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Catalytic Enantioselective Benzilic Ester Rearrangement

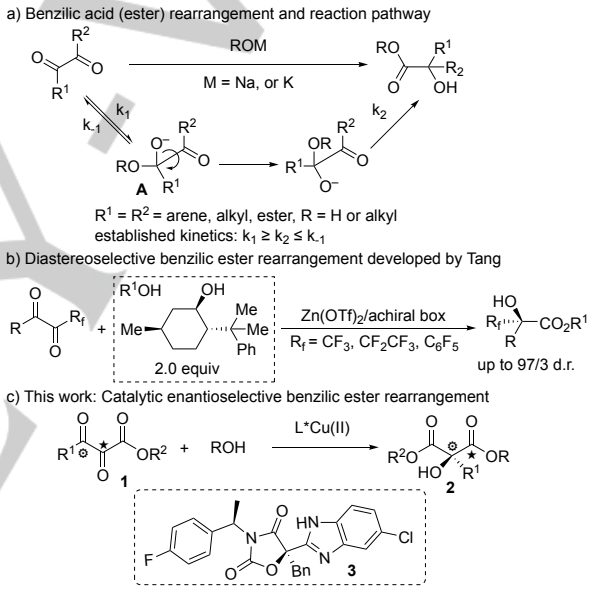
Hua Wu, Qian Wang, and Jieping Zhu*

Abstract: We report the first examples of catalytic enantioselective benzilic ester rearrangement reaction. In the presence of catalytic amount of $Cu(OTf)_2$ and a chiral box ligand under mild conditions, reaction of 2,3-diketoesters with alcohols afforded structurally diverse α-aryl(alkyl) substituted-α-hydroxy malonates (tartronic esters) in good to excellent yields with high enantioselectivities. Preliminary mechanistic studies indicated that hemiketalization, rather than the DKR of hemiketal, was the enantiodetermining step under our reaction conditions.

The development of enantioselective anionotropic 1,2-rearrangement has been a recent focus[1] and the catalytic conditions for the semi-pinacol,[2] pinacol,[3] intramolecular Cannizzaro reaction,[4] α-ketol (acyloin),[5] α-iminol[6] and Meinwald[3c,7] rearrangements have been uncovered for the synthesis of important chiral building blocks that are otherwise difficultly accessible. Despite these notable advances, catalytic enantioselective benzilic acid rearrangement (BAR, Scheme 1a),[8] a prototypical 1,2-anionotropic shift, remains unknown.

Reported in 1838 by von Liebig, the BAR reaction, converting 1,2-diketones to tertiary α-hydroxy acids, is the first rearrangement reaction to be discovered. Together with the benzilic ester rearrangement (BER),[9] they have been the subjects of the extensive mechanistic studies[10] and have been applied to the synthesis of complex natural products[11] as well as the late stage structural modification of bioactive compounds.[12] The accepted mechanism of these rearrangements is depicted in Scheme 1a. Addition of hydroxide/alkoxide to one of the carbonyl groups of *s-trans*-1,2-diketone affords the hydrate/hemiketal **A**. Rotation of the central C-C bond followed by 1,2-shift affords then the α-hydroxy acid/ester. Both kinetic studies and DFT calculations[13] indicates that the hydration/ketalization step is reversible and that the 1,2-migration is the rate-determining step ($k_1 \geq k_2 \leq k_{-1}$). The last step has also been shown to be irreversible[14] unless it is associated with the release of ring strain.[15] Tang and co-workers reported in 2015 an elegant diastereoselective Zn(II)-catalyzed BER reaction using 2 equivalents of (-)-8-phenylmenthol as an alcohol input (Scheme 1b).[16] Unfortunately, all efforts aimed at developing a catalytic enantioselective version of this rearrangement gave the product in very low enantioselectivity (< 10% *ee*).[16]

Different Lewis acids such as Al(III), Zn(II) and Cu(II) salts have been used to catalyze/promote the BAR reaction.[17] Keeping the above mechanistic picture in mind, a dynamic kinetic resolution (DKR) of hemiketal intermediate **A** in the presence of a chiral Lewis acid complex deemed to be a viable approach and we became particularly interested in the BER reaction of vicinal tricarbonyl compounds[18] as this will provide 2-substituted 2-hydroxymalonates (tartronic esters) of high synthetic value.[19] We report herein the first examples of L*Cu(II)-catalyzed asymmetric BER reaction of 2,3-diketoesters **1** affording 2-substituted tartronic esters **2** in high yields and enantioselectivities (Scheme 1c). Application of the present methodology to the synthesis of benzimidazole oxazolidinedione **3**, a nonsteroidal mineralocorticoid receptor antagonist,[20] is also documented. The preliminary experiments indicated that hemiketalization, rather than the DKR of hemiketal, was the enantiodetermining step under our reaction conditions.



Scheme 1. Benzilic acid (ester) rearrangement: Mechanism and state-of-the-art.

By virtue of its multifunctionality, vicinal tricarbonyl compounds have been well exploited in organic synthesis,[21] it is therefore interesting to note that they have rarely been investigated in asymmetric transformation.[22] We began our studies by examining the reaction of a mixture of ethyl 2,2-dihydroxy-3-oxo-3-phenylpropanoate **1a** and its hydrate **1a'** (**1a**/**1a'** = 1:3) with *t*BuOH (20.0 equiv). After initial survey of the reaction parameters (See SI for details), the ligand structure was fine-tuned by performing the reaction in 1,2-dichloroethane (DCE) in the presence of $Cu(OTf)_2$ (0.1 equiv), a chiral ligand (0.12 equiv) at room temperature under air atmosphere. As it is shown in Table 1, the Pybox ligand **L1** was inefficient in catalyzing the transformation (entry 1), while the desired α-hydroxy α-phenyl malonate **2a** was formed in moderate yields with moderate to good enantioselectivities (entries 2-4) when bisoxazolines (**L2**-**L4**, Figure 1) were employed as supporting ligands. Further fine-tuning of ligand structure was focused on those bisoxazolines

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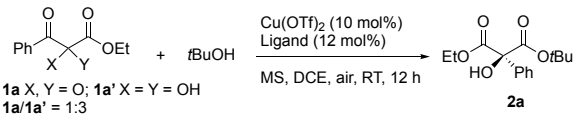
Table 1. Catalytic enantioselective BER reaction of **1a/1a'** with *t*BuOH: Optimization of reaction conditions[a]



1a X, Y = O; **1a'** X = Y = OH
1a/1a' = 1:3

2a

Entry	Ligand	MS	yield[b]	*ee*[c]
1	**L1**	4 Å	trace	–[d]
2	**L2**	4 Å	56	42
3	**L3**	4 Å	57	77
4	**L4**	4 Å	51	78
5	**L5**	4 Å	47	60
6	**L6**	4 Å	64	89
7	**L7**	4 Å	66	92
8	**L8**	4 Å	61	83
9	**L9**	4 Å	82	90
10	**L10**	4 Å	57	94
11	**L11**	4 Å	67	88
12	**L12**	4 Å	65	96
13	**L13**	4 Å	57	88
14	**L14**	4 Å	61	84
15	**L9**	4 Å	79	94[e]
16	**L9**	**4 Å**	**78**	**94**[f]
17	**L9**	3 Å	79	92
18	**L9**	5 Å	50	56
19	**L9**	–	6	-2

[a] **1a** (0.1 mmol), *t*BuOH (2.0 mmol), $Cu(OTf)_2$ (0.01 mmol), Ligand (0.012 mmol), molecular sieves (50 mg), DCE (0.8 mL), air atmosphere, RT, 12 h. [b] Isolated yields. [c] Determined by SFC analysis on a chiral stationary phase. [d] Not detected. [e] 2.0 equivalents of *t*BuOH was used. [f] $Cu(OTf)_2$ (5 mol%) and **L9** (6 mol%) were used. MS = molecular sieves. DCE = 1,2-dichloroethane.

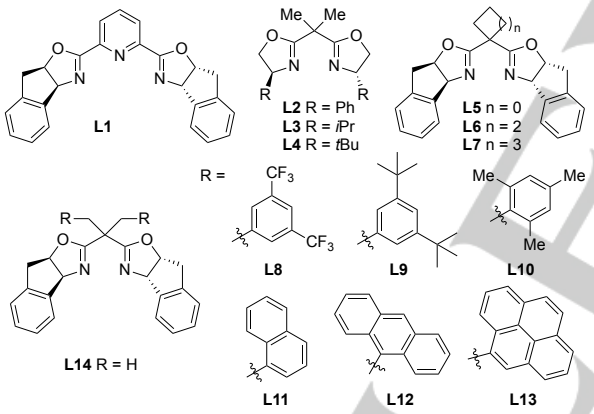


Figure 1. Structure of representative chiral ligands.

derived from (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**L5-L14**)[23] and **L9**[24] stood out taking into consideration of both the yield and *ee* of **2a** (entry 9). Improved enantioselectivity was observed when the amount of *t*BuOH was diminished from 20.0 to 2.0 equivalents (entry 15). Pleasingly, the catalyst loading could be decreased to 5 mol% without impacting the reaction efficiency (entry 16). The presence of molecular sieves (MS) is of utmost importance, with 4 Å MS being optimum (entries 16-19). In its absence, **1a** was recovered together with a trace amount of **2a** and ethyl 2-oxo-2-phenylacetate (46% yield). The latter was also observed as a byproduct under all the conditions examined. Its formation could be accounted for by the benzilic acid rearrangement of hydrate **1a'**. Indeed, when ethyl 2,2-dihydroxy-2-phenylacetate (**1a'**) alone was submitted to the reaction conditions specified in entry 15, 2-oxo-2-phenylacetate was isolated in 35% yield (see SI for mechanistic hypothesis) together with the recovered starting material. Therefore, it seems that hemiketalization of **1a/1a'** and the subsequent BER reaction is faster than the BAR of **1a'**. In accordance with this assumption, **2a** was isolated in similar yield (79%) and *ee* (94%) when pure **1a** was used as a substrate. As vicinal tricarbonyl compounds are easily hydrated, the fact that we can use its hydrate with only a minimum amount of competitive BAR reaction simplified greatly the experimental procedure. While the MS might act as a water scavenger to promote the formation of hemiacetal intermediate, its critical role in the enantioselectivity of the reaction (entries 16-19) is unclear at the present stage of development. Overall, the optimum conditions found consisted of performing the reaction of **1a/1a'** (1.0 equiv) with *t*BuOH (2.0 equiv) in DCE (*c* = 0.125 M) at room temperature in the presence of $Cu(OTf)_2$ (0.05 equiv), chiral bisoxazoline **L9** (0.06 equiv) and 4 Å molecular sieves (50 mg/mmol) under air atmosphere. Under these conditions, **2a** was obtained in 78% yield with 94% *ee* (entry 16).

With the optimized conditions in hand, the scope of this catalytic enantioselective BER reaction was examined (Scheme 2). In addition to tertiary alcohol, secondary alcohol such as isopropanol and cyclopentanol participated in the reaction to give the corresponding 2-substituted tartronic esters (**2c**, **2e**, **2f**) in good yields and enantioselectivities. The Meerwein-Ponndorf-Verley reduction of the diketoester often encountered under classic BER conditions with secondary alcohol was not observed. Methanol participated in the reaction to afford the BER product in good yield with moderate *ee* (*vide infra* Scheme 3a). Reaction of **1a** with (+)-menthol proceeded smoothly to provide the corresponding product **2f** in high yield with excellent diastereoselectivity (81% yield, >20/1 d.r.). 2,3-Diketoesters derived from phenol and primary, secondary as well as tertiary alcohols, such as 2-(trimethylsilyl)ethyl, heptyl, benzyl, isopropyl and *tert*-butyl, were all well-accepted substrates (Scheme 2). Regarding the aryl group of 3-aryl substituted 2,3-diketoesters, the presence of both electron-donating (Me, MeO) and electron-withdrawing groups (F, Br, CF_3, NO_2) at different positions (*para, meta* and *ortho*) of the phenyl ring were well tolerated (**2m-2t**) and excellent enantioselectivity was observed with an aryl group bearing an *ortho* substituent (**2s**, 99% *ee*, **2t**, 96% *ee*). Both α-naphthyl and β-naphthyl as well as heteroarene substituted 2,3-diketoesters participated in this asymmetric 1,2-alkoxycarbonyl shift process to provide the corresponding rearranged products (**2u-2x**). With aliphatic 2,3-diketoesters, conditions have to be slightly re-optimized (See SI for detail). Performing the reaction at 0 °C using bisoxazoline **L12** as ligand, compounds **2y-2aa** were isolated in good yields with good to high enantiopurities. The (*S*)-absolute configuration of **2a** was determined by X-ray crystallographic analysis[25] and the configuration of the other α-hydroxy malonates were assigned by analogy. Performing the gram scale reactions of **1a** (4.0 mmol) and **1o** (5.0 mmol) with *t*BuOH (2.0 equiv) in the presence of only 2.5 mol% of the **L9**-Cu catalyst afforded **2a** and **2t**, respectively, without erosion of yields and *ees*.

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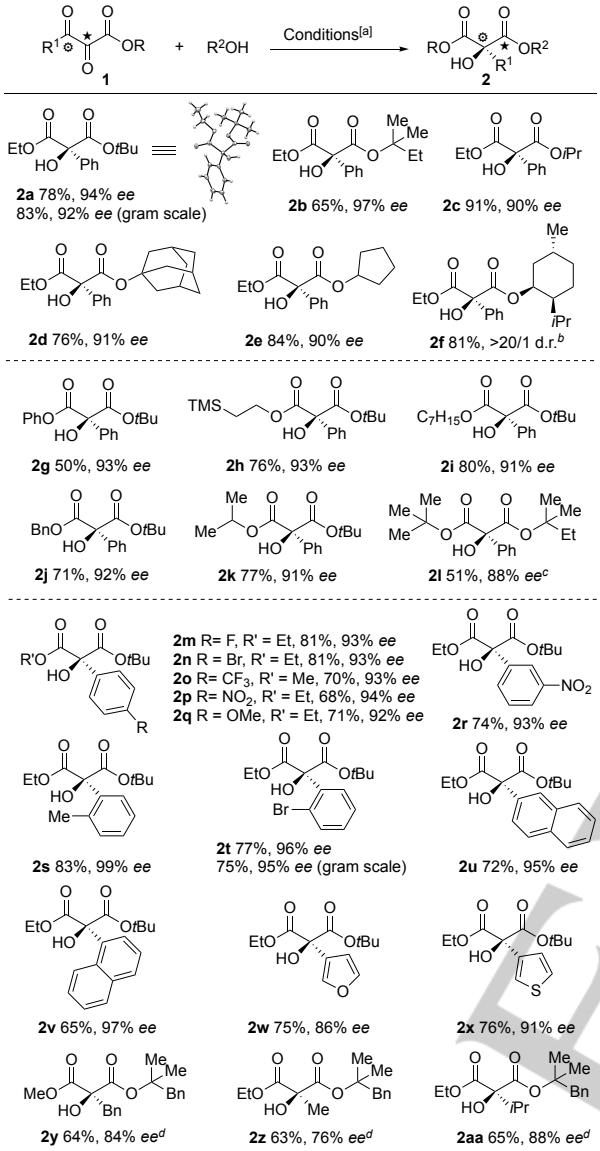
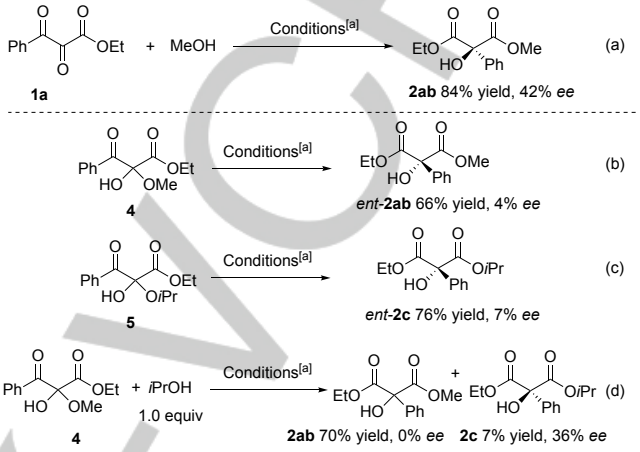
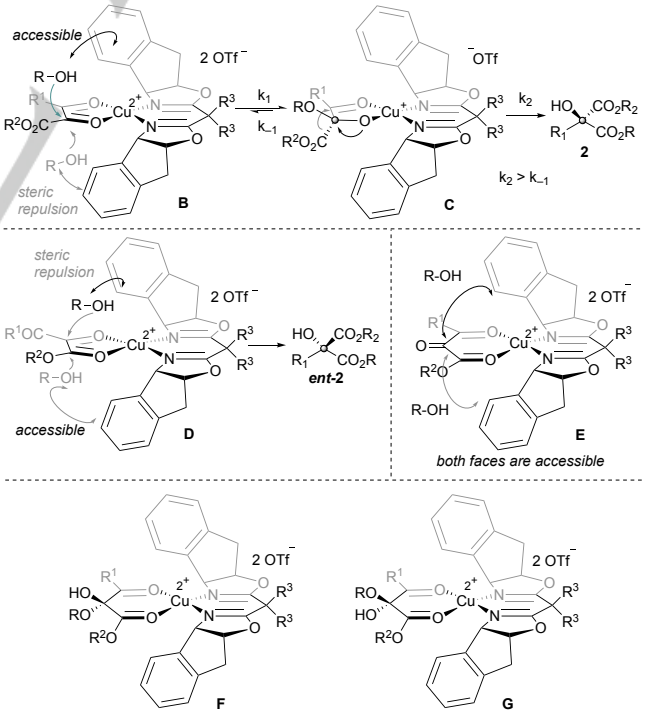


Scheme 2. Scope of catalytic enantioselective BER reaction. [a] Conditions: **1** (0.1 mmol), R^2OH (0.2 mmol, 2.0 equiv), $Cu(OTf)_2$ (5 mol%), **L9** (6 mol%), 4 Å molecular sieves (50 mg), 1,2-dichloroethane (0.8 mL), room temperature, air. The *ee* was determined by supercritical fluid chromatography (SFC) or high performance liquid chromatography (HPLC) analysis on a chiral stationary phase. [b] The d.r. was determined by ^1H NMR. [c] $Cu(OTf)_2$ (0.1 equiv), **L7** (0.12 equiv), at 40 °C. [d] $Cu(OTf)_2$ (10 mol%), **L12** (12 mol%), at 0 °C, 2 days.

Assuming that the 1,2-shift was the kinetically slow step as it was widely accepted for the BAR/BER reactions, dynamic kinetic resolution (DKR) of the hemiketal **A** was the working hypothesis that guided our efforts to render the BER reaction enantioselective (*cf* Scheme 1a). A series of control experiments were carried out in order to understand the reaction course. Under standard conditions, reaction of **1a** with MeOH (2.0 equiv) afforded **2ab** in 84% yield with a moderate 42% *ee* (Scheme 3a). However, submitting the pure hemiketals **4** and **5** to the standard conditions afforded **2ab** (66% yield, -4% *ee*) and **2c** (76% yield, -7% *ee*), respectively, with negligible but reversed enantioselectivity (Scheme 3b, 3c). Finally, reaction of hemiketal **4** and isopropanol under standard conditions provided a mixture of **2ab** (70% yield, 0% *ee*) and **2c** (7% yield, 36% *ee*, Scheme 3d). The results argued against our initial assumption and indicated that, under our conditions, hemiketallization process is an enantiodetermining step and that 1,2-alkoxycarbonyl shift of intermediate **A** (*cf* Scheme 1a) is a fast process ($k_2 > k_{-1}$).



Scheme 3. Control experiments. [a] Conditions: **1a**, or **4**, or **5** (0.1 mmol), $Cu(OTf)_2$ (5 mol%), **L9** (6 mol%), 4 Å molecular sieves (50 mg), 1,2-dichloroethane (0.8 mL), room temperature, air. For equation (d), *i*PrOH (0.2 mmol, 2.0 equiv) was added.



Scheme 4. Stereochemical model.

On the basis of aforementioned results, a plausible pathway leading to the observed stereochemical outcome is illustrated in

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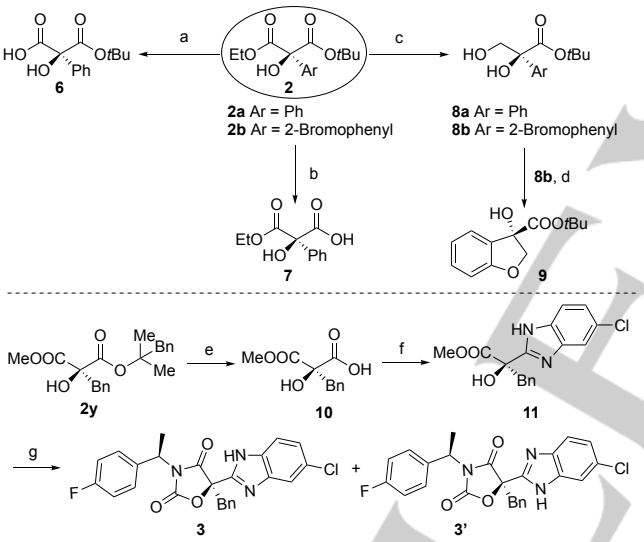
Scheme 4. Coordination of **L9**-Cu(OTf)$_2$ to 2,3-diketoester **1** would afford a square-planar Cu(II) complex **B**,[26] where the adjacent diketo group adopts an s-*cis* conformation. Nucleophilic addition of alcohol to the sterically more accessible *Re* face of the central carbonyl group would afford Cu(II) species **C** with a conformation preorganized for the subsequent 1,2-suprafacial migration of the alkoxycarbonyl group to generate, after decomplexation, the product **2** with the observed absolute configuration. On the other hand, if bidentate coordination of the **L9**-Cu(OTf)$_2$ took place between the central and the ester carbonyl groups as shown in the intermediate **D**, the preferred *Si*-face attack of alcohol would afford the ***ent*-2**. In the six-membered chelate **E**, the central carbonyl group lies along the C_2 axis of the box ligand and therefore, high enantioselectivity would not be expected.[27] Overall, a stereochemical model involving the complex **B** matched best with the experimental results.[22a,28] On the other hand, when the pre-synthesized hemiketal was submitted to the reaction conditions, the six-membered chelates **F/G** might be formed[29] and the ester group in these two diastereomeric intermediates would migrate without kinetic preference to afford a racemic compound in accordance with the experimental results.



Scheme 5. Post-transformation and application to the synthesis of bioactive compound. Reaction conditions: (a) **2a**, NaOH, EtOH/H_2O, RT, 88% yield; (b) **2a**, TFA, DCM, RT, 93% yield; (c) **2a** or **2b**, $LiBH_4$, EtOH/THF, 0 °C, **8a** 63% yield; **8b** 61% yield; (d) **8b**, CuI (0.1 equiv), *t*BuOLi (3.0 equiv), 1,4-dioxane, 100 °C, 40%; (e) TFA/DCM, RT, 3 h, 82% yield; (f) 4-chlorobenzene-1,2-diamine, HATU, diisopropylethyl amine, DMF, RT, 12 h, then acetic acid, 70 °C, 3 h, 51% yield over two steps; (g) (*R*)-1-fluoro-4-(1-isocyanatoethyl)benzene, NaOH, THF, 40 °C, 12 h, 75% yield (10/1 d.r.).

The functionality of α-aryl substituted tartronic ester **2** allowed multiple orthogonal chemical transformations (Scheme 5). Thus, treatment of **2a** with sodium hydroxide or trifluoroacetic acid (TFA) afforded two *pseudo* enantiomeric carboxylic acids **6** and **7**, respectively, in excellent yields. Chemoselective reduction of ethyl esters **2a** and **2b** with lithium borohydride furnished the 2-arylglycerates **8a** and **8b**, respectively. Cu-catalyzed cycloetherification of **8b** afforded dihydrobenzofurane **9** in non-optimized 40% yield.

To further illustrate the synthetic potential of the present method, synthesis of benzimidazole oxazolidinedione **3** was undertaken. Chemoselective hydrolysis of *tert*-butyl ester of **2y** afforded the carboxylic acid **10** in 82% yield. Amidation of **10** with 4-chlorobenzene-1,2-diamine followed by acid-promoted cyclization of the resulting amide provided the benzimidazole **11** in 51% yield over two steps. Sodium hydroxide-promoted cyclocondensation of **11** with (*R*)-1-fluoro-4-(1-isocyanatoethyl)benzene gave compound **3**, a nonsteroidal mineralocorticoid receptor antagonist, in 75% isolated yield (Scheme 8).[20] We note that two resonance structures of the benzimidazole (**3** and **3**') are clearly observable within ^{1}H NMR time scale.

In conclusion, we have developed the first catalytic enantioselective benzilic ester rearrangement (BER) reaction. In the presence of catalytic amount of Cu(OTf)$_2$ and a chiral box ligand under mild reaction conditions, reaction of 2,3-diketoesters with alcohols afforded structurally diverse α-substituted-α-hydroxy malonates in good to excellent yields with high enantioselectivities. Although the acyclic hemiketal is in general configurationally unstable, we believe that, under our conditions, the hemiketalization is an enantio-determining step against the widely accepted reaction mechanism of the BAR/BER reactions.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest

Keywords: asymmetric synthesis • benzilic ester rearrangement • 2,3-diketoester • tartronic esters • chiral copper catalyst

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Asymmetric Synthesis

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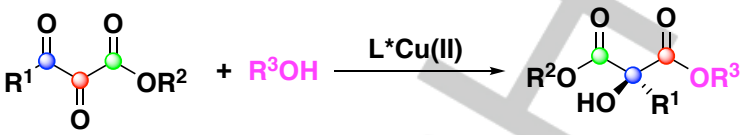
Catalytic Enantioselective Benzilic Ester Rearrangement



Paradigm shift *hemiketal formation is the enantio-determining step against commonly accepted mechanism of the title rearrangement*