Synthesis of \(\beta\)-Hydroxy \(\alpha\)-Amino Acids Through Brønsted Base-Catalyzed \(\text{syn}\)-Selective Direct Aldol Reaction of Schiff Bases of Glycine \(\text{o}\)-Nitroanilide

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**ABSTRACT:** Here we report the highly enantio- and \(\text{syn}\)-selective synthesis of \(\beta\)-hydroxy \(\alpha\)-amino acids from glycine imine derivatives under Brønsted base (BB) catalysis. The key of this approach is the use of benzophenone-derived imine of glycine \(\text{o}\)-nitroanilide as a pronucleophile, where the \(\text{o}\)-nitroanilide framework provides an efficient hydrogen-bonding platform that accounts for nucleophile reactivity and diastereoselectivity.

Due to their prevalence in natural products, including antibiotics and enzyme inhibitors and their presence as structural components of many biologically active products, \(\beta\)-hydroxy \(\alpha\)-amino acids are compounds of high interest in medicinal chemistry. Thus, different approaches for their enantioselective synthesis have been reported, most of them relying on the use of glycine derivatives. Among these and since their introduction by O'Donnel and Eckrich in 1978, glycine Schiff bases stand up as the most appealing substrates due to their bench stability. In this context, the asymmetric aldol reaction of glycine Schiff bases is very effective for the production of \(\beta\)-hydroxy \(\alpha\)-amino acids because, concomitant to the assembly of the 1,2-aminoalcohol functionality during the carbon–carbon bond forming step, up to two vicinal stereogenic centers are created in a single synthetic operation. In 1991, Miller and Gasparski reported the first catalytic direct aldol reaction of benzophenone imines of glycine esters using phase-transfer catalysis. The method leads to \(\text{anti}\)-adducts but in low diastereoselectivities and negligible enantiomeric excesses. Following this report, other protocols involving phase-transfer catalytic conditions, metal catalysis, or the use of lithium/\((-\text{)}\)-sparteine have also been described. Among these, the only report concerning the enantioselective direct synthesis of \(\text{syn}\)-isomers from glycine Schiff bases has been documented, as far as we know, by Trost using a zinc-ProPhenol catalyst. The reaction works well for \(\alpha\)-substituted aldehydes but provides less satisfactory enantioselectivities for linear alky aldehydes.

Herein we report the first aldol reaction of Schiff bases of glycine derivatives by Brønsted base (BB) catalysis, which provides \(\text{syn}\) \(\beta\)-hydroxy \(\alpha\)-amino acids in high diastereoselectivity. The key for this development is the use of a glycine \(\text{o}\)-nitro anilide derivative in combination with an ureidopeptide-based BB catalyst.

Benzophenone imines of glycine esters have shown to be very efficient substrates with applications in many transformations. However, their use in enantioselective synthesis has been mainly limited to metal and phase transfer catalysis, while their development in organocatalysis remains essentially unexplored. The main reason that can account for this deficiency is the relatively low acidity of the methylenic carbon, which precludes enolate generation through deprotonation by the weak BB catalysts usually employed. Only recently, three examples have been documented (Figure 1a) in which this problem has been solved by using more acidic structural analogues as fluorenone imine (A), 2-hydroxybenzophenone imine (B), and (R)-3-hydroxy-[1,1′-binaphthalene]-2-carbaldehyde imine (C) of glycine derivatives. The increased acidity of these iminoesters is the result of structural modifications on the imine function by the incorporation of motifs that promote either stabilization of the corresponding conjugate base by extensive charge delocalization (A) or intramolecular hydrogen bonding as in B and C. It was our consideration that the installation of an \(\text{o}\)-nitroaniline motif in the carboxyl terminus might be another possibility to increase \(\alpha\)-carbon acidity of glycine Schiff bases (Figure 1b). It has been reported that \(\text{o}\)-nitroanilides of simple carboxylic acids exhibit intramolecular hydrogen bonding between the oxygen of the nitro group and the hydrogen of the amide moiety, largely facilitating hydrolysis by...
Scheme 1. Aldol Reaction between Nitroanilides 1−3 and Hydrocinnamaldehyde 4a Promoted by Brønsted Base Catalysts

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Better diastereoselectivity was achieved (entries 3 and 4), but the enantioselectivity of product 5a was still poor. To improve stereocontrol through the incorporation of additional H-bond donors under the reaction, we focused on ureidopeptide-derived Brønsted bases previously developed by us. It was gratifying to observe that the new variants C5, C6, and C7 provided 5a with diastereomeric ratios greater than 98:2 and in each case with good enantioselectivity (entries 5, 6, and 8).

References

1. Previous work: Structural modification on the imine function

2. This work: Structural modification on the carboxylic acid function

Figure 1. (a) Previously developed Schiff bases of glycine for Brønsted base (BB) catalysis. (b) Schiff base of glycine 7-nitroanilide proposed as a pronucleophile for BB catalysis.

Figure 2. Representative H-bonding interactions of 1 in the solid state. View of the molecular structure of 1 with 50% probability displacement ellipsoids.

Analysis also showed an additional hydrogen bonding (2.234 Å) between the o-aromatic hydrogen and the carbonyl oxygen. Therefore, while amides are known to be reluctant to enolization,21 we expected these structural features should render substrate 1 quite promising for Brønsted base-promoted stereoselective transformations.

Initially, our approach was evaluated from the reaction of benzophenone imine 112 with hydrocinnamaldehyde 4a (Scheme 1) mediated by squaramides C1 and C2.23 Using these bases, the reaction indeed proceeded to give the aldol product 5a after one-pot reductive workup, but with very poor diastereoselectivity and negligible enantioselectivity for the major syn isomer, albeit good for the minor isomer (Table 1, entries 1 and 2). Using the parent ureas, C3 and C4, much better diastereoselectivity was achieved (entries 3 and 4), but the enantioselectivity of product 5a was still poor. To improve stereocontrol through the incorporation of additional H-bond donors during the reaction, we focused on ureidopeptide-derived Brønsted bases previously developed by us.26 It was gratifying to observe that the new variants C5, C6, and C7 provided 5a with diastereomeric ratios greater than 98:2 and in each case with good enantioselectivity (entries 5, 6, and 8).

References
Further improvement was achieved using catalyst C6 and carrying out the reaction at 0 °C, and 5a was obtained in 77% isolated yield and 94% ee (entry 7). Although in these reactions, the formation of small amounts (10–15%) of the cyclized product 5a was also observed, its reductive workup also furnished the amino alcohol derivative 5a. Likewise, iminoamides 2 and 3 upon treatment with 4a in CH2Cl2 at 0 °C led to products 6a and 7a in less than 24 h with good isolated yields and stereoselectivities, Table 1. The best result was attained for the latter, which was obtained essentially as a single syn-diastereomer and with excellent enantioselectivity.

The scope of the new glycine amide reagent 3 to the synthesis of syn-β-hydroxy α-amino acids was next examined from a selection of representative enolizable aldehydes (Table 2). With the exception of α-branched aldehydes such as isobutyaldehyde and cyclohexanecarboxaldehyde, which were inert to this system, results were consistently good. As the data in Table 2 show, syn-β-hydroxy α-amino acids bearing short and long linear chains, which cannot be accessed by the above known methods, vide supra, may be prepared with very good yields and ee values. Isovaleraldehyde and aldehydes bearing side chains with functional groups (e.g., ester, carbamate, and ether) are equally tolerated to give the respective syn-isomer with good enantioselectivity. Importantly, in every case under these reaction conditions, self-aldo products from the corresponding enolizable aldehyde 4 were not detected. Likewise, product 7a was chemically and stereochemically unchanged when exposed to treatment with aldehyde 4b at room temperature in the presence of both Et3N (20 mol %) and Schreiber achiral diarylthiourea23 (20 mol %) for 24 h, thus indicating product stability.

The absolute configuration of the adducts was established by X-ray analysis of compound 10 derived from the reaction of 3 with hydrocinnamaldehyde, Scheme 2, and by assuming a uniform reaction mechanism. On the other hand, treatment of aldo product 7a with 2 equiv of (Boc)2O led to 11, which upon Evans hydrolytic conditions provided the carboxylic acid 12 along with N-Boc nitroaniline.

The above experimental results clearly show that benzophenone imines of glycine o-nitroanilides are acidic enough to react in BB-catalyzed reactions under soft enolization conditions. To further prove the significance of the intra-molecular hydrogen bonding in o-nitroanilides 1–3,31 benzophenone imines 13, 14, and 15 were prepared and subjected to treatment with 4a under the above conditions (Scheme 3), and in no case was a reaction observed. Likewise, in an attempt to strengthen the hydrogen bonding, compound 16 with an additional nitro group in the para position of the aromatic ring was also prepared. While, in this case, the reaction proceeded, product 17 was obtained in a modest yield and in an almost racemic form.

### Table 2. Scope of the Aldol Reaction of 3 with Aldehydes 4 Assisted by C6

| Entry | Aldehyde | Yield | Ee (%) |
|-------|----------|-------|--------|
| 1     | 4a       | 92.8% | 90%    |
| 2     | 4b       | 98.2% | 90%    |
| 3     | 4c       | 98.2% | 90%    |
| 4     | 4d       | 98.2% | 90%    |
| 5     | 4e       | 98.2% | 90%    |
| 6     | 4f       | 98.2% | 90%    |
| 7     | 4g       | 98.2% | 90%    |
| 8     | 4h       | 98.2% | 90%    |
| 9     | 4i       | 98.2% | 90%    |
| 10    | 4j       | 98.2% | 90%    |

“Reactions conducted on a 0.2 mmol scale in 0.4 mL of CH2Cl2 (mol ratio N-(diaryl)methylene)glycine o-nitroanilide 3/aldehyde/catalyst 1:3:0.2). Conversion determined by the disappearance of the starting N-(diaryl)methylene)glycine o-nitroanilide. Yield of the isolated major isomer. Diastereomeric ratio determined by 1H NMR (300 MHz) analysis on the crude product. Enantiomeric excess determined by hPLC. Ar: 4-CF3C6H4.
An effective organocatalytic direct access to syn-β-hydroxy α- amino acids is reported. The strategy is based on Schiff bases of glycine o-nitroanilide, wherein the o-nitroanilide motif is key for enolate generation by a soft Brønsted base allowing direct reaction with aldehydes under efficient diastereo- and enantiocontrol. Further applications of both

the nitroanilide tether and the catalyst and/or variants may be easily anticipated.

### EXPERIMENTAL SECTION

#### General Information.

All nonaqueous reactions were performed under an inert atmosphere using oven-dried glassware, and the mixtures were magnetically stirred. Yields refer to chromatographically purified and spectrophotometrically pure compounds, unless otherwise stated. Heat requiring reactions were performed using a hot plate with a sand or an oil bath and a condenser. Reactions requiring low temperatures were performed using cooling bath circulators, Huber T100E, and acetone or isopropanol baths. Organic layers washed with aqueous phases were dried over MgSO₄ or Na₂SO₄ and filtered through cotton. Organic solvents were evaporated under reduced pressure using rotavapor Büchi R-100, R-200, and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents, a vacuum pump, Telstar Top-3 (≈ 0.3 mmHg), was employed. Reagents were purchased from different commercial suppliers (Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.), stored as specified by the manufacturer, and used without previous purification unless otherwise stated. Triethylamine was purified by distillation. When anhydrous solvents were required, they were dried following established procedures. Dichloromethane was dried over CaH₂, and tetrahydrofuran was dried by filtration through activated alumina (powder 150 mesh, pore size 58 Å, basic Sigma-Aldrich) columns. Reactions and flash chromatographic columns were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Biolamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1g) in 100 mL of water (limited lifetime), followed by heating and charring with 1% w/w ninhydrin in ethanol followed by heating. Chromatographic purification was performed on Merck ROCC 60 silica gel 40–63 μm as stationary phase and a suitable mixture of solvents (typically hexane: ethyl acetate or dichloromethane/methanol) as eluent. Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotations (SR) (α⁻¹) are reported in deg cm² g⁻¹; concentrations (c) are quoted in g/100 mL; D refers to the D line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

Melting points were determined in open capillaries in a Stuart SHP3
melting point apparatus and were uncorrected. NMR spectra were recorded using a Bruker Avance 300 (300 MHz for 1H, 75 MHz for 13C) spectrometer, Bruker 400 spectrometer (400 MHz for 1H, 100 MHz for 13C), or Bruker AV-500 spectrometer (500 MHz for 1H, 125 MHz for 13C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually CDCl3, 1H (δ = 7.26) and 13C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad singlet. Coupling constants (J) are reported in hertz (Hz). The MestreNova Mnova 8.1 program was used to process and edit the registered spectra. Mass spectra were recorded on an ESI-ion trap mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, ultra high-performance liquid chromatography—mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2, or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU). Enantiomeric excesses were determined using analytical high-performance liquid chromatography (HPLC) performed on Waters 600-E (equipped with 2996 and 2998 photodiode array UV detector) employing Daicel columns (IA, IF) and Phenomenex Lux (cellulose 3 μm, amylose 3 μm). The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using diffractometers for monocrystals. Aliphatic aldehydes 4a, 4b, 4c, 4d, 4e, and 4f are commercially available and were purchased from commercial suppliers. Aldehydes 4g, 4h, 4i, and 4j were prepared following literature procedures. All aldehydes were dissolved in CH2Cl2 treated with an aqueous saturated solution of NaHCO3 and subsequently distilled before their use in the aldol reaction.

**Synthesis of Catalysts.** Bifunctional organocatalysts C1, C2, C3, C4, and C5 were prepared following reported procedures. Catalysts C5, C6, and C7 were synthesized following a modification of the procedures previously reported.

**Synthesis of Catalysts C5, C6, and C7.**

**a. Preparation of N-Protected i-tert-Leucine.**

In the first step, pyridine (0.9 mL, 11 mmol, 1.1 equiv) was added to a stirred solution of p-nitrophenyl chloroformate (2.2 g, 11 mmol, 1.1 equiv) in dichloromethane (13.6 mL). The white slurry was cooled to 0 °C and the corresponding alcohol (10 mmol, 1 equiv) was slowly added in the same temperature. After addition, the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into H2O (100 mL) and washed with Et2O (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over MgSO4 and concentrated under reduced pressure. The residue was used in the next step without further purification.

In the second step, to a stirred solution of i-tert-leucine (1.31 g, 10 mmol, 1 equiv) in 10% Na2CO3 (26 mL) and dimethylformamide (10 mL) was added a solution of the corresponding carbonate (10 mmol, 1 equiv) in dimethylformamide (30 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h and at room temperature for 16 h. The reaction mixture was poured into H2O (100 mL) and washed with Et2O (3 × 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (5 × 50 mL), dried over MgSO4, and concentrated under reduced pressure.

To a cooled solution of the corresponding N-protected α-amino acid (5 mmol, 1 equiv) in dry THF (20 mL) were added isobutyl chloroformate (0.65 mL, 5 mmol, 1 equiv) and N-methylmorpholine (0.6 mL, 5 mmol, 1 equiv) at −20 °C. The mixture was stirred at the

The title compound was prepared from 9-anthracenemethanol (2.08 g, 10 mmol) following the general procedure. Purification by flash column chromatography on silica gel (hexane/EtOAc, 70:30) afforded the title compound as a white solid. Yield: 88% (3.2 g, 8.8 mmol). All of the spectroscopic data were coincident with those previously reported. 1H NMR (300 MHz, CDCl3): δ = 8.52 (s, 1H), 8.38 (d, J = 8.9 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 7.65–7.58 (m, 2H), 7.53–7.46 (m, 2H), 6.18 (q, J = 12.1 Hz, 2H), 5.24 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 10.2 Hz, 1H), 1.01 (s, 9H).

**S-(3,3-Dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino)butanoic Acid.**

The title compound was prepared from 1-naphthalenemethanol (1.58 g, 10 mmol) following the General Procedure. Purification by flash column chromatography on silica gel (hexane/EtOAc, 80:20) afforded the title compound as a white solid. Yield: 88% (2.8 g, 8.8 mmol). Mp: 131–135 °C. 1H NMR (300 MHz, CDCl3): δ = 10.10 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 8.8 Hz, 2H), 7.49 (dt, J = 27.2, 7.3 Hz, 4H), 5.60 (q, J = 12.3 Hz, 2H), 5.40 (d, J = 9.5 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 1.02 (s, 9H). 13C{1H} NMR (75 MHz, CDCl3): δ = 176.6, 156.4, 133.8, 131.7, 129.5, 128.8, 127.6, 126.7, 126.07, 125.4, 123.7, 65.6, 62.3, 34.7, 26.6. UPLC-DAD-QTOF, HRMS (ESI) m/z [M + Na]+ calcd for C18H21NO4Na, 338.1368; found, 338.1369.

**S-(3,3-Dimethyl-2-(((naphthalen-2-ylmethoxy)carbonyl)amino)butanoic Acid.**

The title compound was prepared from 2-naphthalenemethanol (1.58 g, 10 mmol) following the general procedure. Removal of the remaining phenol was not possible by column chromatography. Therefore, after the work-up described in the general procedure, the crude was dissolved in Et2O (30 mL) and basified with NaHCO3 saturated aq. solution. The aqueous phase was washed with Et2O (3 × 20 mL), acidified with concentrated HCl, and extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over MgSO4 and evaporated under reduced pressure to afford the title compound as a white solid. Yield 48% (1.5 g, 4.8 mmol). All of the spectroscopic data were coincident with those previously reported. 1H NMR (300 MHz, CDCl3): δ = 7.92–7.74 (m, 4H), 7.58–7.36 (m, 3H), 5.47 (d, J = 9.4 Hz, 1H), 5.30 (s, 2H), 4.26 (d, J = 9.6 Hz, 1H), 1.04 (s, 9H).

**b. General Procedure for Isocyanate Synthesis and Coupling with the Amine.**

To a cooled solution of the corresponding N-protected α-amino acid (5 mmol, 1 equiv) in dry THF (20 mL) were added isobutyl chloroformate (0.65 mL, 5 mmol, 1 equiv) and N-methylmorpholine (0.6 mL, 5 mmol, 1 equiv) at −20 °C. The mixture was stirred at the
same temperature for 20 min. Then, a suspension of NaOAc (0.48 g, 7.5 mmol, 1.5 equiv) in 5 mL of H2O was added, and the reaction mixture was stirred at the same temperature for 30 min. The organic layer was separated and evaporated, and the residue was dissolved in CH2Cl2 (30 mL) and washed with water (15 mL). The organic phase was dried over MgSO4, filtered, and concentrated in vacuo to give a yellow oil, which was dissolved in dry CH2Cl2 (10 mL). The resulting solution was stirred at 40 °C under nitrogen for 1–2 h. The reaction was monitored by IR analysis until the disappearance of the azide band (from azide \(-N=\) to isocyanate \(-N\equiv\)). After isocyanate generation, (1S,2S)-2-((piperidin-1-yl)cyclohexan-1-amine was isolated by flash column chromatography on silica gel (Hex/EtOAc 80:20) as a white solid. Yield: 63% (1.7 g, 3.1 mmol). Mp: 146 °C.

To the title compound was prepared from (S)-2-(((anthracen-9-ylmethoxy) carbonyl)amino)-3,3-dimethyl butanoic acid (1.8 g, 5.0 mmol) and was isolated by flash column chromatography on silica gel (hexane/EtOAc, 90:10) as a white solid. Yield: 61% (1.06 g, 2.14 mmol). Mp: 170–172 °C. \([\alpha]_{D}^{25} = -15.6 (c 1, CHCl3).\) 1H NMR (500 MHz, DMSO-d6, 70 °C): \(\delta = 8.67 (s, 1H), 8.37 (d, J = 8.7 Hz, 2H), 8.12 (d, J = 8.0 Hz, 2H), 7.62–7.57 (m, 2H), 7.58–7.49 (m, 2H), 7.21 (d, J = 9.1 Hz, 1H), 6.11–6.00 (m, 2H), 5.79 (s, 1H), 5.17 (s, 1H), 2.55–2.50 (m, 1H), 2.33–2.22 (m, 1H), 2.02–1.94 (m, 1H), 1.75 (d, J = 8.2 Hz, 1H), 1.70–1.60 (m, 2H), 1.58–1.47 (m, 1H), 1.38 (s, 4H), 1.25 (s, 2H), 1.16–1.08 (m, 3H), 0.82 (s, 9H). 13C{1H} NMR (126 MHz, DMSO-d6): \(\delta = 157.3, 155.5, 134.9, 132.7, 127.9, 127.7, 127.6, 126.3, 126.2, 125.7, 125.6, 125.4, 125.3, 124.1, 124.0, 119.5, 75.7, 59.3, 53.9, 53.4, 36.1, 34.5, 26.3, 25.4, 25.1. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calc for C33H45N4O3, 545.3492; found, 545.3506.

**Preparation of Ketimines of Glycine Nitroanilides.**

The imine hydrochlorides employed for the study were prepared by adapting literature procedures. Dry diethyl ether (50 mL) was added to a three-necked round-bottom flask equipped with a reflux condenser containing magnesium powder (434 mg, 20 mmol, 1 equiv) and iodine (20 mg). The resulting suspension was heated to mild reflux, and the corresponding bromobenzene was added dropwise (20 mmol, 1 equiv). The resulting mixture was stirred at the same temperature for 2 h, resulting in the dissolution of the magnesium and the darkening of the solution. Then, the corresponding benzonitrile (20 mmol, 1 equiv) was added dropwise to the solution, and the mixture was allowed to stir at the same temperature for 16 h, resulting in the formation of a white salt. Thus, 3-C-ClSiC (2.5 mL, 20 mmol, 1 equiv) was added dropwise with vigorous stirring after removing the heating, and the resulting mixture was stirred at room temperature for 16 h. A brown solid formed as a result, and the mixture was concentrated under reduced pressure and dissolved in benzene in order to filter off the salts. Benzene was then removed under reduced pressure, the resulting crude was dissolved in dry diethyl ether (10 mL), and the mixture was cooled to −78 °C. Then, HCl (2 M in Et2O, 10 mL, 20 mmol, 1 equiv) was added, the resulting suspension was allowed to warm to room temperature over 30 min, and the solid was filtered, washed with diethyl ether, and dried under an IR lamp in order to afford the desired product.

**Preparation of Ketimines of Glycine Nitroanilides.**

Naphthalen-2-yl-methyl(1S,2)-2,2-dimethyl-1-(3-(2S)-2-((piperidin-1-yl)cyclohexyl)ureido)propylcarbamate C5.

The imine hydrochlorides employed for the study were prepared by adapting literature procedures. Dry diethyl ether (50 mL) was added to a three-necked round-bottom flask equipped with a reflux condenser containing magnesium powder (434 mg, 20 mmol, 1 equiv) and iodine (20 mg). The resulting suspension was heated to mild reflux, and the corresponding bromobenzene was added dropwise (20 mmol, 1 equiv). The resulting mixture was stirred at the same temperature for 2 h, resulting in the dissolution of the magnesium and the darkening of the solution. Then, the corresponding benzonitrile (20 mmol, 1 equiv) was added dropwise to the solution, and the mixture was allowed to stir at the same temperature for 16 h, resulting in the formation of a white salt. Thus, 3-C-ClSiC (2.5 mL, 20 mmol, 1 equiv) was added dropwise with vigorous stirring after removing the heating, and the resulting mixture was stirred at room temperature for 16 h. A brown solid formed as a result, and the mixture was concentrated under reduced pressure and dissolved in benzene in order to filter off the salts. Benzene was then removed under reduced pressure, the resulting crude was dissolved in dry diethyl ether (10 mL), and the mixture was cooled to −78 °C. Then, HCl (2 M in Et2O, 10 mL, 20 mmol, 1 equiv) was added, the resulting suspension was allowed to warm to room temperature over 30 min, and the solid was filtered, washed with diethyl ether, and dried under an IR lamp in order to afford the desired product.
quenched with ice-water (100 mL), and the mixture was extracted with EtOAc (4 × 60 mL). The combined organic phases were dried over MgSO₄, and the solvent was evaporated in vacuo. The residue was coevaporated successively with hexane and diethyl ether, and the resulting solid was crushed with diethyl ether and hexane. This afforded a yellow solid. Yield: 68% (2.01 g, 6.8 mmol). Mp: 128–130 °C. "H NMR (300 MHz, CDCl₃): δ 8.05 (dd, J = 8.6, 1.3 Hz, 1H), 7.82 (dd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.26–7.10 (m, 1H), 7.15 (s, 3H), 4.05 (d, J = 6.1 Hz, 2H), 1.57 (s, 3H), 1.53 (s, 6H). 13C{¹H} NMR (75 MHz, CDCl₃): δ 169.6, 136.6, 134.9, 127.0, 126.5, 124.2, 122.7, 81.8, 46.4, 28.9. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]^+ calc for C₂₁H₁₇N₃O₃, 360.1270; found, 360.1274.

N-Deprotection: To a solution of the previous N-Boc aminoamide (3 mmol) in CH₂Cl₂ (12 mL) was added triethylamine (2.4 mmol, 1 equiv) in CH₂Cl₂ (11 mL) were added benzophenone imine (3 mmol, 1 equiv) and anhydrous MgSO₄ (903 mg, 7.5 mmol, 2.5 equiv). The reaction mixture was stirred at room temperature until consumption of the starting material, then filtered to remove the salts, and evaporated in vacuo. The crude was crushed in diethyl ether/hexane to afford a pure yellow solid. Yield: 75% (1.1 g, 2.25 mmol). Mp: 165–168 °C. "H NMR (300 MHz, CDCl₃): δ 11.94 (s, 1H), 8.85 (d, J = 8.5, 1.2 Hz, 1H), 8.26–8.16 (m, 1H), 7.91 (d, J = 8.1 Hz, 4H), 7.78 (d, J = 8.2 Hz, 4H), 7.70–7.60 (m, 1H), 7.23–7.16 (m, 1H), 3.57 (s, 2H). 13C{¹H} NMR (75 MHz, CDCl₃): δ 172.3, 171.6, 139.4, 137.4, 136.7, 135.5, 135.1, 133.2, 130.2, 130.1, 129.9, 129.5, 128.2, 126.9, 124.5, 123.6, 118.8, 116.1, 107.4, 106.7, 105.9, 105.1, 57.9. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]^+ calc for C₁₉H₁₅N₃O₃, 294.1096; found, 294.1092.

N-Boc glycine a-nitroanilide: It was prepared following the same procedure as in the case of iminoamide 1, but starting from p-nitroaniline (1.38 g, 10 mmol) and was obtained as a white solid. Yield: 69% (1.27 g, 3.9 mmol). "H NMR (300 MHz, CDCl₃): δ 8.21 (d, J = 9.2 Hz, 2H), 7.70 (d, J = 9.2 Hz, 2H), 3.95 (d, J = 6.1 Hz, 2H), 1.49 (s, 9H). All data were consistent with those previously reported.34

N-Deprotection: The same protocol as that described for iminoamide 1 was followed starting from N-Boc glycine p-nitroanilide (885 mg, 3 mmol). Yield: quantitative. Mp: 153–155 °C. "H NMR (300 MHz, CDCl₃): δ 8.21 (d, J = 9.2 Hz, 2H), 7.70 (d, J = 9.2 Hz, 2H), 3.95 (d, J = 6.1 Hz, 2H), 1.49 (s, 9H). All data were consistent with those previously reported.34

To a suspension of the free 2-aminon-N-(2-nitrophenyl)acetamide, prepared as in the case of iminoamide 2, (585 mg, 3 mmol) in CH₂Cl₂ (11 mL) were added bis(4-(trifluoromethyl)phenyl)methane iminium hydrochloride (1.06 g, 3 mmol, 1 equiv) and anhydrous MgSO₄ (903 mg, 7.5 mmol, 2.5 equiv). The reaction mixture was stirred at room temperature until consumption of the starting material, then filtered to remove the salts, and evaporated in vacuo. The crude was crushed in diethyl ether/hexane to afford a pure yellow solid. Yield: 75% (1.1 g, 2.25 mmol). Mp: 165–168 °C. "H NMR (300 MHz, CDCl₃): δ 11.94 (s, 1H), 8.85 (d, J = 8.5, 1.2 Hz, 1H), 8.26–8.16 (m, 1H), 7.91 (d, J = 8.1 Hz, 4H), 7.78 (d, J = 8.2 Hz, 4H), 7.70–7.60 (m, 1H), 7.23–7.16 (m, 1H), 3.57 (s, 2H). 13C{¹H} NMR (75 MHz, CDCl₃): δ 169.5, 168.5, 140.5, 139.0, 136.9, 134.2, 129.0, 127.5, 125.6, 125.9, 125.6, 125.5, 123.6, 122.3, 57.6. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]^+ calc for C₁₉H₁₅N₃O₃F₂, 496.1096; found, 496.1102.

2-((Bis(3,5-bis(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3.

N-Boc glycine p-nitroanilide: It was prepared following the same procedure as in the case of iminoamide 1, but starting from p-nitroaniline (1.38 g, 10 mmol) and was obtained as a white solid. Yield: 69% (1.27 g, 3.9 mmol). "H NMR (300 MHz, CDCl₃): δ 8.21 (d, J = 9.2 Hz, 2H), 7.70 (d, J = 9.2 Hz, 2H), 3.95 (d, J = 6.1 Hz, 2H), 1.49 (s, 9H). All data were consistent with those previously reported.34
N-Boc glycine 2,4-dinitroaryl.:43 Boc-Gly-OH (1.05 g, 6 mmol, 1 equiv) was dissolved in dry DMF (14 mL), and DIPEA (5.2 mL, 30 mmol, 6 equiv) was added at room temperature. Then, 2,4-dinitroaniline (920 mg, 5 mmol, 1 equiv) was added, followed by HATU (2.0 g, 5.5 mmol, 1 equiv). The mixture was stirred at room temperature for 16 h. Then, a solution of EtOAc/H2O (1:1) was added to the reaction mixture, and it was extracted with EtOAc (3 × 50 mL), washed with brine (5 × 30 mL), dried over MgSO4, evaporated under reduced pressure, and purified by flash column chromatography on silica gel (hexane/EtOAc, 90:10) to afford the pure product as a yellow solid. Yield: 77% (1.31 g, 3.85 mmol). Mp: 168–188 °C. 1H NMR (300 MHz, CDCl3): δ 11.39 (s, 1H), 9.12–9.02 (m, 2H), 8.43 (dd, δ = 9.4, 2.6 Hz, 1H), 5.53 (s, δ = 5.7 Hz, 1H), 4.01 (dd, δ = 6.1 Hz, 2H), 1.45 (s, 9H). 13C{1H} NMR (75 MHz, CDCl3): δ 169.8, 164.2, 142.0, 139.3, 135.3, 130.2, 122.3, 122.1, 81.5, 46.0, 28.3. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + Na]+ calcd for C13H14N4O5Na, 363.0917; found, 363.0911.

N-Deprotection: To a solution of the previously obtained N-Boc aminoacid (1.02 g, 3 mmol) in CH2Cl2 (12 mL) was added trifluoroacetic acid (4.5 mL) at 0 °C. The mixture was stirred at room temperature for 30 min until full conversion. The solvents were evaporated, and the residue was coevaporated successively with a mixture of diethyl ether and pentane. Then it was dried in vacuo, and the resulting solid, which was obtained in a quantitative yield, was used in the next step without further purification. Yield: quantitative. Mp: 146–150 °C. 1H NMR (300 MHz, CDCl3): δ 8.97 (d, δ = 2.6 Hz, 1H), 8.57–8.42 (m, 1H), 8.25 (d, δ = 9.2 Hz, 1H), 4.11 (s, 2H). 13C{1H} NMR (75 MHz, CDCl3): δ 166.8, 144.3, 139.3, 136.3, 129.4, 125.4, 121.9, 41.7. UPLC-DAD-QTOF, HRMS (ESI, measured after neutralization) m/z: [M + Na]+ calcd for C13H14N4O5Na, 263.0392; found, 263.0403.

Aminoamide formation: To a suspension of the aminoacid triftluoroacetic salt obtained in the previous step (1.06 g, 3 mmol, 1 equiv) in CH2Cl2 (11 mL) were added benzophenone imine (0.34 mL, 2 mmol, 1 equiv), and the resulting solution was refluxed for 5 h. The mixture was then cooled, dissolved in CH2Cl2 (20 mL), and washed with aqueous 5% NaHCO3 (20 mL). The water phase was extracted with CH2Cl2 (30 mL), and the organic phases were combined and dried over MgSO4. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography on silica gel (eluting with hexane/EtOAc 70:30) to afford the desired product as a viscous orange oil in 70% yield (520 mg, 1.39 mmol). 1H NMR (300 MHz, CDCl3): δ 7.90–7.87 (m, 1H), 7.74–7.57 (m, 2H), 7.54–7.42 (m, 3H), 7.43–7.16 (m, 7H), 7.05–6.95 (m, 1H), 3.92 (s, 2H), 3.25 (s, 3H); Minor rotamer: δ 8.00–7.87 (m, 1H), 7.74–7.57 (m, 2H), 7.54–7.42 (m, 3H), 7.43–7.16 (m, 7H), 7.05–6.95 (m, 1H), 3.92 (s, 2H), 3.35 (s, 3H); 13C{1H} NMR (75 MHz, CDCl3), mixture of rotamers: δ 171.2, 169.2, 146.4, 139.0, 136.8, 135.5, 134.0, 131.5, 130.8, 130.3, 129.4, 129.8, 128.7, 128.6, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 125.5, 125.0, 124.0, 114.1, 56.9, 56.4, 53.4, 38.2, 37.1, 29.5. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C21H17N4O5, 373.1426; found, 373.1425.

Preparation of Benzophenone Imine of Glycine Methyl Ester 13.47 To a suspension of glycine ester hydrochloride (377 mg, 3 mmol, 1 equiv) in DCN (6 mL) was added benzophenone imine (0.5 mL, 3 mmol, 1 equiv). Triethylamine (0.42 mL, 3 mmol, 1 equiv) was then added dropwise, and the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by 1H NMR). The mixture was then diluted with EtO (6 mL), filtered, and washed with H2O (3 × 10 mL) and brine (3 × 10 mL). The combined organic layers were dried over MgSO4 and evaporated to dryness. The crude was obtained with a quantitative yield (759 mg, 3 mmol) and was used without further purification. All of the spectroscopic data were coincident with those described in the literature.45 1H NMR (300 MHz, CDCl3): δ 7.74–7.61 (m, 2H), 7.56–7.42 (m, 4H), 7.43–7.29 (m, 3H), 7.25–7.14 (m, 1H), 4.25 (s, 2H), 3.77 (s, 3H).

Preparation of α-Pyridyl and Phenyl Acetanilides 18–21. Synthesis of 2-(Pyridin-2-yl)acetanilides. General Procedure.
The compound was prepared according to the general procedure starting from 2-(bis(3,5-bis(trifluoromethyl)phenyl)methylene)aminoo-N-(2-nitrophenyl) acetamide 1 (72 mg, 0.2 mmol) and hydrocinnamaldehyde 4a (80 μL, 0.6 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc; 90:10) to afford 5a as a yellow oil. Yield: 71% (70 mg, 0.14 mmol). [α]D20 = +13 (c 1.35, 94% ee, CHCl3). 1H NMR (300 MHz, CDCl3): δ 11.77 (s, 1H), 8.72 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 10.0 Hz, 1H), 7.60 (t, J = 8.6 Hz, 1H), 7.52–7.45 (m, 2H), 7.46–7.31 (m, 4H), 7.31–7.05 (m, 9H), 4.91 (s, 12H), 4.07 (m, 1H), 3.32 (d, J = 3.9 Hz, 2H), 2.86 (m, 1H), 2.67 (m, 1H), 1.88 (m, 1H). 13C{1H} NMR (75 MHz, CDCl3): δ 173.6, 143.0, 142.4, 141.4, 137.1, 135.7, 134.0, 129.0, 128.8, 128.7, 128.6, 127.8, 127.6, 127.4, 126.2, 125.9, 123.7, 122.3, 72.1, 66.8, 65.0, 35.4, 32.4. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C30H30N3O4, 496.2233; found, 496.2236. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/ethanol 90:10; flow rate = 0.5 mL/min; retention times: 18 min (major) and 40 min (minor)).

(25R,3R)-2-(Benzhydrolamino)-3-hydroxy-N-(2-nitrophenyl)-5-phenylpentanamide 6a.

The compound was prepared according to the general procedure starting from 2-(bis(3,5-bis(trifluoromethyl)phenyl)methylene)aminoo-N-(2-nitrophenyl) acetamide 1 (72 mg, 0.2 mmol) and hydrocinnamaldehyde 4a (80 μL, 0.6 mmol) and was isolated by flash column chromatography on silica gel (hexane/EtOAc; 90:10) to afford 6a as a yellow oil. Yield: 77% (70 mg, 0.14 mmol). [α]D20 = 20.8 (c 1, 92% ee, CHCl3). 1H NMR (300 MHz, CDCl3): δ 11.76 (s, 1H), 8.83–8.60 (m, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.71–7.58 (m, 5H), 7.52 (d, J = 1.8 Hz, 4H), 7.36–7.23 (m, 3H), 7.24–7.12 (m,
The compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and hexanal 4d (74 μL, 0.66 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to afford 7c as a yellow oil. Yield: 80% (98 mg, 0.16 mmol). 1H NMR (300 MHz, CDCl3): δ 8.4 (d, J = 8.5 Hz, 1H), 7.86 (s, 4H), 7.66 (q, J = 8.5 Hz, 4H), 7.22 (t, J = 7.8 Hz, 1H), 5.10 (s, 1H), 4.13 (s, 1H), 3.37–3.19 (m, 1H), 1.71–1.47 (m, 2H), 1.41–1.20 (m, 8H), 1.04–0.76 (m, 3H). 13C{1H} NMR (75 MHz, CDCl3): δ 173.5, 146.7, 146.3, 137.5, 136.5, 134.6, 131.0 (q, J = 32.4 Hz), 128.6, 128.2, 126.8, 126.7, 126.5, 126.4, 122.4, 122.2, 73.4, 66.9, 63.8, 34.6, 32.4, 29.8, 26.6, 23.2, 14.7. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calc for C26H24F6N3O4 556.1671; found, 556.1670. The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3 μm i-Cellulose) hexane/isopropanol 95:5, flow rate = 0.5 mL/min. Retention times: major diastereoisomer, 23 min (major) and 29 min (minor); major diastereoisomer, 43 min (minor) and 46 min (major).

(25,3R)-2-(( Bis(4- trifluoromethyl)phenyl) methyl)amino)-3hydroxy-N-(2-nitrophenyl)hexanamide 7e.

The compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and heptanal 4e (84 μL, 0.66 mmol) and was isolated by flash column chromatography on silica gel (hexane/EtOAc, 94:6) as a yellow oil. Yield (diastereomeric ratio 98:2): 76% (95 mg, 0.15 mmol). 1H NMR (300 MHz, CDCl3): δ 11.80 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 9.5 Hz, 1H), 7.65 (d, J = 9.3 Hz, 5H), 7.53 (q, J = 8.4 Hz, 4H), 7.21 (t, J = 7.8 Hz, 1H), 5.11 (s, 1H), 4.05 (d, J = 7.9 Hz, 1H), 3.26 (d, J = 3.1 Hz, 1H), 2.93 (s, 3H), 2.43 (s, 1H), 1.65 (dq, J = 15.0, 7.0 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H). 13C{1H} NMR (75 MHz, CDCl3), major diastereomer: δ 172.7, 146.0, 145.6, 136.8, 135.8, 133.9, 130.5 (q), 128.0, 127.5, 126.1, 126.0, 125.8, 123.7, 121.9, 74.2, 66.2, 64.9, 26.9, 10.4. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calc for C30H32F6N3O4 556.1670. The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3 μm i-Amlose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate = 0.5 mL/min. Retention times: minor diastereoisomer, 31 min (major) and 39 min (minor); major diastereoisomer, 43 min (minor) and 46 min (major).

(25,3R)-2-(( Bis(4- trifluoromethyl)phenyl) methyl)amino)-3-hydroxy-5-methyl-N-(2-nitrophenyl)hexanamide 7f.

The compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and hexanal 4f (64 μL, 0.66 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to afford 7f as a yellow oil. Yield: 78% (91 mg, 0.16 mmol). 1H NMR (300 MHz, CDCl3): δ 11.80 (s, 1H), 8.75 (d, J = 8.5, 12.2 Hz, 1H), 8.23 (dd, J = 8.5, 1.5 Hz, 1H), 7.66 (s, 4H), 7.65–7.60 (m, 1H), 7.54 (q, J = 8.5 Hz, 4H), 7.21 (t, J = 5.10 (s, 1H), 4.13 (s, 1H), 4.05 (d, J = 32.4 Hz), 128.6, 128.2, 126.8, 126.7, 126.5, 126.4, 122.4, 122.2, 73.4, 66.9, 63.8, 34.6, 32.4, 29.8, 26.6, 23.2, 14.7. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calc for C26H24F6N3O4 556.1671; found, 556.12298; found, 556.12279. The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3 μm i-Cellulose) hexane/isopropanol 95:5, flow rate = 0.5 mL/min. Retention times: major diastereoisomer, 19 min (major) and 21 min (minor); major diastereoisomer, 23 min (major) and 29 min (minor).

The compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene) amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and hexanal 4d (74 μL, 0.66 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to afford 7e as a yellow oil. Yield: 78% (91 mg, 0.16 mmol). 1H NMR (300 MHz, CDCl3): δ 11.80 (s, 1H), 8.75 (d, J = 8.5, 12.2 Hz, 1H), 8.23 (dd, J = 8.5, 1.5 Hz, 1H), 7.66 (s, 4H), 7.65–7.60 (m, 1H), 7.54 (q, J = 8.5 Hz, 4H), 7.21 (t, J = 5.10 (s, 1H), 4.13 (s, 1H), 4.05 (d, J = 32.4 Hz), 128.6, 128.2, 126.8, 126.7, 126.5, 126.4, 122.4, 122.2, 73.4, 66.9, 63.8, 34.6, 32.4, 29.8, 26.6, 23.2, 14.7. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calc for C30H32F6N3O4 556.1670. The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3 μm i-Amlose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate = 0.5 mL/min. Retention times: minor diastereoisomer, 31 min (major) and 39 min (minor); major diastereoisomer, 43 min (minor) and 46 min (major).
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The compound was prepared according to the general procedure starting from 2-(bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and tert-butyl (2-hydroxy-4-((2-nitrophenyl)amino)-4-oxobutyl)carbamate 4i (130 mg, 0.6 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc 80:20) to afford 7i as a yellow oil. Yield: 63% (0.13 mmol). δ 1.87 (s, 1H), 8.73 (d, J = 9.8 Hz, 1H), 7.65 (s, 4H), 7.41 (t, J = 7.3 Hz, 1H), 7.58–7.47 (m, 4H), 7.20 (t, J = 8.4 Hz, 1H), 5.09 (s, 1H), 4.66–4.44 (m, 1H), 4.08 (s, 1H), 3.07 (s, 2H), 1.68–1.55 (m, 3H), 1.41 (s, 9H), 1.36–1.12 (m, 5H). 13C{1H} NMR (75 MHz, CDCl3): δ 172.9, 156.4, 154.2, 154.5, 136.9, 135.9, 134.2, 134.1, 130.3 (q, J = 147.8 Hz), 128.1, 127.7, 126.2, 126.1, 125.9, 125.7, 123.7, 122.0, 72.3, 69.2, 66.2, 65.3, 33.2. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C29H28F6N3O4, 596.1984; found, 596.1989. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 90:10, flow rate = 0.5 mL/min, retention times: 26 min (minor) and 29 min (major)).

tert-Butyl (2R,3S)-3-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-2-hydroxy-4-((2-nitrophenyl)amino)-4-oxobutyl)carbamate 7i.

The title compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and tert-butyl (6-oxoethyl)carbamate 4i (130 mg, 0.6 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to afford 7i as a yellow oil. Yield: 63% (0.13 mmol). δ 1.87 (s, 1H), 8.73 (d, J = 9.8 Hz, 1H), 7.65 (s, 4H), 7.41 (t, J = 7.3 Hz, 1H), 7.58–7.47 (m, 4H), 7.20 (t, J = 8.4 Hz, 1H), 5.09 (s, 1H), 4.66–4.44 (m, 1H), 4.08 (s, 1H), 3.07 (s, 2H), 1.68–1.55 (m, 3H), 1.41 (s, 9H), 1.36–1.12 (m, 5H). 13C{1H} NMR (75 MHz, CDCl3): δ 172.9, 156.4, 154.2, 154.5, 136.9, 135.9, 134.2, 134.1, 130.3 (q, J = 147.8 Hz), 128.1, 127.7, 126.2, 126.1, 125.9, 125.7, 123.7, 122.0, 72.3, 69.2, 66.2, 65.3, 33.2. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C29H28F6N3O4, 596.1987; found, 596.2000. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 90:10, flow rate = 0.5 mL/min, retention times: 26 min (minor) and 29 min (major)).

The compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and tert-butyl (6-oxoethyl)carbamate 4i (130 mg, 0.6 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to afford 7i as a yellow oil. Yield: 63% (0.13 mmol). δ 1.87 (s, 1H), 8.73 (d, J = 9.8 Hz, 1H), 7.65 (s, 4H), 7.41 (t, J = 7.3 Hz, 1H), 7.58–7.47 (m, 4H), 7.20 (t, J = 8.4 Hz, 1H), 5.09 (s, 1H), 4.66–4.44 (m, 1H), 4.08 (s, 1H), 3.07 (s, 2H), 1.68–1.55 (m, 3H), 1.41 (s, 9H), 1.36–1.12 (m, 5H). 13C{1H} NMR (75 MHz, CDCl3): δ 172.9, 156.4, 154.2, 154.5, 136.9, 135.9, 134.2, 134.1, 130.3 (q, J = 147.8 Hz), 128.1, 127.7, 126.2, 126.1, 125.9, 125.7, 123.7, 122.0, 72.3, 69.2, 66.2, 65.3, 33.2. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C29H28F6N3O4, 596.1987; found, 596.2000. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 90:10, flow rate = 0.5 mL/min, retention times: 26 min (minor) and 29 min (major)).

The compound was obtained following the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide 3 (99 mg, 0.2 mmol) and tert-butyl 4-oxobutan-2-one 4d (96 mg, 0.6 mmol, 3 equiv) and was isolated by flash column chromatography on silica gel (hexane/EtOAc, 80:20) as a yellow foam. Yield (diastereomeric ratio 97:3): 63% (57 mg, 0.13 mmol). δ 1.87 (s, 1H), 8.73 (d, J = 9.8 Hz, 1H), 7.65 (s, 4H), 7.41 (t, J = 7.3 Hz, 1H), 7.58–7.47 (m, 4H), 7.20 (t, J = 8.4 Hz, 1H), 5.09 (s, 1H), 4.66–4.44 (m, 1H), 4.08 (s, 1H), 3.07 (s, 2H), 1.68–1.55 (m, 3H), 1.41 (s, 9H), 1.36–1.12 (m, 5H). 13C{1H} NMR (75 MHz, CDCl3): δ 172.9, 156.4, 154.2, 154.5, 136.9, 135.9, 134.2, 134.1, 130.3 (q, J = 147.8 Hz), 128.1, 127.7, 126.2, 126.1, 125.9, 125.7, 123.7, 122.0, 72.3, 69.2, 66.2, 65.3, 33.2. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]+ calcd for C30H29F6N3O4, 655.2199; found, 655.2202. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Phenomenex Amilose-1, hexane/isopropanol, 98:2, flow = 1 mL/min; retention times for major diastereomer: 44.4 min (minor), 62.4 min (major)).
The compound was prepared according to the general procedure starting from N-(2-nitrophenyl)-2-(pyridin-2-yl)acetic acid 18 (51 mg, 0.2 mmol) and was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to afford the title product as a yellow oil and as a 50:50 mixture of diastereoisomers. For the mixture of the diastereoisomers follows: Yield: 64% (55 mg, 0.13 mmol). \( ^1H \) NMR (300 MHz, chloroform-\( d_2 \)): \( \delta 8.11, J = 13.0 \text{ Hz}, 1 \text{H}, 8.85−8.71 \text{ (m, 1H), 8.71−8.54 \text{ (m, 1H), 8.32−8.07 \text{ (m, 1H), 7.80−7.55 \text{ (m, 3H), 7.25 (dt, J = 6.6, 1.5 Hz, 2H), 7.22−7.14 \text{ (m, 3H), 7.13−7.08 \text{ (m, 1H), 5.95−5.66 \text{ (m, 1H), 4.24−3.95 \text{ (m, 1H), 3.02−2.47 \text{ (m, 4H), 2.08 \text{ (s, 3H).}} \)\( ^13C \) \( ^1H \) NMR (75 MHz, CDCl\( _3 \))\): \( \delta 171.3, 170.3, 150.4, 149.9, 145.3, 144.6, 138.7, 136.6, 129.3, 129.3, 127.1, 127.0, 126.6, 125.3, 124.4, 124.2, 123.8, 123.6, 122.6, 75.9, 61.8, 36.5, 35.3, 32.4, 22.3. UPLC-DAD-QTOF, HRMS (ESI) \( m/z: [M + H]^+ \) \text{calcd for C}_{38}H_{35}N_{10}O_{11}, 541.2087; found, 541.2076. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF hexane/ethanol 90/10, flow rate = 1.0 mL/min, retention times: 16 min (minor) and 17 min (major)). General Procedure for the Racemic Reactions of Schiff Bases of Glycine Nitroanilide. The corresponding nitroanilide (0.2 mmol, 1 equiv) and 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (0.02 mmol, 20 mol %) were dissolved in dry dichloromethane (0.5 mL) at room temperature. To the mixture was added Et\( _3 \)N (0.02 mmol, 20 mol %), followed by the corresponding aldehyde (0.6 mmol, 3 equiv). The reaction mixture was stirred at room temperature until consumption of the starting material (monitored by \( ^1H \) NMR). To the reaction mixture was added MeOH (0.4 mL), followed by NaBH\( \text{CN} \) (32 mg, 0.5 mmol, 2.5 equiv) and AcOH (24 \( \mu \)L, 0.4 mmol, 2 equiv). The reaction mixture was stirred for 2 h (the reduction of the imine can be followed by \( ^1H \) NMR). The solvents were evaporated under reduced pressure, and the resulting residue was redissolved in dichloromethane and washed with a saturated NaHCO\( _3 \) solution (1 \( \times \) 4 mL). The organic phase was dried over MgSO\( _4 \) and evaporated in vacuo. The crude was purified by flash column chromatography on silica gel. General Procedure for the Aldol Reaction of \( \alpha \)-Pyridyl and Phenyl Acetanilides. To a solution of the corresponding acetanilide (0.2 mmol, 1 equiv) and Et\( _3 \)N (0.02 mmol, 20 mol %) in dry dichloromethane (0.5 mL) was added freshly distilled hydrocinnamaldehyde (80 \( \mu \)L, 0.6 mmol, 3 equiv) (previously washed with a saturated NaHCO\( _3 \) solution) at room temperature. The reaction mixture was stirred at the same temperature until consumption of the starting material (followed by \( ^1H \) NMR). To the reaction mixture was added pyridine/acetic anhydride (2:1, 0.40 mmol), and the resulting mixture was stirred at room temperature overnight. The mixture was then washed with 1 M HCl (1 \( \times \) 4 mL) and saturated NaHCO\( _3 \) solution (1 \( \times \) 4 mL). The organic phase was dried over MgSO\( _4 \) and evaporated in vacuo. 1-[(2-Nitrophenyl)amino]-1-oxo-5-phenyl-2-(pyridin-2-yl)pentan-3-yl acetate 22. The general procedure was followed starting from N-(4-nitrophenyl)-2-(pyridin-2-yl)acetamide 19 (51 mg, 0.2 mmol). After 48 h at rt, the formation of the aldols as a 50:50 mixture of diastereoisomers was observed (50% conversion). The aldols were not isolated. See the \( ^1H \) NMR spectrum of the crude in the Supporting Information. 3-Hydroxy-N,5-diphenyl-2-(pyridin-2-yl)pentanamide 24. The general procedure was followed starting from N-phenyl-2-(pyridin-2-yl)acetamide 20 (42 mg, 0.2 mmol). After 48 h at rt, the formation of a 50:50 diastereomeric mixture of the aldols was observed (33% conversion). The aldols were not isolated. See the \( ^1H \) NMR spectrum of an aliquote in the Supporting Information. General Procedure for the Control Experiments. The corresponding compounds 13−15 (0.2 mmol, 1 equiv) and the corresponding catalyst (0.02 mmol, 20 mol %) were dissolved in dry dichloromethane (0.5 mL) at room temperature, and hydrocinnamaldehyde (0.6 mmol, 3 equiv) was added. When reaction was observed, the work-up described in the general procedure for the asymmetric aldol reactions was followed. Stability of the Reaction Adducts. Imine Hydrolysis and Amine Protection: Synthesis of 10. (25,3R)-2-Amino-3-hydroxy-N-(2-nitrophenyl)-5-phenylpentanamide 9. The isolated product 7a (0.1 mmol, 1 equiv) was dissolved in dry dichloromethane (0.3 mL), and butyraldehyde 4c (0.3 mmol, 3 equiv) was added, followed by the achiral catalyst (10 mg, 0.02 mmol, 20 mol %) and triethylamine (3 \( \mu \)L, 0.02 mmol, 20 mol %). The reaction mixture was stirred at room temperature for 24 h. The crude was purified by flash column chromatography on silica gel. Elaboration of Adducts. The aldol adduct, previous to reduction, (0.2 mmol, 1 equiv) was dissolved in THF (5 mL), and 1 M HCl (0.68 mL, 0.68 mmol, 3.4 equiv) was added at 0 °C. The mixture was stirred at the same temperature for 2 h. Then, after reaction completion (monitored by \( ^1H \) NMR), the solvent was evaporated under reduced pressure, and NaHCO\( _3 \) (sat) was added until pH 8−9. The mixture was extracted with \( \text{CH}_2_2 \) (3 × 10 mL), and brine (10 mL) was added to the aqueous phase, which was extracted again with \( \text{CH}_2_2 \) (3 × 5 mL). The combined organic layers were dried over MgSO\( _4 \) and evaporated under reduced pressure. The crude was used in the next step without further purification. Yield: 80% (52 mg, 0.16 mmol). \( [\alpha]_D^{25} = −8.1 (\epsilon = 2, 94\% \text{ ee, CH}_2Cl_2) \). \( ^1H \) NMR (300 MHz, CDCl\( _3 \)): \( \delta 12.06 (s, 1 \text{H}), 8.79 (d d, J = 8.5 \text{ Hz, 1H), 8.18 (dd, 1H), 7.63 (td, J = 7.6 \text{ Hz, 1H), 7.46−7.01 \text{ (m, 5H), 4.41−4.22 \text{ (m, 1H), 3.46 (d, J = 2.5 \text{ Hz, 1H), 2.95−2.83 \text{ (m, 1H), 2.83−2.61 \text{ (m, 1H), 2.01−1.72 \text{ (m, 2H).}} \)\( ^13C \) \( ^1H \) NMR (75 MHz, CDCl\( _3 \)): \( \delta 173.8, 141.6, 135.7, 134.2, 128.7, 128.6, 126.3, 125.9, 123.6, 122.2, 71.3, 60.0, 55.4, 32.4. UPLC-DAD-QTOF, HRMS (ESI) \( m/z: [M + H]^+ \) \text{calcd for C}_{15}H_{12}N_2O_4, 330.1454; found, 330.1462.
Aminoalcohol 9 (0.2 mmol, 1 equiv) was dissolved in dry THF (1 mL), and 4-bromobenzoyl chloride (0.2 mmol, 1 equiv) was added in one portion, followed by slow addition of triethylamine (0.65 mL, 4.6 mmol, 23 equiv). The reaction mixture was stirred at room temperature for 2 h until complete conversion of the starting material. Then the solvent was evaporated, and the residue was redissolved in dichloromethane, washed with water, and extracted with dichloromethane (2 × 5 mL). The combined organic phases were dried over MgSO₄ and evaporated in vacuo. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 90:10) and affored 10 as a white solid. Yield: 75% (76 mg, 0.15 mmol). Mp: 145–147 °C. [α]D²⁰ = −7.4 (c 2, 92% ee, CH₃Cl). 

H NMR (300 MHz, CDCl₃): δ 11.07 (s, 1H), 8.66 (dd, 1H), 8.16 (dd, J = 8.4, 1.4 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.38–7.12 (m, 6H), 4.92 (s, J = 9.7 Hz, 1H), 4.54–4.39 (m, 1H), 2.86 (s, 1H), 2.78–2.60 (m, 1H), 1.86 (q, J = 8.4 Hz, 2H). 

13C{1H} NMR (75 MHz, CDCl₃): δ 170.1, 167.5, 141.1, 137.2, 135.8, 133.7, 132.2, 129.1, 128.7, 128.5, 127.3, 126.3, 125.9, 124.1, 122.6, 70.3, 58.7, 34.8, 32.1. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₂₃BrN₃O₅; found, 696.3281.

Anilide Cleavage.⁵⁹

Compound 7a (0.2 mmol) was dissolved in dry acetonitrile (0.3 mL), and DMAP (8 mg, 0.06 mmol, 30 mol %) was added, followed by di-tert-butyl dicarbonate (280 mg, 1.2 mmol, 6 equiv). The solution was stirred at room temperature for 16 h. Then, the solvent was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to afford the crude product 11 as a yellow oil. Yield: 88% (122 mg, 0.18 mmol). [α]D²⁰ = −7.9 (c 2, 92% ee, CH₃Cl). 

H NMR (300 MHz, CDCl₃): δ 8.14 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.3 Hz, 2H), 7.56–7.48 (m, 1H), 7.47–7.39 (m, 2H), 7.37–7.07 (m, 13H), 5.25 (t, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 2.79–2.66 (m, 1H), 2.62–2.44 (m, 2H), 2.24–1.98 (m, 1H), 1.41 (s, 9H), 1.19 (s, 9H).

13C{1H} NMR (75 MHz, CDCl₃): δ 176.0, 153.8, 150.6, 145.9, 144.5, 143.1, 141.6, 134.0, 131.7, 129.1, 128.6, 128.5, 127.3, 127.0, 126.0, 125.2, 84.9, 82.3, 76.9, 65.4, 62.2, 33.5, 31.8, 27.9, 27.5. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₀H₁₇BrNO₅; found, 469.3285; 696.3285.

The previous crude product 11 (139 mg, 0.2 mmol) was dissolved in THF/H₂O (3:1, 2 mL). Then, LiOH·H₂O (9 mg, 0.4 mmol, 2 equiv) and 30% H₂O₂ (22 µL, 1 mmol, 5 equiv) were added at 0 °C. The reaction mixture was stirred at room temperature for 48 h, and Na₂SO₄ (252 mg, 2 mmol, 10 equiv) was added. The mixture was then diluted with EtOAc, acidified with 0.5 M HCl, and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (hexane/EtOAc, 80:20) to afford 12 as a yellow oil. Yield: 82% (77 mg, 0.16 mmol). [α]D²⁰ = −9.1 (c 1, 91% ee, CH₃Cl). 

H NMR (300 MHz, CDCl₃): δ 7.48–7.34 (m, 3H), 7.33–6.85 (m, 12H), 5.12–5.02 (m, 1H), 4.88 (s, 1H), 3.33 (d, J = 3.1 Hz, 1H), 2.76–2.58 (m, 1H), 2.58–2.45 (m, 1H), 2.32–2.15 (m, 1H), 2.14–1.90 (m, 1H), 1.46 (s, 9H). 

13C{1H} NMR (75 MHz, CDCl₃): δ 176.2, 153.1, 143.4, 142.3, 141.0, 128.9, 128.8, 128.6, 128.5, 127.8, 127.6, 127.3, 126.6, 126.3, 82.8, 65.9, 61.0, 33.3, 31.8, 29.9, 27.8. UPLC-DAD-QTOF, HRMS (ESI) m/z: [M + H]⁺ calcd for C₁₀H₈NO₄; 476.2437; found, 476.2437.

X-ray Crystallography. Crystals suitable for X-ray crystallography were obtained by crystallization of I from C₂H₅OH of 3 from Et₃O/CHCl₃, and of 10 from CH₂CN. Each sample was dissolved in the minimum amount of the indicated solvent at rt and was allowed to crystallize slowly at the same temperature. Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu Kα radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurements were carried out at 150.01(10) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration, and correction for Lorentz and polarization effects) using the Crysalis software package.⁵⁶,⁵⁷ The structure was solved using SHELXTL⁵¹ and refined by full-matrix least-squares with SHELXL-97.⁵²,⁵³ Final geometrical calculations were carried out with Mercury⁵⁸ and PLATON⁵⁴ as integrated in WinGX.⁵⁵ Complete structural data have been deposited with the Cambridge Crystallographic Data Centre.⁵⁶,⁵⁷

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00406.

Catalyst screening data; X-ray diffraction data for 1, 3, and 10; computational data for the E and Z enolates of ketimine 3; spectroscopic data for all new compounds including ¹H and ¹³C NMR spectra; HPLC chromatograms of all the aldol adducts (PDF)

Accession Codes

CCDC 1977378, 1977381, and 2064298 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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