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Copper Ion-Induced Activation and Asymmetric Benzoylation of 1,2-Diols: Kinetic Chiral Molecular Recognition

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Metal ions embedded in enzymes catalyze various biological transformations as the active centers.[1] An activation of water by metalloenzymes is one of the typical examples. Some metalloenzymes lower the pK_a value of water by the coordination, making it possible to generate hydroxide ion from water at neutral pH.[2] The model studies using dinuclear complexes have recently been reported.[3] In contrast with the activation of water, however, an activation of the hydroxyl group of alcohols has not been well established.[4] We have considered that a coordination of 1,2-diol **1** with an appropriate metal ion (M^{n+}) forms an activated form **A** of **1**, which is transformed with a weak base to the metal alkoxide **B** to be trapped acyl halides (R^2COX) as electrophiles. Provided that M^{n+} is regenerated with a formation of an acylated product **2**, a catalytic cycle concerning with M^{n+} is completed (Scheme 1).

The results thus far obtained based on this concept were an organotin-catalyzed monobenzoylation of 1,2-diols with the first kinetic resolution of terminal 1,2-diols using a chiral organotin catalyst.[5] However, a limitation in a structural modification of organotin compounds has been a barrier to acquire further stereoselectivity for many other diols. We report herein an excellent catalytic ability of copper(II) ion[6] for 1,2-diol activation based on the above-mentioned concept. Since the copper catalysts could be readily modified by chiral ligands, it allowed us to find out the most suited one for the reaction from well-established ligands.[7] That is, (*S*,*S*)-hydrobenzoin[8] ((*S*,*S*)-**1a**) was selectively monobenzoylated with (*R*,*R*)-Ph-BOX-$CuCl_2$[9] as a catalyst with an s[10] value of >645 (Scheme 2).

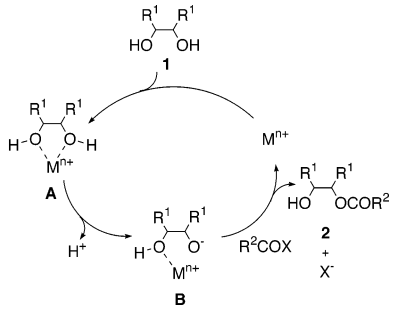
The observed % ee was the highest level of selectivity[10] among the thus-far reported catalytic kinetic resolution of alcohols.[11] The characteristic1,2-diol-selectivity of the new catalytic system was confirmed by the kinetic resolution of *dl*-**1a** in the presence of 1 equiv of *n*-BuOH which afforded (*S*,*S*)-**2a** in 49% yield with 98% ee. This result supports a metal-induced activation concept as shown in Scheme 1.

Table 1 shows the result of a kinetic resolution of various 1,2-diols *dl*-**1b**−**f** using 5 mol % of (*R*,*R*)-Ph-BOX-$CuCl_2$ with a result of *dl*-**1a**.

The selectivity values for *dl*-**1a**−**d** were extremely high irrespective of the character of substituents on their phenyl groups (runs 1−4). Aliphatic diols *dl*-**1e**−**g** also showed useful level of selectively (runs 5−7), although the kinetic resolution of *dl*-**1e**−**g** was not as efficient as that of hydrobenzoin derivatives *dl*-**1a**−**d**.

Interestingly, the selectivity of kinetic resolution of *dl*-**1a** strongly depended on the bulkiness of acylating reagents. When the reaction was carried out using acetyl (s = 1.8), propionyl (s = 4.9), isobutyryl (s = 8.3), and pivaloyl chlorides (s = 11.8),[12] the observed selectivity in the kinetic resolution (Table 3S, Supporting Information) was closely correlated with number of methyl group at the α-position of acetyl moiety.

Scheme 1



Scheme 2

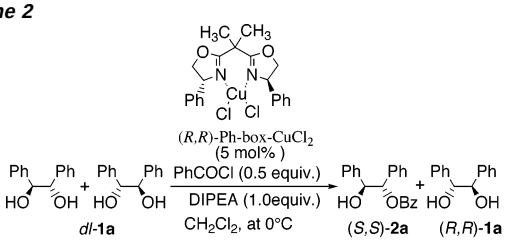


Table 1. Kinetic Resolution of 1,2-Diols[a]

run	1,2-diols	monobenzoylated product **2** yield (%) [b]	ee(%) [c]	selectivity [d]
1	(*dl*)-hydrobenzoin *dl*-**1a**	48	> 99	> 645
2	*p*-Cl-(*dl*)-hydrobenzoin *dl*-**1b**	48	> 99	> 645
3	*p*-CH_3-(*dl*)-hydrobenzoin *dl*-**1c**	47	97	183
4	*p*-CH_3O-(*dl*)-hydrobenzoin *dl*-**1d**	49	98	356
5	 *dl*-**1e**	37	80	14
6	 *dl*-**1f**	49	84	28
7	 *dl*-**1g**	44	77	14

[a] The reaction was carried out with complex (0.05 mmol), diol (1 mmol), diisopropylethylamine (DIPEA, 1 mmol), and benzoyl chloride (0.5 mmol) in CH_2Cl_2 at 0 °C. [b] Isolated yield based on diols. [c] Determined by chiral solid-phase HPLC. [d] Reference 10.

This result suggests that the enantiodiscrimination mainly took place at the acylation step (**2** from **B** in Scheme 1). In fact, the benzoylaion of *dl*-**1a** in the presence of an excess amount (1.5 equiv) of (*R*,*R*)-Ph-box-$CuCl_2$ gave (*S*,*S*)-**2a** with 98% ee with a recovery of (*R*,*R*)-**1a** with 96% ee, whereas a similar experiment using acetyl

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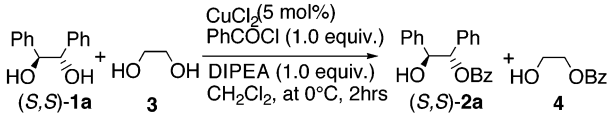
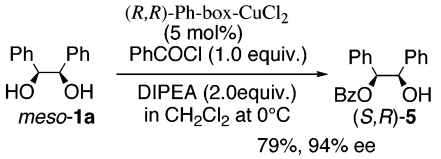
Scheme 3



(*S*,*S*)-**1a** / **3** / PhCOCl = 1 / 1 / 1 without Ph-box **2a** / **4** = 36 / 64
with Ph-box **2a** / **4** = 71 / 29

Scheme 4



chloride afforded **3a** in 20% ee which was comparable with that observed in the catalytic acetylation. The result suggests that (*R*,*R*)-Ph-box-$CuCl_2$ can coordinate with not only (*S*,*S*)-**1a** but also (*R*,*R*)-**1a** to form the corresponding intermediates **B** (Scheme 1). The observed high enantiodiscrimination in the benzoylation of *dl*-**1a** might be primarily explainable in terms of the severe steric repulsion between benzoyl chloride and **B** which might be formed from (*R*,*R*)-**1a** and (*R*,*R*)-Ph-box-$CuCl_2$.

To clarify the other factor responsible for the observed high *s* in the benzoylation of *dl*-**1a**, we carried out a competition reaction between (*S*,*S*)-**1a** and ethyleneglycol **3** in the presence of $CuCl_2$ with or without (*R*,*R*)-Ph-box. In this reaction, the ratios of monobenzoylated products (*S*,*S*)-**2a** to 2-benzoyloxyethanol **4** were 36/64 without (*R*,*R*)-Ph-box and 71/29 with (*R*,*R*)-Ph-box (Scheme 3).[13] This fact suggests a presence of attractive interaction between phenyl rings of (*S*,*S*)-**2a** and of (*R*,*R*)-Ph-box, which also participated to some extent in the benzoylation of *dl*-**1a**.

The presented method was then applied to an asymmetric desymmetrization[14] of *meso*-**1a**, where monobenzoylated **5** was obtained in 79% yield with 94% ee (Scheme 4).

In conclusion, we presented a new chemo- and stereoselective monobenzoylation of 1,2-diols. This is a first example of copper(II) ion-induced enentioselective activation of 1,2-diols. Since the stereoselectivity in the reaction might be readily modified upon ligation, the presented concept may provide an important platform for chemo- and stereoselective manipulation of 1,2-diols in many synthetic works.

This asymmetric benzoylation is completely different in its mechanism from the hitherto-exploited kinetic resolution and desymmetrization of alcohols[11,14] in which acylation reagents such as acyl halides or acid anhydrides are activated by chiral catalysts followed by the reaction of the activated chiral reagents with alcohols. On the contrary, the presented method owns an unique character to recognize 1,2-diols. Further designing of new catalysts based on our concept as well as mechanistic studies (Scheme 1S, Supporting Information) are currently under investigation.

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Supporting Information Available: Typical experimental procedure, analytical data including chiral chromatographic analyses of monobenzoylated products **2a**−**g** and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See Supporting Information Table 2S.
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