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Regioselective Isomerization of 2,3-Disubstituted Epoxides to Ketones: An Alternative to the Wacker Oxidation of Internal Alkenes

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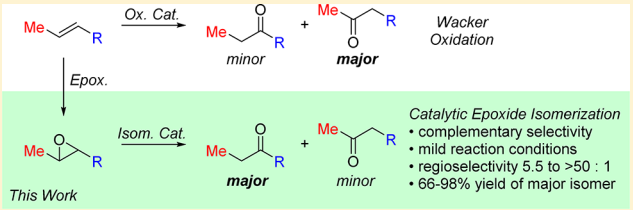
Supporting Information

ABSTRACT: We report an alternative pathway to the Wacker oxidation of internal olefins involving epoxidation of *trans*-alkenes followed by a mild and highly regioselective isomerization to give the major ketone isomers in 66−98% yield. Preliminary kinetics and isotope labeling studies suggest epoxide ring opening as the turnover limiting step in our proposed mechanism. A similar catalytic system was applied to the kinetic resolution of select *trans*-epoxides to give synthetically useful selectivity factors of 17−23 for benzyl-substituted substrates.



INTRODUCTION

The Wacker oxidation is an important, well-established method for the oxidation of terminal alkenes to methyl ketones using Pd catalysts paired with a reoxidant (Figure 1A).[1] This transformation has proven to be functional group tolerant and efficient with a variety of oxidants, making it a very useful tool for synthetic chemists. While the methyl ketone product is generally favored, it has been well-documented[1,2] that the presence of a heteroatom or electron-withdrawing group in the allylic or homoallylic position can change the regioselectivity such that the aldehyde becomes the favored product.[3]

The Wacker oxidation of 2,3-disubstituted alkenes has been slower to develop, mostly due to low activity and poor regioselectivity. Tsuji systematically investigated the internal Wacker oxidation in the 1980s using carbonyl, ether, and ester directing groups to achieve regioselectivity, though with limited yields.[4] Following suit, some researchers who observed aldehyde selectivity for terminal olefins were able to use similar directing groups to achieve regioselective oxidation for internal alkenes.[2a,b] Recently, Grubbs,[5] Sigman,[6] and Kaneda[7] have revisited the Wacker oxidation of internal alkenes by developing systems that reliably oxidize internal olefins with high activity. All found strong directing effects to give oxidation at the distal carbon (Figure 1A). Selectivity dramatically decreased if the directing group was moved farther away than the homoallylic position.[7b] When no electronic bias was present, steric differences were not sufficient to achieve high levels of selectivity, as evidenced by *trans*-2-octene resulting in ratios of 3-octanone (**2a**) and 2-octanone (**3a**) ranging from 1:1 to 1:2.5 (Figure 1B). This is not ideal not only because the modest selectivity lowers the maximum yield of the desired regioisomer, but also because the major product observed in these reactions is a methyl ketone, which would be more efficiently produced from a terminal olefin.

A different pathway resulting in net alkene oxidation is the two-step hydroboration/oxidation sequence. Hydroboration proceeds via concerted *syn*-addition of hydrogen and boron across an olefin in an *anti*-Markovnikov fashion. The organoborane can then be oxidized to the alcohol or directly to the corresponding carbonyl compound.[8] Only a few methods of regioselective hydroboration/oxidation of unsymmetrically 2,3-disubstituted alkenes have been developed, most of which are substrate-controlled. Most commonly, directing groups such as amines[9] or amides[10] have been used, but this limits the applicability and substrate scope of this method. Bulky boron reagents have been shown to improve regioselectivity for specific substrates, but none have been widely studied or applied.[11] In contrast, hydroboration/oxidation of undirected alkenes generally either shows little to no regioselectivity (Figure 1B)[12] or yields the terminally functionalized organoborane via alkene isomerization.[13] Developments by Curran and Vedejs have resulted in improved selectivity for unbiased substrates, but borane migration leads to side products and time-dependent product distributions.[14]

Another two-step alternative to the Wacker oxidation is an epoxidation/isomerization pathway. The atom-economical epoxide rearrangement to carbonyl compounds has been studied using a variety of catalysts for substrates that aid in regioselective ring opening via either a Lewis acid-induced or nucleophilic mechanism (*vide infra*).[15] Epoxidation/isomerization as an alternative to the Wacker oxidation has been introduced by Kulawiec[16] and Che[17] for the regioselective oxidation of aryl-substituted internal and conjugated terminal olefins, respectively. This strategy has not been applied to internal alkenes lacking an electronic bias. Since alkene epoxidation is a well-established reaction, this procedure would only require the development of regioselective isomerization of unbiased epoxides.

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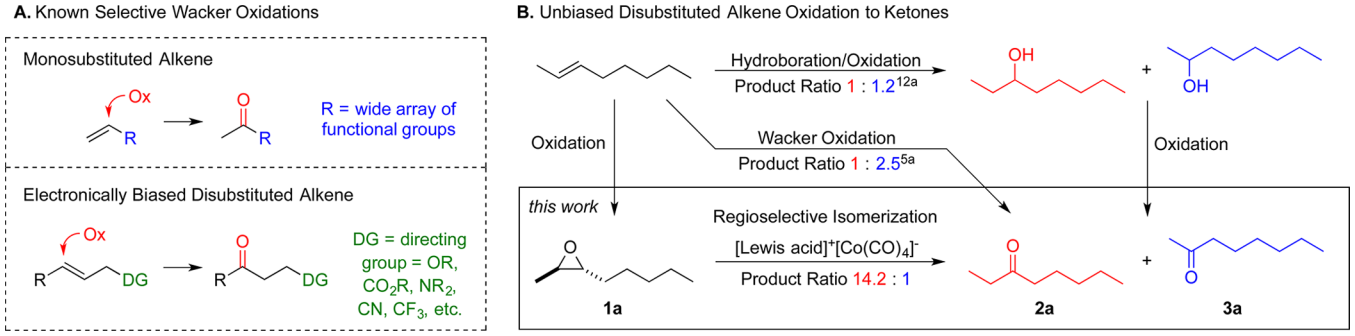


Figure 1. (A) Known substrates for the regioselective Wacker oxidation. (B) Possible pathways for the net oxidation of unbiased disubstituted alkenes to ketones.

On the basis of prior observations that ketone forms as a side product during epoxide carbonylation at low pressures of carbon monoxide,[18] we recently reported the use of a previously developed carbonylation catalyst for the isomerization of terminal epoxides to methyl ketones.[15c] Using this same approach, we hypothesized that catalyst **4**, which is known to catalyze regioselective carbonylation of *trans*-epoxides to *β*-lactones,[19] would similarly accomplish regioselective isomerization to ketones. Herein we report a mild and selective rearrangement of unbiased *trans*-epoxides to ketones.

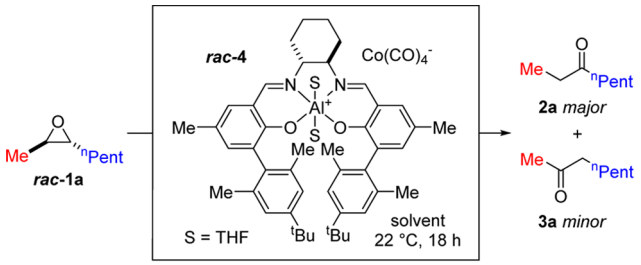
RESULTS AND DISCUSSION

Optimization and Substrate Scope. Optimization of the reaction conditions was done using *trans*-2-octene oxide (**1a**) and **4** (Table 1). $[(salcy)Al(THF)_2]^+[Co(CO)_4]^-$ (salcy = *N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-*rac*-1,2-cyclohexanediamine) was also tested as a catalyst for this reaction, but was found to have no regioselectivity between ketones **2a** and **3a**.[20] A solvent screen revealed that diethyl ether resulted in good activity, high selectivity for ethyl ketone (**2a**), and a low amount of side reactions as evidenced by good agreement between conversion of the epoxide and yield of the products (entries 1−5). More polar, coordinating solvents resulted in lower conversion and yield, presumably due to competitive binding to the metal center. It is unclear at this time why ether improves regioselectivity compared to the more nonpolar solvents. Varying the epoxide concentration from 0.5 to 1.5 M revealed that while regioselectivity was unaffected, the reaction proceeded to full conversion under more dilute conditions (entries 5−7). Surprisingly, a further drop in concentration enabled a reduction in catalyst loading to 2 mol % while further decreasing unwanted side reactions (entries 8−10). Any attempt to further lower the catalyst loading resulted in lower conversion (entries 11 and 12). We suspect that the catalyst decomposes throughout the reaction via a bimolecular pathway due to the observation that the reaction proceeds to higher conversions at lower concentrations. While the reaction should be slower under these dilute conditions due to lower catalyst concentrations, a longer lifetime of **4** accounts for this effect. Visual inspection of the reaction also supports catalyst decomposition, as the solution changes from orange to dark brown and becomes cloudy over time.

Having determined the optimal reaction conditions, we investigated the scope of the reaction. First, symmetrical *trans*-epoxides were isomerized to show the efficiency and high activity of **4**, resulting in very high yields (Table 2). Quantitative GC yields versus dodecane as an internal standard were used for substrates with fewer than 8 carbons due to volatility of the products.

Next, unsymmetrical, unbiased substrates with one methyl and one linear alkyl substituent were investigated and resulted

Table 1. Evaluation of Reaction Conditions for the Regioselective Isomerization of Epoxide 1a by *rac*-4



entry	mol % *rac*-4	solvent	conc 1a (M)	conv[a] 1a (%)	yield 2a + 3a[a]	ratio 2a:3a[a]
1	3	THF	1.0	13	12	12.0:1
2	3	dioxane	1.0	31	25	13.2:1
3	3	toluene	1.0	85	66	12.4:1
4	3	hexanes	1.0	88	76	11.9:1
5	3	Et_2O	1.0	75	69	13.1:1
6	3	Et_2O	1.5	72	58	13.8:1
7	3	Et_2O	0.5	>99	88	13.5:1
8	2	Et_2O	1.0	63	57	13.3:1
9	2	Et_2O	0.5	79	76	13.4:1
10	2	Et_2O	0.25	>99	99	13.5:1
11	1	Et_2O	0.25	43	43	12.9:1
12	1	Et_2O	0.1	62	58	13.4:1

[a]Determined by capillary GC analysis versus dodecane as an internal standard.

Table 2. Isomerization of Symmetrical Substrates[a]

entry	substrate	product	yield (%)
			
1	**1b** (R = Me)	**2b** (R = Me)	95[b]
2	**1c** (R = Et)	**2c**[21] (R = Et)	92[b]
3	**1d** (R = ^{n}Pr)	**2d**[21] (R = ^{n}Pr)	87

[a]Conditions: [epoxide] = 0.25 M in diethyl ether, 2 mol % **4**, 22 °C, 18 h. [b]Quantitative GC yield versus dodecane as an internal standard.

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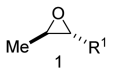
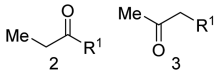
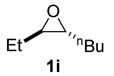
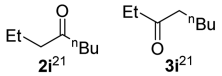
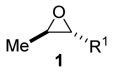
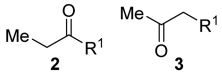
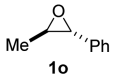
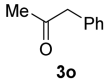
Table 3. Regioselectivity and Substrate Scope[a]

entry	substrate	product(s)	ratio **2**:**3**[b]	yield (%)
	 **1**	 **2** **3**		
1	**1e** (R^1 = Et)	**2e** + **3e** (R^1 = Et)	5.5:1	78[c]
2	**1f** (R^1 = ^{n}Pr)	**2f**[21] + **3f** (R^1 = ^{n}Pr)	10.7:1	98[c]
3	**1g** (R^1 = ^{n}Bu)	**2g** + **3g** (R^1 = ^{n}Bu)	16.6:1	98[c]
4	**1a** (R^1 = ^{n}Pent)	**2a**[21] (R^1 = ^{n}Pent)	14.2:1	78
5	**1h** (R^1 = ^{n}Hex)	**2h** + **3h** (R^1 = ^{n}Hex)	14.3:1	82
6	 **1i**	 **2i**[21] **3i**[21]	3.1:1	98
	 **1**	 **2** **3**		
7[d]	**1j** (R^1 = ^{i}Pr)	**2j** + **3j** (R^1 = ^{i}Pr)	5.8:1	99[e]
8[f]	**1k** (R^1 = CH_2OTBS)	**2k** (R^1 = CH_2OTBS)	>50:1	98
9[g]	**1l** (R^1 = $(CH_2)_3OTBS$)	**2l** (R^1 = $(CH_2)_3OTBS$)	14.6:1	88
10	**1m** (R^1 = Bn)	**2m** (R^1 = Bn)	>50:1	85
11	**1n** (R^1 = *p*-OMeBn)	**2n** (R^1 = *p*-OMeBn)	>50:1	93
12	 **1o**	 **3o**	< 1:>50	83

[a]Conditions: [epoxide] = 0.25 M in diethyl ether, 2 mol % **4**, 22 °C, 18 h. [b]Determined by ^{1}H NMR spectroscopy or GC analysis. [c]Quantitative GC yield versus dodecane as an internal standard. [d]3 mol % catalyst used. [e]Conversion by GC analysis. [f]5 mol % catalyst used at 0.1 M. [g]3.4 mol % catalyst used.

in high regioselectivities for the ethyl ketone **2** over the methyl ketone **3** (Table 3, entries 1−5). These regioselectivities closely tracked with those seen for the corresponding carbonylation using catalyst **4**.[19] Not only is this selectivity opposite to that found by Grubbs and Kaneda for the regioselective Wacker oxidation, but it also allows access to a different major product than that obtained from terminal substrates. For substrate **1a**, for which the optimized conditions yielded a mixture of **2a** and **3a** in 99% yield (Table 1, entry 10), the products were separable by column chromatography such that the major isomer **2a** was isolated in 78% yield (Table 3, entry 4).

When neither alkyl substituent was a methyl group (R = Et, R′ = ^{n}Bu, **1i**, entry 6), regioselectivity dropped off substantially to 3.1:1 favoring the propyl ketone (**2i**[21]). While not ideal, this selectivity is still greater than that seen for the Wacker oxidation of unbiased substrates. We anticipated that increasing the bulk of the R group would improve regioselectivity, but surprisingly the selectivity of **1j** (R^1 = ^{i}Pr, entry 7) was lower compared to that of the ^{n}Pr analogue (**1f**, entry 2). In addition, this substrate required 3 mol % **4** to achieve full conversion.

Some electronically biased substrates were investigated to expand the scope of the reaction. Alcohols protected with the bulky TBS (*tert*-butyl dimethyl silyl) group were tolerated to give ethyl ketones **2k** and **2l** in high isolated yields (entries 8 and 9), though higher catalyst loadings were required. The electronic bias introduced by the silyl ether group would give product **3** (oxidation at the distal carbon) as the major isomer if a regioselective Wacker oxidation was employed on the corresponding alkene, once again showing the complementary nature of the epoxidation/isomerization approach. Also, unlike Kaneda's observation that selectivity dramatically declines as the electronic group is moved farther from the double bond,[7b] regioselectivity remained high for substrate **1l**, in which the OTBS group is three carbons away from the epoxide.

The very high selectivity of benzyl-substituted epoxides (**1m** and **1n**) resulted in sole detection of product **2** using ^{1}H NMR spectroscopy (entries 10 and 11). Aryl substituents, such as the phenyl group in *trans*-*β*-methylstyrene oxide (**1o**, entry 12), promote S_N2 attack at the benzylic position and cause a complete reversal of regioselectivity. The major product **3o** was isolated in high yield, and no minor isomer **2o** was observed. *cis*-Epoxides such as *cis*-2-hexene oxide resulted in low conversion (<40%) and relatively low selectivity (2.4:1) at standard reaction conditions.

Mechanistic Investigations. We propose the nucleophilic mechanism shown in Figure 2 based on the work by

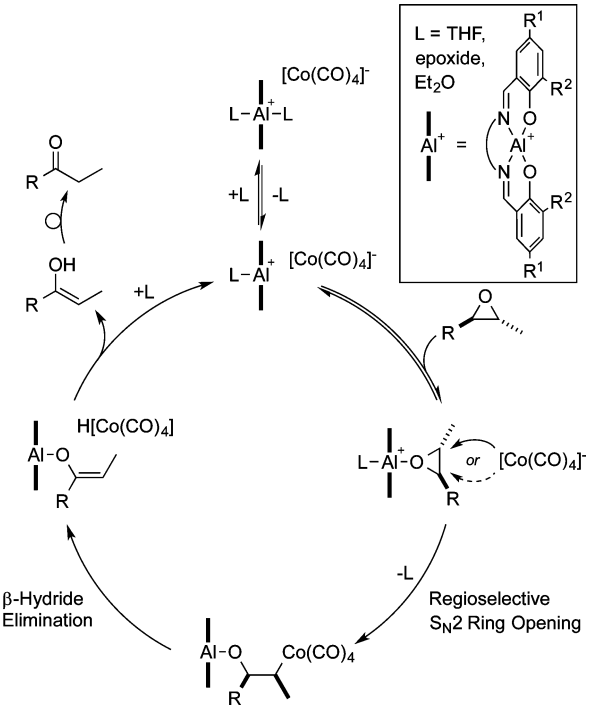


Figure 2. Proposed catalytic cycle for regioselective isomerization of *trans*-epoxides to ketones using ***rac*-4**.

Eisenmann[22] and Kagan[23] on $[Co(MeOH)_6][Co(CO)_4]_2$ as well as our own previous mechanistic observations for the isomerization of terminal epoxides.[15c] After the displacement of a solvent molecule on the Lewis acid by an epoxide, $Co(CO)_4^-$ regioselectively ring opens the epoxide via an S_N2 mechanism to give the corresponding alkoxide complex. *β*-Hydride elimination followed by enolate protonation[24] regenerates the active catalyst, and tautomerization of the enol produces the ketone as the major product. As previously observed,[15c] we confirmed that the presence of both the Lewis acid and the nucleophilic anion was necessary to enact this transformation,[20] ruling out the carbocation-mediated mechanism of the Meinwald rearrangement[25] solely activated by a Lewis acid.[15]

Preliminary kinetic studies using **1a** suggest that the reaction is first order in catalyst and zeroth order in substrate.[20] This

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rules out epoxide binding as the rate-determining step, leaving three other possibilities: (1) epoxide ring opening, (2) β-hydride elimination, or (3) protonation of the enolate. Since both the β-hydride elimination and protonation steps involve a proton transfer, a notable primary kinetic isotope effect is expected if one of these steps is rate limiting. A deuterated version of *trans*-2-octene oxide (**1a**-d_2) was synthesized and subjected to identical reaction conditions as **1a**. We observed no primary kinetic isotope effect (Figure 3), and thus, it is

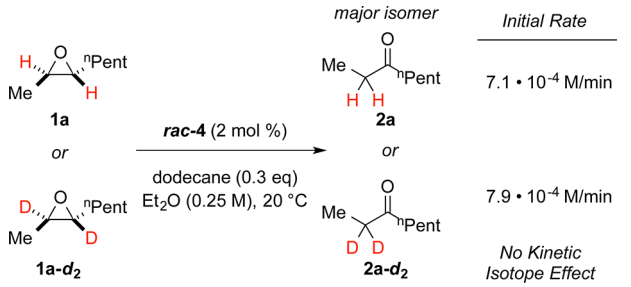

Figure 3. Isotopic labeling studies.

unlikely that these steps are rate determining. Additionally, the deuterated products were isolated to show the expected isotopic labeling in a single α position.[20] This demonstrates the potential for utilizing this reaction as a selective deuteration method, as these products would be difficult to make using current deuteration procedures.[26]

These data are most consistent with S_N2 ring opening of the epoxide as the turnover limiting step for this transformation. This would require that the resting state of the catalyst be after epoxide binding, which could be driven by the relatively poor binding ability of diethyl ether.[27] These observations are also consistent with the similarities seen between this isomerization and the corresponding carbonylation using the same catalyst.[19] The longer reaction times of 2,3-disubstituted epoxide carbonylation as compared to terminal epoxides[19,28] can be rationalized by slower S_N2 attack at a methine (disubstituted epoxide) compared to a methylene (terminal epoxide), and the similar regioselectivities arise from the selectivity determining step also being rate limiting.

Finally, adding an equivalent of 2-butanone relative to epoxide at the beginning of the reaction did not appreciably affect the rate, indicating that there is no product inhibition.[20]

Kinetic Resolution of *trans*-Epoxides. This method was then applied to the kinetic resolution of select *trans*-epoxides.[29] While the kinetic resolution of terminal epoxides has been widely studied and applied by Jacobsen and others,[30] kinetic resolution of internal epoxides remains in its infancy. Chromium salen complexes have been known[31] to catalyze ring opening kinetic resolution of internal *trans*-epoxides, but the substrate scope remains limited to *trans*-butene oxide and aryl epoxides. Few examples in the literature could be found on the resolution of nonaryl 2,3-disubstituted epoxides,[32] and this remains a challenge in the field. Our previous attempts to kinetically resolve epoxides with aluminum salen cobaltate catalysts resulted in low selectivity factors (k_{rel}'s).[33]

We hypothesized that high regioselectivity would be required for high selectivity factors and therefore chose to focus on epoxide **1m** initially. Further optimization of the reaction conditions revealed that a variant of catalyst **4**, in which the methyl group in the para position is substituted with a *tert*-butyl group (catalyst (*S*,*S*)-**5**), gives higher selectivity factors in THF.[20] The reaction is much slower in THF, which helps stop the reaction at the desired level of conversion and hopefully improves selectivity. The concentration of epoxide **1m** was monitored throughout the reaction by analyzing aliquots with chiral GC versus dodecane as an internal standard. All selectivity factors were calculated from at least four points using eq 1.[34] The experimental data for **1m** fit well to an approximate first order k_{rel} of 17 (Figure 4).

$$k_{rel} = \frac{\ln[(1 - conv)(1 - ee)]}{\ln[(1 - conv)(1 + ee)]} \quad (1)$$

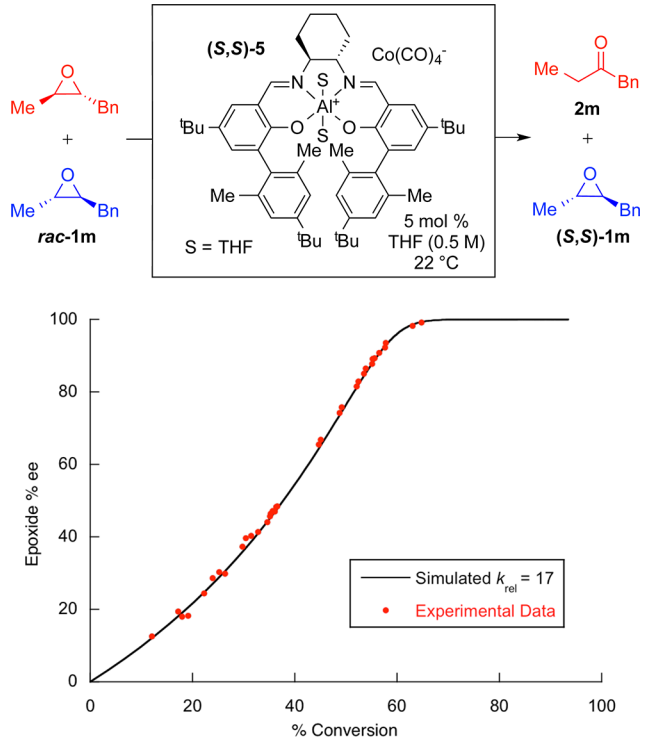

Figure 4. Experimental kinetic resolution data for ***rac*-1m** compared to simulated data.

Encouraged by this result, we investigated how the substitution on the benzyl aromatic ring affects the selectivity factor, but found it had little influence (Table 4). Both sterics and electronics were tested by adding a methyl or methoxy substituent, but in each case the selectivity factor was approximately 20 (entries 2–5).

One feature of isomerization kinetic resolution is that time, not stoichiometry, is used to dictate conversion. We have shown that similar Lewis acid aluminum complexes can be used in conjunction with nucleophiles to enact epoxide ring opening with similar regioselectivities to carbonylation.[35] These results paired with the high selectivities observed in Table 4 provide the opportunity for the development of a nucleophilic ring opening kinetic resolution of internal epoxides in the future.

■ CONCLUSIONS

We have developed a mild and highly regioselective isomerization of *trans*-epoxides to ketones using a [Lewis acid]$^+$[Co(CO)$_4$]$^-$ catalyst previously developed for regioselective carbonylation. This transformation could be useful in organic

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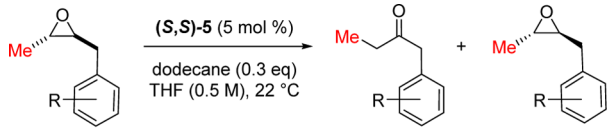
Table 4. Kinetic Resolution of Benzyl-Substituted *trans*-Epoxides[a]



rac-1 2 *S,S*-1

entry	epoxide[29]	conv (%)[b]	% ee[b]	k_{rel}
1	**1m** (R = H)	63	98	17
2	**1p** (R = *o*-Me)	54	85	23
3	**1q** (R = *m*-Me)	59	97	21
4	**1r** (R = *p*-Me)	64	>99	18
5	**1n** (R = *p*-OMe)	65	>99	19

[a]Conditions: [epoxide] = 0.5 M in THF, 5 mol % (*S,S*)-**5**, 22 °C. [b]Determined by chiral GC analysis versus dodecane as an internal standard.

synthesis as part of an epoxidation/isomerization pathway as an alternative to the Wacker oxidation of *trans*-alkenes, which currently suffers from low regioselectivity in the absence of an electronic directing group. Additionally, it can be used as a selective deuteration technique to install two deuterium atoms in a single α position of an aliphatic ketone.

Preliminary kinetic and isotope labeling data suggest epoxide ring opening as the turnover limiting step followed by β-hydride elimination, protonation, and tautomerization to give the desired product. Finally, this method was applied to the kinetic resolution of nonaryl *trans*-epoxides to yield selectivity factors that are synthetically useful ($k_{rel} \approx 20$). To the best of our knowledge, this is the first time a kinetic resolution has been accomplished for benzyl-substituted internal epoxides. On the basis of our mechanistic insights that epoxide ring opening is rate limiting, future work will focus on tuning the nucleophilicity of the anion to achieve higher activity and selectivity as well as further developing the kinetic resolution of internal epoxides using similar catalyst systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10419.

Synthetic procedures, characterization data of all new compounds, and expanded mechanistic and kinetic resolution data (PDF)

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Notes

The authors declare no competing financial interest.

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