Asymmetric Catalysis

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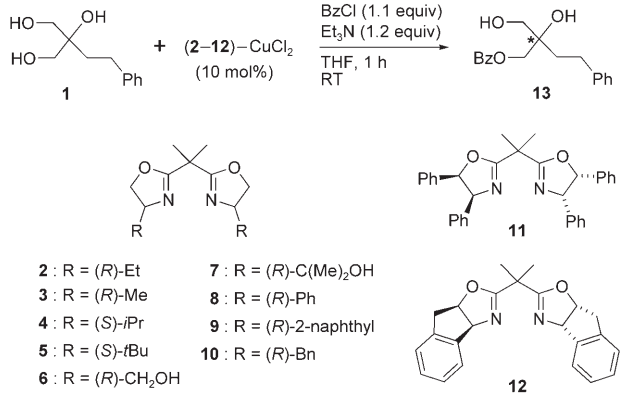
Enantioselective Synthesis of Tertiary Alcohols by the Desymmetrizing Benzoylation of 2-Substituted Glycerols**

*Byunghyuck Jung, Mi Sook Hong, and Sung Ho Kang**

The enantioselective desymmetrization of prochiral compounds has great synthetic potential for the creation of stereogenic centers. Some desymmetrization methods have been exploited to form stereogenic quaternary carbon atoms.[1] Representative examples of methods used for the construction of all-carbon quaternary stereocenters include the Pd-catalyzed cyclization of prochiral dienes,[2] the chiral-amine-promoted intramolecular aldol condensation of triketones,[3] salen–Co-catalyzed intramolecular epoxide opening,[4] the Wittig cyclization of chiral phosphonium salts,[5] the alkylation of ketones mediated by chiral lithium amides,[6] and C–H bond insertion of diazoketones.[7] However, quaternary stereocenters bonded to heteroatoms have rarely been installed by desymmetrization. The following methods have been implemented for the formation of such stereocenters through desymmetrization: the Sharpless epoxidation of dienes,[8] ring-closing metathesis of trienes,[9] the intramolecular nucleophilic cleavage of anhydrides,[10] the Rh-catalyzed conjugate addition–aldol cyclization of enone diketones,[11] a hydroxy-directed Heck cyclization,[12] and an intramolecular Stetter reaction.[13]. As chiral tertiary alcohols are ubiquitous in physiologically valuable natural products and pharmaceuticals, we have been particularly interested in this functionality. In this context, we have been engaged in developing an efficient and versatile asymmetric desymmetrization.[14,15] Herein we describe the enantioselective desymmetrization of prochiral 2-substituted glycerols by monobenzoylation to prepare an array of chiral tertiary alcohols with high stereoinduction.

After an extensive search for prospective asymmetric catalysts, the effective desymmetrization boundaries were investigated by monoprotection of the primary hydroxy groups of the model substrate **1** (30 mM) in the presence of the $CuCl_2$ complex of the diethylbisoxazoline **2**[16] in THF with various combinations of protecting reagents and bases. Higher stereoselectivity was observed with the protecting-reagent/base couples BzCl/Et_3N (84% *ee*), BzCl/*i*Pr_2NEt (78% *ee*), BzCl/*i*Pr_2NH (72% *ee*), BzCl/*t*BuOK (54% *ee*), and TESCl/Et_3N (53% *ee*; TES = triethylsilyl) at room temperature than with other combinations. The most adaptable protocol turned out to be benzoylation with a combination of BzCl and Et_3N. The dependence of the desymmetrizing monobenzoylation on the solvent, reaction temperature, and concentration was examined. It was found that THF was far superior to other solvents, that lowering the reaction temperature exerted an adverse effect on the reaction, and that the optimal concentration of **1** was 60 mM. Under the optimum conditions, the desymmetrizing functionalization of **1** was effected with high enantioselectivity as well as high chemical conversion (Table 1, entry 1).

Table 1: Desymmetrizing monobenzoylation of **1** with complexes of the bisoxazolines **2**–**12** and $CuCl_2$, BzCl, and Et_3N.[a]



Entry	Bisoxazoline	Yield [%] (s.m. [%])[b]	*ee* [%][c]
1	**2**	94 (2)	90 (*R*)
2	**3**	95 (2)	86 (*R*)
3	**4**	80 (10)	76 (*S*)
4	**5**	53 (40)	14 (*S*)
5	**6**	88 (7)	86 (*R*)
6	**7**	60 (28)	58 (*R*)
7	**8**	97	90 (*R*)
8	**9**	89 (5)	88 (*R*)
9	**10**	97	91 (*R*)
10	**11**	97	91 (*S*)
11	**12**	26 (65)	18 (*S*)
12[d]	**10**	78 (15)	87 (*R*)
13[d,e]	**10**	97	92 (*R*)

[a] [**1**] = 60 mM. [b] The values in parentheses refer to the recovery of starting material (s.m.). [c] The configuration of the major enantiomer is given in parentheses. [d] Catalyst **10**–$CuCl_2$: 5 mol%. [e] Et_3N, and the mixture of **1** and BzCl were added simultaneously, dropwise. Bn = benzyl, Bz = benzoyl.

Next, structurally diverse bisoxazolines were surveyed as chiral ligands in the desymmetrization of **1**. Some instructive results are presented in Table 1. In the case of 4-alkyl-substituted bisoxazolines,[17] the stereoselectivity increased

[*] B. Jung, M. S. Hong, Prof. Dr. S. H. Kang
Center for Molecular Design and Synthesis
Department of Chemistry, School of Molecular Science (BK21)
KAIST, Daejeon 305-701 (Korea)
Fax: (+82) 42-869-2810
E-mail: shkang@kaist.ac.kr

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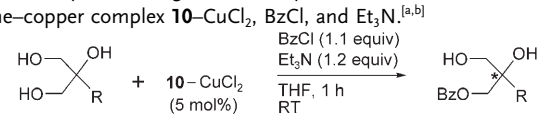
when methyl were replaced with ethyl substituents, and decreased steeply as the substituents became bulkier (Table 1, entries 1–4). The 4-(hydroxyalkyl)-substituted bisoxazolines[18] also seem to dictate the stereoselectivity by a steric rather than an electronic effect (Table 1, entries 5 and 6). We believe that the substituent in the 4-position must have an appropriate size for the catalyst and the substrate to be able to coordinate tightly and must subsequently impose enough steric congestion to promote a high level of stereoinduction. Most of the 4-aryl- and 4-benzyl-substituted bisoxazolines tested[17c,19] showed excellent enantioselectivity to give the products with 88–91% *ee* (Table 1, entries 7–10). Only the use of the indane-fused bisoxazoline **12**[20] led to much lower reactivity and stereoselectivity, presumably as a result of the less flexible fused structure, which may impede effective complexation between the catalyst and the substrate and/or the acylating reagent (Table 1, entry 11). No better results were obtained with bisoxazolines bridged by oxalate, tartrate, phthalate, dibenzofurandicarboxylate, or pyridinedicarboxylate moieties. The dibenzylbisoxazoline **10** was chosen as the best chiral ligand on the basis of desymmetrization efficiency and accessibility (Table 1, entry 9). As it is synthetically worthwhile to modulate the loading amount of the catalyst, various quantities were tried. When the catalyst loading was reduced from 10 to 5 mol%, not only the stereoselectivity but also the chemical conversion decreased (Table 1, entry 12). Fortunately, this problem could be surmounted by adding Et_3N, and the mixture of the substrate **1** and BzCl simultaneously, dropwise over several minutes (Table 1, entry 13). Further amelioration of the desymmetrizing enantiodifferentiation was attempted by testing the efficiency of the catalyst with several different counter anions. However, the chloride anion proved to be the most effective.

The glycerols **14–23** with a variety of substituents in the 2-position were desymmetrized by the established procedure as outlined in Table 2. The asymmetric monobenzoylation proceeded very efficiently with most alkyl substituents. However, the enantioselectivity was a little lower with the bulky isopropyl group (Table 2, entry 4), and both the stereoinduction and the chemical conversion diminished appreciably with the benzyl substituent (Table 2, entry 9). The least satisfying results were obtained with the vinyl and phenyl triols **19** and **20** (Table 2, entries 7 and 8), the asymmetric monobenzoylation of which could not be improved by increasing the quantity of the catalyst.

To overcome the structural limitations of the substrates, another series of catalysts was prepared in situ from $CuCl_2$ and chiral ligands: the oxazoline amides **34–36**, the oxazoline diphenylphosphane **37**, the iminoalcohols **38** and **39**, and the iminooxazolines **40** and **41** (Scheme 1). The desymmetrizing monobenzoylation of **1** was assayed under similar conditions to those used for entry 9 of Table 1, but with 10 mol% of the generated catalysts. Although most catalysts gave products with less than 10% *ee*, when the complex **41**–$CuCl_2$ was used with substrate **1**, compound **13** was formed with a promising 53% *ee* (Table 3, entry 1). When the catalyst loading was tripled from 10 to 30 mol%, the enantioselectivity increased to 90% *ee* (Table 3, entry 2). These results led us to attempt the desymmetrization of **16** and **19–22** under the optimized benzoylation conditions with the new catalyst complex **41**–$CuCl_2$. The enantioselectivities were enhanced by a few percent for the alkyl triols **16** and **22** (Table 3, entries 3 and 7),

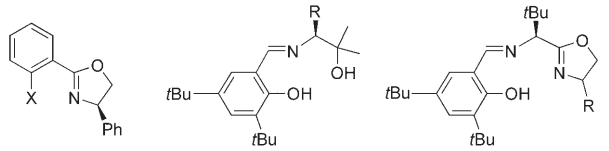
Table 2: Desymmetrizing monobenzoylation of **14–23** with the bisoxazoline–copper complex **10**–$CuCl_2$, BzCl, and Et_3N.[a,b]



14–23 **24–33**

Entry	R (Substrate/Product)	Yield [%] (s.m. [%])[c]	*ee* [%][d,e,f]
1	$(CH_2)_2Ph$ (**1**/**13**)	97	92 (*R*)
2	Me (**14**/**24**)	96	94 (*R*)
3	$(CH_2)_2Me$ (**15**/**25**)	97	92
4	$CHMe_2$ (**16**/**26**)	94	80 (*R*)
5	$(CH_2)_2CHMe_2$ (**17**/**27**)	98	91
6	$CH_2CH{=}CH_2$ (**18**/**28**)	98	92 (*R*)
7	$CH{=}CH_2$ (**19**/**29**)	97	27 (*R*)
8	Ph (**20**/**30**)	67 (30)	30 (*R*)
9	CH_2Ph (**21**/**31**)	68 (27)	67 (*R*)
10	$CH_2OTBDPS$ (**22**/**32**)	94	89
11	$(CH_2)_2OTBDPS$ (**23**/**33**)	94	91 (*R*)

[a] Et_3N and the mixture of substrate and BzCl were added simultaneously, dropwise. [b] [Substrate] = 60 mM. [c] The values in parentheses refer to the recovery of starting material. [d] The configuration of the major enantiomer is given in parentheses. [e] The *ee* value was determined by HPLC analysis with a DAICEL AD-H column. [f] For the determination of absolute configuration, see the Supporting Information. TBDPS = *tert*-butyldiphenylsilyl.



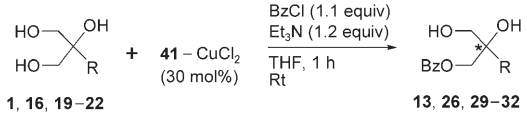
34 : X = NHBz
35 : X = NHAc
36 : X = $NHSO_2Ph$
37 : X = PPh_2

38 : R = *t*Bu
39 : R = Ph

40 : R = α-Ph
41 : R = β-Ph

Scheme 1. Chiral ligands for desymmetrizing benzoylation.

Table 3: Desymmetrizing benzoylation of **1**, **16**, and **19–22** with the complex of ligand **41** and $CuCl_2$, BzCl, and Et_3N.[a]



1, **16**, **19–22** **13**, **26**, **29–32**

Entry	Substrate	Product	Yield [%] (s.m. [%])[b]	*ee* [%][c]
1[d]	**1**	**13**	74 (22)	53 (*R*)
2	**1**	**13**	91 (6)	90 (*R*)
3	**16**	**26**	85 (10)	83 (*R*)
4	**19**	**29**	94	81 (*R*)
5	**20**	**30**	94	80 (*R*)
6	**21**	**31**	91 (7)	86 (*R*)
7	**22**	**32**	90 (5)	93

[a] [Substrate] = 60 mM. [b] The values in parentheses refer to the recovery of starting material. [c] The configuration of the major enantiomer is given in parentheses. [d] Quantity of **41**–$CuCl_2$: 10 mol%.

and substantially for the benzyltriol **21** (Table 3, entry 6), relative to those observed with the complex **10**–$CuCl_2$. The most remarkable results were procured with the vinyl- and phenyl-substituted triols **19** and **20**: Improvements of at least 50% *ee* were observed (Table 3, entries 4 and 5).

In conclusion, we have developed a highly enantioselective monobenzoylation of prochiral 2-substituted 1,2,3-propanetriols to provide access to a variety of chiral tertiary alcohols with up to 94% *ee*. The desymmetrizing functionalization was elaborated by using two complementary asymmetric catalysts, the dibenzylbisoxazoline–copper complex **10**–$CuCl_2$ and the iminooxazoline **41**–$CuCl_2$. The former is compatible with 2-alkyl-substituted substrates, and the latter is very effective for substrates with vinyl, phenyl, and benzyl substituents in the 2-position.

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