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Direct Catalytic Synthesis of Enantiopure 5-Substituted Oxazolidinones from Racemic Terminal Epoxides

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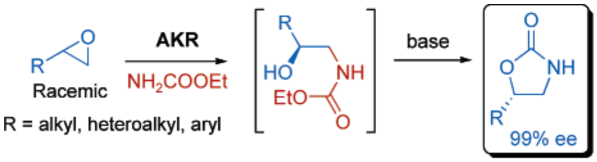
ABSTRACT



AKR = Aminolytic Kinetic Resolution

A venerable scaffold for asymmetric synthesis and drug development, chiral 5-substituted oxazolidinones are obtained in almost enantiomerically pure form (up to 99.9% ee) starting from racemic terminal epoxides. The salient features of this process include the very simple and convenient experimental protocol and the employment of a readily accessible catalyst and inexpensive, easily handled starting materials. An enantioconvergent approach for the total conversion of racemic epoxide into a single stereoisomeric oxazolidinone is also described.

The development of effective asymmetric routes for the synthesis of valuable chiral building blocks in enantiomerically pure form is of pressing current importance, as single-enantiomer small-molecule drugs have a commanding presence in the global pharmaceutical landscape.[1] Chiral 5-substituted oxazolidinones represent a privileged structural motif by virtue of the fact that they are widely used in organic synthesis as chiral auxiliaries,[2] and many of them have relevance from a pharmaceutical point of view because of their interesting biological activity.[3] Such a scaffold is present in a new class of synthetic antimicrobial agents that are extremely effective against Gram-positive bacteria, many strains of which are resistant to traditional antibiotics.[3a] Importantly, the absolute configuration at C-5 of the key 5-substituted oxazolidinone pharmacophore is essential for antibacterial activity. Therefore, simple catalytic methods that allow the rapid generation of collections of enantiopure oxazolidinones would have a significant enabling impact on drug discovery and development.

Chiral 5-substituted oxazolidinones are generally accessible by indirect routes involving preparation of enantioenriched 1-amino-2-ols and subsequent cyclization,[4] but asymmetric entries into these nonproteinogenic derived amino alcohols are relatively uncommon.[5] We report here a direct catalytic synthesis of highly enantioenriched 5-substituted oxazolidinones (up to 99.9% ee) starting from inexpensive racemic terminal epoxides. The presented methodology provides a very simple and practical tool for synthesizing a plurality of structurally and electronically varied 5-substituted oxazolidinones in almost enantiomerically pure form.

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(1) Worldwide sales of single-enantiomer drugs reached more than $159 billion in 2002, and are expected to grow soon. See: Rouhi, A. M. *Chem. Eng. News* **2003**, *81*, 45.

(2) (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3.

(3) (a) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010 and references therein. (b) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529.

(4) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(5) For some leading references, see: (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (b) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510. (c) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241.

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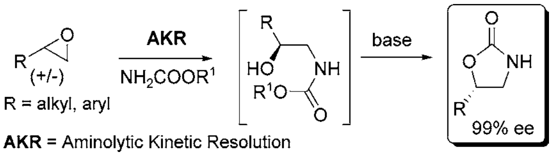
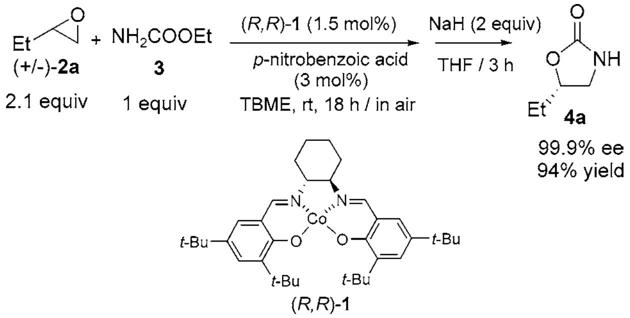
In our recent studies, we discovered that the asymmetric carbamate-based aminolytic kinetic resolution (AKR) of racemic terminal epoxides catalyzed by Jacobsen's (salen)-Co^{III} chiral complex affords *N*-Cbz or *N*-Boc protected 1-amino-2-ols in almost enantiomerically pure form.[6] Considering the synthetic versatility of the carbamate moiety, we envisioned the AKR strategy as a valuable platform for the development of a direct synthesis of enantiopure 5-substituted oxazolidinones.[7] A one-pot reaction sequence could be envisaged wherein a highly selective ring opening of racemic epoxides with carbamate would be followed by an efficient base-mediated in situ cyclization of the aminol intermediate (Scheme 1).

Scheme 1. AKR-Based Strategy for a Direct Conversion of Racemic Terminal Epoxides to Enantiopure 5-Substituted Oxazolidinones



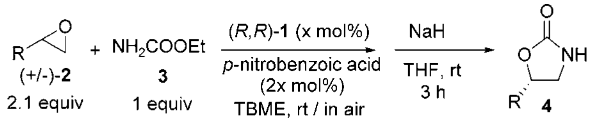
Proof-of-principle was provided through the direct formation of oxazolidinone **4a** starting from racemic 1,2-epoxybutane **2a** (Scheme 2). The effective catalyst for the AKR step was a (salen)Co^{III} complex generated in situ by aerobic oxidation of the catalytically inactive (salen)Co^{II} complex **1** in the presence of *p*-nitrobenzoic acid as the oxidizing agent.[8] A screening among a series of bases has envisaged sodium hydride as the best candidate to promote the subsequent cyclization step. We found that the oxazolidinone formation was clean and fast when using an intermediate bearing an ethyl carbamate moiety.[9] The optimal procedure was achieved by simply mixing (±)-**2a** (2.1 equiv) and urethane **3** (1 equiv) at room temperature with the commercially available complex **1** (1.5 mol % relative to racemic epoxides) and *p*-nitrobenzoic acid (3 mol %) in undistilled *tert*-butyl methyl ether (TBME). Upon completion of the AKR reaction, the sequential one-pot addition of NaH (2 equiv) and THF afforded the enantiopure oxazolidinone **4a** (ee >99%) in 94% isolated yield based on **3**.

Scheme 2. Direct Catalytic Synthesis of Enantiopure Oxazolidinone **4a** from Racemic **2a**



We then sought to test the generality of the presented methodology. A range of 5-substituted oxazolidinones bearing aliphatic substituents was accessed in enantiopure form starting from linear and relatively hindered racemic terminal epoxides (Table 1, entries 1−4). The presence of coordinating functional groups did not appear to affect the efficiency of the system, as ether-containing epoxides **2f**−**g** afforded the corresponding enantiopure oxazolidinones in high yields (entries 5 and 6). Noteworthy, enantiopure *O*-protected oxazolidinone **4g** was reported to be a key intermediate for the synthesis of linezolid (Scheme 3),[10] the first clinically useful oxazolidinone antibacterial agent.[3a]

Table 1. From Racemic Terminal Epoxides to Enantiopure Oxazolidinones[a]

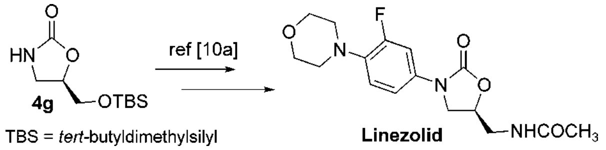


entry	x[b]	R	product	time (h)[c]	yield[d] (%)	ee[e] (%)
1	1.5	CH_3	**4b**	18	97	>99
2	1.5	$(CH_2)_4CH{=}CH_2$	**4c**	18	95	>99
3[f]	4	$c\text{-}C_6H_{11}$	**4d**	40	97	>99
4	4	CH_2Ph	**4e**	40	98	>99
5	2	$CH_2O(i\text{-}Pr)$	**4f**	24	90	>99
6[g]	3	CH_2OTBS	**4g**	36	93	99
7[f]	4	Ph	**4h**	40	90	>99
8[f,h]	5	$4\text{-}ClC_6H_4$	**4i**	60	98	98.7
9[f]	5	$3\text{-}ClC_6H_4$	**4j**	60	97	96.5
10[f]	5	$3\text{-}NO_2C_6H_4$	**4k**	60	94	97.5

[a] Experimental conditions (1 mmol scale): open-air reactions run in undistilled TBME (6 M), using a 2.1:1 ratio of **2** to **3**. The cyclization was performed by subsequent one-pot addition of THF (0.1 M) and 2 equiv of NaH. [b] Catalyst loading relative to racemic epoxide. [c] Reaction time of AKR. [d] Yield of isolated oxazolidinone **4** based on urethane **3**. [e] The ee values of **4** or of the corresponding *N*-benzoyl derivatives were determined by HPLC or by GC analyses on commercially available chiral stationary phases. See the Supporting Information for details. [f] Performed with 2.2 equiv of epoxide. [g] TBS = *tert*-butyldimethylsilyl. [h] Cyclization step: upon completion of the AKR, THF (0.1 M) and 2 equiv of *t*-BuOK were added (rt, 16 h).

Aryl-substituted oxazolidinones were also synthesized in high enantiomeric excess starting from various substituted

Scheme 3



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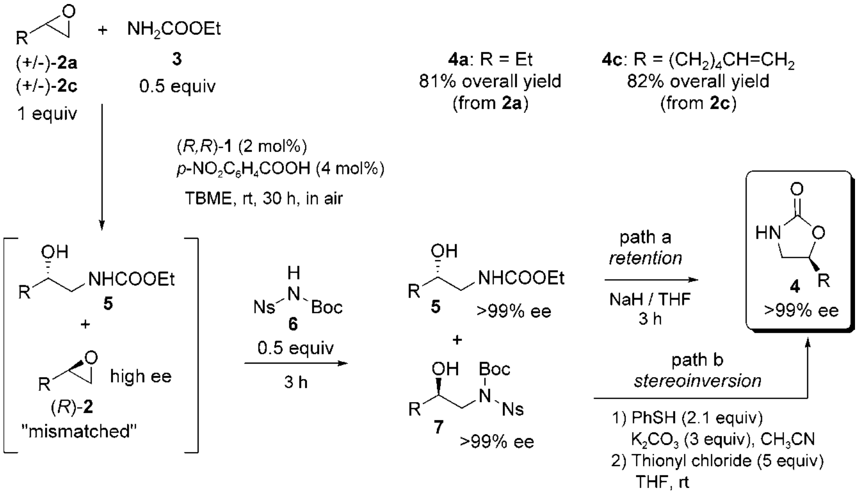
(6) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973.

(7) For a direct preparation of 4,5-disubstituted oxazolidinones based on asymmetric aminohydroxylation of olefins, see: Barta, N. S.; Sidler, D. R.; Somerville, K. B.; Weissman, S. A.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2821.

Scheme 4. Enantioconvergent Strategy for the Total Conversion of Racemic Epoxide into a Single Stereoisomeric Oxazolidinone[a]



[a] Boc = *tert*-butoxycarbonyl, Ns = 2-nitrobenzensulfonyl.

styrene oxide derivatives (entries 7−10). It is noteworthy that, despite the fact that the ring opening of aromatic epoxides might be plagued by conflicting steric and electronic factors, the AKR step proceeded with complete regioselectivity for the terminal position, thus providing only the 5-substituted isomers **4h**−**k**.[11]

The impressive results obtained in the presented direct synthesis of oxazolidinones stem from the extraordinary scope and selectivity of the AKR strategy.[12] However, kinetic resolutions have the significant disadvantage of a 50% maximum yield. To overcome this limitation, we sought to use the unreacted epoxide through a separate pathway in an enantioconvergent reaction sequence (Scheme 4).[13] The exceptionally high selectivity of the (*R*,*R*)-(salen)Co-catalyzed AKR allowed the formation of both the aminol product **5** and the "mismatched" epoxide (*R*)-**2** in very high optical purity at 50% conversion.[14] Recently, it was reported that the same catalyst was able to promote the nonselective ring-opening of terminal epoxides with a different nitrogen-based nucleophile such as *N*-Boc sulfonamide **6**.[15] These considerations suggested the possibility for the (salen)Co^{III} complex to catalyze an highly stereoselective AKR step with urethane **3** and a sequential one-pot stereospecific ring-opening of the enantioenriched "mismatched" epoxide with **6**. The pseudo-enantiomeric aminol products **5** and **7** can be easily isolated by chromatography and separately cyclized via a retention (path a, Scheme 4) and an inversion (path b)[16] pathway, respectively, affording the same enantiomer of the enantiopure oxazolidinone **4** (ee 99%) in high overall yield starting from racemic epoxide. Proof-of-principle for the enantioconvergent strategy was provided through the synthesis of enantiopure oxazolidinones **4a** and **4c**.

In summary, a general, direct, catalytic method for the synthesis of a wide assortment of enantiopure 5-substituted oxazolidinones has been devised. We are hopeful that the ready access to these important building blocks in enantiopure form through a convenient and easy experimental protocol will be useful for the chemical community.

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, full characterization, and copies of both chiral HPLC or GC analyses and proton spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The identity of the counterion for the (salen)Co^{III} catalyst proved to be crucial in terms of both reactivity and selectivity: among different counterions tested (e.g. acetate, tosylate, triflate) 4-nitrobenzoate has been found to provide the best catalyst. For a recent discussion on this topic, see: Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.

[9] The presence of a different group on the carbamate moiety (e.g., *tert*-butyl, benzyl) had a negative effect on the rate and the efficiency of the cyclization step.

[10] (a) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963. See also: (b) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681. For recent advances on *N*-arylation of oxazolidinones, see: (c) Nandakumar, M. V. *Adv. Synth. Catal.* **2004**, *346*, 954. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.

[11] Ring-opening of electron-rich styrene oxide derivatives (e.g., 3-MeOC$_6$H$_4$) with urethane occurred with modest regioselectivity to afford a mixture of isomeric amino alcohol adducts.

[12] For an evaluation of the exceptionally high selectivity of the AKR (selectivity factors exceeding 3000 for selected substrates) see ref 6 and the Supporting Information.

[13] For a review on this topic, see: Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron*: *Asymmetry* **1999**, *10*, 107.

[14] This scenario represents an ideal case and is very rare for a kinetic resolution promoted by a chemo-catalyst. During the AKR, one enantiomer is transformed quickly and the other is unreactive, thus the reaction comes to a standstill at 50% conversion; therefore, over-resolution is not possible.

[15] Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952. As reported, high regiocontrol for the terminal position was achieved only in the ring-opening of aliphatic epoxides with sulfonamide **6**.

[16] Conversion of **7** to oxazolidinone **4** was achieved by sequential deprotection/stereoinversion steps in good overall yield (71−79%, nonoptimized): (1) nosyl deprotection (PhSH/K$_2$CO$_3$/CH$_3$CN); (2) cyclization with stereoinversion (SOCl$_2$/THF), see the Supporting Information for details.