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Enantioselective Formation of *tert*-Alkylamines by Desymmetrization of 2-Substituted Serinols

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Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract: Novel enantioselective desymmetrization of 2-substituted 2-amino-1,3-propanediols has been established to generate asymmetric quaternary carbon centers comprising an amino group. Enantioselective as well as chemical conversion proved to be greatly dependent on the protecting group of the amino group in the substrate, desymmetrizing reagent, base, solvent, and naturally, catalyst. The highly effective desymmetrization has been implemented by using N-benzoylated substrates with benzoyl chloride and triethylamine in the presence of tetraphenylbisoxazoline (**24**)–$CuCl_2$ complex in THF at ambient temperature. An extensive survey of catalysts revealed that dimethylmalonate-bridged bisoxazoline–$CuCl_2$ complexes were superior. Among them, the tetraphenylbisoxazoline (**24**)–$CuCl_2$ complex turned out to work most efficiently with a wide array of the substrates. All the examined substrates, with the exception of 2-phenylserinol **36**, were desymmetrized in the presence of **24**–$CuCl_2$ complex to give high enantioselectivities ranging from 85 to 95% *ee*. Complementary use of the diisopropylbisoxazoline (**22**)–$CuCl_2$ complex has remedied the mediocre desymmetrization of **36** to give a significantly improved enantioselectivity from 63 to 83% *ee*.

Keywords: alkylamines · desymmetrization · Lewis acids · organic chemistry · stereoselectivity

Introduction

Biologically potent small molecules embedded with nitrogen-comprising stereogenic quaternary centers (*tert*-alkylamines) are ubiquitous in natural products and pharmaceuticals, such as manzacidins, sphingofungins, lactacystin,[1] sorbinil,[2] and MK801 (dizociline).[3] In addition, optically pure *tert*-alkylamino acids have recently become an active research subject because their geometric constraints exert pronounced effects on the three-dimensional conformations of their incorporated peptides.[4] It is of great value and a significant challenge to synthesize such structurally (as well as physiologically) intriguing compounds as a result of the difficult installation of the chiral centers. Most of the stereogenic *tert*-alkylamines have been generated by utilizing the preexisting asymmetric centers of substrates themselves or chiral auxiliary-attached substrates.[5] In recent years, their enantioselective formation has been developed through alkylation of alanine and glycine esters,[6] allylic alkylation of azlactones,[7] and cyanide addition to ketoimines[8] in the presence of chiral catalysts. Asymmetric desymmetrization methods have been exploited as powerful synthetic means to engender enantiomerically enriched stereocenters bonded to heteroatoms from *meso* stereoisomers. The structural features of these compounds have been mainly limited to hydroxyl-containing carbonic groups.[9,10,11] However, desymmetrization has rarely been documented to synthesize chiral *tert*-alkylamine building blocks.[12] Herein, we report a highly effective enantioselective monobenzoylation of 2-substituted 2-benzamido-1,3-propanediols by catalytic desymmetrization to install chiral quaternary carbon centers.

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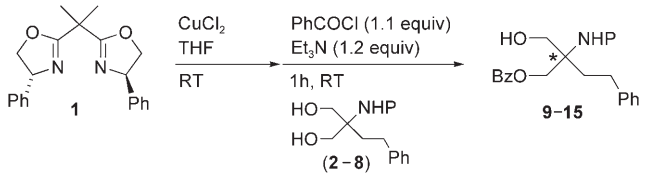
Results and Discussion

In consideration of their easy accessibility and the potential synthetic versatility of the desymmetrization products, 2-substituted serinols were selected as substrates. It was planned that these substrates would be desymmetrized under basic benzoylation conditions in the presence of a chiral Lewis acid catalyst. Choice of the amino protecting group was considered to be critical because its electronic and steric environments certainly have a great influence on the coordination bond strengths and the spatial arrangement in the complex among the substrate, catalyst, and/or benzoylating reagent. With initial use of the benzyloxycarbonyl (Cbz) group as the N-protecting group, the N-Cbz-serinol **2** was extensively investigated in the search for a prospective asymmetric catalyst. The model survey suggested bisoxazoline–$CuCl_2$ complexes, which were pioneered for kinetic recognition of 1,2-diols by Matsumura et al,[11e] would be the most effective catalysts. From this group of complexes, diphenylbisoxazoline (**1**)–$CuCl_2$[13] was employed with benzoyl chloride in the monobenzoylation of **2** to examine the dependence of the desymmetrization on solvents and bases. The experimental data indicated that when using Et_3N as the base, the highest chemical conversion was obtained in THF; however, the lowest conversion was obtained when using other ethereal solvents. Hindered amine bases, such as 2,6-lutidine and iPr_2NEt, displayed much inferior reactivity. The best enantioselectivity (though far from ideal) and chemical conversion were reached with Et_3N in THF (Table 1, entry 1).

Table 1. Desymmetrization of **2**–**8** by using 10 mol% of **1**–$CuCl_2$ complex.



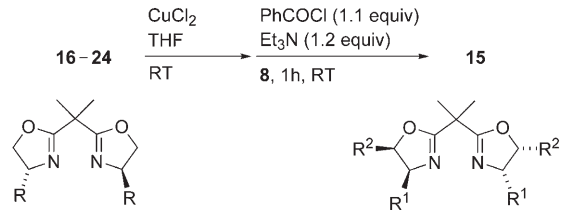
Entry	P	Substrate/product	Yield [%][a]	*ee* [%]
1	Cbz	**2**/**9**	74 (24)	53
2	$PhSO_2$	**3**/**10**	38 (32) [15]	58
3	*p*Ns[b]	**4**/**11**	39 (25) [35]	71
4	Ph_2PO	**5**/**12**	55 (40)	55
5	CF_3CO	**6**/**13**	13 (0)	57
6	Boc[c]	**7**/**14**	6 (48)	49
7	PhCO	**8**/**15**	66 (28)	80
8[d]	PhCO	**8**/**15**	0 (97)	-
9[e]	PhCO	**8**/**15**	38 (56)	69

[a] Percentage of recovered starting material in parentheses; percentage of dibenzoate in square brackets. [b] *p*Ns = *p*-nitrobenzenesulfonyl. [c] Boc = *tert*-butoxycarbonyl. [d] In the absence of complex. [e] The reaction was carried out at −20 °C.

The intrinsic stereoselection in the desymmetrization of **2** was screened by varying the amino protecting group under the modulated conditions. As shown in Table 1, the sulfonamides **3** and **4** were desymmetrized with high stereoinduction but with insufficient chemical conversion and with the formation of considerable amounts of the corresponding dibenzoates (entries 2 and 3). While the monobenzoylation of the phosphinamide **5**, the trifluoroacetamide **6**, and the *tert*-butyl carbamate **7** resulted in moderate stereoselection, the reaction with the latter two substrates proceeded with extensive decomposition (entries 4–6). The best desymmetrization was attained with the benzamide diol **8** (entry 7). As the reaction was not forwarded at all in the absence of catalyst, the background reaction certainly had little adverse effect on the enantioselectivity (entry 8). Lowering the reaction temperature turned out to be detrimental to the desymmetrization (entry 9). Besides benzoyl chloride, some other protecting reagents (Bz_2O, AcCl, Ac_2O, and TESCl; TES = triethylsilyl) were surveyed but no better one could be found.

In the pursuit of further improvement of the asymmetric monobenzoylation, our efforts were focused on elaborating the most effective catalyst by scouting a wide array of chiral bisoxazoline ligands. Representative results are presented in Table 2. Perusal of the results reveals that a specific size of the 4-substituent in the bisoxazoline seems to be advantageous for the enhanced stereoinduction and chemical conversion. It is reasoned that while a smaller substituent itself could not impose influential steric congestion to discern the two hydroxymethyl groups of the substrate, a bulkier substituent might impede a proximal approach of the substrate to the catalyst. With the exception of the diisopropylbisox-

Table 2. Desymmetrization of **8** by using 10 mol% of (**16**–**24**)–$CuCl_2$ complexes.



Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	**1**	66 (28)	80 (*R*)
2	**16**	27 (63)	20 (*R*)
3	**17**	71 (20)	84 (*R*)
4	**18**	11 (88)	44 (*R*)
5	**19**	42 (50)	30 (*R*)
6	**20**	49 (50)	0
7	**21**	38 (57)	2 (*R*)
8	**22**	29 (70)	78 (*S*)
9	**23**	31 (64)	15 (*S*)
10	**24**	73 (22)	84 (*S*)
11[c]	**1**	74 (20)	84 (*R*)
12[c]	**17**	72 (22)	87 (*R*)
13[c]	**24**	74 (20)	90 (*S*)
14[d]	**24**	94	92 (*S*)

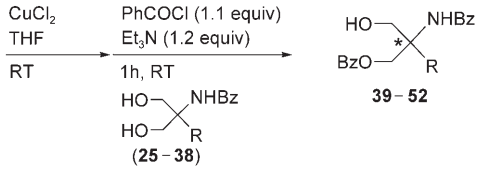
[a] Percentage of recovered starting material in parentheses. [b] Major configuration in parentheses. [c] 20 mol% of complex. [d] 20 mol% of **24**–$CuCl_2$ complex, 2.0 equiv of BzCl and 1.5 equiv of Et_3N.

azoline **22**, the bisoxazolines that induced high enantioselectivity also produced high chemical yield (entries 1, 3, 8 and 10). The value for the percentage *ee* with 4-alkyl-substituted bisoxazolines[14] increased from methyl to ethyl and isopropyl substituents, but dropped drastically when using a *tert*-butyl substituent (entries 2, 3, 8 and 9). In the cases of 4-aryl-substituted bisoxazolines,[15] remarkable asymmetric induction was achieved when using a phenyl substituent, but the bulkier naphthyl substituent yielded almost a racemate (entries 1, 7 and 10). As **1**, **17**, and **24** pertained to the most effective ligand group with similar potency, their assessment was carried out by using increasing amounts of the corresponding catalysts. The maximal *ee* values were gained with 20 mol% of the catalysts, among which **24**–$CuCl_2$ complex brought about the highest stereoinduction, though the differences were marginal (entries 11–13). Furthermore, application of greater quantities of benzoyl chloride and Et_3N drove the monobenzoylation to completion (entry 14). In addition, the ligand recovery was practiced by decomplexing the **24**–$CuCl_2$ catalyst with 25 mol% of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine to recover more than 85% of the bisoxazoline **24**.

Structurally diversified N-benzoyl serinols **25**–**38** were desymmetrized by the established procedure as described in entry 14 of Table 2. Outstanding asymmetric monobenzoylations were carried out with most of the substrates as illustrated in Table 3. A variety of alkyl substituents comprising silyloxy, benzyloxy, phenyl, and vinyl groups are tolerable, irrespective of their sizes and electronic properties (entries 1–9). Vinylic and acetylenic substituents are also effective, albeit **34** and **35** gave slightly lower *ee* values, which were still higher than a 14:1 enantiomeric ratio (entries 10–12). Among the aryl-substituted substrates **36**–**38**, the desymmetrization of only the phenyl-substituted substrate **36** proceeded with significantly lowered enantioselectivity (entries 13, 15 and 16). In consequence of our endeavor to restore the stereoselectivity, the ligand was switched from **24** to **22** to give a substantially improved enantioselectivity of 83% *ee* (entry 14).[16] To establish whether or not the improved enatioselectivity stemmed from a kinetic resolution or the intrinsic stereoselection, the monobenzoate **50** with an 83% *ee* value was treated under desymmetrization conditions (described in entry 14 of Table 3) to give the corresponding dibenzoate in 10% yield along with 85% of recovered **50** with 84% *ee*. Consequently, the intrinsic stereoselection seemed to be responsible for the observed enhancement.

A plausible mechanism of the desymmetrization is proposed based on the assumption that the substrate works as a tridentate ligand to the catalyst to form a pyramidal-shaped complex, the electrophilic Cu^{II} atom of which coordinates with benzoyl chloride from the open-bottomed face for the activation of the benzoyl group (Figure 1, pathway A). The subsequent benzoyl transfer to the equatorial hydroxyl group renders the observed configuration. On the other hand, the desymmetrization through the other diastereomerically arranged complex is conceived to be in a higher energy state because it causes steric interactions between the apical hydroxymethyl group and the phenyl substituent in the oxazoline ring (pathway B). Furthermore, in the process of the benzoyl transfer to the equatorial hydroxyl group, severe steric congestion, between the pending benzoyl chloride and the phenyl substituent in the other oxazoline ring, is expected to disfavor pathway B.

Table 3. Enantioselective monobenzoylation of **25–38** by using 20 mol% of **24**–$CuCl_2$ complex.



Entry	R	Substrate/product	Yield [%][a]	*ee* [%][b]
1	CH_2CH_2Ph	**8**/**15**	94	92 (*S*)
2	Me	**25**/**39**	96	91
3	Et	**26**/**40**	95	95 (*S*)
4	CH_2-*c*Hx[c]	**27**/**41**	95	92
5	*i*Bu	**28**/**42**	98	90
6	$CH_2OTBDPS$	**29**/**43**	96	92 (*R*)
7	$(CH_2)_3OBn$	**30**/**44**	92	94
8	Bn	**31**/**45**	94	90 (*S*)
9	$CH_2CH{=}CH_2$	**32**/**46**	96	92
10	$CH{=}CH_2$	**33**/**47**	93	92 (*S*)
11	(*E*)-$CH{=}CHCO_2Et$	**34**/**48**	95	88 (*S*)
12	$C{=}CSiMe_3$	**35**/**49**	96	87
13	Ph	**36**/**50**	80 (14)	63 (*S*)
14[d]	Ph	**36**/**50**	87 (6)	83 (*S*)
15[d,e]	*p*ClPh	**37**/**51**	97	85
16[d,f]	*p*MePh	**38**/**52**	97	88

[a] Percentage of dibenzoate in parentheses. [b] Major configuration in parentheses (see the Supporting Information). [c] *c*Hx = cyclohexyl. [d] 20 mol% of **22**–$CuCl_2$ complex, 4.0 equiv of BzCl, and 3.0 equiv of Et_3N. [e] Similar results were obtained when using 20 mol% of **24**–$CuCl_2$ complex, 3.0 equiv of PhCOCl, and 2.0 equiv of Et_3N. [f] 97% yield and 85% *ee* were obtained when using 20 mol% of **24**–$CuCl_2$ complex, 3.0 equiv of PhCOCl, and 2.0 equiv of Et_3N.

Conclusion

Highly enantioselective formation of *tert*-alkylamines has been established by desymmetric benzoylation of 2-substituted serinols in the presence of the bisoxazoline–$CuCl_2$ complexes. The most effective ligands have been demonstrated to be tetraphenylbisoxazoline (**24**) for the serinols containing 2-alkyl, alkenyl, and alkynyl substituents, and diisopropylbisoxazoline (**22**) for the 2-arylserinols. Construction of nitrogen-attached quaternary carbon centers with high stereoinduction has rarely been realized and pertains to one of the most difficult synthetic issues. Our desymmetrization approach to generate enantiomerically enriched amino functional groups provides uniquely remarkable solution. Furthermore, this functionality is embedded in a variety of physiologically significant natural products and pharmaceuticals. With this in mind, the developed protocol is expected to offer great synthetic utility and versatility in terms of enantioselectivity and structural diversity in the synthesis

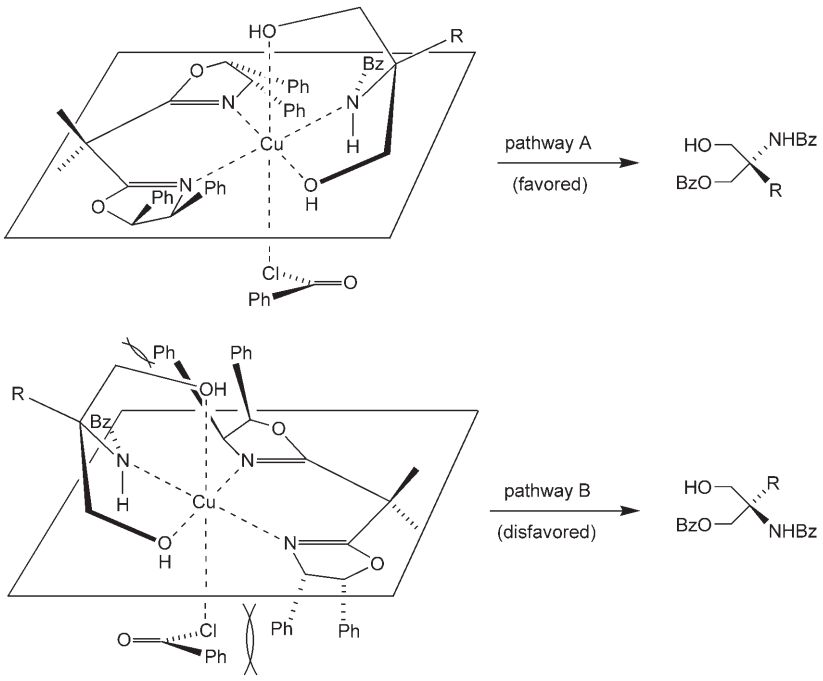


Figure 1. A plausible pathway for the desymmetrization.

and development of these compounds. In addition, the beneficial features of this methodology for practical applications include the facile accessibility of the ligands and substrates, mild reaction conditions, feasible experimental manipulation, and short reaction times.

Experimental Section

General information: NMR spectra were obtained on a Bruker DPX300 spectrometer (300 MHz for ^{1}H NMR spectra, 75 MHz for ^{13}C NMR spectra) and measured in $CDCl_3$. Chemical shifts were recorded in ppm relative to internal standard $CDCl_3$, and coupling constants were reported in Hz. High-resolution mass spectra were recorded on VG Autospec Ultima and JMS-700 spectrometers. 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 columns DAICEL AD-H, AS-H, OD-H, and OJ-H. The eluting solvent was a mixture of 2-propanol and hexane. All reactions were carried out in oven-dried glassware under a N_2 atmosphere. All solvents were distilled from the indicated drying reagents just before use: Et_2O and THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), and MeCN, 1,4-dioxane and DMF (CaH_2). The normal workup included extraction, drying over Na_2SO_4, and evaporation of volatile materials in vacuo. Purification by column chromatography was performed by using Merck (Darmstadt, Germany) silica gel 60 (230≈400 mesh).

Representative procedure for the preparation of serinol 8: Tris(hydroxymethyl)aminomethane was converted to the known N-Boc-protected acetonide alcohol.[17] The structures of the alcohol and the subsequent intermediates are shown in the Supporting Information. Et_3N (0.64 mL, 4.59 mmol), *p*TsCl (*p*Ts=*p*-toluenesulfonyl; 875 mg, 4.59 mmol), and 4-(dimethylamino)pyridine (46 mg, 0.38 mmol) were added in sequence at room temperature to the alcohol (1 g, 3.83 mmol) dissolved in CH_2Cl_2 (10 mL), and the tosylation was carried out at that temperature for 1 h. After quenching the reaction mixture with saturated aqueous NH_4Cl (10 mL), workup with CH_2Cl_2 (5 mL, ×3) and chromatographic purification (EtOAc/hexane 1:5) afforded the tosylate (2.014 g, 92% yield). NaH (60% dispersion in mineral oil, 316 mg, 7.92 mmol) was added to the tosylate (2.742 g, 6.60 mmol) in THF (20 mL) portionwise at 0°C. After stirring the reaction mixture at 0°C for 20 min and then at room temperature for 40 min, it was quenched with H_2O (20 mL) at 0°C and worked up with EtOAc (10 mL, ×3). Column chromatography (EtOAc/hexane 1:3) of the crude product furnished the N-Boc-aziridine (1.567 g, 98% yield). BnMgBr (1.0 M in THF, 12.3 mL, 12.3 mmol) was then added to CuI (234 mg, 1.23 mmol) in THF (5 mL) at −78°C and the resulting mixture was reacted at that temperature for 15 min. The aziridine (1 g, 4.11 mmol) dissolved in THF (5 mL) was injected into the prepared Grignard reagent at −78°C and the reaction temperature was raised from −78 to 0°C over a period of 1 h. After quenching the reaction with saturated aqueous NH_4Cl (10 mL), followed by a workup with EtOAc (5 mL, ×3), the residue was purified by column chromatography (EtOAc/hexane 1:10) to give the protected serinol with a 2-phenylethyl substituent (1.334 g, 97% yield). The protected serinol (500 mg, 1.49 mmol) was demasked by using concentrated HCl (2 mL) in MeOH (5 mL) at room temperature for 7 h. After evaporation of all the volatile materials in vacuo, the residue was dissolved in CH_2Cl_2 (5 mL), and Et_3N (0.62 mL, 4.45 mmol) and benzoyl chloride (0.21 mL, 1.82 mmol) were added to the solution at 0°C. After the reaction mixture had been stirred at 0°C for 30 min and then at room temperature for 3 h, it was quenched with saturated aqueous NH_4Cl (5 mL) and worked up with CH_2Cl_2 (5 mL, ×3). Chromatographic purification (EtOAc/hexane 1:2) delivered the serinol **8** (361 mg, 81% yield) along with the monobenzoate benzamide (84 mg, 14%).

***N*-(1-Hydroxy-2-(hydroxymethyl)-4-phenylbutan-2-yl)benzamide (8)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65–7.21 (10H, m), 6.62 (1H, s), 4.04 (2H, d, J=3.8 Hz), 3.76 (2H, d, J=3.8 Hz), 2.78–2.73 (2H, m), 2.16–2.11 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.5, 141.5, 134.4, 131.7, 128.6, 128.3, 126.9, 126.1, 65.9, 61.5, 34.5, 29.7 ppm; HRMS (EI): m/z: calcd for $C_{18}H_{21}NO_3$: 299.1521; found: 299.1514.

***N*-(1,3-Dihydroxy-2-methylpropan-2-yl)benzamide (25)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79–7.76 (2H, m), 7.54–7.43 (3H, m), 6.66 (1H, s), 3.89 (2H, d, J=3.8 Hz), 3.75 (2H, d, J=3.8 Hz), 1.37 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.6, 134.4, 131.7, 128.6, 126.9, 67.5, 59.0, 19.8 ppm; HRMS (EI): m/z: calcd for $C_{11}H_{15}NO_3$: 209.1052; found: 209.1072.

***N*-(1-Hydroxy-2-(hydroxymethyl)butan-2-yl)benzamide (26)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.80–7.77 (2H, m), 7.55–7.45 (3H, m), 6.61 (1H, s), 3.98 (2H, d, J=3.8 Hz), 3.71 (2H, d, J=3.8 Hz), 1.82 (2H, q, J=2.5 Hz), 0.99 ppm (3H, t, J=2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.8, 134.6, 131.7, 128.6, 126.9, 65.4, 61.5, 25.1, 7.7 ppm; HRMS (EI): m/z: calcd for $C_{12}H_{17}NO_3$: 223.1208; found: 223.1223.

***N*-(1-Cyclohexyl-3-hydroxy-2-(hydroxymethyl)propan-2-yl)benzamide (27)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.77–7.74 (m, 2H), 7.55–7.44 (3H, m), 6.52 (1H, s), 4.04 (2H, d, J=3.8 Hz), 3.70 (2H, d, J=3.8 Hz), 1.81–1.64 (7H, m), 1.57–1.48 (1H, m), 1.30–1.06 ppm (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.3, 134.6, 131.7, 128.7, 126.8, 66.5, 61.8, 41.0, 35.1, 33.0, 26.2, 26.0 ppm; HRMS (EI): m/z: calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1847.

***N*-(1-Hydroxy-2-(hydroxymethyl)-4-methylpentan-2-yl)benzamide (28)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83–7.75 (2H, m), 7.55–7.43 (3H, m),

6.56 (1H, s), 4.05 (2H, d, $J=3.8$ Hz), 3.70 (2H, d, $J=3.8$ Hz), 1.84–1.82 (1H, m), 1.68 (1H, d, $J=2.0$ Hz), 1.02 (3H, s), 1.00 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.5$, 134.7, 131.7, 128.6, 126.8, 66.5, 61.7, 42.1, 24.6, 23.6 ppm; HRMS (EI): m/z: calcd for $C_{14}H_{21}NO_3$: 251.1521; found: 251.1511.

***N*-(1-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-2-(hydroxymethyl)propan-2-yl)benzamide (29)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.79$–7.76 (2H, m), 7.68–7.65 (4H, m,), 7.48–7.39 (9H, m), 7.31 (1H, s), 3.92 (2H, d, $J=3.9$ Hz), 3.86 (2H, s), 3.64 (2H, d, $J=3.9$ Hz), 1.12 ppm (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 135.5, 134.0, 132.1, 131.9, 130.2, 128.7, 128.0, 126.9, 64.2, 63.3, 61.8, 26.9, 19.2 ppm; HRMS (EI): m/z: calcd for $C_{27}H_{33}NO_4Si$: 463.2179; found: 463.2163.

***N*-(5-(Benzyloxy)-1-hydroxy-2-(hydroxymethyl)pentan-2-yl)benzamide (30)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.73$–7.71 (2H, m), 7.47–7.23 (8H, m), 7.09 (1H, s), 4.46 (2H, s), 3.87 (2H, d, $J=2.9$ Hz), 3.59 (2H, d, $J=2.9$ Hz), 3.47 (2H, t, $J=1.4$ Hz), 1.86–1.83 (2H, m), 1.71–1.64 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.8$, 137.8, 134.5, 131.6, 128.7, 128.5, 128.4, 128.0, 127.0, 73.2, 70.3, 65.4, 61.4, 29.5, 23.3 ppm; HRMS (EI): m/z: calcd for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1793.

***N*-(2-Benzyl-1,3-dihydroxypropan-2-yl)benzamide (31)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.69$–7.66 (2H, m), 7.53–7.30 (8H, m), 6.62 (1H, s), 3.92 (2H, d, $J=3.9$ Hz), 3.68 (2H, d, $J=3.9$ Hz), 3.09 ppm (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.7$, 135.9, 134.4, 131.8, 130.4, 128.7, 128.6, 127.3, 126.9, 64.9, 61.6, 37.6 ppm; HRMS (EI): m/z: calcd for $C_{13}H_{17}NO_3$: 235.1365; found: 235.1351.

***N*-(1-Hydroxy-2-(hydroxymethyl)pent-4-en-2-yl)benzamide (32)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.77$–7.74 (2H, m), 7.55–7.43 (3H, m), 6.72 (1H, s), 5.87–6.11 (1H, m), 5.31–5.26 (2H, m), 3.96 (2H, d, $J=3.9$ Hz), 3.69 (2H, d, $J=3.9$ Hz), 2.53 ppm (2H, d, $J=2.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.5$, 134.3, 132.7, 131.8, 128.7, 126.9, 120.2, 65.5, 60.7, 37.5 ppm; HRMS (EI): m/z: calcd for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1227.

***N*-(1-Hydroxy-2-(hydroxymethyl)but-3-en-2-yl)benzamide (33)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.85$–7.82 (2H, m), 7.57–7.46 (3H, m), 6.93 (1H, s), 6.04–5.94 (1H, m), 5.40 (1H, d, $J=3.5$ Hz), 5.30 (1H, d, $J=5.7$ Hz), 3.88–3.76 ppm (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$, 136.2, 134.2, 131.9, 128.7, 127.0, 116.5, 66.0, 64.2 ppm; HRMS (EI): m/z: calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1037.

***(E)*-Ethyl 4-benzamido-5-hydroxy-4-(hydroxymethyl)pent-2-enoate (34)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.85$–7.82 (2H, m), 7.58–7.47 (3H, m), 7.11 (1H, s), 7.02 (1H, d, $J=5.3$ Hz), 5.99 (1H, d, $J=5.3$ Hz), 4.20 (2H, t, $J=2.3$ Hz), 3.88–3.75 (4H, m), 1.29 ppm (3H, t, $J=2.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.2$, 165.9, 145.8, 133.7, 132.1, 128.7, 127.1, 122.7, 65.5, 63.6, 60.8, 14.1 ppm; HRMS (EI): m/z: calcd for $C_{15}H_{19}NO_5$: 293.1263; found: 293.1281.

***N*-(1-Hydroxy-2-(hydroxymethyl)-4-(trimethylsilyl)but-3-yn-2-yl)benzamide (35)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.82$–7.79 (2H, m), 7.56–7.48 (3H, m), 6.75 (1H, s), 4.08–4.04 (2H, m), 3.98–3.91 (2H, m), 3.65–3.68 (2H, m), 0.21 ppm (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.9$, 134.0, 132.0, 128.7, 127.1, 102.1, 91.3, 66.6, 59.8, 1.01 ppm; HRMS (EI): m/z: calcd for $C_{15}H_{21}NO_3Si$: 343.1291; found: 343.1277.

***N*-(1,3-Dihydroxy-2-phenylpropan-2-yl)benzamide (36)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.09$–8.05 (2H, m), 7.54–7.33 (8H, m), 4.88 (1H, d, $J=2.7$ Hz), 4.55 (1H, d, $J=2.7$ Hz), 3.96 (1H, d, $J=3.8$ Hz), 3.78 ppm (1H, d, $J=3.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$, 139.1, 134.1, 132.0, 128.9, 128.8, 127.8, 127.1, 126.1, 67.6, 65.9 ppm; HRMS (EI): m/z: calcd for $C_{16}H_{17}NO_3$: 291.1291; found: 291.1298.

***N*-(2-(4-Chlorophenyl)-1,3-dihydroxypropan-2-yl)benzamide (37)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.89$–7.86 (2H, m), 7.60–7.48 (3H, m), 7.39–7.32 (4H, m), 4.11 (2H, d, $J=3.9$ Hz), 4.99 (2H, d, $J=3.9$ Hz), 3.67 ppm (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.5$, 137.5, 133.7, 133.5, 132.1,128.8, 128.7, 127.6, 127.0, 67.3, 65.1 ppm; HRMS (EI): m/z: calcd for $C_{16}H_{16}ClNO_3$: 305.0819; found: 305.0808.

***N*-(1,3-Dihydroxy-2-p-tolylpropan-2-yl)benzamide (38)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.89$–7.86 (2H, m), 7.58–7.47 (3H, m), 7.31–7.20 (5H, m), 4.18–4.12 (2H, m), 4.03–3.96 (2H, m), 3.77–3.72 (2H, m), 2.35 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$, 137.5, 136.0, 134.2, 132.0, 129.6, 128.7, 127.1, 126.0, 67.6, 65.7, 20.9 ppm; HRMS (EI): m/z: calcd for $C_{17}H_{19}NO_3$: 285.1365; found: 285.1352.

General procedure for the enantioselective desymmetrization: Tetraphenylbisoxazoline (97 mg, 0.2 mmol) in THF (8 mL) was added to $CuCl_2$ (26 mg, 0.2 mmol), which had been dried under vacuum (0.5 mmHg) at 120 °C for 5 h, and the resulting mixture was complexed at that temperature for 2 h. The serinol (1.0 mmol) in THF (16 mL), Et_3N (0.21 mL, 1.5 mmol), and benzoyl chloride (0.23 mL, 2.0 mmol) were injected to the generated catalyst, and the mixture was desymmetrized at room temperature for 1 h. After quenching the benzoylation with saturated aqueous NH_4Cl (5 mL), workup with EtOAc (5 mL, ×3) and subsequent chromatographic separation rendered the monobenzoate.

2-Benzamido-2-(hydroxymethyl)-4-phenylbutyl benzoate (15): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.08$–8.05 (2H, m), 7.73–7.70 (2H, m), 7.51–7.44 (6H, m), 7.29–7.22 (5H, m), 6.78 (1H, s), 4.82 (1H, d, $J=3.8$ Hz), 4.61 (1H, d, $J=3.8$ Hz), 4.58 (1H, s), 3.96–3.95 (2H, m), 2.85–2.71 (2H, m), 2.50–2.44 (1H, m), 2.26–2.21 ppm (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 167.1, 141.4, 134.3, 133.5, 131.8, 129.7, 129.3, 128.6 (two carbon atoms), 128.3, 127.2, 126.9, 126.1, 66.1, 65.4, 61.3, 34.3, 29.9 ppm; HRMS (EI): m/z: calcd for $C_{25}H_{25}NO_4$: 403.1783; found: 403.1772.

2-Benzamido-3-hydroxy-2-methylpropyl benzoate (39): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.08$–8.06 (2H, m), 7.80–7.77 (2H, m), 7.62–7.43 (6H, m), 6.81 (1H, s), 4.66 (1H, dd, $J=3.8$, 7.6 Hz), 3.85 (1H, dd, $J=4.0$, 9.3 Hz), 1.56 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 167.1, 134.4, 133.4, 131.6, 129.6, 128.5 (two carbon atoms), 127.7, 127.0, 67.0, 66.8, 58.6, 19.5 ppm; HRMS (EI): m/z: calcd for $C_{18}H_{19}NO_4$: 313.1314; found: 313.1331.

2-Benzamido-2-(hydroxymethyl)butyl benzoate (40): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.07$–8.04 (2H, m), 7.80–7.77 (2H, m), 7.62–7.45 (6H, m), 6.71 (1H, s), 4.76 (1H, d, $J=3.8$ Hz), 4.56 (1H, d, $J=3.8$ Hz), 3.91–3.89 (2H, m), 2.14–2.12 (1H, m), 1.98–1.96 (1H, m), 1.04 ppm (3H, t, $J=2.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$, 167.0, 134.5, 133.4, 131.7, 129.7, 128.6, 128.5, 126.9, 126.6, 66.0, 65.2, 61.4, 25.3, 7.8 ppm; HRMS (EI): m/z: calcd for $C_{19}H_{21}NO_4$: 327.1470; found: 327.1463.

2-Benzamido-3-cyclohexyl-2-(hydroxymethyl)propyl benzoate (41): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.07$–8.04 (2H, m), 7.77–7.75 (2H, m), 7.61–7.44 (6H, m), 6.71 (1H, s), 4.78 (1H, d, $J=3.8$ Hz), 4.55 (1H, d, $J=3.8$ Hz), 3.93–3.92 (2H, m), 1.91 (2H, t, $J=1.9$ Hz), 1.72–1.65 (5H, m), 1.27–1.07 ppm (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$, 166.9, 134.4, 133.4, 132.2, 131.8, 129.7, 128.6, 128.5, 126.9, 65.5, 64.3, 60.5, 37.1, 31.5, 25.2, 22.6, 14.0 ppm; HRMS (EI): m/z: calcd for $C_{24}H_{29}NO_4$: 395.2097; found: 395.2079.

2-Benzamido-2-(hydroxymethyl)-4-methylpentyl benzoate (42): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.07$–8.04 (2H, m), 7.79–7.76 (2H, m), 7.62–7.44 (6H, m), 6.73 (1H, s), 4.80 (1H, d, $J=3.8$ Hz), 4.55 (1H, d, $J=3.8$ Hz), 3.98–3.88 (2H, m), 1.98–1.87 (3H, m), 1.06–1.00 ppm (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 167.2, 134.5, 133.5, 131.7, 129.7, 129.4, 128.7, 128.5, 126.9, 66.7, 65.8, 61.6, 40.9, 24.7, 23.7 ppm; HRMS (EI): m/z: calcd for $C_{21}H_{25}NO_4$: 355.1784; found: 355.1773.

2-Benzamido-3-(*tert*-butyldiphenylsilyloxy)-2-(hydroxymethyl)propylbenzoate (43): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.96$–7.93 (2H, m), 7.79–7.76 (2H, m), 7.65–7.25 (16H, m), 7.14 (1H, s), 4.85 (1H, d, $J=3.6$ Hz), 4.54 (1H, d, $J=3.6$ Hz), 4.06 (1H, d, $J=3.3$ Hz), 3.95–3.94 (2H, m), 3.76 (1H, d, $J=3.3$ Hz), 1.10 ppm (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 166.3, 135.5, 134.2, 133.2, 132.3, 131.9, 130.0, 129.7, 129.6, 128.7, 128.4, 127.9, 126.9, 63.7, 63.2, 62.7, 61.9, 26.8, 19.2 ppm; HRMS (EI): m/z: calcd for $C_{34}H_{37}NO_4Si$: 567.2441; found: 567.2457.

2-Benzamido-5-(benzyloxy)-2-(hydroxymethyl)pentyl benzoate (44): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.98$–7.95 (2H, m), 7.70–7.67 (2H, m), 7.52–7.19 (11H, m), 6.98 (1H, s), 4.70 (1H, d, $J=3.8$ Hz), 4.53 (1H, d, $J=3.8$ Hz), 4.42 (2H, s), 3.88–3.83 (2H, m), 3.44 (2H, t, $J=4.0$ Hz), 2.09–2.04 (1H, m), 1.91–1.84 (1H, m), 1.75–1.67 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.7$, 166.8, 138.0, 134.4, 133.3, 131.7, 129.7, 129.6, 128.6 (two carbon atoms), 128.5, 128.4, 127.7, 127.0, 73.0, 70.1, 65.9, 65.7, 60.9, 29.9, 23.5 ppm; HRMS (EI): m/z: calcd for $C_{27}H_{29}NO_5$: 447.2046; found: 447.2058.

2-Benzamido-2-benzyl-3-hydroxypropyl benzoate (45): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06–8.03$ (2H, m), 7.72–7.29 (13H, m), 6.59 (1H, s), 4.67 (1H, d, $J = 3.8$ Hz), 4.47 (1H, d, $J = 3.8$ Hz), 3.99–3.97 (1H, m), 3.90–3.88 (1H, m), 3.47 (1H, d, $J = 4.5$ Hz), 3.23 ppm (1H, d, $J = 4.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.5$, 166.9, 135.5, 134.4, 133.5, 131.8, 130.5, 129.7, 129.3, 128.7, 128.6 (two carbon atoms), 127.1, 126.9, 65.5, 65.3, 61.4, 37.5 ppm; HRMS (EI): *m*/*z*: calcd for $C_{24}H_{23}NO_4$: 389.1627; found: 389.1606.

2-Benzamido-2-(hydroxymethyl)pent-4-enyl benzoate (46): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.08–8.05$ (2H, m), 7.78–7.75 (2H, m), 7.62–7.45 (6H, m), 6.77 (1H, s), 5.96–5.94 (1H, m), 5.29–5.24 (2H, m), 4.77 (1H, d, $J = 3.8$ Hz), 4.56 (1H, d, $J = 3.8$ Hz), 3.94–3.90 (2H, m), 2.91–2.84 (1H, m), 2.63–2.56 ppm (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.4$, 166.9, 134.4, 133.4, 132.2, 131.8, 129.7, 129.4, 128.6, 128.5, 126.9, 120.2, 65.7, 65.6, 60.6, 37.1 ppm; HRMS (EI): *m*/*z*: calcd for $C_{20}H_{21}NO_4$: 339.1471; found: 339.1459.

2-Benzamido-2-(hydroxymethyl)but-3-enyl benzoate (47): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06–8.04$ (2H, m), 7.84–7.81 (2H, m), 7.62–7.45 (6H, m), 7.01 (1H, s), 6.16–6.07 (1H, m), 5.43–5.37 (2H, m), 4.79 (1H, d, $J = 3.8$ Hz), 4.65 (1H, d, $J = 3.8$ Hz), 3.96–3.92 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.0$, 167.1, 135.5, 134.1, 133.6, 131.9, 129.7, 129.3, 128.7, 128.6, 127.0, 116.9, 66.3, 66.1, 63.3 ppm; HRMS (EI): *m*/*z*: calcd for $C_{19}H_{19}NO_4$: 325.1314; found: 325.1293.

(*E*)-2-Benzamido-5-ethoxy-2-(hydroxymethyl)-5-oxopent-3-enyl benzoate (48): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03–8.01$ (2H, m), 7.80–7.78 (2H, m), 7.58–7.42 (6H, m), 7.12 (1H, d, $J = 5.3$ Hz), 7.05 (1H, s), 6.08 (1H, d, $J = 5.3$ Hz), 4.76–4.69 (2H, m), 4.18 (2H, q, $J = 1.7$ Hz). 3.96 (1H, d, $J = 3.0$ Hz), 3.88 (1H, d, $J = 3.0$ Hz), 1.25 ppm (t, 3H, $J = 1.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.7$, 167.3, 165.7, 144.3, 133.7 (two carbon atoms), 132.1, 129.8, 129.0, 128.7, 128.6, 127.1, 123.0, 65.5, 65.1, 62.3, 60.7, 14.1 ppm; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{23}NO_6$: 397.1525; found: 397.1509.

(*E*)-2-Benzamido-5-ethoxy-2-(hydroxymethyl)-5-oxopent-3-enyl benzoate (49): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.11–8.08$ (2H, m), 7.82–7.79 (2H, m), 7.61–7.44 (6H, m), 6.84 (1H, s), 4.84 (2H, s), 4.10–4.07 (2H, m), 0.17 ppm (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.5$, 166.7, 134.0, 133.4, 131.9, 129.8, 129.5, 128.6, 128.4, 127.1, 101.3, 91.5, 66.3, 65.2, 58.3, 0.2 ppm; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{25}NO_4Si$: 395.1553; found: 395.1542.

2-Benzamido-3-hydroxy-2-phenylpropyl benzoate (50): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.13–8.11$ (2H, m), 8.00–7.97 (2H, m), 7.66–7.39 (12H, m), 5.15 (2H, d, $J = 3.9$ Hz), 5.01 (2H, d, $J = 3.9$ Hz), 4.74–4.69 (1H, m), 4.47–4.40 (1H, m), 4.28–4.22 ppm (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.1$, 167.2, 138.5, 134.0, 133.6, 132.0, 129.7, 129.2, 128.8, 128.7, 128.5, 127.9, 127.1, 126,1, 67.9, 67.5, 65.1 ppm; HRMS (EI): *m*/*z*: calcd for $C_{20}H_{21}NO_4$: 339.1471; found: 339.1487.

2-Benzamido-2-(4-chlorophenyl)-3-hydroxypropyl benzoate (51): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03–8.00$ (2H, m), 7.88–7.85 (2H, m), 7.62–7.37 (11H, m), 4.96 (1H, d, $J = 3.9$ Hz), 4.85 (1H, d, $J = 3.9$ Hz), 4.25 (1H, d, $J = 4.0$ Hz), 4.13 ppm (1H, d, $J = 4.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.0$, 167.3, 137.0, 133.8, 133.7 (two carbon atoms), 132.1, 129.7, 129.0, 128.9, 128.7, 128.6, 127.7, 127.1, 67.8, 67.0, 64.5 ppm; HRMS (EI): *m*/*z*: calcd for $C_{23}H_{20}ClNO_4$: 409.1081; found: 409.1089.

2-Benzamido-3-hydroxy-2-p-tolylpropyl benzoate (52): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02–8.00$ (2H, m), 7.88–7.85 (2H, m), 7.60–7.21 (11H, m), 5.03 (1H, d, $J = 3.9$ Hz), 4.87 (1H, d, $J = 3.9$ Hz), 4.30 (1H, d, $J = 4.0$ Hz), 4.12 (1H, d, $J = 4.0$ Hz), 2.36 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.1$, 167.2, 137.7, 135.5, 134.1, 133.5, 131.9, 129.7, 129.6, 128.7, 128.5, 128.4, 127.1, 126.0, 67.8, 67.5, 64.9, 20.9 ppm; HRMS (EI): *m*/*z*: calcd for $C_{24}H_{23}NO_4$: 389.1627; found: 389.1613.

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