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Catalytic Asymmetric Acyloin Rearrangements of α-Ketols, α-Hydroxy Aldehydes, and α-Iminols by *N,N′*-Dioxide–Metal Complexes

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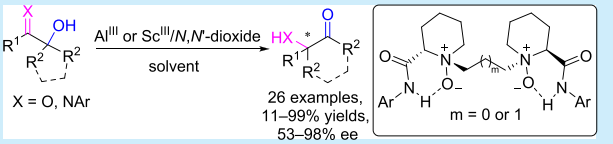
ABSTRACT: A highly enantioselective acyloin rearrangement of cyclic α-ketols has been developed with a chiral Al(III)–*N,N′*-dioxide complex as catalyst. This strategy provided an array of optically active 2-acyl-2-hydroxy cyclohexanones in moderate to good yields with high enantioselectivities. The asymmetric isomerizations of acyclic α-hydroxy aldehydes and α-iminols were achieved as well under modified conditions, affording the corresponding chiral α-hydroxy ketones and α-amino ketones in moderate results. Moreover, further transformations of product to enantioenriched diols were carried out.



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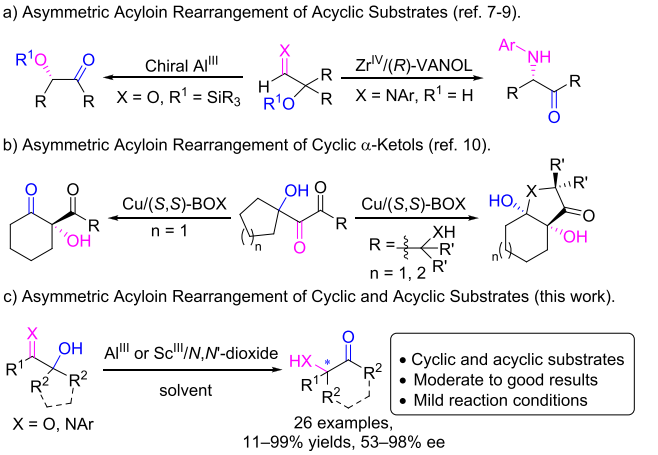
The acyloin rearrangement is the transformation of an α-hydroxycarbonyl compound into its structural isomer through 1,2-carbon-to-carbon migration.[1] Since the seminal report from Prins and Shoppee in 1943,[2] acyloin rearrangement has been gradually utilized to construct otherwise inaccessible molecular frameworks, especially for the synthesis and structural modification of natural products.[3] However, the reversibility of such transformations under either acidic, basic, or thermal conditions[4] hampered its wide application in organic synthesis. In view of the high value of the enantioenriched α-hydroxy ketones and α-amino ketones,[5] the development of catalytic asymmetric versions of such processes was intriguing but highly challenging.

In 2003, Brunner and Kagan et al. first disclosed their efforts toward the asymmetric α-ketol rearrangement. A moderate ee value was obtained for the isomerization of 1-benzoylcyclopentanol after screening plenty of catalysts.[6] In 2007, the Maruoka group described the asymmetric rearrangement of α,α-dialkyl-α-siloxy aldehydes to α-siloxy ketones by using a chiral aluminum catalyst (Scheme 1a, left).[7] In 2014, Wulff et al. reported zirconium/VANOL complex accelerated asymmetric α-iminol rearrangements with wide substrate scope (Scheme 1a, right).[8] Three years later, the first example of organocatalytic enantioselective acyloin rearrangement of α,α-disubstituted α-hydroxy acetals was achieved by Zhu and co-workers.[9] Very recently, the same group developed copper/Box catalyzed highly enantioselective cyclic α-hydroxy ketone rearrangement and sequential kinetic resolution processes (Scheme 1b).[10] Enantioenriched 2-acyl-2-hydroxy cyclohexan-1-ones, dihydroxyhexahydro-benzofuranones, and dihydroxyhexahydro-cyclohepta-furanones were delivered in 35–99% yield with 79–98% ee. Nevertheless, this still leaves much room for improvement in terms of substrate scope and catalyst. As part of our ongoing interest in asymmetric rearrangements[11] and

Scheme 1. Chiral Lewis Acid Mediated Acyloin Rearrangements



intrigued by the well-established platform of chiral metal–*N,N′*-dioxide catalysts,[12] we envisioned that this kind of chiral Lewis acid had the potential to be effective in promoting the acyloin rearrangement of α-iminol or α-ketol through coordination and activation of vicinal difunctional groups.[13] Herein, we wish to describe our efforts along this line. The chiral Al(III)–*N,N′*-dioxide complex was identified to be an efficient catalyst to promote enantioselective acyloin rearrangement of cyclic α-

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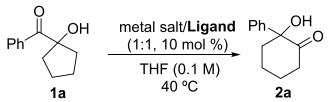
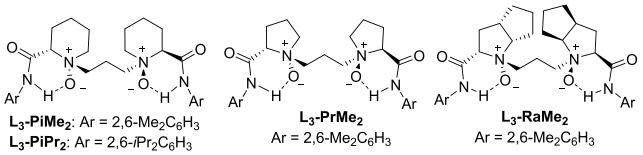
ketols, and various 2-aryl-2-hydroxy cyclohexanones were readily afforded in moderate to good yields with high enantioselectivities. Moreover, under slightly modified conditions, the asymmetric isomerizations of acyclic α-hydroxy aldehydes and α-iminols were achieved as well.

Initially, 1-benzoylcyclopentanol **1a** was selected as the model substrate to optimize the reaction conditions (Table 1).[6,14] First,

Table 1. Optimization of Reaction Conditions for the Asymmetric Rearrangement of Cyclic α-Ketol 1a





L3-PiMe2: Ar = 2,6-$Me_2C_6H_3$
L3-PiPr2: Ar = 2,6-*i*$Pr_2C_6H_3$

L3-PrMe2
Ar = 2,6-$Me_2C_6H_3$

L3-RaMe2
Ar = 2,6-$Me_2C_6H_3$

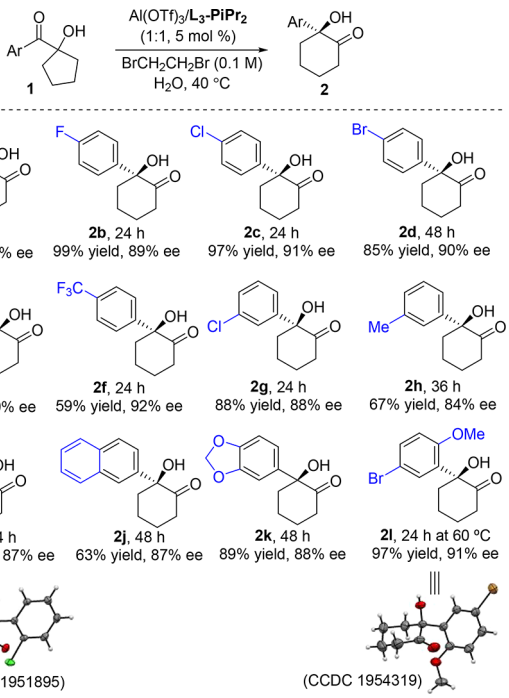
entry[a]	metal salt	ligand	yield (%)[b]	ee (%)[c]
1	$Fe(OTf)_3$	**L3-PiMe2**	48	53
2	$In(OTf)_3$	**L3-PiMe2**	49	27
3	$Al(OTf)_3$	**L3-PiMe2**	47	55
4	$Al(OTf)_3$	**L3-PiPr2**	50	87
5	$Al(OTf)_3$	**L3-PrPr2**	39	85
6	$Al(OTf)_3$	**L3-RaPr2**	28	69
7[d]	$Al(OTf)_3$	**L3-PiPr2**	69	87
8[d,e]	$Al(OTf)_3$	**L3-PiPr2**	99	91
9[d,e,f]	$Al(OTf)_3$	**L3-PiPr2**	98	91

[a]Unless otherwise noted, the reactions were performed with the metal salt/ligand (1:1, 10 mol %) and **1a** (0.1 mmol) in THF (1.0 mL) at 40 °C for 24 h. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]$BrCH_2CH_2Br$ (1.0 mL) was used as the solvent. [e]H_2O (3 μL) was added. [f]5 mol % of catalyst loading.

different metal salts were investigated in the presence of *N*,*N*′-dioxide **L3-PiMe2**. It was pleasant to find that *in situ* formed chiral Lewis acid catalysts could promote the rearrangement of compound **1a** under mild conditions,[6] and $Al(OTf)_3$ gave better results than $Fe(OTf)_3$ and $In(OTf)_3$ in terms of enantioselectivity (entries 1−3, 55% ee vs 53% ee, 27% ee). To our delight, increasing the steric hindrance of the amide substituents from 2,6-$Me_2C_6H_3$ to 2,6-*i*$Pr_2C_6H_3$ resulted in higher enantioselectivity (entry 4, 87% ee vs 55% ee). Then, representative *N*,*N*′-dioxides with different skeletons were examined. **L3-PiPr2** derived from L-pipecolinic acid was proved to be superior to L-proline-derived **L3-PrPr2** or L-ramipril-based **L3-RaPr2** (entries 5 and 6, 87% ee vs 85% ee, 69% ee). The subsequent survey of solvents indicated that $BrCH_2CH_2Br$ could provide an improved yield compared to THF (entry 7, 69% yield vs 50% yield; for more details, see SI, Page 7). Interestingly, the addition of water (3 μL, ca. 1.7 equiv) into the reaction system led to further improvement in the yield and enantiomeric excess (entry 8, 99% yield, 91% ee.).[15] When the reaction was carried out with 5 mol % catalyst loading, both the yield and enantioselectivity were maintained (entry 9).

With the optimal reaction conditions in hand, the substrate scope of 1-aroylcyclopentanols was next examined (Scheme 2). It was found that the substituent pattern and the electronic property of the aryl moiety displayed a limited influence on the enantioselectivity (**2a**−**2l**, 84−92% ee). However, the strong

Scheme 2. Substrate Scope of Cyclic α-Ketols 1[a]



[a]The reactions were carried out with $Al(OTf)_3$/**L3-PiPr2** (1:1, 5 mol %) and **1** (0.1 mmol) with H_2O (3 μL) in $BrCH_2CH_2Br$ (1.0 mL) at 40 °C for the indicated time. Isolated yields. Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase.

electron-withdrawing group (for instance, CF_3) at the *para*-position (**2f**) or methyl substituent at the *meta*-position (**2h**) in the substrate led to diminished yields (59% yield and 67% yield, respectively). To get more insight into the reaction, the product **2f** was subjected to the standard reaction system, and the very trace of starting compound **1f** was observed; the ee value did not change.[4] It is worth mentioning that 2-naphthyl-containing substrate **1j** proceeded the migration process smoothly under the standard conditions, affording the desired product **2j** in decent yield (63%) with good enantiomeric excess (87% ee). Meanwhile, piperonyl-substituted α-hydroxy ketone was suitable as well, and the corresponding product **2k** was isolated in 89% yield with 88% ee. For the reaction of **1l** with the disubstituted aryl ring, elevated reaction temperature (60 °C) was necessary, and product **2l** was obtained with good outcomes (97% yield, 91% ee). The absolute configurations of the products **2i** and **2l** were both determined to be (*S*) configuration by X-ray crystallography analysis, which were consistent with the configurations of chiral **2a**, **2e**, **2f**, and **2j**, by comparing the optical rotation data in the previous report.[16] The configurations of other products were assigned by comparing with the CD spectrum of compound **2i**.

Encouraged by the satisfactory results of cyclic α-ketol, we attempted to apply the current system to the rearrangement of α-hydroxy aldehydes **3** (Scheme 3). Unfortunately, only a trace amount of the desired rearranged product was afforded with 11% ee under the above optimized reaction conditions. After modification of the reaction parameters, including the use of **L3-PiMe2** as the ligand and $Br_2CHCHBr_2$ as solvent, lower reaction temperature (30 °C), and addition of 4 Å MS (10 mg), the yield and enantioselectivity of this transformation reached a satisfactory level (54% yield, 82% ee) after 48 h (see details in

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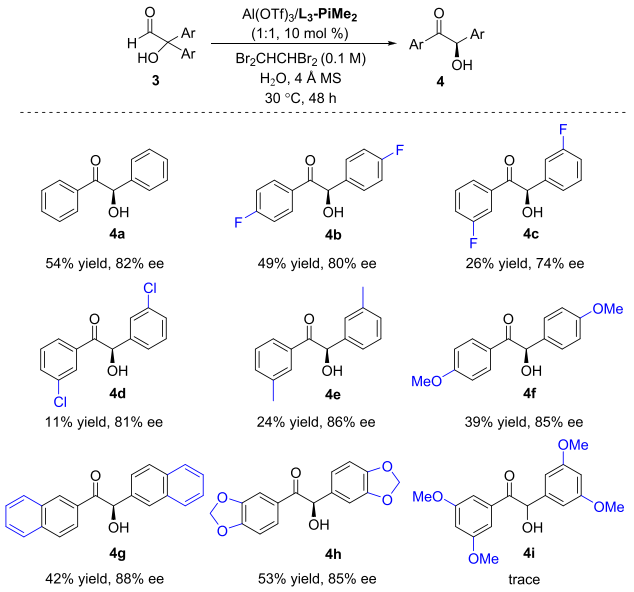
Scheme 3. Substrate Scope of Acyclic α-Hydroxy Aldehydes 3[a]

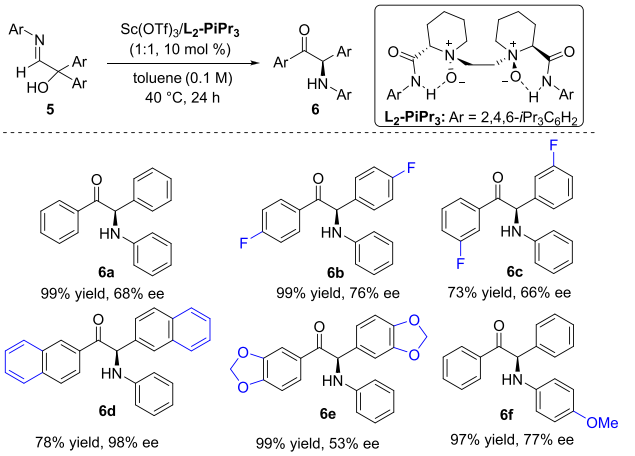


[a]The reactions were carried out with $Al(OTf)_3$/**L_3-PiMe$_2$** (1:1, 10 mol %), **3** (0.1 mmol) with H_2O (3 μL), and 4 Å MS (10 mg) in $Br_2CHCHBr_2$ (1.0 mL) at 30 °C for 48 h. Isolated yields. Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase.

SI).[17] Under these conditions, representative α-hydroxy aldehydes **3** were tested. Although the enantioselective control of such rearrangement was in the good level, a notable difference in the reactivity was observed. Generally, aryl-substituted alcohols with substituents at the *ortho*- or *para*-position furnished the expected products in higher yields than that with *meta*-substituted ones (**4c**−**4e**, **4i**). The absolute configurations of products **4a**−**4g** were determined to be (*R*) by comparing the optical rotation with the previous report.[18]

The asymmetric rearrangement of α-hydroxy aldimines was explored as well. The acyclic 1,1-diphenyl-2-(phenylimino)-ethanol **5a** was selected as the model substrate.[8a] After extensive investigation, we concluded that excellent ee but moderate yield of the corresponding product **6a** was obtained when the In(OTf)$_3$/**L$_2$-PiPr$_3$** complex was employed as the catalyst (41% yield, 93% ee, see SI for details). The low yield of the In(III)-mediated process resulted from the unknown side reaction. Comparatively, the use of $Sc(OTf)_3$ as the metal precursor afforded a high yield but moderate enantioselectivity (99% yield, 68% ee). Then the substrate scope of α-hydroxy aldimines was examined with Sc^{III} as the catalyst (Scheme 4; see Scheme S1 in page 13 of SI for the results of In(III)-mediated reactions). Similarly, the fluoro substituent at *meta*-position **5c** exhibited lower reactivity than that with a *para*-substituted one, **5b**. Of note, substrate **5d** containing 2-naphthyl rings isomerized to the product **6d** in good yield with excellent enantioselectivity (78% yield, 98% ee). Although high yield (99% yield) was obtained for α-hydroxy aldimine **5e** bearing an electron-rich Ar group, slightly lower enantiomeric excess (53% ee) was given. Another substituent, for example, *N*-MeOC$_6$H$_4$-protected aldimine, was compatible in this system, generating the desired rearranged product **6f** in 97% yield with 77% ee. The absolute configurations of the products **6a**, **6b**, and **6f** were determined

Scheme 4. Substrate Scope of Acyclic α-Hydroxy Aldimines 5[a]

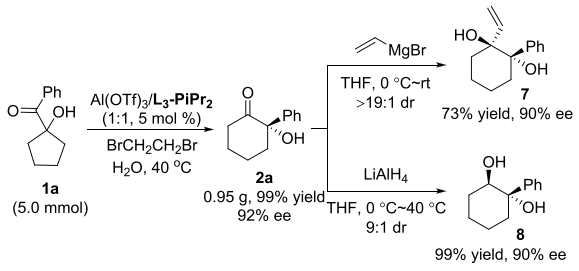


[a]The reactions were carried out with $Sc(OTf)_3$/**L_2-PiPr$_3$** (1:1, 10 mol %) and **5** (0.1 mmol) in toluene (1.0 mL) at 40 °C for 24 h. Isolated yields. Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase.

to be (*R*) by comparing the optical rotation with the previous report.[8a]

To exhibit the practicability of this methodology, a gram-scale synthesis of **2a** was performed under the standard reaction conditions with 5.0 mmol of **1a**, and the corresponding product **2a** was isolated in 99% yield with 92% ee. The transformations of the product were performed as well. Treatment of the chiral compound **2a** with vinylmagnesium bromide gave rise to the diol compound **7** in 73% yield with >19:1 dr (Scheme 5).[16b] Similarly, reduction of the compound **2a** with $LiAlH_4$ provided diol compound **8** in high yield with 9:1 dr and 90% ee.[16b]

Scheme 5. Gram-Scale Synthesis of 2a and Its Further Transformations



In summary, we have realized the acyloin rearrangements of cyclic α-ketols, as well as α-hydroxy aldehydes and aldimines, with chiral *N*,*N*′-dioxide complexes of Al(III) or Sc(III) salts under mild reaction conditions. The corresponding chiral α-hydroxy ketones and α-amino ketones were produced in moderate to good yields with high enantioselectivities. Further studies on other asymmetric rearrangement reactions are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01626.

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Experiment procedures, full spectroscopic data for all new compounds, and copies of ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$ NMR, and HPLC spectra (PDF)

Accession Codes

CCDC 1951895 and 1954319 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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