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Regioselective Carbonylation of *trans*-Disubstituted Epoxides to *β*-Lactones: A Viable Entry into *syn*-Aldol-Type Products

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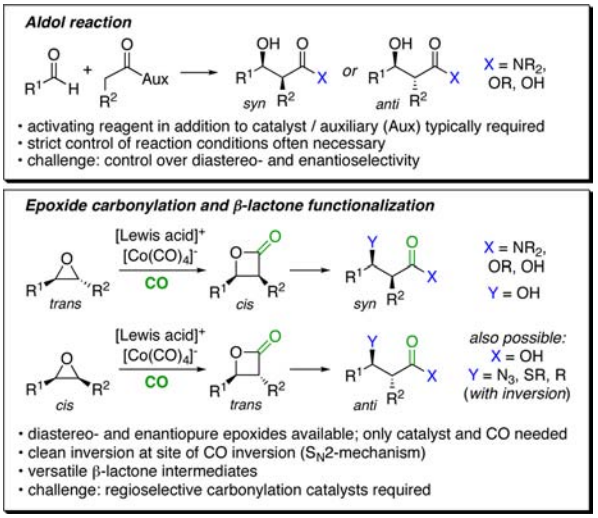
Supporting Information

ABSTRACT: Two new catalysts are reported for the regioselective carbonylation of *trans*-disubstituted epoxides to *cis*-*β*-lactones. The two catalysts display high and opposing selectivities, which generally are difficult to achieve for this class of epoxides. The resulting *β*-lactones are well-defined precursors for a wide variety of aldol-type compounds. Altogether, carbonylation of disubstituted epoxides is established as a viable and economical entry into *syn*- and *anti*-aldol products.

The aldol reaction and its diverse array of products are of great importance in the synthesis of complex molecules and industrial processes.[1] Noteworthy features of this transformation are the formation of a C−C bond and the concomitant creation of two contiguous stereocenters. Aldol products derived from so-called *propionate aldol reactions* (R^2 = Me in Scheme 1) are of special interest,[2] and thus many excellent methods for their synthesis exist.[3] A common deficiency of these methods, however, is the use of stoichiometric amounts of an activating agent, e.g. a base, to facilitate the reaction. Furthermore, strict control of reaction conditions and additional auxiliaries or catalysts are often needed to induce high levels of relative and absolute stereocontrol.[3] Taken together, these attributes can be disadvantageous in terms of cost and operational simplicity.

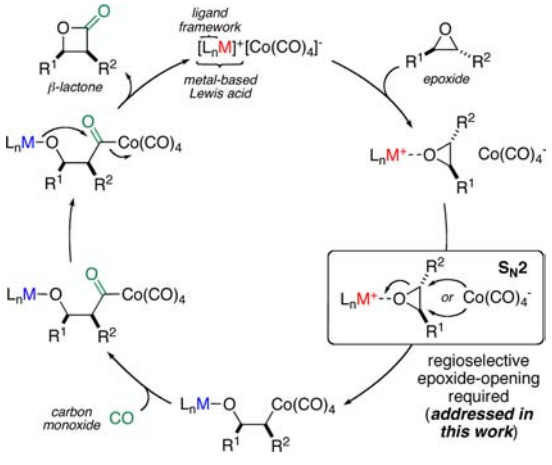
Scheme 1. Epoxide Carbonylation with Subsequent *β*-Lactone Functionalization as a Versatile Alternative to the Aldol Reaction



An alternative approach to the same line of products utilizes *α*,*β*-disubstituted *β*-lactones. Due to their inherent reactivities, they can easily be converted into a wide variety of stereochemically well-defined aldol compounds (Scheme 1), or rearranged to structures otherwise inaccessible via aldol reactions.[4,5] Of the methods available for the synthesis of *α*,*β*-disubstituted *β*-lactones,[4] most require lactonization of a corresponding acyclic precursor.[6] However, these precursors themselves are typically derived from aldol reactions.[7] Another popular approach is the catalyzed (formal) [2+2]-cycloaddition of ketenes to carbonyl compounds. This transformation gives *β*-lactones directly, often with excellent stereoselectivity.[8] Drawbacks are the need to synthesize both reaction partners separately, the use of stoichiometric amounts of an activating agent, and careful control of the reaction parameters.

An attractive alternative method to obtain the *β*-lactones is the carbonylation of vicinally disubstituted epoxides using catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ (Schemes 1 and 2).[9,10] The epoxides are readily available in diastereo- and enantioenriched forms,[11] and the S_N2 mechanism of the carbonylation reaction transforms stereochemistry predictably.[12] However, known carbonylation catalysts show low regioselectivity with vicinally disubstituted epoxides, leading to

Scheme 2. Simplified Mechanism of Epoxide Carbonylation Using [Lewis Acid]$^+$[Co(CO)$_4$]$^-$ Catalysts, and the Problem of Regioselectivity



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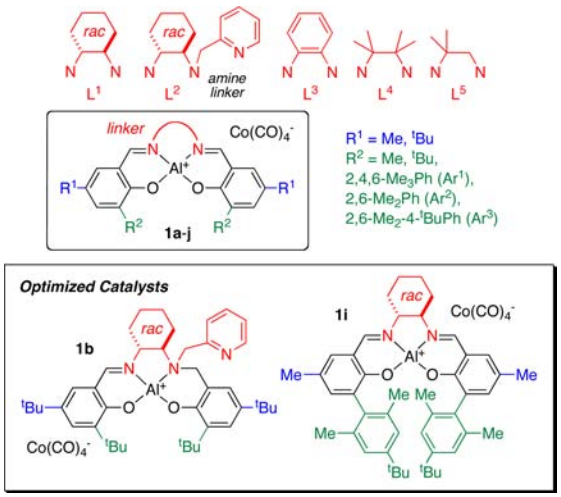
a mixture of products. This is attributed to an unselective S_N2 reaction between the epoxide and the cobaltate anion (Scheme 2).

Opening unbiased vicinally disubstituted epoxides regioselectively using an intermolecular S_N2 reaction is generally very challenging.[13] Consequently, very few selective catalysts exist for such a reaction.[14,15] With the intent to address these problems, we herein report two new carbonylation catalysts that carbonylate *trans*-disubstituted epoxides with good to excellent regioselectivities. The catalysts display opposing selectivities, allowing the synthesis of either regioisomer of the β-lactone. Overall, this method provides access to a large group of more complex α,β-disubstituted β-lactones starting from epoxides and CO, and as such is a convenient and economical entry into a large variety of *syn*- and *anti*-aldol-type products (Scheme 1).

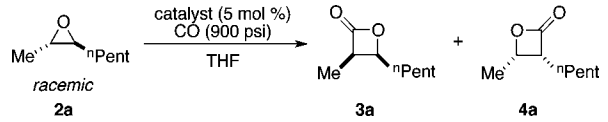
Initial studies focused on identifying a ligand framework for the Lewis acidic metal ion that could impart high degrees of regioselectivity in the carbonylation of *trans*-epoxides (Chart 1). Methyl-substituted epoxides such as **2a** were chosen as

Chart 1. [Lewis Acid]$^+$[Co(CO)$_4$]$^-$ Catalysts Explored in This Study



substrates because the resulting β-lactones **3** and **4** are both of interest. Lactone class **3** serves as a precursor for biologically important propionate aldol products.[2] Lactones **4** give aldol-type products based on acetaldehyde, which can be a troublesome electrophile in aldol reactions due to its suspected carcinogenicity and propensity to hydrate or oligomerize. The salen framework seemed to be a good starting point for ligand development because of its highly modular nature and known ability to form complexes that catalyze carbonylation reactions.[9,12b] Previously reported salen-based carbonylation catalysts, however, showed poor activity at ambient temperature, and a modest contrasteric preference for β-lactone **4a** (Table 1, entry 1).[16] Consequently, a redesign of the ligand was necessary. Changing the ligand structure from the salen-type to a salalen-type ($\mathbf{L}^2$) increased the preference for **4a** to more synthetically useful levels (entry 2). Use of a salalen ligand also allowed for the incorporation of an additional pyridine donor ligand. Based on prior mechanistic studies,[12b] this was expected to facilitate the rate-determining step in the catalytic cycle, thus improving the low activity of catalysts such as **1a** at room temperature. Catalyst **1b** proved useful for the enhanced

Table 1. Evaluation of Carbonylation Catalysts for the Regioselective Carbonylation of *trans*-Epoxide 2a[a]



entry	linker	R^1	R^2	catalyst	ratio[b] **3a:4a**	conv[b] (%)
1	$\mathbf{L}^1$	^{t}Bu	^{t}Bu	**1a**	1:1.6	5
2[c]	$\mathbf{L}^2$	^{t}Bu	^{t}Bu	**1b**	1:4.0	>95
3	$\mathbf{L}^1$	Me	Me	**1c**	1.4:1	9
4	$\mathbf{L}^1$	Me	Ar^1	**1d**	10.1:1	40
5	$\mathbf{L}^3$	Me	Ar^1	**1e**	11.5:1	23
6	$\mathbf{L}^4$	Me	Ar^1	**1f**	2.3:1	87
7	$\mathbf{L}^5$	Me	Ar^1	**1g**	6.7:1	71
8	$\mathbf{L}^1$	Me	Ar^2	**1h**	11.5:1	40
9	$\mathbf{L}^1$	Me	Ar^3	**1i**	11.5:1	>95
10	$\mathbf{L}^3$	Me	Ar^3	**1j**	10.1:1	35

[a]Conditions: [**2a**] = 0.5 M, 22 °C, 20 h. [b]Determined by ^{1}H NMR/GC analysis from crude reaction mixture. [c]Benzene as solvent and 7.5 mol % **1b** used. See Supporting Information for complete table.

production of **4a**, yet a carbonylation catalyst that would strongly favor formation of regioisomer **3a** was still more desirable. A first indication of how this could be achieved came in the form of catalyst **1c** (entry 3). The small size of the substituents R^1 and R^2 in this catalyst gave rise to a small shift in selectivity toward **3a**. A subsequent adjustment of the steric hindrance in R^2 then gave rise to very good selectivity, yet catalyst activity was still only moderate (entry 4). Variation of the diamine linker yielded unsatisfactory results (entries 5−7). However, fine-tuning the steric size of the aryl group in R^2 (entries 8 and 9) led to catalyst **1i**, which in THF showed the best activity and selectivity in producing **3a**.[16] Although only low-quality X-ray crystals of **1i** could be obtained to date (R = 0.0707, w$R2$ = 0.1832), their analysis indicates that the ligand coordinates in the salen-typical *trans*-planar geometry around the Al^{3+} ion, albeit in a rather distorted fashion.[16,17] Lastly, changing the diamine linker in **1i** to $\mathbf{L}^3$ resulted in lower activity (entry 10).

Catalysts **1b** and **1i** were subsequently tested for the regioselective carbonylation of a variety of *trans*-disubstituted epoxides **2** (Tables 2 and 3). GC or ^{1}H NMR analysis of crude reaction mixtures indicated full conversion of starting material to lactone with both catalysts in almost all cases. The resulting regioisomeric β-lactone products **3** and **4** could be separated from one another either directly via column chromatography or after their conversion into the corresponding ester derivatives **5** and **6** by quenching the reaction with MeOH/NaOMe. The latter approach showcases how the obtained β-lactones can readily be converted into related aldol moieties with well-defined stereochemistry.

Carbonylation of *trans*-epoxides **2** with catalyst **1b** gave good preference for β-lactones **4** (Table 2), with ratios **3**:**4** falling in the range from 1:3.0 to 1:4.6. Interestingly, **1b** displayed an almost steady increase in regioselectivity for epoxides **2a**−**e** (Table 2, entries 1−5). This seems counterintuitive because longer alkyl chains should shield their side of the epoxide more from nucleophilic attacks than shorter ones. In line with this expectation, epoxides with sterically more demanding substituents R such as **2f** gave no formation of any lactone when exposed to **1b** (entry 6). Nevertheless, the contrasteric selectivities achieved with **1b** are without precedence for this

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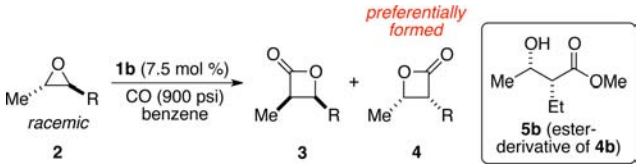
Table 2. Regioselective Carbonylation of *trans*-Disubstituted Epoxides to β-Lactones Using 1b[a]



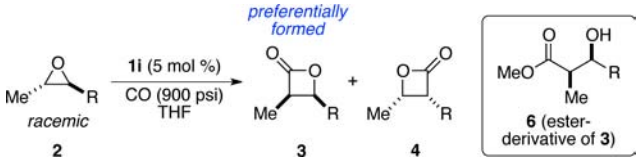
entry	R (epoxide)	ratio[b] 3:4	isolated product	isolated yield (%)
1[c]	Et (**2b**)	1:3.0	**5b**	63
2	^{n}Pr (**2c**)	1:3.7	**4c**	60
3[c]	^{n}Bu (**2d**)	1:3.5	**4d**	65
4	^{n}Pent (**2a**)	1:4.0	**4a**	68
5	^{n}Hex (**2e**)	1:4.6	**4e**	71
6	$(CH_2)_3$OTBS (**2f**)	n.d.	**4f**	<5[b]

[a]Conditions: [**2**] = 0.5 M, 22 °C, 22 h. All reactions gave full conversion (GC or ^{1}H NMR analysis), except for **2f** (<5%). Yields refer to isolated products. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]5 mol % of **1b** used. n.d. = not determined. TBS = ^{t}BuMe$_2$Si.

group of epoxides, and cannot readily be explained by invoking an inherent steric or electronic bias.

In comparison to **1b**, catalyst **1i** generally showed higher regioselectivities in the carbonylation of *trans*-epoxides **2**, with ratios **3**:**4** typically exceeding 10.0:1 in favor of **3** (Table 3).

Table 3. Regioselective Carbonylation of *trans*-Disubstituted Epoxides to β-Lactones Using 1i[a]



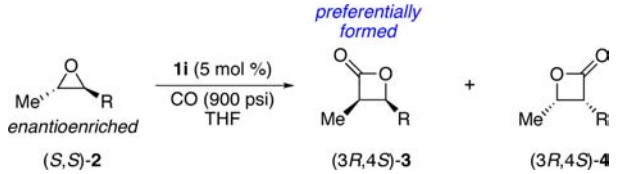
entry	R (epoxide)	ratio[b] 3:4	isolated product	isolated yield (%)
1	Et (**2b**)	6.1:1	**6b**	60
2	^{n}Pr (**2c**)	11.5:1	**6c**	68
3	^{n}Bu(**2d**)	13.3:1	**6d**	74
4	^{n}Pent (**2a**)	11.5:1	**6a**	79
5	^{n}Hex (**2e**)	13.3:1	**6e**	85
6	$(CH_2)_3$OTBS (**2f**)	19.0:1	**6f**	75
7[c]	$(CH_2)_2$OTBS (**2g**)	24.0:1	**6g**	81
8[d]	CH_2OTBS (**2h**)	>50:1	**3h**	92
9	CH_2Ph (**2i**)	>50:1	**3i**	84
10	^{i}Pr (**2j**)	10.1:1	**3j** + **4j**[b]	45[b]

[a]Conditions: [**2**] = 0.5 M, 22 °C, 20 h. All reactions gave full conversion (GC or ^{1}H NMR analysis), except for **2j** (45%). Yields refer to isolated products. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]7.5 mol % **1i** used. [d]10 mol % **1i** used. TBS = ^{t}BuMe$_2$Si.

Only epoxide **2b** gave a lower ratio of 6.1:1 (entry 1). Given the similarity of the epoxide substituents in **2b** (Me vs Et), this is still a very good ratio, and underscores the ability of **1i** to effectively enhance even small degrees of steric bias contained in **2**. In contrast to the trend observed with **1b**, epoxides **2a,c–e** showed little variation in regioselectivity as the length of the alkyl chain was altered (entries 2–5). As expected, *trans*-epoxides **2** with sterically more demanding substituents R gave even better selectivities toward β-lactones **3** (entries 6–9). In the cases of **2h,i**, this additional bias was strong enough to form lactones **3h,i** almost exclusively, with only trace amounts of **4h,i** being detected via ^{1}H NMR spectroscopy. However, placement of steric bulk immediately adjacent to the epoxy group (**2j**, entry 10) gave a mixture of **3** and **4** and relatively poor conversion. Likewise, *trans*-epoxides with sterically very similar substituents such as *trans*-2-butyl-3-ethyloxirane (**2k**) gave rather low selectivities when using **1i**.[18]

Given the good performance of **1i**, its ability to regioselectively carbonylate enantioenriched *trans*-epoxides was investigated next. The use of enantioenriched epoxides is very attractive because several excellent methods for their preparation exist,[11] and stereochemistry is reliably converted during carbonylation reactions.[12] A potential pitfall, however, lies in the fact that **1i** is typically used as a racemate. This can lead to matched/mismatched combinations[19] between the enantioenriched epoxide and the two enantiomers of the racemic catalyst, thus potentially diminishing the good selectivities observed before with racemic epoxides. To explore this scenario, highly enantioenriched (*S,S*)-**2e** (>95% ee) and (*S,S*)-**2i** (99% ee) were synthesized and carbonylated using racemic versions of **1i** (Table 4). Good regioselectivities and

Table 4. Regioselective Carbonylation of Enantioenriched *trans*-Disubstituted Epoxides (*S,S*)-2e,i[a]



entry	R (epoxide)	catalyst	ratio[b] 3:4	conv[b] (%)
1	^{n}Hex (*S,S*-**2e**)	*rac*-**1i**	13.3:1	>95
2	^{n}Hex (*S,S*-**2e**)	(*S,S*)-**1i**	1.6:1	80
3	^{n}Hex (*S,S*-**2e**)	(*R,R*)-**1i**	32.3:1	>95
4	CH_2Ph (*S,S*-**2i**)	*rac*-**1i**	>50:1	>95
5	CH_2Ph (*S,S*-**2i**)	(*S,S*)-**1i**	13.4:1	56
6	CH_2Ph (*S,S*-**2i**)	(*R,R*)-**1i**	>50:1	>95

[a]Conditions: [**2**] = 0.5 M, 22 °C, 20 h. [b]Conversion to lactone, determined by ^{1}H NMR analysis of crude reaction mixture.

activities were retained with both enantioenriched epoxides when using *rac*-**1i** (Table 4, entries 1 and 4). These results document that *rac*-**1i** is well suited for the regioselective carbonylation of enantioenriched *trans*-epoxides, which ultimately leads to enantioenriched aldol-type products. The use of enantiopure catalysts also allowed for the identification of matched/mismatched pairs between the epoxide and the carbonylation catalyst. As Table 4 shows, *trans*-epoxides with (*S,S*)-configuration constitute a mismatched pair with (*S,S*)-**1i**, leading to significantly reduced selectivity and activity (entries 2 and 5). The matched case with (*R,R*)-**1i**, however, improved further on the already good selectivity and produced the preferred regioisomer **3** almost exclusively (entries 3 and 6).

It is currently unclear why (*R,R*)-**1i** preferentially interacts with (*S,S*)- instead of (*R,R*)-*trans*-epoxides, and how the catalyst is able to induce such high levels of regioselectivity. Steric interactions presumably play a major role in both processes. Moreover, it is reasonable to assume that, once the epoxide is bound to the Lewis acid, the movement of its substituent R is conformationally restricted. This restriction

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then probably confines R to positions that shield its corresponding epoxy methine carbon from nucleophilic attacks, thus favoring ring-opening of the epoxide at the observed position.

In summary, two new carbonylation catalysts **1b** and **1i** are reported that convert *trans*-disubstituted epoxides **2** into the corresponding regioisomeric β-lactones **3** and **4**. Due to the regioselectivities displayed by **1b** and **1i**, only one of the two β-lactone regioisomers is predominantly produced in these reactions. Moreover, the two catalysts show opposing regioselectivities, and thus provide access to a large variety of α,β-disubstituted β-lactones starting from readily available epoxides and carbon monoxide. In addition, these features are retained with enantiopure epoxides, and regioselectivity can be improved even further by matching the right enantiomers of catalyst and epoxide. Lastly, this work constitutes a major advance toward regioselective intermolecular S_N2 ring-opening reactions of vicinally disubstituted epoxides. Current work focuses on the regioselective carbonylation of disubstituted *cis*-epoxides, as well as the development of enantiopure catalysts for the synthesis of enantioenriched β-lactones.[20]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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