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A Highly Efficient and Enantioselective Intramolecular Cannizzaro Reaction under TOX/Cu(II) Catalysis

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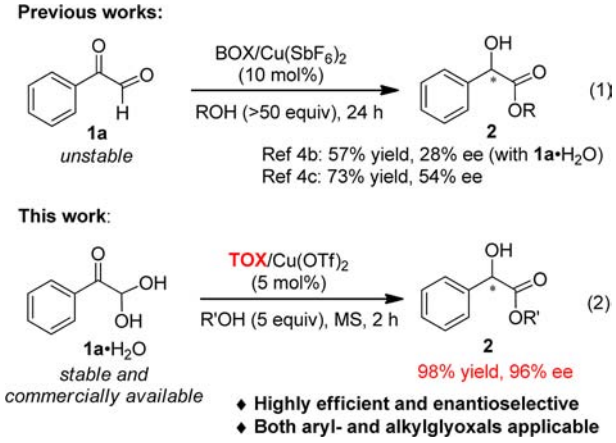
Supporting Information

ABSTRACT: An asymmetric intramolecular Cannizzaro reaction of aryl and alkyl glyoxals with alcohols has been realized with an unprecedented high level of enantioselectivity, on the basis of a newly developed congested TOX ligand and a gradual liberation protocol of active glyoxals from glyoxal monohydrates. Preliminary results suggested a mechanism of enantioselective addition of alcohols to glyoxals contributing most to the stereoselectivity, other than by the dynamic kinetic resolution of hemiacetal intermediates.

The intramolecular Cannizzaro reaction of α-keto aldehydes to α-hydroxy carboxylic acid (mandelic acid) derivatives has been well-known since 1897.[1] Typically, harsh conditions such as strong bases and high temperature are required, while later, reactions conducted under milder conditions in the presence of Lewis acid catalysts were established.[2] By employing chiral ligands, the asymmetric version of this reaction may provide a unique access to optically active α-hydroxy carboxylic acid derivatives which are of significant synthetic and pharmaceutical importance.[3] However, this asymmetric process was still a quite challenging problem due to low enantioselective induction.[4] The first catalytic asymmetric version appeared in 1992, in which Nishinaga et al. obtained 13.5% ee by using 2,2′-diamino-1,1′-binaphthalene (DABN)-derived Schiff-base/cobalt(II) complex as a catalyst.[4a] In 2000, Morken and co-workers reported a systematic study on this reaction by screening a spectrum of Lewis acids and chiral ligands such as BOX and BINAP, and achieved up to 33% ee with Ph-BOX/Cu(OTf)$_2$.[4b] Later on, Ishihara et al. optimized this catalytic system further and found that the use of anhydrous phenylglyoxal and Cu(SbF$_6$)$_2$ can increase the reaction efficiency.[4c] Even though the improvement of enantioselectivity was limited, 54% ee and 73% yield represent the best results so far (Scheme 1, eq 1).[5]

Recently, we found that a type of sterically hindered trisoxazoline (TOX) ligands newly designed in our lab exhibited high efficiency in this reaction, giving an unprecedented high level of enantioselectivity (96% ee, Scheme 1, eq 2). Notably, a slow substrate-release strategy has been established, leading to nearly quantitative yield in a short reaction time, as well as the discovery of an alternative chirality control step in this asymmetric transformation. Herein, we report our preliminary results on this subject.

Scheme 1. Asymmetric Cannizzaro Reaction of Glyoxals



We commenced our study by employing phenylglyoxal as the model substrate and ^{t}Bu-BOX/Cu(OTf)$_2$ as the catalyst.[6] The Cannizzaro reaction was first carried out in 1,2-dichloroethane (DCE) with a toluene solution of anhydrous phenylglyoxal and 50 equiv of *tert*-butanol, according to the literature conditions.[4c] Obtained was 50% ee, but the reaction was slow and messy (Table 1, entry 1), which may result from the oligomerization of phenylglyoxal and other side reactions.[1b,4a] We conceived that keeping the highly active phenylglyoxal at a lower concentration may suppress the oligomer formation, and the commercially available phenylglyoxal monohydrate (**1a**·H$_2$O) in combination with molecular sieves (MS) could be used for this goal, which would gradually release the unstable phenylglyoxal along the reaction by removing water. To our delight, this change led to a fast and clean reaction and also a simplified operation (entry 2). Spurred by this success, we next focused on the ligand screening. Ligands **L3b** and **L3c** (entries 3 and 4), possessing a typical aryl and oxazolinyl side arm modification, respectively,[7] were examined first. Gratifyingly, in comparison with the parent ^{t}Bu-BOX ligand, the introduction of the two kinds of side arm groups both significantly increased the reaction efficiency (entries 3 and 4). Notably, TOX **L3c** greatly improved the enantioselectivity to 73% ee (entry 4). After solvent screening,[8] DCM was found to give a slightly better enantioselectivity (entry 5 vs entry 4). After an extensive screening of a number of TOX ligands, bulky ^{t}Bu-TOX was

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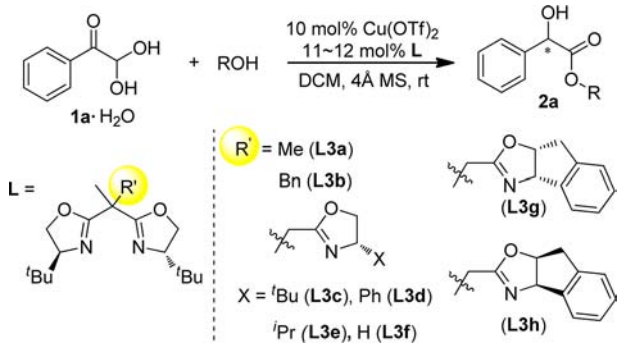
Table 1. Reaction Optimization[a]



entry	ROH	L	t (h)	yield (%)[b]	ee (%)[c]
1[d,e]	^{t}BuOH (50 equiv)	L3a	24	/	50
2[e]	^{t}BuOH (50 equiv)	L3a	2	68	50
3[e]	^{t}BuOH (50 equiv)	L3b	2	99	47
4[e]	^{t}BuOH (50 equiv)	L3c	2	99	73
5	^{t}BuOH (50 equiv)	L3c	2	99	74
6	^{i}PrOH (50 equiv)	L3c	2	91	37
7	Et_2CHOH (50 equiv)	L3c	2	99	76
8	Et_3COH (50 equiv)	L3c	2	99	81
9	$^iPr_2CHOH$ (50 equiv)	L3c	2	99	90
10	$^iPr_2CHOH$ (5 equiv)	L3c	2	99	88–92
11[f]	$^iPr_2CHOH$ (5 equiv)	L3c	2	99	94
12[f]	$^iPr_2CHOH$ (5 equiv)	L3d	2	97	92
13[f]	$^iPr_2CHOH$ (5 equiv)	L3e	2	99	96
14[f]	$^iPr_2CHOH$ (5 equiv)	L3f	35	79	31
15[f]	$^iPr_2CHOH$ (5 equiv)	L3g	2	97	96
16[f]	$^iPr_2CHOH$ (5 equiv)	L3h	35	89	58
17[f,g]	$^iPr_2CHOH$ (5 equiv)	L3e	2	98	96

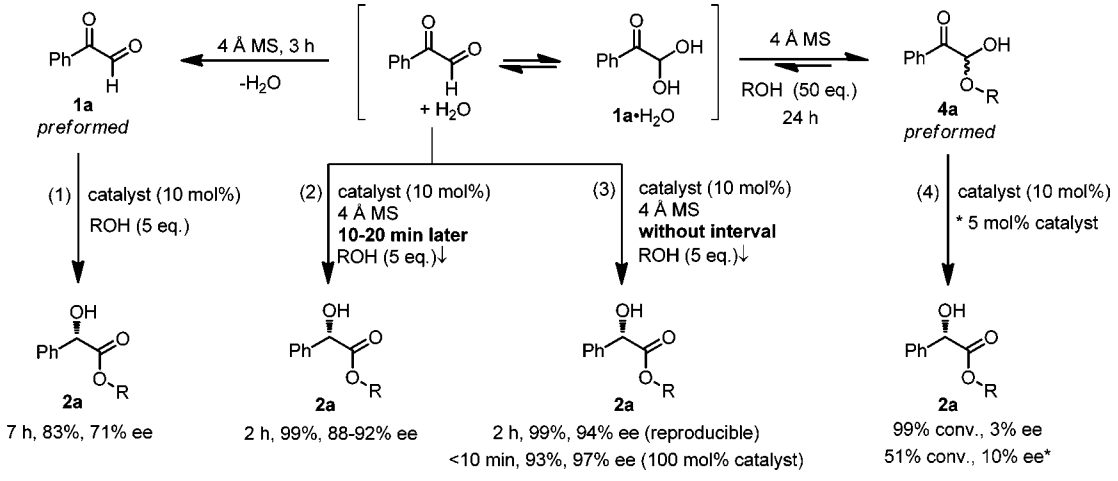
[a]0.2 mmol scale, 0.1 M, MS (200 mg), ROH was added last after **1a** with a 10–20 min interval, N_2. [b]Isolated yield. [c]Determined by chiral HPLC. [d]With anhydrous **1a**. [e]The reaction was performed in DCE (1,2-dichloroethane). [f]Alcohol was added immediately after **1a**.[8] [g]5 mol % of catalyst.

identified as the best, superior to other scaffolds.[8] This trend indicated a steric demand in the stereochemical control. Therefore, more bulky alcohols which probably lead to a better stereocontrol were examined. As anticipated, the enantioselectivity improved gradually as the sizes of alcohols increase (entries 6–9), and 90% ee could be achieved with 2,4-dimethylpentan-3-ol ($^iPr_2CHOH$) (entry 9). Furthermore, the alcohol loading can be reduced from 50 equiv to 5 equiv without loss of efficiency, but the ee values were not exactly reproducible, varying in the range of 88–92% ee (entry 10).

This observation inspired us to perform a close examination over several reaction protocols, and the results are very startling (Scheme 2). Reaction 1 utilizing preformed anhydrous glyoxal **1a** gave a messy reaction with 71% ee. In contrast, reaction 2 under the present conditions using glyoxal monohydrate directly afforded a quantitative yield and much better enantioselectivity, albeit with a small variation in the ee value. In this protocol, the alcohol was added last, with a 10–20 min interval after mixing the catalyst and substrate. After repeating the reaction several times, we realized that this interval may be the reason for the ee changes. Reaction 3 was thus designed for comparison, in which the alcohol was added immediately after adding substrate. To our great pleasure, this protocol gave a reproducible and even better result (94% ee, also see entry 11 in Table 1), and the reaction at a 100 mol % catalyst loading can raise the selectivity to 97% ee. We thus suspected that the difference in enantioselectivity between reaction 1 and reaction 2 may be caused by the different extent of noncatalyzed formation of racemic hemiacetal **4a**,[4b] as in reaction 1 the highly active anhydrous glyoxal was largely excessive in relation to the catalyst, while the active glyoxal in reaction 2 was liberated gradually and kept at a relatively lower concentration. As a consequence, there should be more racemic hemiacetal formed in reaction 1, leading to a lower ee. This hypothesis was well supported by the control reaction 4, in which as racemic hemiacetal **4a** was preformed (>98% NMR yield) before the addition of the catalyst, the product was almost racemic (3% ee). And the enantioselectivity at 51% conversion was also quite low (10% ee).[8] This result strongly suggested that the *high* enantioselectivity observed under our conditions may be not dominated by the dynamic kinetic resolution of the hemiacetals, which was proposed previously for the BOX/Cu(II) system.[4b,c]

To further probe the reaction mechanism, we performed the crossover experiments with 1-deuterated phenylglyoxal and 2-naphthylglyoxal (Scheme 3a), and no incorporation of deuterium into the naphthyl product was observed. The reaction run in CD_3OD also gave no deuterium incorporation

Scheme 2. Optimization and Comparison of Reaction Protocols (Catalyst: L3c/Cu(OTf)$_2$; R = CH(^{i}Pr)$_2$)



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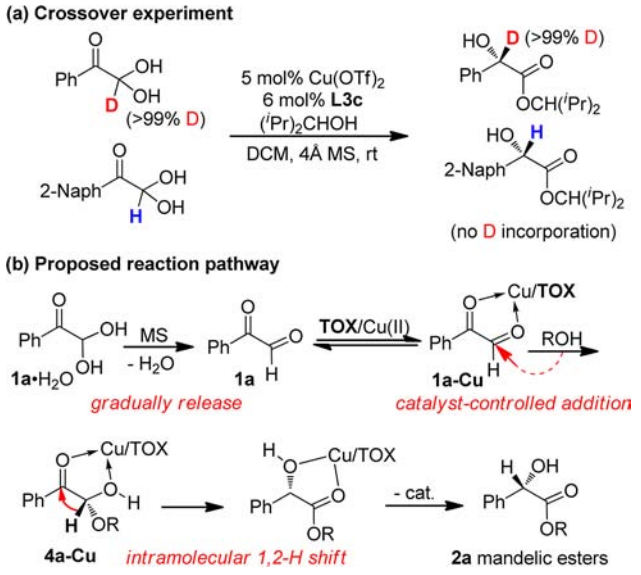
Scheme 3. Crossover Experiment and Reaction Route

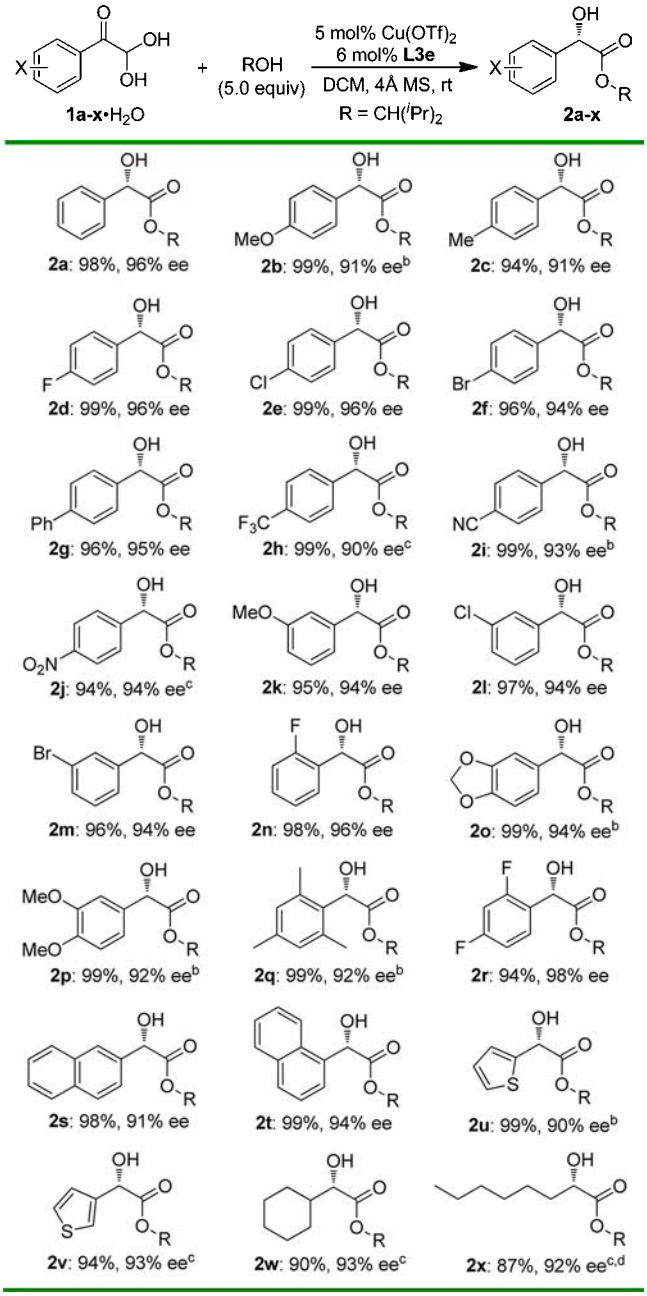


at the α-carbon position of the ester group in the product. Both deuterium-label experiments were in accord with an intramolecular 1,2-hydride shift mechanism.[4b,9] A reaction route was thus proposed as shown in Scheme 3b. In view of the aforementioned results in Scheme 2, the chiral induction occurs at the catalyst-controlled alcohol-addition step, rather than via dynamic kinetic resolution (DKR) of hemiacetal **4a**.[10] In fact, in reaction 4, even at low conversion which normally favors the kinetic resolution product, the ee remained very low (11% ee at 5% conversion).[8] The better stereocontrol with trisoxazoline (TOX) ligands over the addition of the alcohol to **1a-Cu** could be explained in terms of a more congested environment created around the reactive site with the assistance of the additional *tert*-butyl oxazoline, while typical bisoxazoline (BOX) ligands lack such a side arm regulator.[7d,m]

The effect and importance of the additional oxazoline group became more significant when several TOX ligands containing a different side arm oxazoline (**L3c**–**L3h**) were compared together. As shown in Table 1 (entries 11–15), in contrast to the high ee (92–96%) obtained with ligands **L3c**–**L3e** and **L3g**, **L3f** that lacks a substituent at the pendant oxazoline, resulted in a sharp drop in enantioselectivity by ca. 60% ee (entry 14). This is consistent with the aforementioned steric demand in the stereochemical control step, the alcohol-addition step. A strong match/mismatch effect between the scaffold and pendant oxazoline chirality was also observed (entries 15 and 16), which further manifested the influence of the pendant group on the stereoselectivity. The homochiral ligand **L3g** afforded a faster reaction and a much better selectivity (96% ee vs 58% ee). In addition, the catalyst loading of **L3e**/$Cu(OTf)_2$ can be reduced to 5 mol %, and **L3e** as a solid is easy to handle (entry 17). Under the optimized conditions, the reaction scope was investigated next.

As shown in Table 2, the reaction worked well with a range of arylglyoxals, and various functional groups such as -OMe, -F, -Cl, -Br, CF_3, NO_2 were all well tolerated. In general, high yields and enantioselectivities can be accomplished regardless of the electronic nature of the aryl groups and the substitution patterns. In particular, substrate **1j** containing a NO_2 group which is usually susceptible to reductive conditions,[11] and sterically hindered 2,4,6-trisubstituted substrate **1q**, both can be

Table 2. Reaction Scope[a]



[a]0.4 mmol scale, 0.1 M, 4 Å MS (80 mg), **1a**/ROH: 1/5, 5 mol % catalyst. [b]10 mol % catalyst. [c]20 equiv of alcohol was used. [d]With 20 mol % catalyst.

smoothly converted to the desired products in high yields and selectivities. Remarkably, the current catalytic system is also compatible with alkylglyoxals (**1w** and **1x**), furnishing aliphatic α-hydroxy acid derivatives in high optical purity, an important type of intermediate for the synthesis of many natural products and bioactive molecules.[12] To our knowledge, the aliphatic substrates have never been employed before in the asymmetric Cannizzaro reaction. In addition, the product can be easily converted to the corresponding methyl ester in nearly quantitative yields with conservation of enantioselectivity by treatment with BF_3·2MeOH.[8] The corresponding methyl esters of **2a** and **2w** were used to determine the absolute configuration

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of the products by comparing their optical rotations with the literature values; other products were assigned by analogy.

In summary, the asymmetric intramolecular Cannizzaro reaction of glyoxals has been realized for the first time with high efficiency and high levels of enantioselectivity by combining TOX/copper catalysis with a slow substrate-release protocol. The catalytic system is mild and efficient, and compatible with both aryl- and alkylglyoxals, allowing a facile access to a variety of α-hydroxy carboxylic acid derivatives with high optical purity. Preliminary results suggested that the high enantioselectivity observed in the present reaction was mainly dominated by the catalyst-controlled face-selective addition of alcohols to coordinated glyoxals. Further mechanistic study and the extension of the present catalytic system to other redox and 1,2-shift reactions are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterizations, analytical data of products, and spectra of NMR and HPLC. 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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