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Chromium catalyzed kinetic resolution of 2,2-disubstituted epoxides

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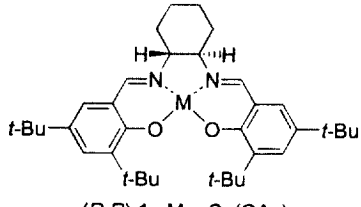
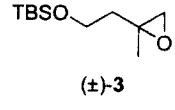
Abstract

Chiral (salen)Cr(III) complex **2** is an efficient catalyst for the kinetic resolution of 2,2-disubstituted epoxides. The scope and limitations of this methodology are described.

Recently, we reported highly effective methods for the asymmetric ring opening of epoxides catalyzed by cobalt complex **1**[1] and chromium complex **2**.[2] In particular, the hydrolytic kinetic resolution (HKR) with catalyst **1** has been shown to provide access to a wide variety of monosubstituted terminal epoxides in >99% ee. We became interested in extending this methodology to 2,2-disubstituted epoxides,[3,4] a particularly challenging substrate class for kinetic resolution, but one that holds special interest since the resolved epoxides could be elaborated readily to valuable optically-active tertiary alcohols.[5] In the context of the total synthesis of taurospongin A, we recently examined the kinetic resolution of epoxide (±)-**3**. While this substrate proved unreactive under HKR conditions with catalyst **1**, the kinetic resolution in the presence of (salen)Cr catalyst **2** and HN_3 proved successful.[6] We have carried out further investigations of the substrate scope for the kinetic resolution of 2,2-disubstituted epoxides catalyzed by (salen)Cr complex **2**, and we described our results herein.



(*R,R*)-**1** : M = Co(OAc)
(*R,R*)-**2** : M = Cr(N_3)



(±)-**3**

Treatment of (±)-**3** with 0.55 equiv. of HN_3 (generated by combining equimolar amounts of $TMSN_3$ and 2-propanol)[7] in TBME in the presence and 2 mol% of catalyst **2** led to complete consumption of

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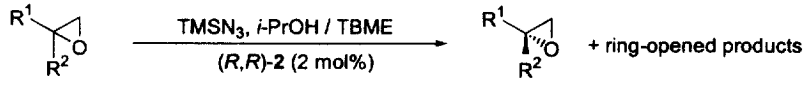
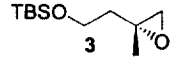
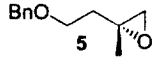
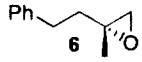
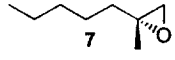
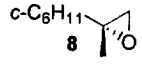
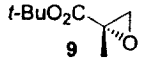
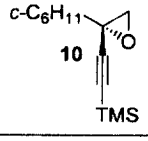
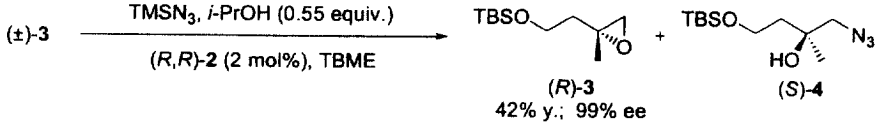
Table 1
Kinetic resolution of 2,2-disubstituted epoxides catalyzed by (*R*,*R*)-**2**



Entry	Epoxide	HN_3 (equiv)[a]	Yield[b]	ee
1	 **3**	0.55	42%	99%[c]
2	 **5**	0.55	44%	95%[d]
3	 **6**	0.60	44%	97%[d]
4	 **7**	0.55	42%	99%[e]
5	 **8**	0.50	46%	98%[e]
6[f]	 **9**	0.55	46%	85%[e]
7[g]	 **10**	0.70	48%	80%[e]

[a] Equivalents of $TMSN_3$ and 2-propanol. [b] Isolated yield of the epoxide based on racemic epoxide. [c] Determined by chiral GC analysis of the corresponding primary methyl ether. [d] Determined by chiral HPLC analysis. [e] Determined by chiral GC analysis. [f] Reaction was performed without additional solvent for 24 h at rt. [g] Reaction was performed without additional solvent for 24 h at rt with 5 mol% of catalyst **2**.

HN_3 within 6 h, with formation of azidoalcohol **4** and recovery of *R*-**3** in 99% ee and 42% yield by flash chromatography (Eq. 1).



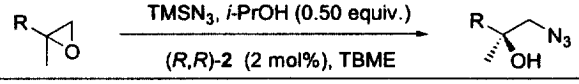
(1)

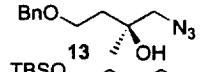
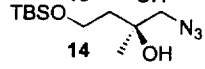
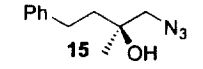
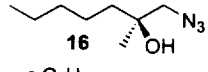
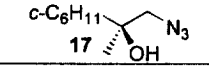
These reaction conditions have proven effective for the preparation of a variety of 2,2-disubstituted epoxides in high enantiomeric excess (Table 1).[8] Epoxides bearing substituents with significantly different steric properties proved to be excellent substrates (e.g. methyl versus cyclohexyl, entry 5). More remarkable, catalyst **2** also proved effective in the resolution of epoxides bearing substituents with similar steric and electronic properties (e.g. methyl versus *n*-pentyl, entry 4). While catalyst **2** efficiently differentiated between methyl groups and alkyl chains, epoxide **11** failed to give good regio- and enantioselectivity. For more sterically demanding epoxides, such as epoxide **12**, no reaction was observed.

11 **12**

The methacrylate derivative **9** displayed only moderate reactivity; however, good levels of conversion

Table 2
Kinetic resolution of 2,2-disubstituted epoxides catalyzed by (*R,R*)-**2**: Formation of azido alcohols



Entry	Azido alcohols	Yield[a]	ee
1	 **13**	46%	93%[b]
2	 **14**	47%	90%[c]
3	 **15**	45%	92%[d]
4	 **16**	44%	95%[e]
5	 **17**	40%	99%[e]

[a] Isolated yield of the azido alcohol based on racemic epoxide. [b] Determined by chiral HPLC analysis. [c]Determined by chiral GC analysis of the corresponding primary methyl ether. [d]Determined by chiral HPLC analysis of the azido *O*-acetate derivative. [e] Determined by chiral GC analysis.

were attainable by performing the reaction in the absence of additional solvent, and the epoxide was recovered in 85% ee (Table 1, entry 6). Although epoxides bearing terminal alkyne substituents proved to be completely unreactive under the reaction conditions, TMS-protected alkynes were acceptable substrates. Thus, kinetic resolution of epoxide **10** afforded the desired enantioenriched epoxide in 48% yield and 80% ee, although 0.7 equiv. of $TMSN_3$ and 2-propanol and 5 mol% of catalyst **2** were required. In the case of substrates **10** and **11**, it was not possible to attain higher enantiomeric excesses in the recovered epoxides simply by extending reaction times or using excess reagents. Although the reasons for this are not yet clear, it may be due to competitive catalyst destruction by HN_3 in the kinetic resolution of these less reactive substrates.

The azido alcohol products of this kinetic resolution are also synthetically valuable chiral building blocks, as they can be derivatized into β-amino tertiary alcohol derivatives.[9] Good regioselectivity was observed with epoxides listed in Table 1, with the expected primary azide products predominating. For example, when epoxide **5** was treated with 0.5 equiv. of $TMSN_3$ and 2-propanol and 2 mol% of catalyst **2**, azido alcohol **13** was produced in 46% yield and 93% ee (Table 2). The regioisomer resulting from an internal attack of the azide was obtained in 4% yield and 20% ee.[10] All attempts to increase either the yield or the enantiomeric excess of the latter product were unsuccessful. Similar results were obtained with other epoxides, with a small amount (4–6%) of the tertiary azide product recovered in low ee in all cases.[11] However, primary azido alcohols **14–17** were obtained in good yield and enantiomeric excess.

The kinetic resolution of 2,2-disubstituted epoxides has considerable potential as a synthetic strategy, given that the resulting enantioenriched epoxides can be elaborated further to afford optically active tertiary alcohols that can be difficult to access otherwise using existing asymmetric methods. The effective resolution of epoxides bearing sterically-similar substituents also provides another example of the remarkable enantiodiscrimination attainable with metal salen-based catalysts.

Representative procedure:[12] (−)-(*R*)-1-Methyl-1-pentyloxirane (**6**). To a solution of (±)-1-methyl-1-pentyloxirane (**6**) (2.20 g, 17.2 mmol) in TBME (6.0 mL) was added (*R,R*)-**2** (220 mg, 0.343 mmol).

The resulting brown mixture was stirred for 5 min at rt, then cooled to 0°C. To this mixture, was added 2-propanol (730 μL, 9.44 mmol), followed by $TMSN_3$ (1.30 mL, 9.44 mmol). The brown mixture was warmed to rt and stirred for 6 h. The solvent was removed under reduced pressure, and the residue is purified by flash chromatography (5% ether/pentane) providing the desired enantioenriched epoxide as a colorless liquid (925 mg, 42% yield). $[\alpha]_D$ −10.65 (*c*, 3.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.60 (d, *J*=5 Hz, 1H), 2.57 (d, *J*=5 Hz, 1H), 1.62–1.55 (m, 2H), 1.50–1.24 (m, 6H), 1.30 (s, 3H), 0.89 (t, *J*=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 53.6, 36.6, 31.7, 24.8, 22.4, 20.7, 13.8; IR (NaCl, film) 2960, 2935, 2860, 1460, 1390, 905, 800 cm^{-1}; HMRS (CI^+) calcd for $C_8H_{20}NO$ $[M+NH_4]^+$: 146.1545. Found: 146.1539. The enantiomeric excess was determined to be ≥99% (≥200:1) by chiral GC analysis (γ-TA, 35°C isothermal, t_R 13.04 (major), 16.26 (minor)).

Acknowledgements

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References

1. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (b) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773–776.
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3. For selected examples of kinetic resolution of 2,2-disubstituted epoxides, see: (a) Orru, R. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, *54*, 859–874. (b) Orru, R. V. A.; Osprian, I.; Kroutil, W.; Faber, K. *Synthesis* **1998**, 1259–1263. (c) Osprian, I.; Kroutil, W.; Mischitz, M.; Faber, K. *Tetrahedron: Asymmetry* **1997**, *8*, 65–71. (d) Lakner, F. J.; Hager, L. P. *J. Org. Chem.* **1996**, *61*, 3923–3925.
4. For selected examples of preparation of 2,2-disubstituted epoxides, see: (a) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *J. Org. Chem.* **1999**, *64*, 1772–1773. (b) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187–192. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
5. For selected examples of preparation of optically-active tertiary alcohols, see: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446. (b) Tietze, L. F.; Görlitzer, J. *Synthesis* **1998**, 873–878.
6. Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624–9625.
7. See Ref. 6. This procedure allows the in-situ generation of an exact amount of HN_3 which is essential in the context of a kinetic resolution. See also: Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309–5312.
8. Racemic epoxides **3**, **4** and **8** have been prepared by epoxidation of the corresponding alkene. Racemic epoxides **5**, **6** and **7** were obtained by methylene sulfur ylide transfer on the corresponding ketone. Epoxide **9** was produced by addition of the lithium anion of TMS-acetylene to the corresponding α-bromo ketone.
9. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875. Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935–952.
10. The regioisomeric ring-opened products were easily separable by flash chromatography.
11. This could be the result of two reaction pathways: one resulting from the addition of the azide at the terminal position in high selectivity and another slower pathway involving a less-selective internal attack. We also observed a variation of the ratio of regioisomers with time; at the beginning of the reaction, the more selective pathway was predominant, while at the end (~50% conversion), both pathways occurred. The competition between multiple pathways leads to a complex kinetic resolution that cannot be easily expressed in terms of k_{rel}. The standard equation for k_{rel} assumes the presence of only two diastereoisomeric pathways and also that the reaction is first order in both enantiomers of the substrate.
12. Full experimental details for all substrates are available upon request: jacobsen@chemistry.harvard.edu.