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Reaction Optimization Using Solid-Phase Catalysis-CD HTS: *N*b-Imidazoline–Cu(I)-Catalyzed Asymmetric Benzoylation of 1,2-Diols

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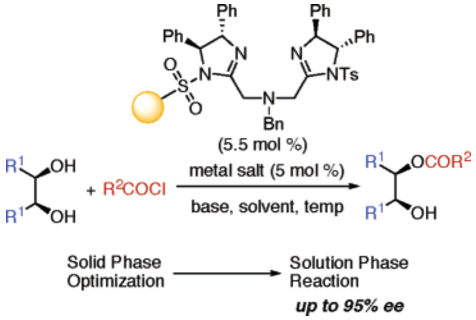
ABSTRACT



Catalytic asymmetric benzoylation of 1,2-diols has been developed using a solid-phase asymmetric catalyst. The reaction conditions were optimized by the screening of different metal salts, solvents, bases, and temperatures. High-throughput screening was performed using circular dichroism detection, and the results revealed that *N*b-imidazoline–copper(I) in combination with diisopropylethylamine was able to catalyze with high enantioselectivity, giving the monobenzoylated products in high yields and excellent enantiomeric excesses of up to 95% ee.

Practically useful catalysts that combine high activity with good stereoselectivity have been produced as a result of detailed optimization of the reaction conditions. The complex optimization process involves numerous combinations of parameters (i.e., temperature, solvent, and/or concentration), which is an obstacle to rapid development of the catalysts. As such, establishment of a simple and general guideline would be helpful for modern research.[1] To explore novel asymmetric catalysts, we have developed a new high-throughput screening (HTS) method, in which the asymmetric reaction from achiral substrate **A** to chiral product **B** is catalyzed by solid-phase catalyst **C**, and the asymmetric induction is directly monitored by a circular dichroism (CD) detector (Figure 1).[2] Though the system has been developed

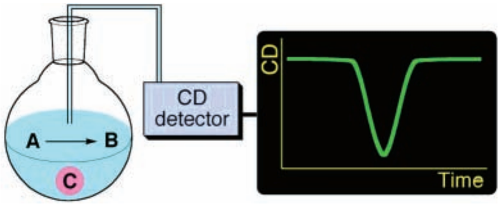


Figure 1. High-throughput screening of solid-phase asymmetric catalysts using circular dichroism.

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[1] Representative general reviews: (a) Stefan, D.; Stefan, B. *Synthesis* **2001**, 1431−1449. (b) de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799−811.

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for the discovery of new asymmetric catalysis using a combinatorial library of polymer-supported chiral ligands, we envision that the HTS would enable the rapid optimization of asymmetric catalysis even for a single polymer-supported chiral ligand.

In recent efforts to create new chiral ligands, we have succeeded in developing the *N*-tethered bis(imidazoline) ligand **1** (Figure 2).[3] For example, the **1**−Cu(OTf)$_2$ catalyst showed activity in promoting the monobenzoylation of racemic 1,2-diol. Although the enantiomeric excess (ee) of the product was moderate, this preliminary result prompted us to further explore the potential of the *N*b-imidazoline ligand.[4]

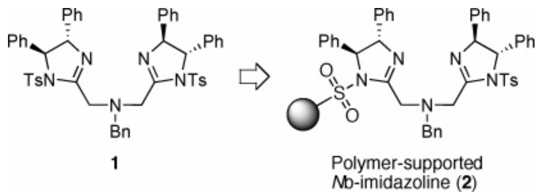
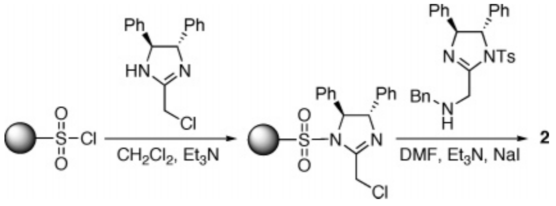


Figure 2. *N*-Tethered bis(imidazoline) ligands: *N*b-imidazoline (**1**) and polymer-supported *N*b-imidazoline (**2**).

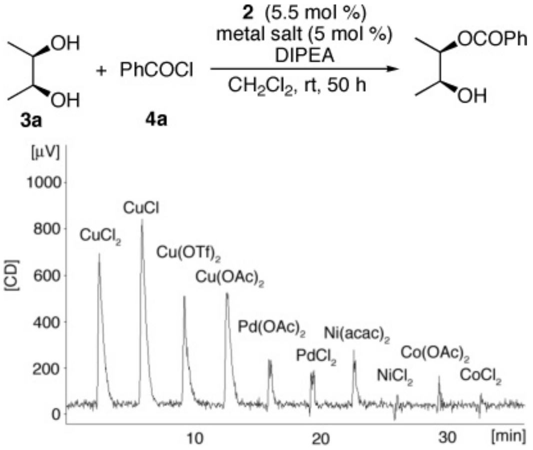
To perform the new reaction optimization, we prepared polymer-supported *N*b-imidazoline (**2**) as shown in Scheme 1. After immobilization of chloromethyl imidazoline onto the polystyrylsulfonyl chloride, a nucleophilic substitution using aminomethyl imidazoline provided the polymer-supported *N*b-imidazoline (**2**). The construction of **2** was confirmed by the analysis of ^{13}C-PST/MAS NMR[5] and IR spectra.

Scheme 1. Synthesis of Polymer-Supported *N*b-Imidazoline (**2**)



With the polymer-supported *N*b-imidazoline ligands in hand, we studied the Cu-catalyzed enantioselective monobenzoylation of *meso*-1,2-diols. The importance of asymmetric desymmetrization of diols in obtaining biologically important products has promoted recent advances, but the catalytic and nonenzymatic asymmetric desymmetrization of *meso*-diols is still limited.[6] In the first screening to find the lead catalyst, various kinds of metal salts were examined as in Scheme 2.

Scheme 2. Polymer-Supported *N*b-Imidazoline (**2**)−Metal Salt Catalyzed Asymmetric Benzoylation of *meso*-2,3-Butanediol



Direct monitoring of the asymmetric reaction using CD detection clearly indicated that the most effective catalyst was the **2**−CuCl catalyst. The efficiency of the asymmetric catalyst was found to decrease somewhat in the order [Cu] > [Pd] ∼ [Ni] > [Co]. Despite the fact that recent reports based on Matsumura's pioneering work[6c] have focused on the Cu(II) catalysis, the HTS results show that the Cu(I) complex has high catalytic activity. Conventional purification by silica gel column chromatography and analysis using chiral stationary phase HPLC revealed that the 2-CuCl catalyst provided the adduct in 64% yield with 61% ee. Thus, the asymmetric conversion yield (ACY),[2] given as the square root of the chemical yield multiplied by the enantiomeric excess, was 62%. This result is better than that obtained using **2**−CuCl$_2$ (29% yield, 52% ee, ACY 39%).

The optimization in Scheme 3 indicated that CHCl$_3$ and CH$_2$Cl$_2$ were appropriate solvents. Conventional analysis revealed that the reaction in CH$_2$Cl$_2$ provided the adduct in 60% yield with 60% ee; the adduct was provided in CHCl$_3$

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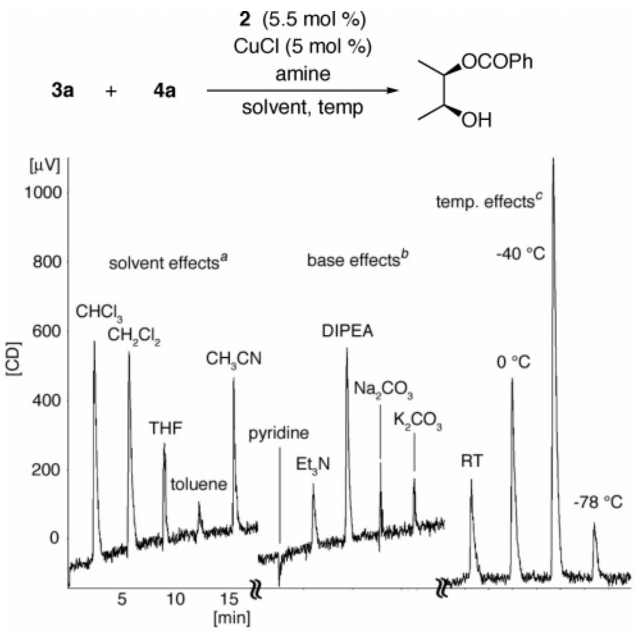
(3) Arai, T.; Mizukami, T.; Yokoyama, N.; Nakazato, D.; Yanagisawa, A. *Synlett* **2005**, 2670−2672.

(4) Recent progresses on chiral ligands containing the imidazoline motif: (a) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783−785. (b) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1500−1503. (c) Manges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713−4716. (d) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595−598. (e) Casey, M.; Smyth, M. P. *Synlett* **2003**, 102−106. (f) Guiu, E.; Claver, C.; Benet-Buchholz, J.; Castillón, S. *Tetrahedron: Asymmetry* **2004**, *15*, 3365−3373. (g) Bastero, A.; Claver, C.; Ruiz, A.; Castillón, S.; Daura, E.; Bo, C.; Zangrando, E. *Chem. Eur. J.* **2004**, *10*, 3747−3760. (h) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller. M. *Org. Lett*, **2005**, *7*, 3393−3396. (i) Weiss, M. E.; Fischer, D. F.; Xin, Z.-q.; Jautze, S.; Schweizer, W. B.; Peters, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 5694−5698.

(5) Arai, T.; Fujiwara, A.; Watanabe, M.; Yokoyama, N.; Fujito, T.; Deguchi, K.; Yanagisawa, A. *Tetrahedron Lett.* **2006**, *47*, 1673−1677.

(6) Several impressive examples of nonenzymatic asymmetric benzoylation of *meso*-1,2-diol have been described: (a) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397−400. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529−3532. (c) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052−2053. (d) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383−3385. (e) Mazet, C.; Köhler, V.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4888−4891.

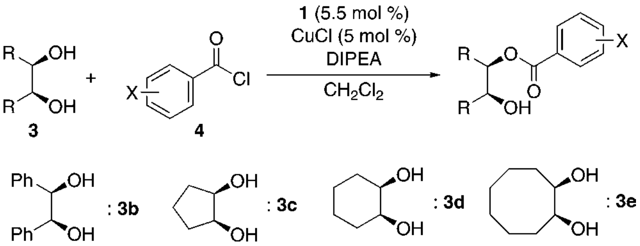
Scheme 3. Optimization of Reaction Conditions: Solvent, Base, and Temperature Effects[a]



[a] Key: (a) examined at rt for 48 h with DIPEA as the base; (b) examined in CH_2Cl_2 at rt for 48 h; (c) examined in CH_2Cl_2 with DIPEA as the base (48 h at rt, 0 °C, and −40 °C, 120 h at −78 °C).

in 68% yield with 54% ee. In terms of base, diisopropylethylamine (DIPEA) was apparently the best choice. Regarding temperature, reducing the temperature from rt to −40 °C dramatically improved the efficiency of the asymmetric reaction. Conventional analysis revealed that the reaction at −40 °C gave the product in 79% yield with 80% ee (ACY = 79%). The reaction at −78 °C was quite slow, and only trace amounts of the adduct were obtained even after 120 h.

Table 1. *N*b-Imidazoline (**1**)−CuCl-Catalyzed Asymmetric Benzoylation of *meso*-1,2-Diols

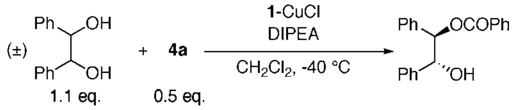


entry	diol	benzoyl chloride	*T* (°C)	time (h)	yield (%)	ee (%)
1	**3a**	**4a**	−40	47	97	95
2	**3a**	**4b** (X = 2-CH_3)	−40	50	98	94
3	**3a**	**4c** (X = 3-CH_3)	−40	51	91	89
4	**3a**	**4d** (X = 4-CH_3)	−40	50	89	93
5	**3a**	**4e** (X = 4-Br)	−40	50	74	92
6	**3a**	**4f** (X = 4-OCH_3)	−40	26	87	93
7	**3b**	**4e**	−40	94	51	68
8	**3b**	**4e**	−78	91	59	80
9	**3c**	**4f**	−40	55	69	61
10	**3d**	**4e**	−40	54	16	65
11	**3d**	**4e**	0	19	72	80
12	**3e**	**4f**	−40	52	72	76
13	**3e**	**4f**	−78	70	76	86

The optimized conditions were applied to the well-defined **1**-Cu(I) catalysis, and the scope and generality is summarized in Table 1. The simple benzoyl chloride (**4a**) as well as the substituted benzoyl chlorides provided adducts with similar high levels of enantiomeric excess up to 95% ee (entries 1−4). Moreover, both electron-deficient and electron-sufficient benzoyl chlorides were useful (entries 5 and 6). The cyclic diols were also benzoylated with good enantioselectivities (entries 9−13), although the appropriate temperature depended on the reactivity of the substrates. For example, the temperature had to be increased to 0 °C for *meso*-1,2-cyclohexanediol (**3d**) to get sufficient yield.

Finally, the optimized catalyst system consisting of *N*b-imidazoline (**1**), CuCl, and DIPEA was applied to the kinetic resolution of racemic 1,2-diol in CH_2Cl_2. The reaction of *rac*-hydrobenzoin with **4a** was catalyzed smoothly at −40 °C to give the monobenzoylated product in 94% yield (based on **4a**) with 92% ee (Scheme 4).[6,7]

Scheme 4. Kinetic Resolution of Racemic 1,2-Diol



1 (5.5 mol %), CuCl (5 mol %), 72 h: y. 81%, 91% ee
1 (11 mol %), CuCl (10 mol %), 43 h: y. 94%, 92% ee

In conclusion, we have demonstrated a new protocol for rapid optimization of reaction conditions to obtain the most ideal catalyst. Research on new and powerful asymmetric catalysis is under progress using the solid catalysis-CD HTS system.

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Supporting Information Available: Experimental procedure and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Kinetic resolution of racemic diols using Cu complex: (a) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325−2328. (b) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879−1882. See also ref 6c.