Kinetic Resolution of Epoxides

Kinetic Resolution of Epoxides by a C–C Bond-Forming Reaction: Highly Enantioselective Addition of Indoles to *cis*, *trans*, and *meso* Aromatic Epoxides Catalyzed by [Cr(salen)] Complexes**

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Epoxides are valuable intermediates in organic synthesis. Elaboration of optically active epoxides by selective ring-opening reactions with nucleophiles and radicals in the presence of Lewis acids or Lewis bases provides access to a variety of enantiomerically enriched compounds.[1] Currently, enantioenriched *cis* and *trans* epoxides can be efficiently

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prepared by catalytic epoxidation.[2] However, the ready accessibility of epoxides in racemic form renders kinetic resolution an attractive alternative route to optically active epoxides.[3] In particular, racemic terminal epoxides have been used as substrates in kinetic-resolution reactions promoted by [Cr(salen)Cl] and [Co(salen)OAc] (Figure 1) with

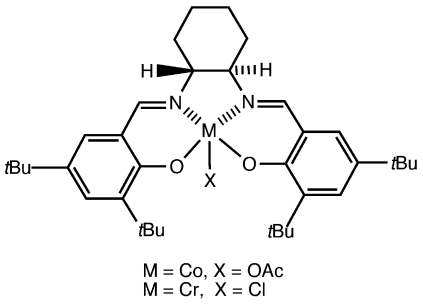
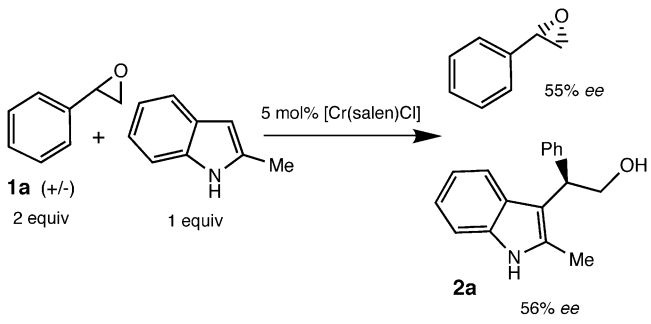


Figure 1. Metal salen complexes.

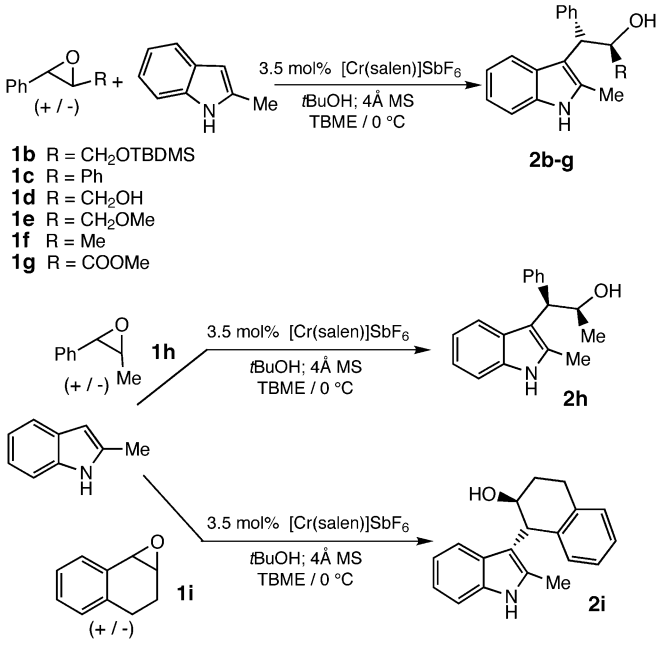
remarkable results.[4] However, 1,2-disubstituted epoxides are still challenging substrates for kinetic resolution,[5] and a general kinetic resolution of both *cis* and *trans* aromatic epoxides catalyzed by metal salen complexes has been not reported.[6] Here we present the first method for the catalytic kinetic resolution of both *cis* and *trans* aromatic epoxides, based on a C–C bond-forming reaction with indoles.[7] Moreover, the methodology is also effective in the desymmetrization of *meso* aromatic epoxides, which provides access to highly enantioenriched indolyl derivatives.[8]

During our studies on indium halides as Lewis acid catalysts we discovered that $InBr_3$ can promote ring opening of aromatic epoxides with indoles.[9] Considering the ability of [Cr(salen)Cl] (Figure 1, M = Cr, X = Cl) to generate a suitable chiral environment,[10] we tested the possibility of using this complex in the asymmetric ring opening of racemic styrene oxide derivatives with indoles. The reaction was performed at room temperature in noncoordinating solvents (CH_2Cl_2 or *tert*-butyl methyl ether (TBME), 0.3 M) with 5 mol% of (*R*,*R*)-[Cr(salen)Cl] as catalyst (Scheme 1) and commercially available 2-methylindole as the nucleophile.[11] Under these conditions, after complete consumption of 2-methylindole, the unconsumed styrene oxide and the indolyl



Scheme 1. Reaction of racemic styrene oxide with 2-methylindole catalyzed by [Cr(salen)Cl].

derivatives **2a** were isolated with enantiomeric excesses of 55 and 56%, respectively.[12] To apply this novel reaction to the kinetic resolution of 1,2-disubstituted epoxides, *trans*-1-[(*tert*-butyldimethylsilyloxy)]-3-phenyloxirane (**1b**) was chosen as a model substrate. Reaction of racemic epoxide **1b** (2 equiv) with 2-methylindole (1 equiv) was performed in the presence of [Cr(salen)Cl] (5 mol%) in TBME. Although the desired ring-opened product **2b** was isolated with high enantioselectivity (*ee* = 78%), the *trans* aromatic epoxide **1b** was in general rather unreactive (70% conversion over 5 days). To increase the reactivity of the system we used cationic [Cr(salen)] complexes, prepared by exchange with silver salts by following the protocol of Jacobsen et al.[13] We found that [Cr(salen)]SbF_6 in the presence of 4 Å molecular sieves (MS), TBME as solvent, and *t*BuOH (1 equiv relative to 2-methylindole) led to complete consumption of 2-methylindole over 16 h (Scheme 2). The unconsumed epoxide (*R*,*R*)-



Scheme 2. Kinetic resolution of *cis* and *trans* aromatic epoxides with 2-methylindole.

1b and the corresponding indolyl derivative **2b** were isolated with the same enantiomeric excess (77%). Then 1,2-disubstituted aromatic epoxides **1b–i** were treated with 2-methylindole under these optimized conditions. An excess of epoxide (3 equiv) and a reaction temperature of 0 °C ensured that the ring-opened product was obtained with high enantiomeric excess (Table 1). Both *cis* and *trans* aromatic epoxides reacted with complete regioselectivity to give the corresponding indolyl derivatives **2b–i** in high yields and with good enantioselectivity values (up to 91% *ee*; Table 1, entry 1).[14] *Cis* aromatic epoxides were more reactive than *trans* epoxides. It is noteworthy that the stereochemical outcome of this kinetic resolution is strictly dependent on the stereochemistry of the starting epoxides. In fact, the *trans* and *cis* β-methylstyrene oxides **1f** and **1h** gave the ring-opened

Table 1: Kinetic resolution of aromatic epoxides with 2-methylindole.[a]

Entry	Epoxide	*t* [h]	Yield [%][b]	*ee* of **2** [%][c]	*s*[d]
1	**1b**	16	96	91	30
2	**1c**	48	82	86	15
3	**1d**	40	93	87	25
4	**1e**	24	98	86	23
5	**1f**	36	99	72	10
6	**1g**	30	85	80	13
7	**1h**	18	95	80	13
8	**1i**[d]	24	97	83	16

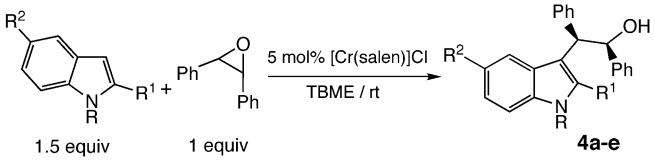
[a] Reactions were carried out with 1 equiv of 2-methylindole, 3 equiv of racemic epoxide, 1 equiv of *t*BuOH, and 3.5 mol% [Cr(salen)]SbF_6 relative to the racemic epoxide. [b] Yield of **2** after chromatographic purification. [c] Enantiomeric excesses were evaluated by HPLC analysis; see Supporting Information. [d] Selectivity factor. [e] [Cr(salen)Cl] (3.5 mol% relative to the epoxide) was used as catalyst.

products **2f** and **2h** with *S* and *R* absolute configuration of the benzylic stereocenter, respectively.

A useful feature of kinetic resolution is that the enantiopurity of the unconverted substrate can be enhanced through higher substrate conversion. Indeed, while reactions applied to prochiral substrates give products with constant enantioselectivity, the enantiomeric excesses obtained in kinetic resolutions are a function of conversion. Therefore, to obtain high enantiomeric excesses, the selectivity factor must be evaluated.[15]

In principle, this kinetic resolution could represent a general method for the preparation of both *cis* and *trans* aromatic epoxides with high *ee* values starting from racemic substrates. This concept was demonstrated by the reaction of selected *cis* and *trans* epoxides (Scheme 3). Table 1 lists the selectivity factors for treatment of the epoxides with 2-methylindole. By adjusting the amount of 2-methylindole on the basis of the selectivity factor, it was possible to isolate the unconverted epoxides with high enantioselectivity and in satisfactory yields (24–36%).[16] *Trans* epoxides **1b** and **1c** were isolated in high enantiomeric excesses (91 and 96%, respectively), while the more reactive *cis* epoxides **1h** and **1i** were isolated in enantiomerically pure form (*ee* > 99%). To the best of our knowledge this is the first example of kinetic resolution of both *cis* and *trans* aromatic epoxides by a C–C bond-forming reaction.[17]

Finally, this [Cr(salen)]-catalyzed addition of indoles to epoxides was also applied to the asymmetric ring opening (ARO) of *meso*-stilbene oxide. In this case the commercially available [Cr(salen)Cl] (5 mol%) proved to be effective in catalyzing the highly selective ARO of *meso*-stilbene oxide in the presence of different substituted indoles (Scheme 4). The corresponding indolyl derivatives **4a–e** were isolated in excellent yield and high enantioselectivity (yield 95–98%; 90–98% *ee*, Table 2).



3a R = H, R^1 = H, R^2= H
3b R = Me, R^1 = H, R^2= H
3c R = H, R^1 = Me, R^2 = H
3d R = Me, R^1= Me, R^2 = H
3e R = H, R^1 = H, R^2 = OMe

Scheme 4. Asymmetric ring opening of *meso*-stilbene oxide with indoles.

Table 2: ARO of *meso*-stilbene oxide with indoles.

Entry	Indole	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**3a**	36	98	93
2	**3b**	30	96	96
3	**3c**	36	98	98
4	**3d**	36	95	97
5	**3e**	36	95	90

[a] Yield of **4** after chromatographic purification; [b] Enantiomeric excesses were evaluated by HPLC; see Supporting Information.

In summary, we have developed a highly effective methodology for the kinetic resolution of 1,2-disubstituted aromatic epoxides, based on a C–C bond-forming reaction. The method uses 2-methylindole as the resolving agent, and both the indolyl derivatives and the unconverted epoxides are obtained in high enantiomeric excess. Further studies on the mechanistic and practical aspects of this new kinetic-resolution procedure are in progress.

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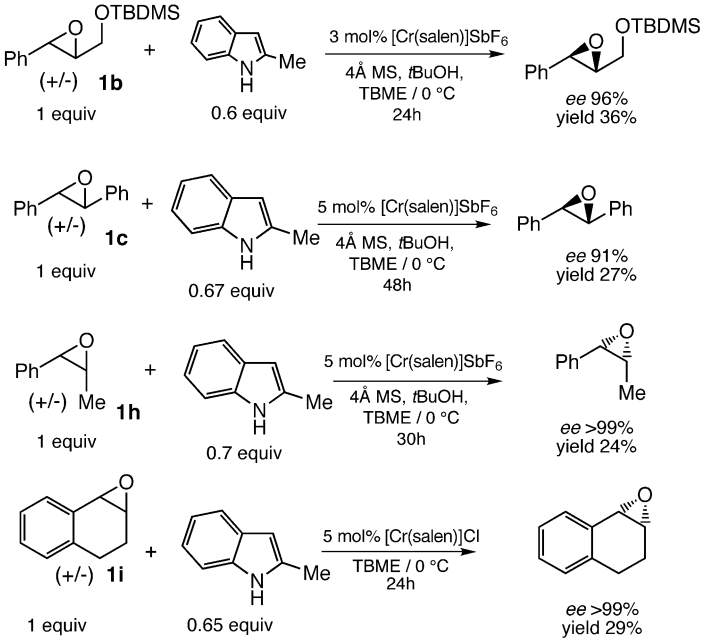
Keywords: aromatic epoxides · asymmetric catalysis · indoles · kinetic resolution · N,O ligands



Scheme 3. Highly enantioselective kinetic resolution of aromatic epoxides.

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[11] Other indoles (indole; 1-methyl-, 5-methoxy-, 5-bromo-, 5-benzyloxy-, and 5-nitroindole) were less reactive than 2-methyindole.

[12] Interestingly, the absolute configuration of isolated **1a** was the opposite of that in other kinetic resolutions carried out with [Cr(salen)] and [Co(salen)] complexes, and this indicates that a different mechanism is probably operative in this case. For [Co(salen)]-catalyzed kinetic resolution, see S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307 – 1315. For kinetic resolution employing [Cr(salen)], see ref. [7e].

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[14] Absolute configurations of products **2a**, **2f**, and **2i** were established by HPLC analysis by comparing the retention times with those of authentic samples; for all other products the absolute configuration was assigned by analogy.

[15] The lower limit of the selectivity factor s for the epoxides was estimated by using the equation $s = \ln[1-c(1+ee)]/\ln[1-c(1-ee)]$ in the reaction with 2-methylindole (*ee* is the percentage enantiomeric excess of the ring-opened products; yields of ring-opened products were used for conversion c.

[16] The amount of 2-methylindole was adjusted to obtain the maximum yield possible with the highest enantiomeric excess for the unconverted epoxides. As we use 0.6–0.7 equiv of 2-methylindole, the maximum theoretical yield is 30–40 %.

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