sought to extend the use of this catalyst to the carbamate-based AKR of terminal epoxides. However, reaction of (±)-glycidyl phenyl ether **4** (2.2 equiv) with *tert*-butyl carbamate **3a** (1 equiv) in the presence of complex **1** (0.016 equiv, 1.5 mol % relative to racemic epoxide) in CH_2Cl_2 led to no conversion (entry 1, Table 1). Thus, we turned our attention to the Jacobsen's (salen)Co^{III}−OAc complex **2a** that had been demonstrated to be a highly effective and enantioselective catalyst for the hydrolytic kinetic resolution of racemic terminal epoxides.[7] Use of the acetate complex **2a**, prepared by aerobic oxidation of the catalytically inactive (salen)Co^{II} complex **2** in the presence of acetic acid, afforded the *N*-Boc-protected amino alcohol **5a** in moderate yield but in very high optical purity (96% ee, entry 3). In situ generation of **2a** under AKR conditions by suspension of **2** in the solvent and addition of HOAc under an aerobic atmosphere resulted in a more reactive system (entry 4).

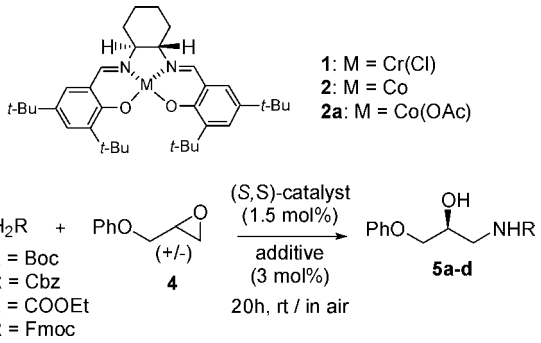
The identity of the counterion[8] for the (salen)Co^{III} catalyst and the reaction solvent proved to be crucial in terms of both reactivity and selectivity: performing the reaction in *tert*-butyl methyl ether (TBME) in the presence of complex **2** (1.5 mol %) and *p*-nitrobenzoic acid (3 mol %) as the oxidizing additive resulted in 85% conversion of **3a** after 20 h and formation of **5a** in enantiomerically pure form (entry 7). The optimized procedure (2 mol % of **2**, 4 mol % of additive, entry 8) afforded enantiopure product **5a** in 99% isolated yield based on carbamate after 24 h at room temperature.[9]

The AKR of **4** is also effective with different nucleophiles such as benzyl carbamate **3b**, urethane **3c** and 9-fluorenyl-methyl carbamate **3d** (entries 9−11). In particular, the reaction of **3b** and **3d** proceeds with very high selectivity (s = selectivity factor = 865 and 610, respectively)[10] although a slight decrease in reactivity is observed. The extension of the AKR strategy to various carbamates represents an important feature from a synthetical standpoint, providing orthogonal sets of easily removable *N*-protecting groups.

The asymmetric AKR catalyzed by (salen)Co^{III} complex displays extraordinary scope, as a wide range of structurally and electronically varied terminal epoxides **6** can be opened with *tert*-butyl carbamate **3a** providing enantiopure *N*-Boc-protected 1,2-amino alcohols **7a**−**i** in high yield and complete regioselectivity for the terminal position; the results are reported in Table 2.

Both linear (entries 1−3) and relatively hindered (entry 4) aliphatic epoxides undergo AKR with extraordinary selectivity. The presence of coordinating functional groups does not appear to affect the efficiency of the system, as

Table 1. Kinetic Resolution of Racemic **4** with Carbamates[a]



entry	3	cat.	additive	solvent	conv (%)[b]	ee[c] (%)	s[d]
1	**a**	**1**	none	CH_2Cl_2	0		
2	**a**	**2**	none	CH_2Cl_2	0		
3	**a**	**2a**	none	CH_2Cl_2	45	96	
4	**a**	**2**	AcOH	CH_2Cl_2	65	96	
5	**a**	**2**	*p*-nitrobenzoic acid	CH_2Cl_2	80	>99	
6	**a**	**2**	*p*-nitrobenzoic acid	THF	65	98	
7	**a**	**2**	*p*-nitrobenzoic acid	TBME	85	>99	
8[e]	**a**	**2**	*p*-nitrobenzoic acid	TBME	>95 (99)[f]	98.9	450
9[g]	**b**	**2**	*p*-nitrobenzoic acid	TBME	95 (93)[f]	99.5	865
10[e]	**c**	**2**	*p*-nitrobenzoic acid	TBME	>95 (97)[f]	99.0	470
11[h]	**d**	**2**	*p*-nitrobenzoic acid	TBME	75 (67)[f]	99.5	610

[a] Experimental conditions (1 mmol scale): open-air reactions run in undistilled solvent (5 M) for 20 h using a 2.2:1 ratio of **4** to **3** and 1.5 mol % of catalyst relative to racemic epoxide. [b] Determined by ^{1}H NMR of the crude mixture and based on consumption of **3**. [c] The ee values were determined by HPLC on Chiralpak AD-H column. [d] Selectivity factor; see ref 10 for details. [e] 2 mol % of **2**, 4 mol % of additive, and 24 h reaction time. [f] Number in parentheses indicates yield of isolated product based on **3**. [g] 4 mol % of **2**, 8 mol % of additive, and 24 h reaction time. [h] 4 mol % of **2**, 8 mol % of additive, and 50 h reaction time.

(6) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173.

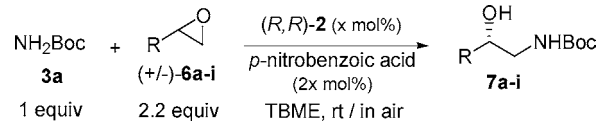
(7) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(8) See footnote 24 in ref 7b. See also ref 15.

(9) Small amounts of 1,2-diol and *p*-nitrobenzoate addition product were also generated, presumably as a result of adventitious water and counterion addition. For the latter path, see: Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773. The use of molecular sieves to inhibit diol production had no significant effects.

(10) 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 (set to equal the isolated yield). Given the high selectivity of AKR ($s > 400$), the absolute magnitudes of s factors are certainly lacking precision; see the Supporting Information for details.

Table 2. AKR of Terminal Epoxides with *tert*-Butyl Carbamate **3a**[a]



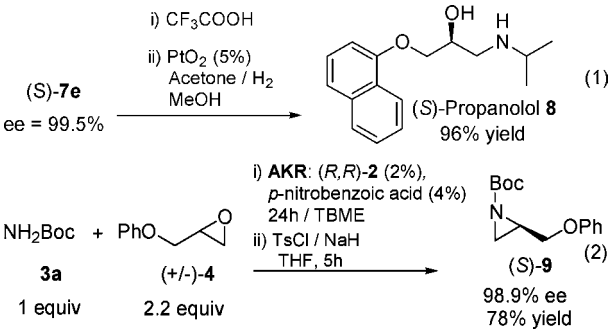
entry	x[b]	R	time (h)	yield[c] (%)	ee[d] (%)	s[e]
1	2	CH_3, **6a**	24	99	99.3	725
2	2	$(CH_2)_3CH_3$, **6b**	24	99	99.2	630
3	2	$(CH_2)_4CH{=}CH_2$, **6c**	24	99	99.7	1700
4	4	*c*-C_6H_{11}, **6d**	24	84	99.9	>3000
5	4	CH_2O(1-naphthyl), **6e**	24	95	99.5	900
6[f]	4	CH_2Cl, **6f**	24	87	99.9	>3000
7	4	C_6H_5, **6g**	36	90	99.9	>3000
8[g]	5	C_6H_5, **6g**	48	52	99.5	540
9	5	*p*-BrC_6H_4, **6h**	48	76	99.8	1690
10	5	*o*-$NO_2C_6H_4$, **6i**	48	62	99.8	1460

[a] Experimental conditions (1 mmol scale): open-air reactions run in undistilled TBME (5 M) using a 2.2:1 ratio of **6**/**3a**. [b] Catalyst loading relative to racemic epoxide. [c] Yield of isolated product based on **3a**. [d] The ee values of **7** or of the corresponding *O*-benzyl derivatives were determined by HPLC on Chiralpak AD-H or AS-H columns; see the Supporting Information for details. [e] Selectivity factor; see ref 10 for details. [f] Performed at 0 °C using benzyl carbamate **3b**. [g] Performed using carbamate **3b** to afford *N*-Cbz-protected amino alcohol **7gb**.

both 1-naphthyl glycidyl ether and epichlorohydrin afford the corresponding 1-amino-2-ols **7e** and **7f** in good yield and in enantiomerically pure form (entries 5 and 6).

The viability of the AKR strategy is illustrated by the practical synthesis of enantiopure (*S*)-propanolol **8** (Scheme 2, eq 1), a widely used anti-hypertensive drug (*β*-blocker).[11]

Scheme 2. Practical Utility of the AKR Strategy



Moreover, given the versatility of the *N*-protected aminol products, a wide range of synthetically useful transformations can be envisaged. For example, the highly enantioenriched *N*-Boc protected aziridine **9** can be easily synthesized in good yield (78% based on **3a**) starting from racemic epoxide **4** using a practical one-pot procedure (Scheme 2, eq 2).

(11) Klunder J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710.

Noteworthy, the AKR of styrene oxide **6g** proceeds with complete regioselectivity for the terminal position, affording the enantiopure *N*-Boc-protected aminol in good yield (entry 7). The use of benzyl carbamate **3b** results in a lower reactivity (entry 8), although the high regio- and enantiocontrol of the process is preserved. Various substituted styrene oxide derivatives display similar behavior, generating only one isomer in enantiomerically pure form (entries 9 and 10). These results add significant importance to the AKR strategy since aromatic epoxides represent a challenging class of substrates for kinetic resolutions as conflicting steric and electronic factors generally affect the regioselectivity in the ring opening of terminal epoxides.[12] Moreover, 1-aryl-2-amino ethanol isomers, precursors of pharmaceutically significant compounds,[13] are difficult to achieve by carbamate-based asymmetric aminohydroxylation of olefins.[14]

The exceptionally high levels of selectivity observed in the AKR are consistent with other highly selective (salen)Co^{III}-catalyzed kinetic resolutions of terminal epoxides in which a peculiar, bimolecular, nearly perfect chiral recognition mechanism is operating.[15] A thorough investigation to elucidate the mechanism of catalysis is underway and will be reported in due course.

In summary, the presented (salen)Co^{III}-catalyzed aminolytic kinetic resolution of racemic terminal epoxides with carbamates provides a general and straightforward method for the synthesis of enantiopure (ee ≥ 99%) *N*-protected 1,2-amino alcohols.[16] Importantly, the AKR uses easily removable *N*-protecting groups, an easily accessible catalyst and inexpensive, easily handled starting materials. The reactions are conveniently carried out at room temperature, under an air atmosphere and with a small amount of catalyst and solvent. All these positive practical features[17] render the AKR a potentially useful method for large-scale applications.

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Supporting Information Available: Experimental procedures, full characterization, and copies of both HPLC analyses and proton spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048322L

(12) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086. See also ref 3a.
(13) For a recent example, see: Nesterenko, V.; Putt, K. S.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 14672.
(14) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207. See also ref 13.
(15) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360. See also ref 12.
(16) Also the unreacted epoxides can be recovered in high ee (>90%).
(17) For practical considerations on kinetic resolution strategy, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth., Catal.* **2001**, *343*, 5.