Chiral imine copper chloride-catalyzed enantioselective desymmetrization of 2-substituted 1,2,3-propanetriols

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Catalytic enantioselective desymmetrization of meso-2-substituted glycerols has been developed to secure a novel synthetic route to chiral tertiary alcohols. The transformation has been realized by monobenzylation using benzoyl chloride and triethylamine in the presence of the imine ligand (25)-CuCl₂ complex in THF at ambient temperature. The desymmetrization turned out to be greatly dependent on acylating reagent, base, solvent, and needless to say, catalyst. Extensive screening of chiral ligands led us to combine bromopyridinecarboxaldehyde 1 and phenyloxazoline amine 12 derived from *tert*-leucine, the bromo and phenyl substituents of which proved to be indispensable. All of the substrates have been desymmetrized to the corresponding monobenzoates with high enantioselectivity up to 96% enantiomeric excess. The catalytic system allows broad structural diversity of substrates and its synthetic versatility has been demonstrated by an efficient synthetic route to a known key precursor 68 of triazole antifungals.

bromopyridinecarboxaldehyde | chiral tertiary alcohols |
meso-2-substituted glycerols | phenyloxazoline amine

The enantioselective construction of chiral quaternary carbon centers belongs to one of the most challenging issues in synthetic organic field (1–3). Among them, the hydroxyl-containing centers have attracted considerable attention because of their highly versatile utility as chiral building blocks. The optically active tertiary alcohols are prevalent in many physiologically significant natural products and pharmaceuticals, and are usually considered as the most abstruse structural components to be elaborated in their synthesis.

Although the chiral functionality has been often installed through asymmetric epoxidation (4–6) and dihydroxylation (7, 8), several enantioselective methodologies have emerged in recent years, such as cyanohydrin formation (9–18), organometallic addition (19–38), aldol condensation (39–42) and epoxide opening (43–45). Because most of the reported methods have their own limit of application, it is worthwhile to expand the functionalization scope, especially in terms of the substrate diversity. The enantioselective desymmetrization of meso molecules is conceived to be another prospective means in the asymmetric transformation. So far, meso compounds have been mostly, if not all, desymmetrized to engender tertiary stereogenic centers (46–53). It is of great value and significance to develop asymmetric desymmetrization creating chiral quaternary centers. In this context, we have investigated desymmetric monoacylation of meso-2-substituted 1,2,3-propanetriols using various chiral catalysts. Here, we describe unprecedented catalytic desymmetric monobenzylation of the substrates to procure the corresponding tertiary alcohols efficiently with high enantioselectivity. We also present its synthetic application to triazole antifungal agents.

Results and Discussion

Preliminary survey for the proposed desymmetrization directed us to use a basic acylation rather than an acidic one. The

following extensive scouting of a suitable catalyst to impose a chiral environment around the triol substrates under basic conditions revealed that its structural motif could be devised by a combination of pyridinecarboxaldehydes and monooxazolines derived from *tert*-leucine, as described in Scheme 1. Initially, a corresponding tridentate imine ligand 15 was prepared from bromopyridinecarboxaldehyde 1 and ethyloxazoline amine 7, and subsequently complexed with transition metal cations *in situ* to explore the asymmetric monoacylation. Some representative experimental data for the substrate 34 are summarized in Table 1. Great dependence of the reaction was observed on solvents, metal salts, acylating reagents, and bases. Although a racemic mixture of the monobenzoates 35 (54) was formed in toluene and CH₂Cl₂, better enantioselectivity was secured in ethereal solvents, among which THF proved to be far superior. The choice of other reagents turned out to be benzoyl chloride, CuCl₂, and Et₃N as shown in entry 5 of Table 1.

To scrutinize the most effective ligand structure, ethyloxazoline amine 7 was first condensed with pyridinecarboxaldehydes 2–6, substituted variously at the 6-position (55, 56), to confer the imine ligands 16–20 (Scheme 1). The asymmetric monobenzylation was performed in the presence of the catalysts generated from 16–20 and CuCl₂. The substituent effect is outlined in Table 2. It is noted that, although the unsubstituted pyridine-containing imine ligand 16 rendered a racemic mixture (Table 2, entry 2), substantially better stereoselectivity was induced using the imine 17–20, installed with the more sterically demanding or electronically influential substituents (Table 2, entries 3–6). Interestingly, the bromo imine ligand 15 gave rise to the highest enantioselectivity as well as chemical conversion, probably due to in part the matched electronic effect for complexation (Table 2, entry 1). In addition, an adverse effect was observed by lowering the reaction temperature (Table 2, entries 1, 7, and 8).

The next structural modification was applied to the oxazoline subunit. Accordingly, an array of the oxazoline amines 8–14 and 28–30 were prepared, and coupled with bromopyridinecarboxaldehyde 7 to supply the tridentate ligands 21–27 and 31–33 (Scheme 1). To confirm the stereochemical matching between the substituents in the oxazoline amines, the desymmetrization was implemented in the presence of the copper catalysts generated from the imines 21 and 22 com-

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Abbreviation: ee, enantiomeric excess.

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Scheme 1. Formation of chiral imine ligands.

prising 4*S* configurations of the substituents in the oxazoline rings. The low enantioselectivity presented in Table 3 indicates that the two substituents of **21** and **22** have mismatched stereochemical configurations, respectively (Table 3, entries 2 and 3). Scrutiny of the experimental outcomes in Table 3 discloses that the stereoselectivity decreases when the bulkiness of the substituents in the oxazoline ring exceeds a certain size. In the series of 4-alkyl substitution, the enantioselectivity increases from methyl group to ethyl (Table 3, entries 1 and 4), and decreases considerably from ethyl to the bulkier isopropyl and benzyl (Table 3, entries 1, 5, and 7). In the cases of 4-aryl substitution, the stereoselectivity becomes lower from the phenyl group to the bulkier naphthyl (Table 3, entries 6 and 8), and with 5-substituents (Table 3, entries 9–11). It is conceived that the bulkier substituents may impede the formation of the tightly bound coordination bonds between the catalysts and the substrate. Because the pursuing ligand structure was settled as the phenyloxazoline imine **25** (Table 3, entry 6), its optimal loading amount was adjusted to 20 mol% to give rise to a superb desymmetrization (Table 3, entries 12 and 13).

To garner rudimentary knowledge concerning to the racemic background reaction and the catalyst function, the benzoylation was performed in the absence of the complex and in the presence

of 20 mol% of only the chiral ligand **25**. Although the reaction proceeded by 11% under the former conditions, the latter rendered **35** in 17% yield with 4% enantiomeric excess (ee) (Table 3, entries 14 and 15). Comparison of the two data reveals that **25** itself works as a chiral activator, although not so efficient. It consists of pyridine and *tert*-leucine-derived oxazoline moieties, which presumably serve as activator and stereoinducer, respectively. The assumption leads us to propose a plausible mode of action of the catalyst (**25**-CuCl₂). It is proposed that the catalyst coordinates the substrate to form the square planar complex, the electrophilic Cu(II) of which interacts with benzoyl chloride from the bottom face for steric reasons to activate the benzoyl group (Fig. 1). Subsequently benzoyl transfer to the nucleophilic pyridine group strengthens the benzoyl reactivity further and the resulting benzoylpyridinium intermediate reacts with the pending primary hydroxyl group at the bottom side to yield the predicted enantiomer **35** as the major. This scenario also rationalizes the fact that **31** and **32**, having 5α-substituents, elicit even lower asymmetric induction, due to the enhanced steric congestion at the bottom face.

With the established enantioselective monobenzoylation method in hand, variously substituted triols **36–48** were desymmetrized. Remarkable enantioselectivity was consummated with

Table 1. Desymmetrization of 34 using 10 mol% of 15-CuCl₂ complex

$ \begin{array}{c} \text{CuCl}_2 \text{ solvent} \\ \text{rt} \rightarrow \text{PhCOCl (1.1 equiv), rt} \\ \text{Et}_3\text{N (1.2 equiv), 1h} \\ \text{HO-CH(OBn)-CH(OBn)-CH}_2\text{OH (34)} \rightarrow \text{BzO-CH(OH)-CH(OH)-CH}_2\text{OBn (35)} \end{array} $			
Entry	Solvent	% Yield*	% ee
1	PhMe	67 (11) [†]	0
2	CH ₂ Cl ₂	70 (15)	3
3	Et ₂ O	43 (48)	12
4	1,4-dioxane	34 (60)	12
5	THF	89 (5)	68
6 [‡]	THF	71 (24)	47
7 [§]	THF	35 (41)	21
8	THF	32 (63)	2

*Percentage of recovered sm in parentheses.

[†]12% of meso-dibenzoate was formed.

[‡]*i*-Pr₂NEt was used instead of Et₃N.

[§]CH₃COCl was used instead of PhCOCl.

^{||}35% of monoacetates and 17% of meso-diacetate were formed.

^{||}ZnCl₂ was used instead of CuCl₂.

all of the substrates as displayed in Table 4. Although desymmetrization of propenyl carbinol **44** and propargyl alcohol **45** proceeded with rather lower % ee values, although still higher than 10:1 (Table 4, entries 10 and 11), this unusual catalyst tolerates a broad scope of substrate structures, comprehending alkyl (Table 4, entries 1–8), olefinic (Table 4, entries 9 and 10), acetylenic (Table 4, entry 11), and aryl (Table 4, entries 12–14) (57) substituents at the quaternary carbon, and a wide range of steric and electronic factors in the substituents. The synthetic utility of our developed desymmetrization method was demonstrated by highly enantioselective synthesis (58–62) of a common intermediate **68** to triazole antifungal agents such as Sch 45450, ZD 0870, and voriconazole (63–65) (Scheme 2). Triol **64**, acquired from difluorophenyl bromide **62** and ketone **63** via Grignard reaction, was subjected to the aforementioned protocol to give benzoate **65** with 96% ee quantitatively. After mesylation of **65**, the generated mesylate **66** was treated with triazole **67** in the presence of methanolic Na₂CO₃ to supply a known key intermediate diol **68** to triazole antifungals in 80% overall yield.

Conclusion

Enantiomerically enriched tertiary alcohols have been readily prepared by desymmetric monobenzylation of meso-2-

Table 3. Desymmetric benzylation of 34 using 10 mol% of (21–27, 31–33)-CuCl₂ complexes

$ \begin{array}{c} \text{CuCl}_2 \text{ THF} \\ \text{rt} \rightarrow \text{PhCOCl (1.1equiv)} \\ \text{Et}_3\text{N (1.2equiv)} \rightarrow \text{35} \end{array} $			
Entry	Ligand	% Yield*	% ee
1	15	89 (5)	68
2	21	85 (11)	6 [†]
3	22	88 (6)	6 [†]
4	23	87 (11)	47
5	24	89 (6)	21
6	25	99	87
7	26	90 (5)	12
8	27	92 (4)	23
9	31	90 (4)	49
10	32	36 (62)	9
11	33	91 (4)	75
12 [‡]	25	96	63
13 [§]	25	99	93
14	–	11 (85)	–
15	25	17 (80)	4

*Percentage of recovered sm in parentheses.

[†]5 major configuration.

[‡]5 Mol% of 25-CuCl₂ complex.

[§]20 Mol% of 25-CuCl₂ complex.

^{||}In the absence of complex.

^{||}20 Mol% of 25 without CuCl₂.

substituted 1,2,3-propanetriols in the presence of the chiral imine-CuCl₂ complex. The imine **25** has been produced by condensation of bromopyridinecarboxaldehyde **1** and phenylloxazoline amine **12** from *tert*-leucine. Both the formation of the imine ligand **25** and the enantioselective desymmetrization of triols with a quaternary carbon are novel and unique. The developed catalytic process has been saliently effective in terms of substrate diversity as well as asymmetric induction. Its other advantageous features include feasible accessibility to substrates and the ligand components, simple experimental operation, mild reaction conditions, and short reaction times. Considering that there are numerous physiological beneficial organic molecules possessing tertiary hydroxyl functionality such as triazole antifungals, voglibose, fosterecin, dysiherbaine, and azithromycin, it has considerable potential to provide efficient and versatile synthetic functionalization in natural product synthesis and drug development.

Table 2. Desymmetric benzylation of 34 using 10 mol% of (15–20)-CuCl₂ complexes

$ \begin{array}{c} \text{CuCl}_2 \text{ THF} \\ \text{rt} \rightarrow \text{PhCOCl (1.1equiv)} \\ \text{Et}_3\text{N (1.2equiv)} \rightarrow \text{35} \end{array} $			
Entry	Ligand	% Yield*	% ee
1	15	89 (5)	68
2	16	42 (45)	0
3	17	65 (30)	62
4	18	62 (29)	52
5	19	71 (23)	60
6	20	82 (13)	60
7 [†]	15	87 (5)	66
8 [‡]	15	72 (19)	62

*Percentage of recovered sm in parentheses.

[†]The reaction was carried out at –10°C.

[‡]The reaction was carried out at –30°C.

Fig. 1. A plausible intermediate.

Table 4. Enantioselective benzoylation of 36–48 using 20 mol% of 25-CuCl₂ complex

Entry	R	Substrate/product	% Yield	% ee*
1	CH ₂ CH ₂ OBn	34/35	99	93(R)
2	Me	36/49	99	95(R)
3	<i>n</i> -Bu	37/50	99	95
4	<i>i</i> -Pr	38/51	99	90(R)
5	<i>i</i> -Bu	39/52	99	92
6	Bn	40/53	99	94(R)
7	CH ₂ CH=CH ₂	41/54	99	93(R)
8	CH ₂ OBn	42/55	99	93
9	CH=CH ₂	43/56	99	90(R)
10	C(Me)=CH ₂	44/57	99	83
11	C≡CSiMe ₃	45/58	81 [†]	87(R)
12	Ph	46/59	99	92(R)
13	<i>p</i> -MeOPh	47/60	99	91
14	<i>p</i> -ClPh	48/61	99	94

*Major configuration in parentheses.

[†]12% of recovered sm.

Materials and Methods

General Information. NMR spectra were obtained on Bruker AVANCE 400 spectrometer (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR) and measured in CDCl₃. Chemical shifts were recorded in ppm relative to internal standard CDCl₃, and coupling constants were reported in Hz. The high resolution mass spectra were recorded on VG Autospec Ultima spectrometer. The enantioselectivities were determined by HPLC. HPLC measurements were done on a DIONEX model equipped with P580G pump, UV 525 detector (Thermo Science, Waltham, MA) measured at 254 nm, and chiral column DAICEL AD-H. Eluting solvent was a mixture of 2-propanol and hexane. Optical rotations were measured on a polarimeter (JASCO, Tokyo, Japan) in a 10-cm cell. All reactions were carried out in oven-dried glassware under a N₂ atmosphere. All solvents were distilled from the indicated drying reagents right before use: Et₂O and THF (Na, benzophenone), CH₂Cl₂ (P₂O₅), and MeCN and 1,4-dioxane (CaH₂). The normal work-up included extraction, drying over Na₂SO₄ and evaporation of volatile materials *in vacuo*. Purification by column chromatography was performed

using Merck (Darmstadt, Germany) silica gel 60 (≈230–400 mesh).

Representative Procedure for the Preparation of the Oxazoline Amine

12. Cbz protected *L*-tert-leucine (200 mg, 0.75 mmol) was reacted with 2-chloro-4,6-dimethoxy-1,3,5-triazine (145 mg, 0.82 mmol) and 4-methylmorpholine (0.24 ml, 2.18 mmol) in THF (4 ml) at room temperature for 1 h. To the resulting solution was added (*R*)-phenylglycinol (103 mg, 0.75 mmol) at room temperature and the mixture was stirred at room temperature for 10 h. Aqueous work-up with EtOAc (5 ml, three times) followed by chromatographic purification (EtOAc/hexane = 1/2) afforded the corresponding amide (269 mg, 93% yield). The amide (269 mg, 0.70 mmol) dissolved in CH₂Cl₂ (5 ml) was consecutively tosylated and cyclized using *p*-toulensulfonyl chloride (146 mg, 0.77 mmol) and Et₃N (0.29 ml, 2.08 mmol) in the presence of 4-dimethylaminopyridine (9 mg, 0.07 mmol) at room temperature for 24 h, and then the reaction was quenched with saturated aqueous NH₄Cl (5 ml). Work-up with EtOAc (5 ml, three times) and the subsequent chromatographic purification (EtOAc/hexane = 1/5) furnished the Cbz-protected monooxazoline amine (241 mg, 94% yield). The protected amine (241 mg, 0.66 mmol) was stirred under hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (24 mg) in MeOH (5 ml) at room temperature for 5 h. After filtering the mixture through celite (0.8 g) followed by evaporation of the volatile materials *in vacuo*, the residue was chromatographically purified (MeOH/CH₂Cl₂ = 1/20) to give the oxazoline amine **12** (145 mg, 95% yield).

Representative Procedure for the Preparation of the Triol 34. To allylmagnesium bromide (1.0 M in Et₂O, 6.9 ml, 6.90 mmol) in THF (10 ml) was added 1,3-dihydroxyacetone acetone **63** (300 mg, 2.31 mmol) in THF (5 ml) through a cannula at 0°C. The reaction proceeded at 0°C for 1 h, and then was quenched with saturated aqueous NH₄Cl (10 ml). Work-up with Et₂O (5 ml, three times) and chromatographic separation (EtOAc/hexane = 1/5) yielded the allyl adduct (290 mg, 73% yield). Ozone was bubbled into the allyl compound (290 mg, 1.69 mmol) in MeOH (7 ml) at –78°C for 10 min, and subsequently the resulting products were reduced with NaBH₄ (70 mg, 1.85 mmol) at 0°C for 20 min. After quenching the reaction mixture with saturated aqueous NH₄Cl at 0°C for 30 min, work-up with EtOAc (5 ml, three times) and the following chromatographic purification (EtOAc/hexane = 5/1) offered the diol (230 mg, 77% yield). After treatment of the diol (230 mg, 1.31 mmol) with NaH (60% dispersion in mineral oil, 78 mg, 1.95 mmol) in a 4:1 mixture of THF and DMF (5 ml) at 0°C for 20 min, the resulting solution was reacted with benzyl bromide (0.17 ml, 1.40 mmol) in the presence of (*n*-Bu)₄NI (48 mg, 0.13 mmol) at room temperature

Scheme 2. Enantioselective synthetic route to a key precursor **68** of triazole antifungals.