JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Desymmetrization of 2,2-Disubstituted 1,3-Propanediols

Ji Young Lee, Young Suk You, and Sung Ho Kang*

Molecular-Level Interface Research Center, Department of Chemistry, KAIST, Daejeon 305-701, Korea

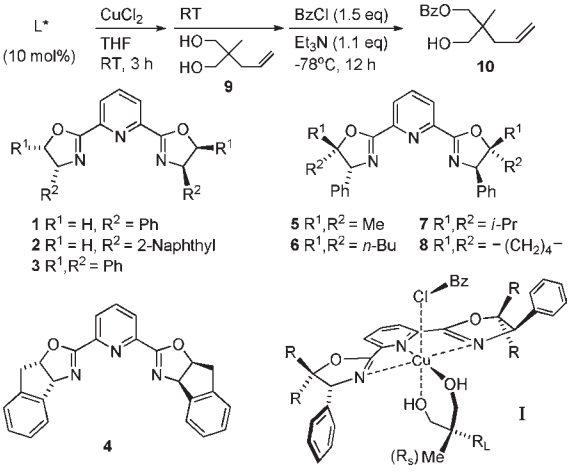
Supporting Information

Enantioselective desymmetrization of symmetric molecules is an economical way to generate chirality. The process is effected by differentiation of two enantiotopic groups and is advantageous due to the relatively facile preparation of the starting substrates. Among the stereogenic carbon centers, the formation of quaternary centers directly bonded to heteroatoms or all-carbons is particularly challenging.[1] In trying to construct all-carbon quaternary stereocenters, one is fighting innate steric congestion. Catalytic desymmetrization has been applied rarely to forming such carbon stereocenters.[2] Most of the known approaches to them suffer from the narrow substrate scope and/or low enantioselectivity.[3] They have been implemented through aldol cyclization,[4] Pd-catalyzed coupling reactions,[5] Diels−Alder cycloaddition,[6] Rh-activated C−H bond insertion and cyclization,[7] and Cu-induced tosylation.[8] It is of great significance and synthetic utility to develop a desymmetrization method producing the quaternary sterocenters with the enhanced substrate scope and enantioselectivity. Herein, we describe a catalytic asymmetric desymmetrization of 2,2-disubstituted 1,3-propanediols to build the corresponding all-carbon quaternary stereocenters.

Previously, we reported the enantioselective desymmetrization of glycerols and serinols to synthesize *tert*-alcohols[9] and *tert*-alkylamines,[10] the stereochemical outcomes of which might be rationalized by analyzing the chelated intermediates between the Cu-catalysts and the substrates through the two heteroatoms at 1,2- rather than 1,3-positions. In the present desymmetrization of 2,2-(all-carbon)disubstituted 1,3-propanediols, the substrates can coordinate with the catalyst through only the two hydroxyl groups at 1,3-positions. Since their pro-stereogenic centers are located at 2-positions and farther from the chiral ligand in the 1,3-chelated complexes, their desymmetrization is destined to remain a substantial synthetic challenge. With the inherent difficulty associated with the 1,3-diols in mind, the desymmetrization of the model substrate **9** was extensively assayed under benzoylation conditions by changing or adjusting the chiral ligand, base, temperature, etc. Eventually, the pyridinebisoxazoline **1**[11] was identified to reach the relatively superior enantioselectivity, proposing this skeleton as the main structural frame for the prospective chiral ligand (entry 1, Table 1).

A wide array of functionalized pyridinebisoxazolines (Pybox) was primed and scouted in search of the optimal ligand in the desymmetrization of **9**.[12] Some informational outcomes are summarized in Table 1. In the beginning, the two phenyl substituents of **1** were replaced by alkyl, benzyl, and 2-naphthyl. While a racemic mixture of monobenzoates was obtained with the $(alkyl)_2$-Pybox and $(Bn)_2$Pybox, $(2\text{-naphthyl})_2$Pybox **2** afforded them

Table 1. Desymmetrization of 9 Using Pybox (L*)-$CuCl_2$ Complexes



entry	L*	% yield (% sm)[a]	% ee
1	**1**	64 (32)	65
2	**2**	60 (36)	61
3	**3**	62 (36)	50
4	**4**	45 (53)	2
5	**5**	66 (30)	61
6	**6**	80 (17)	76
7	**7**	47 (50)	14
8	**8**	54 (40)	73
9[b]	**6**	98	89

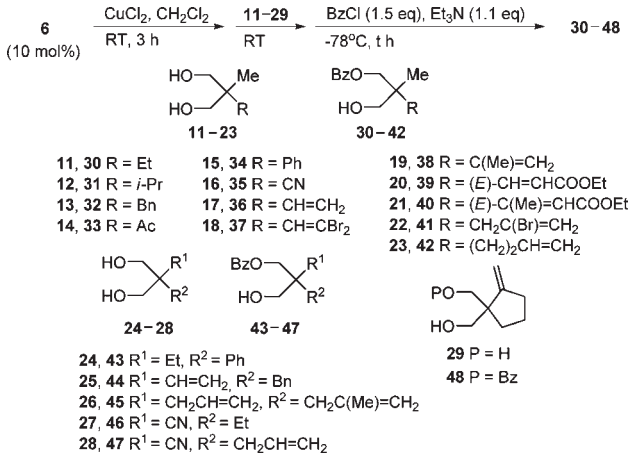
[a] Recovered sm in parentheses. [b] CH_2Cl_2 was used as solvent instead of THF.

with a moderate but somewhat inferior stereoselectivity to that for **1** (entry 2). The next examination with the tetrasubstituted Pybox **3** and **4** revealed that both are less effective than **1**, and intriguingly they have distinctively different capability in ligand function (entries 3 and 4). At this point, we surmised that the Pybox-Cu(II) catalyst makes an octahedral complex with the 1,3-diol and benzoyl chloride to transfer the benzoyl cation to the proximate hydroxyl group, in which the tridentate Pybox is

Received: November 17, 2010
Published: January 25, 2011

dx.doi.org/10.1021/ja1103102 | J. Am. Chem. Soc. 2011, 133, 1772–1774

Table 2. Desymmetrization of 11−29 Using Pybox (6)-$CuCl_2$ complex



entry	substrate/product	reaction time (t h)	% yield (% sm)[c]	% ee[d,e]
1	**9/10**	12	98	89
2	**11/30**	12	95 (2)	84 (*R*)
3	**12/31**	5	96 (2)	94 (*R*)
4	**13/32**	3	99	95 (*R*)
5	**14/33**	12	85 (10)	95 (*R*)
6	**15/34**	3	98	83 (*R*)
7[a]	**16/35**	5	73 (10)	99 (*R*)
8	**17/36**	20	91 (7)	54 (*R*)
9	**18/37**	3	99	97 (*R*)
10	**19/38**	12	97	96 (*R*)
11	**20/39**	12	95 (3)	85 (*R*)
12	**21/40**	12	95 (2)	98 (*R*)
13	**22/41**	15	93 (3)	92
14	**23/42**	12	98	94
15[b]	**24/43**	12	98	49 (*R*)
16[b]	**25/44**	12	88 (5)	84
17[b]	**26/45**	12	91 (5)	51
18[a]	**27/46**	12	67 (15)	98
19[a]	**28/47**	18	72 (18)	98
20	**29/48**	20	92 (5)	87

[a] The reaction was carried out with BzCl (1.5 equiv) and $(i\text{-Pr})_2$NEt (1.2 equiv) in a 20:1 mixture of PhMe and CH_2Cl_2. [b] PhMe was used as solvent. [c] Percentage of recovered sm in parentheses. [d] Determined by HPLC analysis using DAICEL chiral columns (see Supporting Information [SI]). [e] Absolute configuration of the major enantiomer in parentheses (see SI).

situated equatorially, benzoyl chloride axially, and the substrate both equatorially and axially. In the proposed transition state, the smaller group of the substrate is expected to occupy the space near the 4-phenyl substituent of the oxazoline ring based on sterics. Thus, we inferred that enough room should be secured in the space to accommodate the smaller methyl substituent. The inference suggested that the ineffectiveness of **4** as a chiral ligand could be ascribed to the conformationally inflexible planarity of the indanyl substituents. We designed the attachment of two substituents at the 5-position of the oxazoline ring in order to force the phenyl group perpendicularly to the ring to allow for extra room as shown in the intermediate **I** (Table 1). A survey of several substituents led us to elaborate the most effective chiral ligand **6** comprising *n*-butyl groups (entry 6). Furthermore, changing the solvents from THF to CH_2Cl_2 enhanced both the stereoinduction and chemical conversion (entry 9). On the other hand, methyl groups seem to be rather small for the intended phenyl conformation, whereas isopropyl groups themselves are too bulky (entries 5 and 7). In addition, the chloride anion worked best among the catalyst anions. When 5, 15, or 20 mol % of **6** was loaded, **10** was procured in a little lower yield (95%) with a slightly lower ee value (88%).

Diverse 1,3-diols **11**−**29** were desymmetrized under the asymmetric monobenzoylation conditions as detailed by entry 9 of Table 1. Outstanding desymmetrization was attained especially with most of the 2-methyl 1,3-diols as depicted in Table 2. Remarkably, the small ethyl group in **11** was distinguished from the methyl group with higher than 10:1 er (entry 2). In contrast, why the bulkier substituent-containing diols **15** and **20** were monobenzoylated with somewhat lower enantioselectivity than estimated from other substrates is not readily explained (entries 6 and 11). While the chirality generation from the vinyl diol **17** proceeded with a moderate stereoselection probably due to the smaller size difference between the two pendants, replacement of the vinyl group by the bulkier β,β-dibromovinyl (**18**) and α-methylvinyl (**19**) resulted in respectably higher % ee values (entries 8−10). As for **20** and **21**, attachment of a methyl substituent to the conjugated ester branch of **20** augmented the % ee value significantly from 85 to 98 (entries 11 and 12). This similar proclivity was observed to a lesser extent with a β-bromo substituent in the allyl diols **9** and **22** (entries 1 and 13). Scrutiny of the experimental data reveals that the stereoselectivity was enhanced with the 2-methyl diols having the second substituent with α- or β-branches (entries 3, 5, 9, 10, 12, and 13). The 2-cyano diols **16**, **27** and **28** were desymmetrized more stereoselectively by 20−25% ee in toluene than in CH_2Cl_2 (entries 7, 18, and 19). In practice a 20:1 mixture of toluene and CH_2Cl_2 was used to enhance solubility. Little difference in stereoselectivity was found between this mixture and toluene. It is unlikely that the superb enantioselectivity for the cyano diols can be rationalized simply by considering the relative sizes of their substituents. Since considerable amounts (15−25%) of the corresponding dibenzoates were formed with Et_3N in the monobenzoylation of the cyano diols, the base was switched to $i\text{-Pr}_2$NEt. With significant suppress of the side reaction, 4−7% of the dibenzoates still formed. In order to clarify whether kinetic resolution was responsible for the observed excellent stereoselectivity, ee values from the reaction of **28** were analyzed every 4 h and found to be consistent, excluding this possibility. Somewhat lower material balances for the cyano diols are partially ascribed to separation difficulty from the Pybox ligand and their higher solubilities in water. As expected, the desymmetrization of the diols bearing two substituents different from the methyl group proceeded with reduced stereoinduction (entries 15−17). Also, the enantiotopic differentiation of **24** and **25** was found to be more effective in toluene (entries 15 and 16). It is worth mentioning that the monobenzoylation of the methylenylcyclopentane diol **29** was consummated with a noteworthy 87% ee value (entry 20).

We have established an asymmetric monobenzoylation of readily accessible symmetric 2,2-disubstituted 1,3-diols to install all-carbon quaternary stereocenters. The most efficient chiral ligand turned out to be the Pybox **6** having 4-phenyl and 5,5-di-*n*-butyl substituents, thought to enable the two phenyl and

dx.doi.org/10.1021/ja1103102 |*J. Am. Chem. Soc.* 2011, 133, 1772–1774

oxazolidine planes to cross vertically in securing the reserved space for the smaller substituent of the substrate.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
shkang@kaist.ac.kr.

■ ACKNOWLEDGMENT

This work was supported by Midcareer Researcher program through an NRF grant funded by the MEST (2010-0000780) as well as by the MEST (2010-0001957). This paper is dedicated with respect to the memory of Prof. Chi Sun Hahn.

■ REFERENCES

(1) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (e) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(2) (a) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139. (b) Teng, X.; Cefalo, D. R.; Shrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779. (c) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421. (d) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149. (e) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (f) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509.

(3) (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

(4) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(5) (a) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108. (b) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1249. (c) Takenaka, K.; Nakatsuka, S.; Tsujihara, T.; Koranne, P. S.; Sasai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2492.

(6) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

(7) (a) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(8) Demizu, Y.; Kubo, Y.; Matsumura, Y.; Onomura, O. *Synlett* **2008**, 433.

(9) (a) Jung, B.; Kang, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 1471. (b) Jung, B.; Hong, M. S.; Kang, S. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2616.

(10) Hong, M. S.; Kim, T. W.; Jung, B.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 3290.

(11) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.

(12) See SI for the results using the previously employed chiral ligands.