HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 995 - 1000. © The Japan Institute of Heterocyclic Chemistry
Received, 25th March, 2008, Accepted, 28th May, 2008, Published online, 2nd June, 2008. COM-08-S(N)59

KINETIC RESOLUTION OF 1,2-DIOLS USING NITROGEN-TETHERED BISIMIDAZOLINE-COPPER(I) CATALYZED BENZOYLATION

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – Nitrogen-tethered bisimidazoline (*N*b-imidazoline) ligand was utilized in the Cu(I)-catalyzed benzoylation of 1,2-diols. With the assistance of *i*-Pr_2NEt, the reaction of *rac*-1,2-diols with *o*-methylbenzoyl chloride was smoothly catalyzed by *N*b-imidazoline-CuCl in CH_2Cl_2 to give the corresponding *o*-methylbenzoylated secondary alcohols in up to 79% ee.

Because the hydrogen-bonding network plays a key role in regulating biological phenomena, the development of an efficient synthetic method for producing chiral diols has been receiving much attention. The kinetic resolution of alcohols by nonenzymatic asymmetric catalysis[1-6] would be the most fundamental procedure for supplying such optically active *vic*-diol compounds directed toward the synthesis of biologically significant molecules.[7-20]

We have recently designed and synthesized a new type of X-tethered bisimidazoline ligand that shows diversity of R^1 to R^4, X, and linker length (n).[21] The use of various metal salts would generate a series of imidazoline-metal complexes (Figure 1).

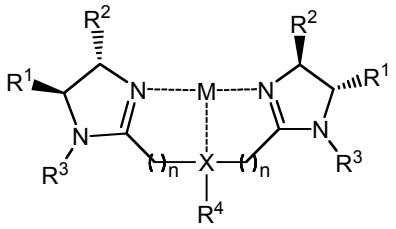
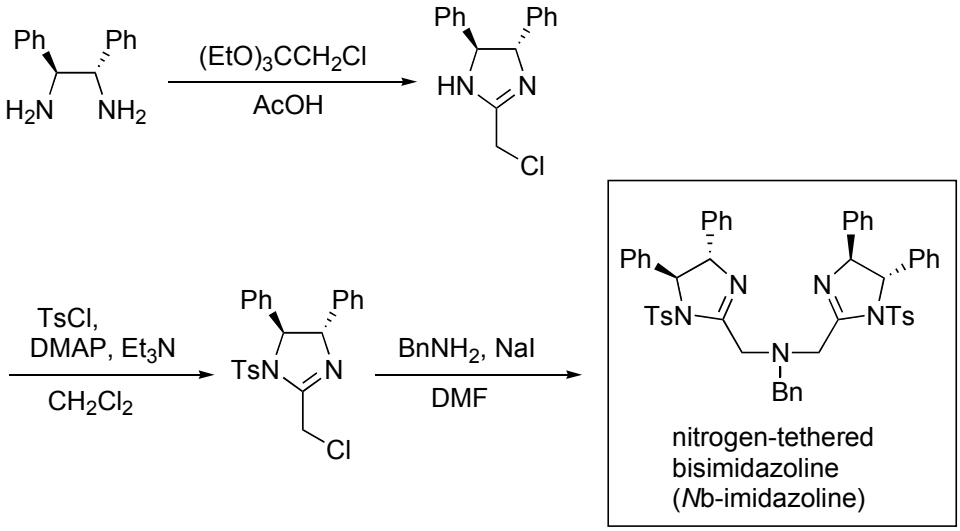


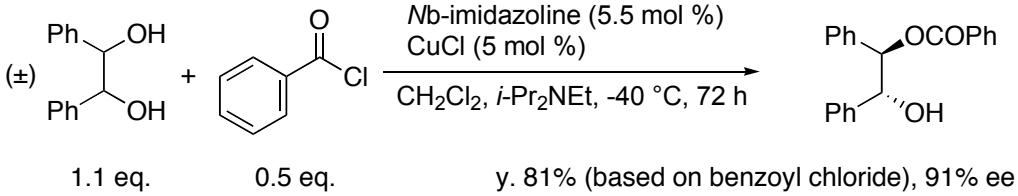
Figure 1. X-Tethered bisimidazoline ligand-metal complex

The synthesis of nitrogen-tethered bisimidazoline (*N*b-imidazoline) is summarized in Scheme 1. After the construction of a heterocyclic chloromethylated imidazoline from commercially available chiral (*S*,*S*)-diphenylethylenediamine, two molecules of the tosyl derivative were connected by substitution using benzylamine.



Scheme 1. Synthesis of nitrogen-tethered bisimidazoline (*N*b-imidazoline).

In the course of our study on the catalytic ability of newly developed *N*b-imidazoline, we succeeded in developing an efficient asymmetric desymmetrization of *meso*-diols[22] using a novel reaction optimization system called "solid-phase catalysis CD-HTS."[23] We have also reported one example of the kinetic resolution of *rac*-1,2-diphenylethanediol using *N*b-imidazoline-CuCl catalyst (Scheme 2).[22]



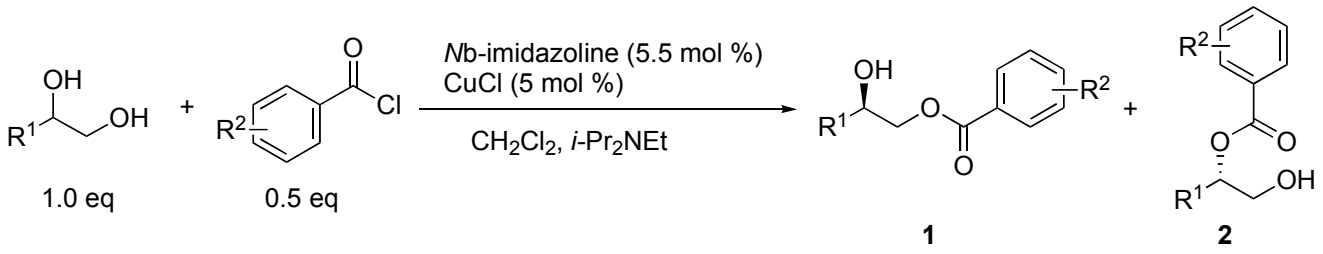
Scheme 2. Kinetic resolution of *rac*-1,2-diphenylethanediol.

We report herein the application of this fascinating catalyst system to the kinetic resolution of *rac*-1,2-diols .

We started our experiment with the simple application of the original catalyst system developed for the desymmetric benzoylation of *meso*-diols. The reaction of *rac*-3,3-dimethyl-1,2-butanediol with benzoyl chloride was examined using 5 mol% *N*b-imidazoline-CuCl; however, the reaction at -40 °C in CH_2Cl_2 gave benzoylated secondary alcohol (**1**) in 58% yield and only 52% ee (Table 1, entry 1). When the

reaction was carried out at -78 °C, the result was disappointing in that enantioselectivity was decreased further to 36% ee (Table 1, entry 2). The use of *p*-Br-benzoyl chloride, which showed better enantioselectivities in some cases in the desymmetrization of *meso*-diols, gave results similar to those using benzoyl chloride (Table 1, entry 3). Although initial attempts at the simple application of the original catalyst system resulted in moderate enantioselectivities, the generality of the catalyst system using several kinds of *rac*-1,2-diols was confirmed as summarized in Table 1.

Table 1. Kinetic Benzoylation of 1,2-Diols Using *N*b-Imidazoline-CuCl Catalyst



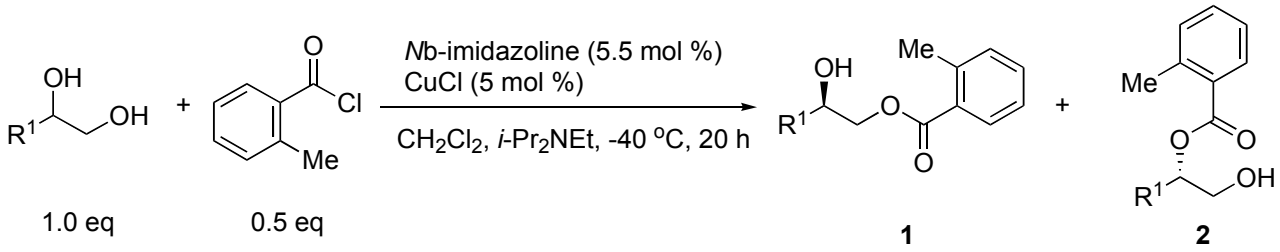
Entry	R^1	R^2	Temp (°C)	Time (h)	Yield (%)[a] (**1**/**2**)	ee (%) (**1**/**2**)
1	*t*-Bu	H	-40	14	58/4	52/61
2	*t*-Bu	H	-78	94	70/18	36/ND
3	*t*-Bu	*p*-Br	-40	14	58/14	51/80
4	Me	H	-40	33	76/14	47/73
5	Et	H	-40	22	80/8	44/73
6	Bu	H	-40	20	78/12	43/92
7	Ph	H	-40	22	80/12	42/ND

[a]Yields are based on benzoyl chlorides. ND: not determined.

Interestingly, although benzoylated primary alcohol (**2**) was the minor product, it recorded higher enantioselectivities (ranging from 61% ee to 92% ee) than major product **1**. The migration of benzoyl group and the formation of the bisbenzoylated products were negligible under the current reaction conditions. Compared with the benzoylation route for **1**, that for **2** has to occur on sterically hindered secondary alcohol. This prompted us to conduct further experiments using sterically hindered benzoyl chloride derivatives to improve stereoselectivity. To our delight, the enantioselectivity of the product was improved; for example, the reaction of *rac*-3,3-dimethyl-1,2-butanediol with *o*-methylbenzoyl chloride using 5 mol% *N*b-imidazoline-CuCl catalyst gave the product in 43% yield and 73% ee (Table 2, entry 1). In this reaction, the minor product of secondary alcohol was obtained only in trace amount. Encouraged by this result, the generality of the reaction using *o*-methylbenzoyl chloride was examined,

and the results are summarized in Table 2.[24]

Table 2. Kinetic Resolution of *rac*-1,2-Diols Catalyzed by *N*b-Imidazoline-CuCl Complex



Entry	R^1	Yield (%) (**1**/**2**)[a]	ee (%) (**1**/**2**)
1	*t*-Bu	86/trace	73/-
2	Me	62/14	78/89
3	Et	78/20	79/89
4	*n*-Bu	68/22	75/97
5	Ph	72/14	61/98

[a]Yields are based on *o*-methylbenzoyl chloride.

When 1,2-butanediol was utilized in the asymmetric *o*-methylbenzoylation, the enantiomeric excess of **1** reached 79% ee (Table 2, entry 3). Not only aliphatic substrates (Table 2, entries 1-4) but also the phenyl-substituted substrate was converted into the target *o*-methylbenzoylated secondary alcohol with reasonable enantioselectivity (Table 2, entry 5).[25]

One possible mechanism for the generation of regio- and enantioselectivity in the *N*b-imidazoline-CuCl catalyzed benzoylation of *rac*-1,2-diols was proposed, as shown in Figure 2. Using chiral (*S*,*S*)-*N*b-imidazoline, the (*R*)- or (*S*)-enantiomer of 1,2-diol would form the diastereomeric catalyst-substrate complex. When the 1,2-diol coordinates to the Cu atom in a bidentate manner, a total of four complexes are possible (**A** to **D**) in Figure 2. Of the four possible coordination manners, **B** and **C** exhibit significant steric repulsion between phenyl group on *N*b-imidazoline and R group of the substrate. Thus, the equilibrium should lean toward the formation of **A** and **D**, respectively. At this stage, in the benzoylation of diols using Cu catalyst, the hydroxyl group would be activated by the Lewis acidity of the Cu cation. Because the Jahn-Teller effect made the equatorial site more acidic than the axial site, the OH group existing at the equatorial site would smoothly react with benzoyl chloride.[26, 27] Structure **A** satisfies the requirements for benzoylation from the less-hindered primary alcohol via equatorial coordination. The formation of (*R*)-enriched benzoylated secondary alcohol **1** using (*S*,*S*)-*N*b-imidazoline-CuCl catalyst is also well explained by **A**.

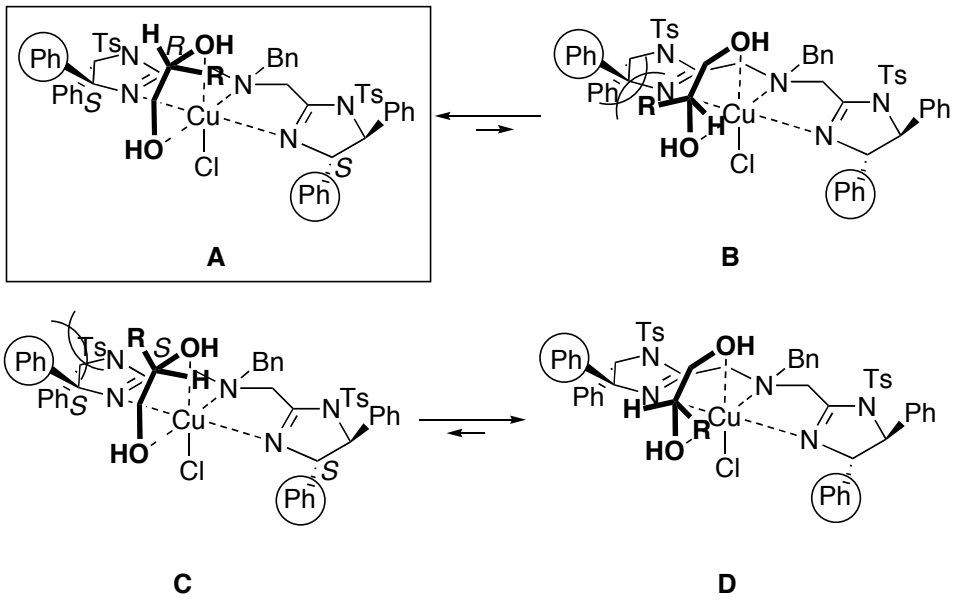


Figure 2

In summary, we have succeeded in developing an efficient kinetic resolution of *rac*-1,2-diols using the *N*b-imidazoline-CuCl catalyst. Because the non-enzymatic approach is practically useful, the current approach would be the method of choice for the synthesis of chiral 1,2-diols. Further applications of fascinating *N*b-imidazoline-metal complexes in asymmetric catalysis are in progress.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in Aid for Scientific Research on Priority Areas (No. 19028007, "Chemistry of Concerto Catalysis") from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a grant from the Uehara Memorial Foundation.

REFERENCES AND NOTES

1. G. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412.
2. S. France, D. J. Duerrin, and S. J. Miller, *Chem. Res.*, 2003, **103**, 2985.
3. E. Vedejs and M. Jure, *Angew. Chem. Int. Ed.*, 2005, **44**, 3974.
4. P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138.
5. V. B. Birman, E. W. Uffman, H. Jiang, X. Li, and C. J. Kilbane, *J. Am. Chem. Soc.*, 2004, **126**, 12226.
6. A. C. Spivey, D. P. Leese, F. Zhu, S. G. Davey, and R. L. Jarvest, *Tetrahedron*, 2004, **60**, 4513.
7. T. Kawabata, M. Nagato, K. Takasu, and K. Fuji, *J. Am. Chem. Soc.,* 1997, **119**, 3169.
8. T. Oriyama, K. Imai, T. Sano, and T. Hosoya, *Tetrahedron Lett.*, 1998, **39**, 3529.
9. F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, and Y. Matsumura, *J. Org. Chem.*, 2000, **65**, 996.

10. Y. Matsumura, T. Maki, S. Murakami, and O. Onomura, *J. Am. Chem. Soc.,* 2003, **125**, 2052.
11. S. Mizuta, M. Sadamori, T. Fujimoto, and I. Yamamoto, *Angew. Chem. Int. Ed.*, 2003, **42**, 3383.
12. E. Vedejs, O. Daugulis, and N. Tuttle, *J. Org. Chem.*, 2004, **69**, 1389.
13. K. Ishihara, Y. Kosugi, and M. Akakura, *J. Am. Chem. Soc*., 2004, **126**, 12212.
14. A. Gissibl, M. G. Finn, and O. Reiser, *Org. Lett.*, 2005, **7**, 2325.
15. C. Mazet, V. Köhler, and A. Pfaltz, *Angew. Chem. Int. Ed*., 2005, **44**, 4888.
16. C. Mazet, S. Roseblade, V. Köhler, and A. Pfaltz, *Org. Lett.,* 2006, **8**, 1879.
17. S. Yamada, T. Misono, Y. Iwai, A. Masumizu, and Y. Akiyama, *J. Org. Chem.*, 2006, **71**, 6872.
18. K. Matsumoto, M. Mitsuda, N. Ushijima, Y. Demizu, O. Onomura, and Y. Matsumura, *Tetrahedron Lett*., 2006, **47**, 8453.
19. D. Nakamura, K. Kakiuchi, K. Koga, and R. Shirai, *Org. Lett*., 2006, **8**, 6139.
20. B. Jung, M. S. Hong, and S. H. Kang, *Angew. Chem. Int. Ed.,* 2007, **46**, 2616.
21. T. Arai, T. Mizukami, N. Yokoyama, D. Nakazato, and A. Yanagisawa, *Synlett,* 2005, 2670.
22. T. Arai, T. Mizukami, and A. Yanagisawa, *Org. Lett.,* 2007, **9**, 1145.
23. T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, and A. Yanagisawa, *Angew. Chem. Int. Ed.,* 2006, **45**, 5978.
24. Typical experimental procedure (Table 2, entry 3): *N*b-imidazoline (7.3 mg, 8.25 μmol) and CuCl (0.74 mg, 7.5 μmol) were stirred for 3 h at rt in CH_2Cl_2 (1.5 mL) under Ar atmosphere. To the solution were added 1,2-butanediol (11 μL, 0.15 mmol), *i*-Pr_2NEt (25.7 μL, 0.15 mmol), and *o*-methylbenzoyl chloride (9.7 μL, 0.075 mmol) at -40 °C. After stirring for 20 h, the solution was poured onto water and the aqueous layer was extracted with $CHCl_3$ (10 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* after filtration. The residual crude product was purified by silica gel chromatography (hexane:EtOAc = 3:1) to give the product. The ee of the adduct was determined by chiral stationary phase HPLC analysis (Daicel Chiralpak AS-H).
25. In the reaction using pheny-l,2-ethanediol, when the major secondary alcohol **1** was obtained in 36% yield with 54% ee and the minor primary alcohol **2** was obtained in 7% yield with 73% ee, the (*S*)-enriched starting diol was recovered in 41% with 29% ee.
26. B. J. Hathaway and D. E. Billing, *Coord. Chem. Rev.,* 1970, **5**, 143.
27. D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, and C. W. Downey, *J. Am. Chem. Soc.,* 2003, **125**, 12692.