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Enantioselective Acyloin Rearrangement of Acyclic Aldehydes Catalyzed by Chiral Oxazaborolidinium Ion

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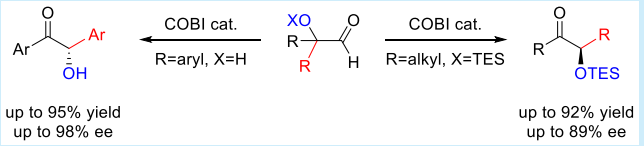
ABSTRACT: A catalytic enantioselective acyloin rearrangement of acyclic aldehydes to synthesize highly optically active acyloin derivatives is described. In the presence of a chiral oxazaborolidinium ion catalyst, the reaction provided chiral α-hydroxy aryl ketones in high yield (up to 95%) and enantioselectivity (up to 98% ee). In addition, the enantioselective acyloin rearrangement of α,α-dialkyl-α-siloxy aldehydes produced chiral α-siloxy alkyl ketones in high yield (up to 92%) with good enantioselectivity (up to 89% ee).



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The acyloin rearrangement,[1−5] involving 1,2-aryl or -alkyl migration to the carbonyl group, is a useful synthetic method for structural reorganization of organic molecules that renders the synthesis of various natural products feasible.[6,7] Through the acyloin rearrangement, α-hydroxy ketone (acyloin)[8] can be easily synthesized as a versatile building block[8b,9] for many natural products and pharmaceuticals.[8b,10] However, the inherent reversibility of this reaction involving an equilibrium between two isomers[1b] has made it highly challenging to develop catalytic enantioselective rearrangements.

To overcome this limitation, asymmetric acyloin rearrangements of aldehyde moieties have been developed.[2,3] Because the released steric and strain factors of ketones provide a thermodynamic advantage compared with aldehydes, the system undergoes a unidirectional reaction toward ketone products.[1b] Currently there are three examples of enantioselective acyloin rearrangements of acyclic aldehyde derivatives such as protected aldehydes or aldimine compounds.[2b−d] In 2007, the Maruoka group reported a chiral-organoaluminum-catalyzed enantioselective rearrangement of α,α-dialkyl-α-siloxy aldehydes (Scheme 1A, a).[2d] In 2014, the Wulff group developed an asymmetric α-iminol rearrangement of α-hydroxy aldimines catalyzed by a zirconium/VANOL complex (Scheme 1A, b).[2c] Three years later, chiral phosphoramides were used to catalyze the asymmetric rearrangement of α-hydroxy acetals, as reported by the Zhu group (Scheme 1A, d).[2b] To the best of our knowledge, there is only one example of an asymmetric acyloin rearrangement using acyclic α-hydroxy aldehyde.[2a] Very recently, the Feng group reported the enantioselective acyloin rearrangement of α-hydroxy aldehydes using an aluminum/*N*,*N*′-dioxide complex as the catalyst (Scheme 1A, c). However, enantioenriched aromatic acyloins were obtained in low yield (11−54%) with 74−88% ee. Thus, the development of a new catalytic reaction is highly desired to improve the yield and enantioselectivity of acyloin and broaden its substrate scope.

Recently, our group reported the catalytic asymmetric acyloin rearrangement of cyclic aldehydes[3] in the presence of a chiral oxazaborolidinium ion[11,12] (COBI) as a Lewis acid catalyst (Scheme 1B, a). The catalytic acyloin rearrangement of cyclopropyl aldehydes, which were formed through enantioselective cyclopropanation of siloxyacrolein with diazo esters, provided highly optically active cyclobutanones (81−98% ee) with excellent diastereomeric ratios (up to >20:1). Inspired by these encouraging results, we envisioned that the reaction of acyclic aldehydes would provide chiral acyloins under similar conditions. Herein we report a broadly applicable enantioselective acyloin rearrangement of acyclic aldehydes catalyzed by the COBI catalyst.

Initially, the asymmetric acyloin rearrangement of α,α-diphenyl-α-trimethylsiloxy aldehyde **1a** was examined in the presence of 20 mol % COBI catalyst **3a** activated by trifluoromethanesulfonic imide (Table 1, entry 1). When the reaction was carried out at −40 °C in toluene, the optically active α-trimethylsiloxy ketone **2a** was obtained in 92% yield with 60% ee. First, changing the solvent to dichloromethane led to improved enantioselectivity (Table 1, entry 2). In a screen of various catalyst structures, the simple catalyst **3a** with Ar = R = phenyl yielded the best result (Table 1, entries 2−4). Although catalyst **3b** afforded **2a** in good yield, the reaction time for rearrangement was excessive (Table 1, entry 3). Because α-triethylsiloxy ketone **2b** was obtained with a

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Scheme 1. Enantioselective Catalytic Acyloin Rearrangement of Various Aldehyde Compounds

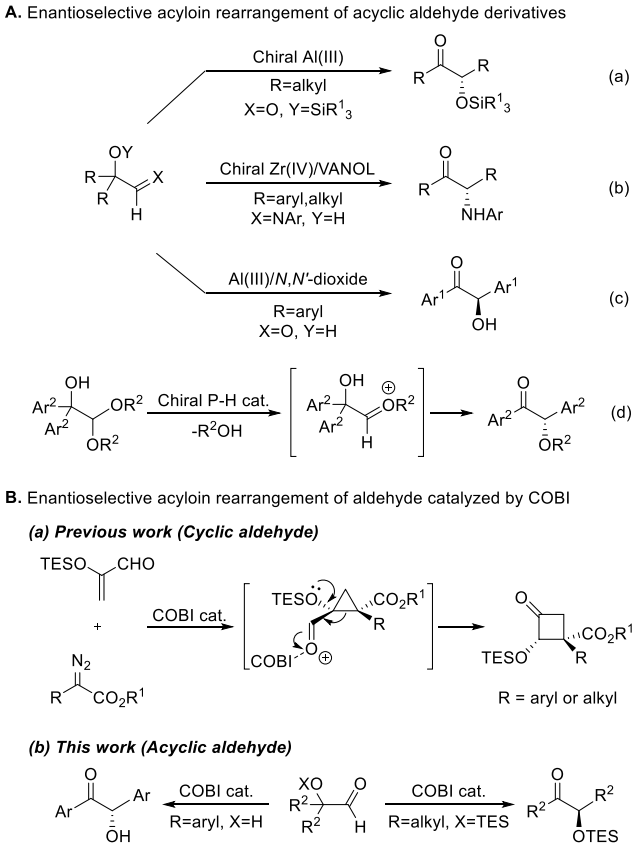
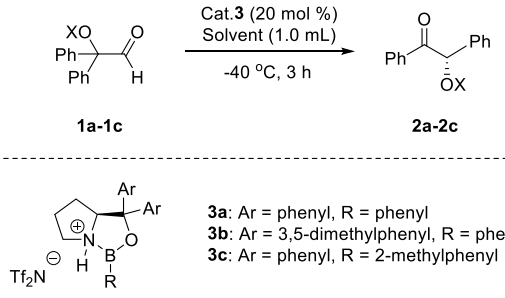


Table 1. Optimization of the Enantioselective Acyloin Rearrangement of Aldehydes 1[a]



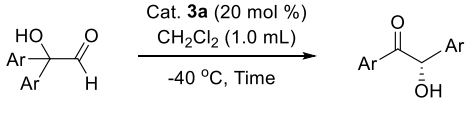
entry	X	2	3	solvent	yield (%)[b]	ee (%)[c]
1[d]	TMS[e]	2a	3a	PhMe	92	60
2	TMS	2a	3a	CH_2Cl_2	90	63
3[d]	TMS	2a	3b	CH_2Cl_2	90	64
4[d]	TMS	2a	3c	CH_2Cl_2	50	14
5	TES[f]	2b	3a	CH_2Cl_2	95	27
6	H	2c	3a	CH_2Cl_2	90	98

[a]The reactions were performed with aldehyde **1** (0.2 mmol) in the presence of catalyst **3** (20 mol %) in the solvent (1.0 mL) for 3 h at −40 °C. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The reaction was conducted for 18 h. [e]Trimethylsilyl. [f]Triethylsilyl.

dramatically diminished enantioselectivity of 27% (Table 1, entry 5), we thought that a sterically less hindered group was needed. Gratifyingly, introduction of a hydroxy group into aldehyde **1** produced α-hydroxy ketone **2c** in 90% yield with an improved enantioselectivity of 98% (Table 1, entry 6).

After optimization of the reaction conditions for the enantioselective acyloin rearrangement, we evaluated the scope of the reaction with a range of α,α-diaryl-α-hydroxy aldehydes (Table 2). The reaction of electron-rich aldehydes **1**

Table 2. Scope of α,α-Diaryl-α-hydroxy Aldehydes 1[a]



entry	2	Ar	time (h)	yield (%)	ee (%)
1	2c	Ph	3	90 (86[b])	98 (98[b])
2	2d	4-MePh	12	88	98
3	2e	4-MeOPh	12	83	95
4[c]	2f	4-FPh	12	85	95
5[c,d]	2g	4-ClPh	12	80	96
6[c,d]	2h	4-BrPh	12	70	95
7	2i	2-MePh	1	93	98
8	2j	2-MeOPh	1	88	90
9	2k	3-MePh	18	86	98
10[e]	2l	1-naphthyl	1	95	94
11[c,e]	2m	2-naphthyl	18	85	92

[a]The reactions of α-hydroxy aldehydes **1** (0.2 mmol) were performed in the presence of catalyst **3a** (20 mol %) in dichloromethane (1.0 mL) at −40 °C. All yields refer to isolated products. The ee values were determined by chiral HPLC analysis. [b]On a 1.0 mmol scale. [c]The reaction was conducted at 0 °C. [d]40 mol % catalyst was used. [e]2.0 mL of dichloromethane was used.

provided highly optically active products **2** in excellent yields (Table 2, entries 2, 3, and 7−11). However, the rearrangement of halogenated aldehydes **1** showed very low conversion at −40 °C. When the reaction was performed at 0 °C, acyloins **2f−h** were obtained in high yield and ee (Table 2, entries 4−6). The (*S*) absolute configurations of **2c−m** were confirmed through a comparison of the optical rotation data of **2c−m** with literature values (see the Supporting Information).

Encouraged by the promising results illustrated in Table 2, we next investigated the reaction of α-aryl-α-phenyl-α-hydroxy aldehydes to investigate their migratory aptitude (Table 3). Under the optimized conditions, a mixture of α-hydroxy ketones **2n** and **2n′** was obtained with moderate selectivity (3:1), preferring migration of the *p*-tolyl group in 40% yield with excellent enantioselectivity (Table 3, entry 1). Changing the *p*-tolyl group to a sterically more hindered *o*-tolyl group improved the migratory selectivity to 4.5:1 (Table 3, entry 3). When the strong electron-donating *p*-methoxyphenyl substituted aldehyde **1q** was used, the migratory selectivity increased to 10:1 (Table 3, entry 4).[2a] The unreacted **1q** was recovered in 35% yield with 99% ee (*s* factor = 16).[13] These results matched well with the migration order for the pinacol rearrangement.[2d,14,15a]

To further investigate the substrate scope of the present catalytic system, we performed the catalytic asymmetric acyloin rearrangement with α,α-dibenzyl-α-hydroxy aldehyde **4a**. However, the best conditions for α,α-diaryl aldehydes were not the optimal conditions for α,α-dialkyl aldehydes. Because of easy dimerization of **4a** with the COBI catalyst system, protected α-triethylsiloxy aldehyde **4b** was considered as a substrate for the rearrangement. While the reaction of **4a** provided the dimer product in 90% yield, the reaction of **4b**

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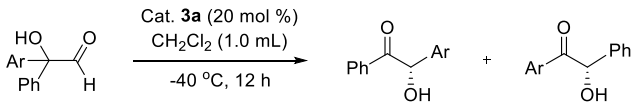
Table 3. Enantioselective Acyloin Rearrangement of α-Aryl-α-phenyl-α-hydroxy Aldehydes 1[a]



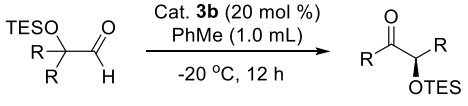
1 2 2'

entry	2	Ar	2:2′	yield (%)	ee (%)
1	**2n**	4-MePh	3:1	40	96 (98[b])
2	**2o**	2-naphthyl	1.9:1	69	95 (97[b])
3[c]	**2p**	2-MePh	4.5:1	40	96 (93[b])
4[d,e]	**2q**	4-MeOPh	10:1	58	92 (99[b])

[a]The reactions of α,α-aryl phenyl-α-hydroxy aldehydes **1** (0.2 mmol) were performed in the presence of catalyst **3a** (20 mol %) in dichloromethane (1.0 mL). All yields refer to the total yields of products **2** and **2′**. The ee values were determined by chiral HPLC analysis. Except for the values in parentheses, all of the ee values are the results for acyloin **2**. [b]ee of **2′**. [c]The reaction was conducted for 4 h at −78 °C. [d]The reaction was conducted for 0.5 h at −78 °C. [e]The ee of recovered **1q** was determined by chiral HPLC analysis after reduction of the aldehyde using $NaBH_4$ (1.0 equiv).

proceeded well in the presence of catalyst **3b** in toluene at −20 °C to afford the rearranged product **5b** in 92% yield with 86% ee (Table 4, entries 1 and 2; for details, see the Supporting Information[15b]). With the modified optimization, the range of α,α-dialkyl-α-siloxy aldehydes was examined. As shown in Table 4, regardless of the electronic properties of the substituents on the benzyl group, optically active acyloins **5** were obtained (Table 4, entries 3−7). Notably, our catalytic system successfully yielded simple alkyl substrate **5h** with good enantioselectivity (Table 4, entry 8).

Table 4. Scope of α,α-Dialkyl-α-siloxy Aldehydes 4[a]



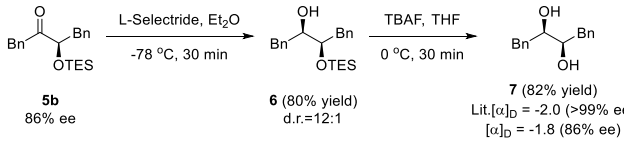
4 5

entry	5	R	yield (%)	ee (%)
1[b]	**5a**	Bn	<10[c]	–
2	**5b**	Bn	92 (90[d])	86 (86[d])
3	**5c**	4-MeOBn	84	76
4[e]	**5d**	4-FBn	90	86
5[f]	**5e**	4-ClBn	80	82
6[e,f]	**5f**	2-BrBn	88	89
7[e]	**5g**	2-naphthyl-CH_2	87	86
8	**5h**	$(CH_3)_2CHCH_2$	87	78[g]

[a]The reactions of α-siloxy aldehydes **4** (0.2 mmol) were performed in the presence of catalyst **3b** (20 mol %) in toluene (1.0 mL) at −20 °C. All yields refer to isolated products. The ee values were determined by chiral HPLC analysis. [b]The reaction was conducted with the α,α-dibenzyl-α-hydroxy aldehyde. [c]A 90% yield of dimerized products was obtained. [d]On a 1.0 mmol scale. [e]The reaction was conducted for 18 h. [f]The reaction was conducted at 0 °C. [g]Determined by chiral HPLC after removal of the TES protecting group followed by reprotection with 3,5-dinitrobenzoate.

The obtained α-hydroxy aryl ketone (benzoin) moieties are known to be valuable intermediates that can be used for the preparation of functionalized compounds such as chiral diols, diol derivatives, amino alcohols, etc.[2b,16] The diastereomeric selective reduction of α-hydroxy alkyl ketone **5b** to confirm the absolute structure is illustrated in Scheme 2. The reduction of

Scheme 2. Reduction of 5b and Removal of the Triethylsilyl Group of 6



5b with L-Selectride generated polar Felkin−Anh product[17] **6** with a high diastereomeric ratio (12:1). The triethylsilyl group of **6** was removed with tetrabutylammonium fluoride (TBAF) to afford chiral diol **7**. The absolute configuration of **7** was confirmed through a comparison of the optical rotation data for **7** with the literature result,[18] and the (*R*) configurations of all acyloins **5** were assigned accordingly.

The observed stereochemistry for the asymmetric acyloin rearrangement of the aldehyde using COBI catalyst **3a** or **3b** could be explained by pretransition state models **8** or **9** shown in Figure 1. In the case of α,α-diaryl-α-hydroxy aldehydes, the

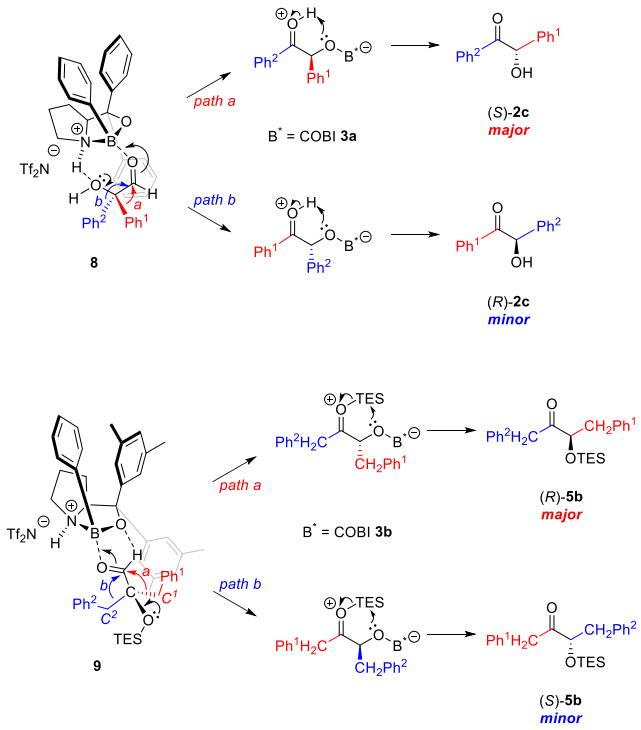


Figure 1. Pretransition state models for enantioselective acyloin rearrangements of α-hydroxy aldehyde **1c** catalyzed by **3a** and α-siloxy aldehyde **4b** catalyzed by **3b**.

hydrogen-bonding coordination of aldehyde **1c** to **3a** represented by **8** was similar to that previously suggested for enantioselective Strecker reactions with aldimines.[19] In pretransition state complex **8**, the aldehyde was placed above the phenyl group of catalyst **3a**, which effectively blocked the *re* face (back) migration of the Ph^2 group of aldehyde **1c**. Carbonyl activation by the COBI catalyst facilitated concerted migration of the Ph^1 group of **1c** (path *a* in pretransition state **8**), generating an oxocarbenium ion intermediate. The proton

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shift provided α-hydroxy ketone **2c** with the (*S*) configuration as the major enantiomer.

Interestingly, the acyloin rearrangement of α,α-dialkyl aldehydes unexpectedly yielded α-siloxy ketone **5b** with the (*R*) configuration. Presumably, the mode of coordination of α,α-dibenzyl-α-siloxy aldehyde **4b** to COBI **3b** was the same as previously postulated for enantioselective 1,2-addition of aldehydes with COBI.[11a] In pretransition state model **9**, the benzyl (CH_2Ph^1) group was placed above the 3,5-dimethylphenyl group of **3b** as a result of π−π interactions between Ph^1 and the 3,5-dimethylphenyl group. At that time, the migrating σ bond ($C-C^1$) was parallel to the carbonyl π bond, while the other σ bond ($C-C^2$) was orthogonal. Because the parallel σ bond could migrate to the carbonyl π bond during the acyloin rearrangement,[6] only the benzyl (CH_2Ph^1) group could participate in the concerted migration pathway (path *a* in pretransition state **9**). As a result, α-siloxy ketone **5b** with the (*R*) configuration was formed as the major enantiomer through silyl group shift.

In summary, we developed a Lewis acid-catalyzed enantioselective acyloin rearrangement of acyclic α,α-diaryl and α,α-dialkyl aldehydes. This synthetic method provided highly optically active α-hydroxy or α-siloxy ketones in high yields. Moreover, the catalytic system was applied to the reaction of differently α,α-disubstituted-α-hydroxy aldehydes and afforded isomeric ketones with good migratory selectivities (up to 10:1) and excellent enantioselectivities. The absolute configurations of the products were predicted using the pretransition state models in Figure 1 and were confirmed by comparison with reported literature. We believe that the resulting acyloins could be valuable precursors for the synthesis of bioactive compounds. Additional extensions of the substrate scope and application of this approach are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00314.

General information, experimental procedures, characterization of products, and full analytical data with spectra (PDF)

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Notes

The authors declare no competing financial interest.

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