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Highly diastereoselective synthesis of arylglycine derivatives via TFA-promoted Friedel–Crafts reactions of phenols with cyclic glyoxylate imines

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Abstract—Optically active α-arylglycine derivatives were synthesized by Brønsted acid (TFA)-promoted Friedel–Crafts reaction of various phenols with chiral cyclic glyoxylate imines (**2a–c**), followed by deprotection with $Pd(OH)_2/C$ under H_2. The diastereoselectivities of the initially formed F–C reaction products are up to 99%.

1. Introduction

There has been considerable interest in the development of synthetic methods to realize non-proteinogenic α-amino acids within the synthetic community due to their potential pharmacological properties and their use as precursors for novel peptide structures.[1] Arylglycines constitute an important class of non-proteinogenic α-amino acids. Glycopeptidic antibiotics,[2] such as vancomycin,[3] are one of the best-studied and most important natural sources of arylglycines. Apart from the interesting naturally occurring arylglycines, there are also a number of synthetic arylglycine derivatives that could serve as a side-chain moiety of semisynthetic penicillins and cephalosporins.[1a] In addition, it was recently discovered that molecules of this type were found to be potent and selective agonists or antagonists of metabotropic glutamate receptors.[4] On the other hand, unlike other amino acids, which can be effectively prepared in enantiomerically pure form,[5] the apparent simplicity of the arylglycine structure is complicated by the ease of racemization at the α-stereocenter,[6] rendering these substances challenging synthetic targets to be obtained in optically pure form.

Recently, a number of reports on the stereoselective synthesis of arylglycine derivatives have appeared covering a wide range of reactions[1] including: enzymatic resolution of racemic arylglycine derivatives,[7] asymmetric Strecker reaction,[8] *C*-arylation of electrophilic chiral glycinate[9] and electrophilic amination of chiral benzylic enolate[10] and some other methods.[6a,11] Although many of these methods offer avenues to access this increasingly important functional array, the subject still constitutes an active area of research, especially because of a number of unsolved aspects related to either the functional diversity and the stereochemistry of the products or the generality of the reaction. The electrophilic aromatic substitution represented by Friedel–Crafts (F–C) reaction is one of the most efficient methods for the formation of carbon–carbon bonds to aromatic rings.[12] However, the use of imines in F–C reaction as electrophiles, which would lead to new and interesting arylglycine derivatives, has received only scant attention.[13] On the other hand, chiral cyclic glyoxylate imines have been shown to be a good chiral template in some asymmetric synthesis,[14] which are able to avoid the equilibrium between *E/Z* isomers existing in acyclic alkyl glyoxylate imines. There is only one example of the use of chiral cyclic glyoxylate imine in F–C-type reaction,[15] but its preparation suffers from a larger number of synthetic steps (7 steps). As part of our program to develop a novel method for the stereoselective synthesis of arylglycine derivatives,[16] we herein describe a highly diastereoselective synthesis of optically active arylglycines via Brønsted acid (TFA)-promoted Friedel–Crafts reaction of phenols with chiral cyclic glyoxylate imines.

2. Results and discussion

The following chiral cyclic glyoxylate imines: dihydro-1,4-oxazin-2-ones **2a–c** (Fig. 1) were synthesized via oxidative rearrangement of oxazolines,[17] which were readily prepared

Keywords: arylglycine; F–C reaction; phenol; chiral cyclic glyoxylate imine; diastereoselective synthesis.
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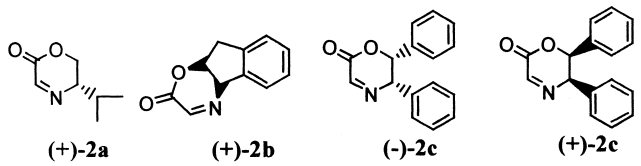
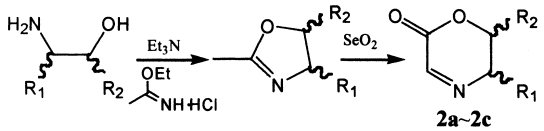


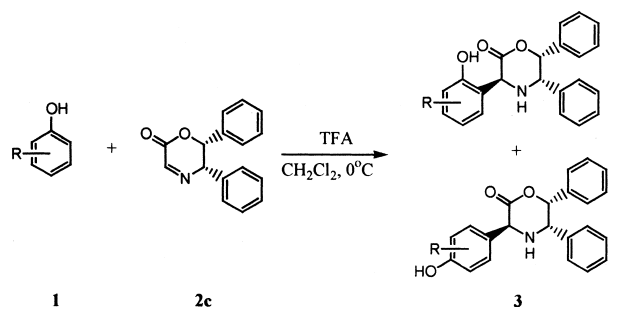
Figure 1.

by condensing L-valinol, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol and (1*R*,2*S*)-(−)-2-amino-1,2-diphenyl-ethanol or its enantiomer with ethyl acetimidate respectively according to Meyers' method[18] (Scheme 1). To the best of our knowledge, these four chiral cyclic glyoxylate imines have never been used as chiral templates on F–C reaction.



Scheme 1.

As illustrated in Scheme 2, the F–C reactions were carried out as shown in the following procedure. To a solution of phenol and chiral cyclic glyoxylate imine in CH_2Cl_2 at 0°C, TFA (5 equiv.) was added dropwise by a syringe. After the reaction mixture was stirred for 3 h at 0°C, usual work-up furnished a residue from which the pure product was obtained after purification by flash chromatography on silica gel. Noteworthy is that the reaction can be carried out in the solvent directly from stock and without protection from air with the same yield and diastereoselectivity of the reaction. It should be mentioned that the properties of the organic solvents play a key role in the F–C reaction. The reaction proceeded smoothly in dichloromethane and toluene with good yield and diastereoselectivity while no product was detected when THF, CH_3CN or 1,4-dioxane was used as solvent.



Scheme 2.

As a preliminary study, we first examined the reactions of 4-*tert*-butyl-phenol (**1a**) with different dihydro-1,4-oxazin-2-ones (**2a**–**c**) under selected reaction conditions for screening purpose. Both chiral cyclic glyoxylate imines (−)-**2a** and (+)-**2b** did not show satisfactory diastereoselectivities (53% and 68% de determined by ^{1}H NMR of the adducts, respectively; Table 1, entries 1 and 2) in the corresponding adducts **3aa** and **3ab**. However, when **1a** was allowed to react with (−)-**2c** or (+)-**2c** instead of **2a** and **2b**, the des of adducts **3ac** and **3ad** can be improved to 99%

Table 1. Reactions of **1a** with **2a**–**c** promoted by TFA

Entry	Phenol	Imine	Product	Yield (%)[a]	De (%)[b]
1	**1a**	(+)-**2a**	**3aa**	73	53
2	**1a**	(+)-**2b**	**3ab**	80	68
3	**1a**	(−)-**2c**	(+)-**3ac**	85	99
4	**1a**	(+)-**2c**	(−)-**3ac**	83	99

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

(entries 3 and 4). In the following experiments, we therefore selected (−)-**2c** as chiral template.

Subsequently, the effects of Brønsted acids[19] as promoter on the F–C reaction were investigated. As depicted in Table 2, similar to the case of TFA, a variety of Brønsted acids can also promote the reaction of **1a** with (−)-**2c** with good yields (83–85%) and excellent diastereoselectivities (99%) (entries 1–4). However, $BrCH_2COOH$, CH_3CO_2H as promoters in the same reaction conditions could not promote the reaction. It could be found from the results in Table 2 that the pK_a value of the Brønsted acid is a crucial factor for promoting the reaction. In contrast to our previous results,[16] which indicated that the Lewis acids used, such as $TiCl_4$ and $Sc(OTf)_3$, can efficiently promote the F–C reaction of phenols with *N*-Tos imino ester and *N*,*O*-acetals, but if $TiCl_4$ or $Sc(OTf)_3$ were employed as promoters in the reaction of phenols with chiral cyclic glyoxylate imines, no reaction took place at all.

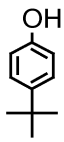
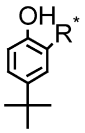
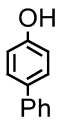
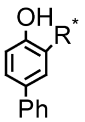
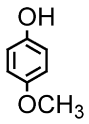
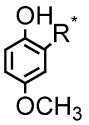
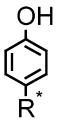
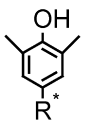
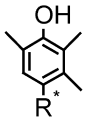
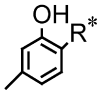
Table 2. Reactions of **1a** with **2c** promoted by acids

Entry	Brønsted acid	pK_a	Product	Yield (%)[a]	De (%)[b]
1	$CF_3CF_2CF_2COOH$	0.17	**3ac**	85	99
2	CF_3COOH	0.25	**3ac**	84	99
3	CCl_3COOH	0.64	**3ac**	84	99
4	$HN(SO_2CF_3)_2$	1.7	**3ac**	83	99
5	$BrCH_2COOH$	2.9	NR		
6	CH_3CO_2H	3.75	NR		

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

To evaluate the scope and limitation of the reaction, a variety of substituted phenols were employed as substrates. Given the results summarized in Table 3, some observations are worthy of comments. The TFA-promoted F–C reaction of **2c** with substituted phenols occurs mainly at the *ortho*- or *para*-position of phenolic hydroxyl group under the reaction conditions depending on the substituted pattern. For the substrates such as **1a**–**1c** in which the 4-position in the aromatic ring was blocked by a substituent, the addition took place exclusively at the *ortho*-position of the phenolic hydroxyl group with 99% de and moderate to good yields (entries 1–3). When simple phenol (**1d**) was used as substrate, *othro*- and *para*-substituted adducts **3dc** and **3dc*** were obtained in 38 and 40% yields with identical 99% de, respectively. The regioisomers **3dc** and **3dc*** were readily isolated by flash chromatography (entry 4). Both 2,6-dimethylphenol **1e** and 2,3,6-trimethylphenol **1f** afforded the *para*-addition products in 80–82 yields and 99% de, respectively (entries 5 and 6), while 2-methyl phenol **1g** provided a mixture of *othro*- and *para*-addition products that were inseparable (entry 7). It was found that substrate

Table 3. Reaction of different phenols **1** with **2c** promoted by TFA

Entry	Phenols	Products	Yield (%)[a]	De (%)[b]
1	**1a** 	**3ac** 	85	99 (S)[c]
2	**1b** 	**3bc** 	41	99 (S)
3	**1c** 	**3cc** 	60	99 (S)
4	**1d** 	**3dc** 	38	99 (S)
		3dc* 	40	99 (S)
5	**1e** 	**3ec** 	82	99 (S)
6	**1f** 	**3fc** 		99 (S)
7	**1g** 	**3gc** 	75	
8	**1h** 	**3hc** 	81	99 (S)

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Configuration of newly formed chiral center.

1h afforded *ortho*-addition product in 81% yield and 99% de (entry 8), and no *para*-adduct was detected from the reaction mixture. The reason for this unique regioselectivity is not clear yet. It is worth mentioning that adduct **3** may serve as a good chiral template for the synthesis of α-alkylated arylglycine derivatives in light of a recent report[20] on the synthesis of enantiopure α,α-disubstituted amino acids. It should be mentioned that anisole and *N*,*N*-dimethylaniline are not suitable for this F–C reaction.

X-ray crystallographic analysis of (−)-**2c** (Fig. 2) provided a basis for understanding of the stereochemistry of the reaction when (−)-**2c** was used as chiral template. Since the phenyl group at 6-position in dihydro-1,4-oxazin-2-one takes up an equatorial position, phenyl group at 5-position is forced to adopt an axial position, shielding *re*-face of the C=N double bond from addition. Thus, the nucleophilic

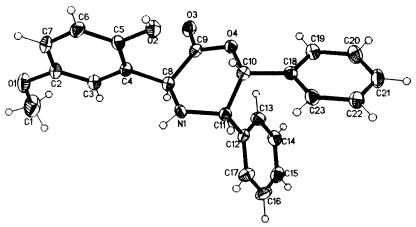


Figure 2. X-ray structure of (−)-**2c**.

attack would take place only from the *si*-face of C=N double bond to afford the addition product with *S* configuration. This is also consistent with an X-ray crystallographic analysis of adduct **3cc** (Fig. 3).

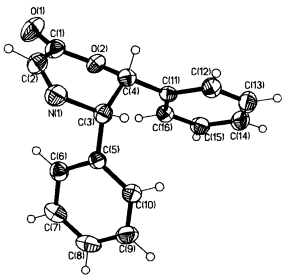
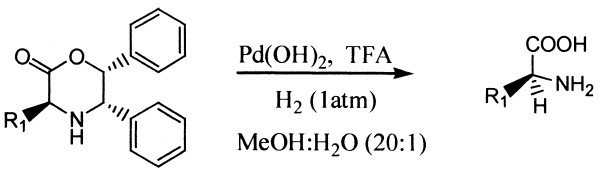


Figure 3. X-ray structure of **3cc**.

The final stage of the study was to remove the chiral template to form the free amino acid without notable racemization.[21] To this end, the adducts **3dc** and **3dc*** were subjected to hydrogenolysis in aqueous methanol using Pearlman's catalyst [$Pd(OH)_2$/C] and TFA under 1 atm of hydrogen gas for 5 h, respectively, and afforded the corresponding amino acids in good yields (Scheme 3). The measured optical rotation values of **4d** and **4d*** were comparable with reported values of D-*p*-hydroxyphenylglycines and D-*o*-hydroxy-phenylglycine (Table 3).[22] Furthermore, considering the sign of optical rotation of **4b** and **4c**, it was further deduced that the absolute configuration of newly formed chiral center of **3cc** is *S* (Table 4).



3dc or **3dc*** **4d** or **4d***

Scheme 3.

Table 4. The optical rotation values of **4d** and **4d***

Entry	Substrate	Product	Yield (%)[a]	$[\alpha]_D$	$[\alpha]_D$ (ref)
1	**3dc**	**4d**	85	+152 (*S*)	−158 (*R*)
2	**3dc***	**4d***	80	+150 (*S*)	−158.4 (*R*)

[a] Isolated yield.

3. Conclusion

In summary, a novel synthesis of useful optically pure arlyglycines by means of TFA-promoted diastereoselective

Friedel–Crafts reaction of a versatile chiral cyclic glyoxylate imine **2c** with various substituted phenols has been developed. The method would allow us to synthesize a variety of highly functionalized optically pure arylglycine derivatives. Further applications of the F–C reaction products **3** to synthesize a range of optically pure α-alkylated arylglycine derivatives are currently under investigation in our laboratory.

4. Experimental

All reactions were performed under a positive atmosphere of dry nitrogen unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). The oxazolines were prepared according to a Ref. 18. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Elemental analyses were performed on a Carlo Elba 1102 Element Analysis instrument. Melting points were determined on a Beijing-Tike X-4 apparatus and were uncorrected. NMR spectra were measured on a Bruker XL-300 (^{1}H, 300 MHz and ^{13}C, 75 MHz) or Bruker XL-400 (^{1}H, 400 MHz and ^{13}C, 100 MHz). IR spectra were taken as neat for liquid compounds and as KBr plates on Perkin–Elmer 500 FT-IR spectrometer. Mass spectra were measured on Bruker APEX-2 FT-ICRMS spectrometer. The crystal X-ray structures were measured on Rigaku R-axis RAPID IP.

4.1. General procedure for the synthesis of chiral cyclic glyoxyate imines

4.1.1. (5*S*,6*R*)-5,6-Diphenyl-5,6-dihydro-[1,4]oxazin-2-one (2c). A solution of (5*S*,6*R*)-2-methyl-4,5-diphenyl-4,5-dihydro-oxazoline (1.46 g, 6.16 mmol) in dry dioxane (60 mL) was added to a suspension of selenium dioxide (854 mg, 7.7 mmol) in dioxane (60 mL), and the mixture was heated at reflux for 75 min. The mixture was cooled to ambient temperature. The mixture was passed through a short column of silica gel and washed several times with ethyl acetate and chromatography on silica gel (eluent: ethyl acetate/light petroleum ether=1:4) to give (−)-**2c** as pale yellow solid (958 mg, 62%); mp: 159–161°C, $[\alpha]_D^{20}=-622$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.18–7.32 (m, 6H), 6.93 (d, *J*=7.0 Hz, 2H), 6.70 (d, *J*=7.5 Hz, 2H), 5.84 (d, *J*=3.7 Hz, 1H), 5.34 (d, *J*=3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.7, 153.1, 130.9, 130.3, 129.1, 128.4, 128.1, 127.3, 126.9, 126.0, 80.7, 66.4. IR 3029, 1739, 1630, 1496, 1452 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48, H, 5.21, N, 5.57%; found: C, 76.84, H, 5.29, N, 5.57%. X-Ray analysis of **2c**: The crystal used for the X-ray study had the dimensions 0.29×0.17×0.08 mm^3. Crystal data: $C_{16}H_{13}NO_2$, *M* 251.27; orthorhombic; space group, $P2_1$ lattice parameters, *a*=5.9439 Å, *b*=8.4943 Å *c*=25.5719 Å; *V*=1291.11 Å^3 *Z*=4; D_{calcd}=1.293 g/cm^3; F_0=528; number of reflections measured=2737, λ=0.7107 Å. CCDC No: 212451.

According to the same procedure, (5*R*,6*S*)-(+)-**2c** was prepared as a pale yellow solid (60%), $[\alpha]_D^{20}=+628$ (*c* 1.0, CH_2Cl_2).

4.1.2. (5*S*)-5-Isopropyl-5,6-dihydro-[1,4]oxazin-2-one (+)-2a. As a colorless oil (70%). $[\alpha]_D^{20}=+96$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.89 (d, *J*=2.8 Hz, 1H), 4.46 (dd, *J*=4.4, 11.7 Hz, 1H), 4.25 (dd, *J*=9.6, 11.6 Hz, 1H), 3.45–3.53 (m, 1H), 1.88–2.00 (m, 1H), 1.06 (t, *J*=6.4 Hz, 6H).

4.1.3. (5*R*, 6*S*)-9,9a-Dihydro-4a*H*-1-oxa-4-aza-fluoren-2-one (+)-2b. As a pale white solid (87%); mp 85–87°, $[\alpha]_D^{20}=+474$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.44–7.47 (m, 1H), 7.30–7.35 (m, 3H), 5.39–5.43 (m, 1H), 5.34–5.38 (m, 1H), 3.43 (dd, *J*=5.4, 16.9 Hz, 1H), 3.25 (dd, *J*=2.6, 16.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 152.8, 151.4, 139.1, 138.3, 128.8, 127.8, 125.1, 124.7, 79.5, 62.7, 38.4. IR 3442, 2970, 1730, 1638 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{11}H_{10}NO_2$: 188.0705; found: 188.0708.

4.2. General procedure for the synthesis of 3

4.2.1. (3*S*,5*S*,6*R*)-3-(5-*tert*-butyl-2-Hydroxy-phenyl)-5,6-diphenyl-morpho-lin-2-one (+)-3ac. To a mixture of **1a** (18 mg, 0.12 mmol) and **2c** (25 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) was added TFA (40 μL, 0.5 mmol) at 0°C. The reaction mixture was stirred at the same temperature until (−)-**2c** was consumed. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether=1:8) to give (+)-**3ac** as a pale yellow solid (34 mg, 85%); mp 90–92°C. de 99%, $[\alpha]_D^{20}=+118$ (*c* 1, CH_2Cl_2). ^{1}H NMR($CDCl_3$) δ 7.18–7.31 (m, 8H), 6.99–7.01 (m, 4H), 6.86 (d, *J*=8.4 Hz, 1H), 5.94 (d, *J*=4.0 Hz, 1H), 5.34 (s, 1H), 4.72 (d, *J*=3.9 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.4, 154.2, 142.9, 136.0, 134.2, 128.4, 128.2, 127.9, 127.6, 126.9, 125.9, 124.1, 118.6, 117.2, 81.2, 58.7, 58.2, 34.0, 31.3. IR 3422, 3033, 2961, 1744, 1598 cm^{-1}. HRMS (FAB) calcd for [M−H$^+$] $C_{26}H_{26}NO_3$: 400.1918; found: 400.1921.

(3*R*,5*R*,6*S*)-(−)-**3ac** as a pale yellow solid (83%), $[\alpha]_D^{20}=-122$ (*c* 1.0, CH_2Cl_2).

4.2.2. 3-(5-*tert*-Butyl-2-hydroxy-phenyl)-5-isopropyl-morpholin-2-one (3aa). As a pale yellow solid (73%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.30 (m, 1H), 7.13, 7.20* (s, 1H), 6.86 (d, *J*=8.3 Hz, 1H), 4.84, 5.11* (s, 1H), 4.51–4.56 (m, 1H), 4.29–4.36 (m, 1H), 2.94–2.97, 2.99–3.02* (m, 1H), 1.82–1.89 (m, 1H), 1.29–1.31 (m, 9H), 1.00–1.08 (m, 6H), * two diastereomeric protons, de 53%; ^{13}C NMR ($CDCl_3$) δ 168.3, 168.0, 154.5, 153.6, 142.7, 142.6, 127.0, 126.7, 124.6, 121.0, 118.8, 116.9, 71.8, 71.5, 62.4, 58.4, 57.5, 53.0, 34.1, 34.0, 31.5, 31.4, 29.8, 29.3, 18.9, 18.8, 18.6. IR 3293, 2962, 1735, 1612 cm^{-1}. HRMS (FAB) cacld for [M+H$^+$] $C_{17}H_{26}NO_3$: 292.1907; found: 292.1904.

4.2.3. 3-(5-*tert*-Butyl-2-hydroxy-phenyl)-4,4a,9,9a-tetrahydro-3*H*-1-oxa-4-aza-fluoren-2-one (3ab). As a pale white solid (80%). ^{1}H NMR ($CDCl_3$) δ 7.26–7.37 (m, 5H), 7.08 (s, 1H), 6.91 (d, *J*=8.5 Hz, 1H), 5.12–5.16 (m, 1H), 5.01 (s, 1H), 4.66 (d, *J*=5.8 Hz, 1H), 3.34, 3.48* (d, *J*=6 Hz, 2H), 1.30 (s, 9H), *two diastereomeric protons, de

68%.; ^{13}C NMR ($CDCl_3$) δ 168.6, 154.5, 142.9, 139.7, 138.6, 129.3, 129.1, 127.8, 127.7, 127.1, 127.0, 126.9, 125.6, 125.3, 124.6, 124.5, 123.8, 117.3, 116.9, 116.7, 80.5, 60.3, 58.1, 57.8, 56.8, 38.8, 37.8, 34.1, 31.4. IR 3750, 3423, 2959, 2868, 1735, 1616 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{21}H_{24}NO_3$: 338.1750; found: 338.1753.

4.2.4. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-biphenyl-3-yl)-5,6-diphenyl-morpholin-2-one (3bc). As a pale yellow solid (41%); mp 107–109°C, de% 99%, $[\alpha]_D^{20}$=+165 (*c* 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J*=7.6 Hz, 2H), 7.52 (s, 1H), 7.45 (t, *J*=7.4 Hz, 2H), 7.22–7.37 (m, 8H), 6.99–7.08 (m, 5H), 6.00 (d, *J*=4.1 Hz, 1H), 5.49 (s, 1H), 4.80 (d, *J*=4.1 Hz, 1H); ^{13}C NMR ($CDCCl_3$) δ 168.0, 156.7, 140.2, 136.1, 134.1, 133.4, 128.8, 128.7, 128.4, 128.2, 128.1, 127.6, 126.8, 126.7, 126.0, 125.9, 119.3, 118.4, 81.3, 58.9, 58.4. IR 3424, 3032, 2925, 2854, 1742, 1650, 1607cmcm^{-1}; HR MS (FAB) calcd for [M+H$^+$] $C_{28}H_{24}NO_3$ 422.1751; found: 422.1750.

4.2.5. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-5-methoxy-phenyl)-5,6-diphe-nylmorpholin-2-one(3cc). As colorless crystals (60%); mp 179–181°C, de 99%, $[\alpha]_D^{20}$=+54 (*c* 0.85, $(CH_3)_2CO$). ^{1}H NMR ($CDCl_3$) δ 7.19–7.28 (m, 7H), 6.82–7.00 (m, 6H), 5.92 (d, *J*=4.0 Hz, 1H), 5.37 (s, 1H), 4.72 (d, *J*=4.1 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 169.6, 152.3, 149.0, 137.9, 136.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 126.9, 116.6, 116.3, 114.5, 84.1, 56.8, 56.4, 55.9. IR 3434, 3340, 2963, 2923, 2853, 1735, 1691, 1636 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{23}H_{22}NO_4$: 376.1543; found: 376.1544. X-ray analysis of **3cc**: The crystal used for the X-ray study had the dimensions 0.33×0.29×0.13 mm^3. Crystal data: $C_{23}H_{21}NO_4$, *M* 375.41; Monoclinic; space group, $P_2(1)$; lattice parameters, *a*=9.7520 Å, *b*=9.6697 Å, *c*=10.2717 Å; *V*=930.52Å^3 *Z*=2; D_{calcd}=1.340 g/cm^3; F_0=396; number of reflections measured=4185, λ=0.7107 Å. CCDC No: 212450.

4.2.6. (3*S*,5*S*,6*R*)-3-(2-Hydroxy-phenyl)-5,6-diphenyl-morpho-lin-2-one (3dc). White solid (31.8%); mp 158–160°C, de 99%, $[\alpha]_D^{20}$=+52.6 (*c* 1.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.17–7.32 (m, 8H), 6.90–7.00 (m, 6H), 5.92 (d, *J*=4.2 Hz, 1H), 5.38 (s, 1H), 4.72 (d, *J*=4.2 Hz, 1H); ^{13}C NMR ($CDCCl_3$) δ 168.2, 157.2, 136.3, 134.2, 130.2, 128.7, 128.4, 128.2, 128.1, 127.6, 127.2, 126.0, 120.3, 119.2, 118.1, 81.3, 58.8, 58.4. IR 3301, 3065, 1742 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{22}H_{20}NO_3$: 346.1437; found: 346.1432.

4.2.7. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-phenyl)-5,6-diphenyl-morpho-lin-2-one (3dc′). As colorless crystals (40%); mp 213–215°C, de% 99%, $[\alpha]_D^{20}$=+101.1 (*c* 0.95, acetone). ^{1}H NMR (d_6-acetone) δ 7.43 (d, *J*=8.6 Hz, 2H), 7.13–7.20(m, 6H), 7.00–7.06(m, 4H), 6.86 (d, *J*=8.6 Hz, 2H), 5.85(d, *J*=4.3 Hz, 1H), 5.13 (s, 1H), 4.82(d, *J*=4.3 Hz, 1H); ^{13}C NMR (d_6-acetone) δ 170.2, 157.9, 139.0, 136.9, 130.2, 129.0, 128.6, 128.4, 128.3, 127.6, 116.1, 83.9, 60.3, 57.6. IR 3361, 3034, 2425, 1705, 1612 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{22}H_{20}NO_3$: 346.1437; found: 346.1432.

4.2.8. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-3,5-dimethyl-phenyl)-5,6-diphe-nyl-morpholin-2-one (3ec). As a white solid (82%); mp 193–195°C, de 99%, $[\alpha]_D^{20}$=+96 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.15–7.27 (m, 8H), 6.93–6.99 (m, 4H), 5.77 (d, *J*=3.9 Hz, 1H), 5.10 (s, 1H), 4.74 (d, *J*=3.9 Hz, 1H), 2.25 (s, 6H); ^{13}C NMR ($CDCCl_3$) δ 170.3, 152.3, 137.6, 135.1, 129.4, 128.3, 128.1, 127.9, 127.7, 127.1, 126.9, 126.7, 123.8, 83.1, 60.0, 57.6, 16.2. IR 3435, 3033, 2921, 1732, 1632 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{24}H_{24}NO_3$: 374.1750; found: 374.1753.

4.2.9. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-2,3,5-trimethyl-phenyl)-5,6-dip-henyl-morpholin-2-one (3fc). As a white solid (80%); mp 176–178°C, de 99%, $[\alpha]_D^{20}$=+158 (*c* 2.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.21–7.30 (m, 6H), 7.04–7.11 (m, 4H), 6.98 (s, 1H), 5.99 (d, *J*=3.9 Hz, 1H), 5.28 (s, 1H), 4.82 (d, *J*=3.9 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCCl_3$) δ 170.9, 152.4, 137.3, 135.8, 134.2, 129.2, 128.7, 128.4, 128.2, 128.1, 127.2, 124.0, 120.5, 85.2, 59.2, 56.6, 16.4, 16.1, 12.7. IR 3443, 3032, 2925, 1731 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{24}H_{24}NO_3$: 388.1907; found: 388.1905.

4.2.10. (3*S*,5*S*,6*R*)-3-(4-Hydroxy-3-methyl-phenyl)- and (3*S*,5*S*,6*R*)-3-(2-hydroxy-3-methyl-phenyl)-5,6-diphenyl-morpholin-2-one (3gc). As a white solid (75%). ^{1}H NMR (d_6-acetone) δ 7.30–7.32 (m, 1H), 7.19–7.21 (m, 1H), 7.12–7.17 (m, 6H), 6.98–7.06 (m, 4H), 6.85 (d, *J*=8.3 Hz, 1H), 6.16, 5.84* (d, *J*=4.3 Hz, 1H), 5.29, 5.08* (s, 1H), 4.96, 4.81* (d, *J*=4.3 Hz, 1H), 2.28 (s, 3H), *two regioisomeric protons (1:2); ^{13}C NMR(d_6-acetone): δ 169.5, 155.1, 138.3, 136.2, 129.5, 129.4, 127.8, 127.6(2C), 127.3, 126.8, 125.4, 124.4, 114.5, 83.0, 59.6, 56.8, 15.5. IR 3339, 3061, 2480, 1704, 1607cmcm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{23}H_{20}NO_3$: 358.1437; found: 358.1433.

4.2.11. (3*S*,5*S*,6*R*)-3-(2-Hydroxy-4-methyl-phenyl)-5,6-diphenyl-morpholin-2-one (3hc). As a white solid (81%); mp 61–63°C, de% 99%. ^{1}H NMR ($CDCl_3$) δ 7.15–7.25 (m, 6H), 7.07 (d, *J*=7.8 Hz, 1H), 6.91–6.97 (m, 4H), 6.75 (s, 1H), 6.70 (d, *J*=7.9 Hz, 1H), 5.89 (d, *J*=4.2 Hz, 1H), 5.33 (s, 1H), 4.68 (d, *J*=4.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 157.0, 140.6, 136.4, 134.4, 128.7, 128.5, 128.2, 128.1, 127.7, 127.2, 126.2, 121.2, 118.6, 116.3, 81.3, 58.7, 58.4, 21.2. IR 3272, 3033, 2923, 1741, 1624 cm^{-1}. HRMS (FAB) calcd for [M+H$^+$] $C_{23}H_{22}NO_3$: 360.1594; found: 360.1602.

4.3. General procedure for synthesis of 4

4.3.1. (*S*)-*o*-Hydroxy-phenylglycine (4d). TFA (16 μL, 0.21 mmol) was added to a mixture of **3dc** (73 mg, 0.21 mmol) and palladium hydroxide (78 mg, 1 equiv. by mass) in aqueous methanol (20:1 MeOH/H_2O, 20 mL mmol^{-1}) under a positive atmosphere of hydrogen (1 atm), the reaction mixture was stirred at ambient temperature for 24 h, then the solution was filtered and the solvent removed in vacuo. Trituration of the crude mixture with ethyl ether, the solid was filtered and dried in vacuo to give **4d** as a white powder (30 mg, 85%); mp 186–188°C, $[\alpha]_D^{20}$=+152 (*c* 1.0, 1N HCl). ^{1}HNMR (d_6-DMSO) δ 7.10–7.16 (m, 2H), 6.78–6.82 (m, 2H), 4.62 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 170.0, 156.3, 129.1, 125.4, 123.2, 119.1, 117.8, 53.9. IR 3417, 3071, 1633, 1462 cm^{-1}. HRMS

(FAB) calcd for $[M+H^+]$ $C_8H_{10}NO_3$: 168.0655; found: 168.0653.

4.3.2. (*S*)-*p*-Hydroxyphenylglycine (4d*). As a white powder (80%); mp 212–214°C, $[\alpha]_D^{20}=+150$ (*c* 1.0, 1*N* HCl). ^1H NMR (d_6-DMSO) δ 7.18 (d, $J=8.2$ Hz, 2H), 6.71 (d, $J=8.0$ Hz, 2H), 4.14 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 169.5, 157.6, 129.4, 127.6, 115.5, 57.9. IR 3421, 3030, 1613, 1515 cm^{-1}. HRMS (FAB) calcd for $[M+H^+]$ $C_8H_{10}NO_3$: 168.0655; found: 168.0655.

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