Co(III)(salen)-catalyzed HKR of two stereocentered alkoxy- and azido epoxides: a concise enantioselective synthesis of (*S*,*S*)-reboxetine and (+)-*epi*-cytoxazone†

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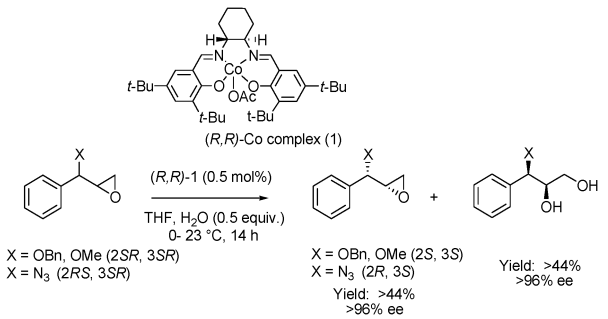
The HKR of racemic *syn*- or *anti*- alkoxy- and azido epoxides catalyzed by Co(salen) complex affords a practical access to a series of enantioenriched *syn*- or *anti*- alkoxy- and azido epoxides and the corresponding 1,2-diols. This strategy has been successfully employed in the concise, enantioselective synthesis of bioactive molecules such as (*S*,*S*)-reboxetine and (+)-*epi*-cytoxazone.

The enantiomerically pure *syn*- or *anti*- alkoxy- and azido epoxides and the corresponding diols are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals and as chiral auxiliaries and ligands.[1] In principle, access to these building blocks may be provided by several methods, such as Sharpless epoxidation and dihydroxylation,[2] as well as other multistep methods.[3] These latter methods necessitate protection/deprotection of various functional groups, thereby limiting the overall yield and the enantioselectivity of the process, particularly unsuitable for atom economic synthesis.

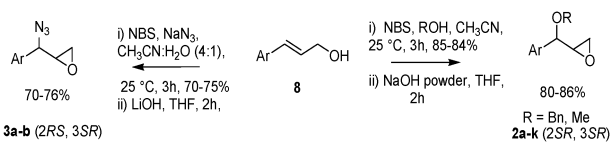
Jacobsen's Hydrolytic Kinetic Resolution (HKR), that uses readily accessible Co-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields, has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects.[4] Despite these achievements, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[5] To the best our knowledge, study related to HKR of *functionalized epoxides* with two stereocentres is rare.[6] In the present work, we have thus extended the scope of the applicable substrates to cover multi-functionalized molecules with two stereocentres. The aim of such an investigation is to access enantiomerically enriched alkoxy- or azido epoxides and diols by a direct and simple method from the respective racemic materials, thus complementing the other tedious routes.[2] Due to their importance as 'building blocks' for the synthesis of highly functionalized molecules, racemic alkoxy or azido epoxides are subjected to HKR with chiral Co-catalysts. We now report a flexible, novel method that employs HKR of racemic alkoxy and azido epoxides to generate two stereocentres of high optical purities in a single step (Scheme 1).



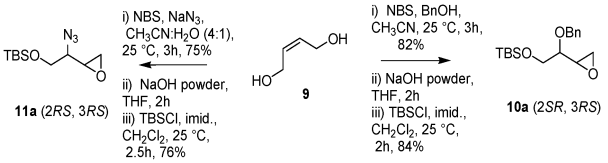
Scheme 1 Co-catalyzed HKR of *syn*-alkoxy and azido epoxides.

We envisioned that application of the HKR method to racemic functionalized epoxides would enable us to obtain both enantiomers of *syn* or *anti* epoxides and 1,2-diols depending upon the chiral ligand chosen. The racemic *syn*- and *anti*-alkoxy and azido epoxides, the substrates for HKR, were then efficiently prepared in highly diastereoselective manner from the corresponding (*E*)- and (*Z*)-allylic alcohols (**8** & **9**), respectively, involving essentially a two-step reaction sequence of NBS-bromination in the presence of alcohols or azides, as the case may be, followed by treatment with base to form the corresponding racemic epoxides (Schemes 2 and 3). In this strategy, the relative stereochemistry between the alkoxy or azido and epoxide groups is established prior to the HKR step itself and in this way a simple asymmetric reaction can be used to form the key enantiomerically pure alkoxy- or azido epoxides with two stereocentres.

To test this proposal, we prepared the *syn*-alkoxy epoxide **2a** from allylic alcohol **8** by a modified procedure reported in the literature.[7]



Scheme 2 Synthesis of racemic *syn*-alkoxy- and azido epoxides.



Scheme 3 Synthesis of racemic *anti*-alkoxy- and azido epoxides.

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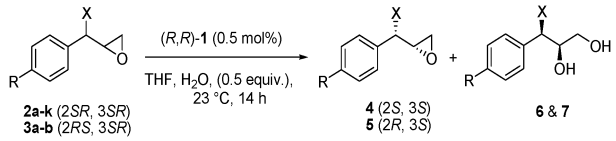
† Electronic supplementary information (ESI) available: Full experimental procedures, ^{1}H NMR, and ^{13}C NMR, spectra of all new compounds. See DOI: 10.1039/c0cc00650e

Table 1 Co-catalyzed HKR of *syn*-benzyloxy- and azido epoxides



			Epoxides			Diols		
2 & 3	R	X	**4 & 5**	Yield (%)[a]	ee (%)[d]	**6 & 7**	Yield (%)[a]	ee (%)
2a	H	OBn	**4a**	45	98	**6a**	44	98[b]
2b	OMe	OBn	**4b**	49	96	**6b**	47	98[b]
2c	Me	OBn	**4c**	48	96	**6c**	45	96[b]
2d	Cl	OBn	**4d**	45	95	**6d**	42	98[c]
2e	Br	OBn	**4e**	44	98	**6e**	47	98[c]
2f	SMe	OBn	**4f**	48	96	**6f**	47	97[c]
2g	H	OMe	**4g**	48	97	**6g**	47	98[b]
2h	OMe	OMe	**4h**	47	98	**6h**	46	97[b]
2i	Me	OMe	**4i**	44	97	**6i**	45	98[b]
2j	Br	OMe	**4j**	45	97	**6j**	42	98[c]
2k	SMe	OMe	**4k**	47	98	**6k**	46	97[c]
3a	H[e]	N_3	**5a**	48	96	**7a**	47	98[b]
3b	OMe[e]	N_3	**5b**	48	98	**7b**	48	97[b]

[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC analysis (see the ESI†). [c] ee determined by Mosher's ester analysis. [d] ee determined by Mosher's ester analysis of the corresponding mono protected diol. [e] Reaction carried at 0 °C.

Initially, when HKR of racemic *syn*-benzyloxy epoxide (**2a**) was performed with (*R*,*R*)-salen Co(OAc) complex (**1**) (0.5 mol%)[8] and H_2O (0.5 equiv.), the corresponding chiral epoxide **4a** (45%) and diol (**6a**) (44%) were isolated in high yields and optical purity. Encouraged by the observation of high enantioselectivity [**4a** (98%) and **6a** (97%)] in this reaction, we examined its scope by subjecting several racemic *syn*-alkoxy- and azido epoxides (**2a–k** & **3a–b)** to HKR, which indeed proceeded smoothly, with complete regiocontrol, to give the respective enantiopure epoxides (**4** & **5**) and diols (**6** & **7**) in excellent yields and ees. Table 1 shows the results of such a study. The reaction exhibited extraordinary generality with respect to the degree of functionalization of epoxides. The configuration of both chiral alkoxy- and azido epoxides (**4** & **5**) and diols (**6** & **7**) was ascertained by comparing their optical rotations with those reported in the literature.[3c,d]

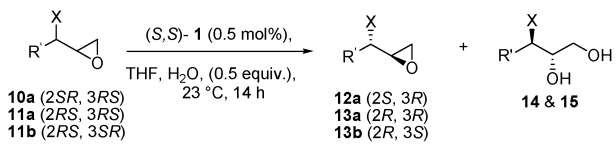
Similarly, *anti*-epoxides (**10a** & **11a**), were readily prepared from *cis*-butenediol **9** by following a three-step reaction sequence (Scheme 3). When subjected to HKR under identical conditions, these racemic epoxides (**10** & **11**) gave the corresponding enantiopure *anti*-epoxides (**12** & **13**) and diols (**14** & **15**) in high isolated yields and ees. The results are presented in Table 2.

A wide range of synthetic applications of this HKR procedure is readily envisaged and is amply illustrated in the short synthesis of (*S*,*S*)-reboxetine (**19**), a selective norepinephrine reuptake inhibitor (NRI),[9] and (+)-*epi*-cytoxazone (**21**), a cytokine modulator.[10] For (*S*,*S*)-reboxetine, chiral epoxide (**4a**) was chosen as the starting material (Scheme 4).

Regiospecific opening of epoxide **4a** with 30% NH_4OH gave amino alcohol **16** in 83% yield, which was condensed with chloroacetyl chloride under basic conditions to afford imide **17** in 72% yield. Alcohol **18** was obtained in 88% yield by a standard sequence of reactions. The transformation of **18** to (*S*,*S*)-reboxetine (**19**) was achieved in 98% ee.

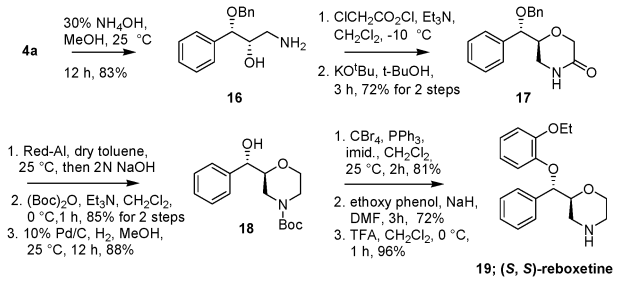
Synthesis of (+)-*epi*-cytoxazone (**21**) was readily achieved in 99% ee from chiral azido diol **7b** in a concise,[2e] two-step reaction sequence which involved azide reduction with PMHS to give amino diol **20**, followed by base-mediated cyclization (Scheme 5).

Table 2 Co-catalyzed HKR of *anti*-benzyloxy epoxides

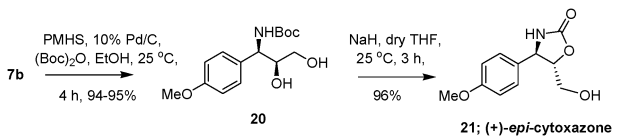


			Epoxides			Diols		
10 & 11	R	X	**12 & 13**	Yield (%)[a]	ee (%)[d]	**14 & 15**	Yield (%)[a]	ee (%)
10a	CH_2OTBS	OBn	**12a**	47	96	**14a**	49	97[c]
11a	CH_2OTBS[e]	N_3	**13a**	48	96	**15a**	46	98[c]
11b	Ph[e]	N_3	**13b**	48	97	**15b**	47	98[b]

[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC analysis (see the ESI†). [c] ee determined by Mosher's ester analysis. [d] ee determined by Mosher's ester analysis of the corresponding mono protected diol. [e] Reaction carried at 0 °C.



Scheme 4 Synthesis of (*S*,*S*)-reboxetine (**19**).



Scheme 5 Synthesis of (+)-*epi*-cytoxazone (**21**).

In summary, the (salen)Co(III)-catalyzed HKR of racemic alkoxy- and azido epoxides provides a highy practical route to enantiopure *syn*- or *anti*-alkoxy- and azido epoxides and the corresponding 1,2-diols in a single step. The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope. We believe that this HKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis of racemic alkoxy- and azido epoxides and the ready availability of catalyst in both enantiomeric forms.

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