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Divergent Reactivity via Cobalt Catalysis: An Epoxide Olefination

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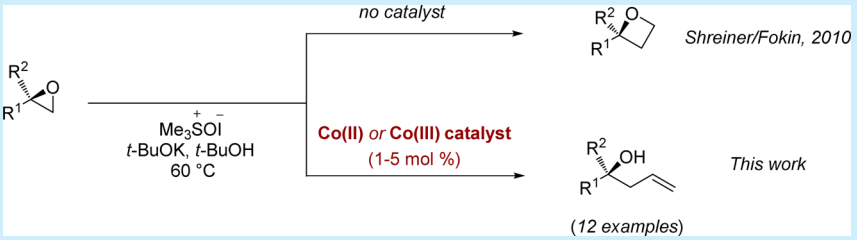
Supporting Information



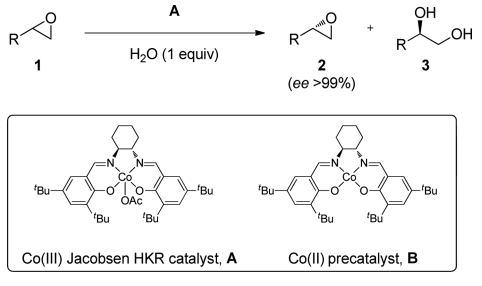
ABSTRACT: Cobalt salts exert an unexpected and profound influence on the reactivity of epoxides with dimethylsulfoxonium methylide. In the presence of a cobalt catalyst, conditions for epoxide to an oxetane ring expansion instead deliver homoallylic alcohol products, corresponding to a two-carbon epoxide homologation/ring-opening tandem process. The observed reactivity change appears to be specifically due to cobalt salts and is broadly applicable to a variety of epoxides, retaining the initial stereochemistry. This transformation also provides operationally simple access to enantiopure homoallylic alcohols from chiral epoxides without use of organometallic reagents. Tandem epoxidation−homologation of aldehydes in a single step is also demonstrated.

Hydrolytic kinetic resolution (HKR) employing the Jacobsen cobalt(III) salen complex **A** (Scheme 1), prepared in situ from cobalt(II) precatalyst **B**, enables robust, scalable, and economical access to enantiopure epoxides. The reaction tolerates a wide variety of terminal epoxides and routinely delivers products of >99% ee on scales suitable for research and process applications.[1] These attributes have encouraged its use in a wide range of transformations for the asymmetric synthesis of complex molecular architectures.[2]

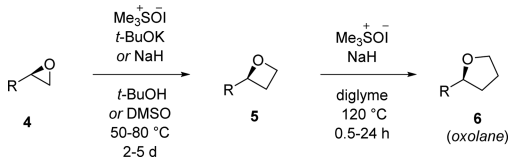
In the context of a synthetic program, we planned to apply the epoxide to oxetane ring-expansion methodology initially described by Okuma (Scheme 2),[3] and reinvestigated in detail by Schreiner and Fokin in 2010,[4] to chiral epoxides readily available via Jacobsen HKR.

The initial conversion of epoxides **4** to oxetanes **5** has been established to proceed cleanly over 2−5 days, at 50−80 °C, using 2−6 equiv of dimethylsulfoxonium methylide.[3] Further ring expansion of oxetanes **5** to oxolanes **6** has also been shown to proceed in moderate to excellent yields but required higher temperatures and prolonged reaction times. Density functional calculations and experimental results have been used to estimate the energy barriers for formation of the key reaction intermediates and relative reactivity trends for 2-monosubstituted and 2,2-disubstituted epoxides and oxetanes.[4] Due to the similar ring-strain energy of oxetanes and epoxides (107 and 114 kJ/mol, respectively),[5] a number of epoxide ring-opening transformations have also been successfully applied to oxetanes using heteroatomic nucleophiles[6] or carbon nucleophiles[7] or by desymmetrization of prochiral 3-substituted oxetanes.[8] Oxetanes are used relatively infrequently in synthesis to date, despite the many methods available for synthesis of homochiral epoxides or other precursors,[9] although there has recently been increased interest in 3-substituted derivatives in a drug discovery context.[10]

Scheme 1. Hydrolytic Kinetic Resolution of Epoxides 1 Using the Jacobsen Cobalt(III) Salen Complex A



Scheme 2. Ring Expansion of Epoxides 4 to Oxetanes 5 Using Dimethylsulfoxonium Methylide, Initially Reported by Okuma,[3] and Extended to Oxolanes 6 by Shreiner and Fokin[4]



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Scheme 3. Divergent Reactivity of (Top) Racemic (±)-7 Giving Oxetane 8 and (Bottom) Enantiopure (*R*)-7, Resolved by Jacobsen HKR, Giving Homoallylic Alcohol 9

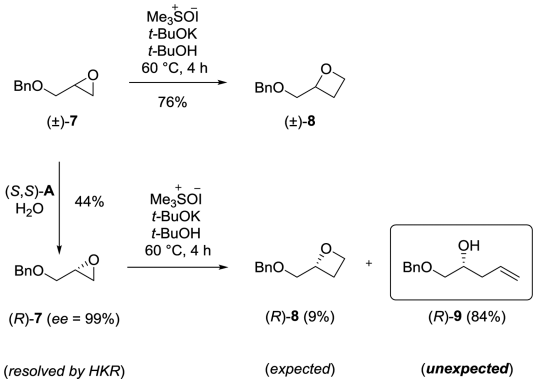
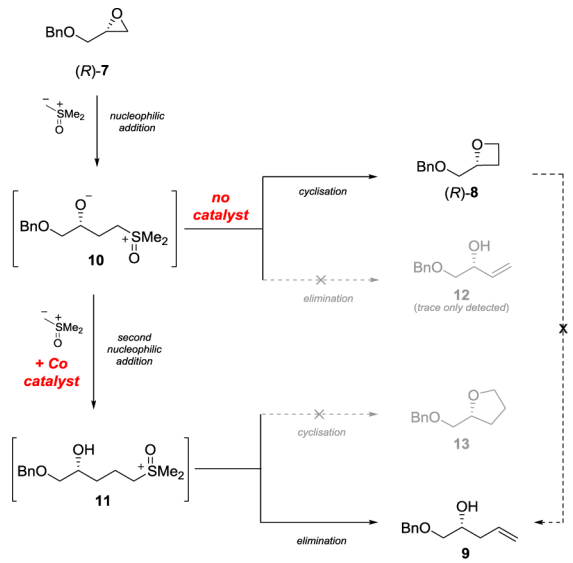


Table 1. Confirmation of the Role of Catalytic Cobalt(II) and -(III) Salts in the Epoxide Olefination

entry	sm	catalyst[a]	oxetane **8** (%)	alcohol **9** (%)
1	(±)-7		76	0
2	(*R*)-7[b]		9	84
3	(*R*)-7[c]		76	0
4	(±)-7	A	0	89
5	(±)-7	B	0	100
6	(±)-8	B	93[d]	0

[a]5 mol %. [b]Resolved by HKR. [c]Purified by Kugelrohr distillation. [d]I.e., no reaction; starting material (±)-**8** recovered.

Scheme 4. Proposed Reaction Pathway for Cobalt-Catalyzed Epoxide Olefination



In order to apply the epoxide to oxetane ring expansion in our synthetic investigations, benzyl-protected epoxide (±)-7 (Scheme 3) was treated with trimethylsulfoxonium iodide (5 equiv) and potassium *tert*-butoxide (5 equiv) in *tert*-butyl alcohol, according to the literature conditions, to give oxetane (±)-**8** in 63% yield after 3.5 days. In our hands, this was improved to 3 equiv of each reagent at 60 °C for 4 h to give oxetane (±)-**8** in 76% yield.

Expecting that (*R*)-**8** would be similarly available from glycidol (*R*)-7, epoxide (±)-7 was resolved under standard HKR conditions using the Co(III) (salen)·OAc catalyst (*S*,*S*)-**A**. Surprisingly, submission of purified (*R*)-7 (99% ee) to the optimized ring-expansion conditions only afforded trace amounts of the expected oxetane (*R*)-**8**, instead delivering homoallylic alcohol **9** in high yield (Table 1, entry 2). Several repetitions confirmed that only batches of the resolved homochiral epoxide (*R*)-7 underwent the side reaction, suggesting that a possible cause was a trace amount of catalyst **A** remaining after purification by flash chromatography.

To investigate this possibility, a sample of (*R*)-7 was repurified by Kugelrohr distillation to remove all traces of catalyst and submitted to the standard reaction conditions. Only oxetane **8** resulted in 76% yield (Table 1, entry 3). Reaction of racemic 7 in the presence of 5 mol % of either the Co(III) (salen)·OAc catalyst **A** (Table 1, entry 4) or Co(II) (salen) precatalyst **B** (Table 1, entry 5) as an additive was found in both cases to afford homoallylic alcohol **9** as the sole product in high yields. Interestingly, the reaction catalyzed by the Co(II) (salen) precatalyst **B** (Table 1, entry 5) appeared to give a cleaner product mixture, in slightly higher yield. Taken together, these data indicate that traces of the cobalt complexes were indeed responsible for the observed divergent reactivity of epoxide 7 under the ring-expansion conditions. Finally, submission of racemic oxetane **8** to the same conditions, with the addition of Co(II) (salen) precatalyst **B** (Table 1, entry 6), only resulted in recovered starting material. This last result indicated that oxetane **8** is *not* an intermediate in the reaction leading to homoallylic alcohol **9**.

Table 2. Lewis Acid Catalyst Screen for Epoxide Olefination[a]

entry	catalyst[b]	**7** (yield, %)	**8** (yield, %)	**9** (yield, %)
1	$BF_3{\cdot}OEt_2$	100[c]		
2	$Sc(OTf)_3$		100[c]	
3	$CoBr_2$			72[d]
4	$CoCl_2$		47[d]	21[d]
5	$FeCl_3$		100[c]	
6	$CoBr_2$/bipy			100[c]
7	$FeCl_3$/bipy		98[d]	

[a]Reagents and conditions: trimethylsulfoxonium iodide (3 equiv), *t*-BuOK (3 equiv), *t*-BuOH, 80 °C, 3 h. [b]5 mol %. [c]Sole component of product mixture by ^{1}H NMR; [d]Isolated yield. bipy = 2,2′-bipyridyl.

On the basis of the studies performed by Shreiner and Fokin, it appears likely that the mechanism initially proceeds through ring-opening of epoxide **7** with dimethylsulfoxonium methylide (Scheme 4) to give an intermediate betaine **10**. In the absence of catalyst, the betaine then preferentially undergoes intramolecular cyclization of the alkoxide, with the loss of DMSO, to afford the oxetane **8** that does not undergo further reaction. Under the basic conditions employed, betaine cyclization theoretically competes with β-deprotonation and elimination of DMSO to afford allylic alcohol **12**. During this study, however, this compound was only observed once as a trace byproduct (<2%). Addition of a cobalt catalyst diverts the course of the reaction, promoting the exclusive formation of homoallylic alcohol **9**. This is likely to proceed via addition of a second equivalent of dimethylsulfoxonium methylide to betaine **10** to give homologated betaine **11**, although the exact mechanism for this is unclear. β-Deprotonation and elimination of DMSO from **11** then yields homoallylic alcohol **9** that does not undergo further reaction. Interestingly, the possible cyclization product **13** was also not observed in any reaction during this study.

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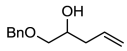
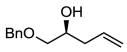
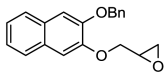
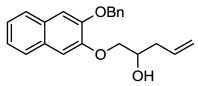
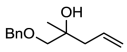
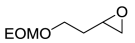
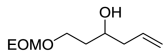
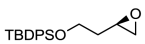
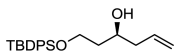
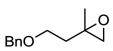
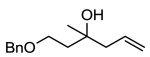
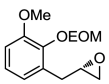
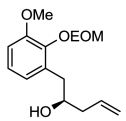
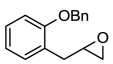
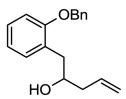
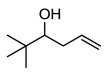
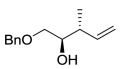
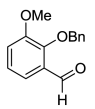
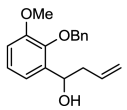
Table 3. Substrate Scope for the Cobalt-Catalyzed Epoxide Homologation−Olefination*

entry	epoxide	product	yield (%)	*ee* % (sm/prod)[a]
1			99	
2			92	99/99
3			82	
4			99	
5			96	
6			51	90/90
7			81	
8			90	99/99
9			77	
10			44[b]	
11			35	[c]
12			43	

*Reagents and conditions: trimethylsulfoxonium iodide (3 equiv), **B** (5 mol %), *t*-BuOK (3 equiv), *t*-BuOH, 80 °C, 3 h. [a]Determined by chiral HPLC or ^{19}F NMR of a Mosher ester derivative; see the Supporting Information. [b]Product volatile. [c]Relative stereochemistry shown for entry 11.

In an effort to clarify the role of catalytic amounts of cobalt in diverting the reaction course, a screen of potential Lewis acid catalysts was carried out using the standard conditions (Table 2). Interestingly, the presence of boron trifluoride prevented ring expansion, returning only epoxide starting material (Table 2, entry 1). Addition of scandium triflate or iron trichloride had no effect on the reaction, which proceeded as normal to the oxetane (Table 2, entries 2, 5, and 7). Remarkably, the reaction was

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selectively diverted to produce homoallylic alcohol **9** instead of oxetane **8** exclusively in the presence of cobalt salts as the sole product in nearly all cases (Table 2, entries 3, 4, and 6). The addition of the bidentate 2,2′-bipyridyl (bipy) ligand appeared to have no influence on the reaction outcome (Table 2, entries 6 and 7). These data suggest that the observed change in reactivity is not due to general Lewis acid catalysis but rather is specific to cobalt salts, out of those in this study. It remains to be clarified whether this is due to a particular ability of cobalt to promote addition of a second equivalent of the sulfoxonium ylid to intermediate betaine **10** to give **11** (Scheme 4) or, more intriguingly, to the possible formation of a nucleophilic vinylcobalt species in situ.

In order to explore the generality of the epoxide olefination, a variety of substrates were investigated (Table 3). Epoxides possessing a variety of substitution patterns were shown to efficiently undergo olefination to the corresponding homoallylic alcohols, in good to excellent yields. Monosubstituted epoxides (Table 3, entries 1−3, 5, 8, and 9) proved to be excellent substrates, in many cases affording nearly quantitative yields. Monosubstituted epoxides possessing bulky substituents gave reduced conversion to the desired products (Table 3, entries 6 and 10). 1,1-Disubstituted epoxides were also well tolerated (Table 3, entries 4 and 7). The reaction of 1,2-disubstituted epoxides also proceeded (Table 3, entry 11), although the reaction was much slower. Due to the use of dimethylsulfoxonium methylide for Corey−Chaykovsky epoxidation of aldehydes, we were interested in investigating the possibility of tandem epoxidation−olefination under cobalt catalysis. Accordingly, an aromatic aldehyde was exposed to the standard reaction conditions (Table 3, entry 12), successfully affording the homoallylic alcohol product expected from the epoxidation−olefination process, in moderate yield. The enantiopurity of the initial epoxides was transferred unchanged to the homoallylic alcohol products, as determined for selected examples by Mosher ester analysis and ^{19}F NMR or chiral HPLC (Table 3, entries 2, 6, and 8).

In summary, a cobalt-catalyzed homologation of epoxides to homoallylic alcohols using dimethylsulfoxonium methylide is reported. The unique catalytic role of cobalt salts was confirmed through a series of control experiments. The reaction demonstrated wide substrate scope, with epoxides possessing a range of substituents being converted to homoallylic alcohols in good to excellent yields, with retention of starting material stereochemistry. Tandem epoxidation−olefination of aldehydes was also demonstrated. Initial investigations showed that the mechanism does not proceed through an oxetane intermediate, but further work is required to elucidate the exact role of the cobalt catalyst in the homologation. Finally, this novel transformation enables convenient synthesis of enantiopure homoallylic alcohols from readily available chiral epoxides without the use of organometallic reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03514.

^{1}H and ^{13}C NMR spectra for novel compounds, ^{19}F NMR, and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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