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Large Scale Synthesis of Chiral (3*Z*,5*Z*)-2,7-Dihydro-1*H*-azepine-Derived Hamari Ligand for General Asymmetric Synthesis of Tailor-Made Amino Acids

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Supporting Information

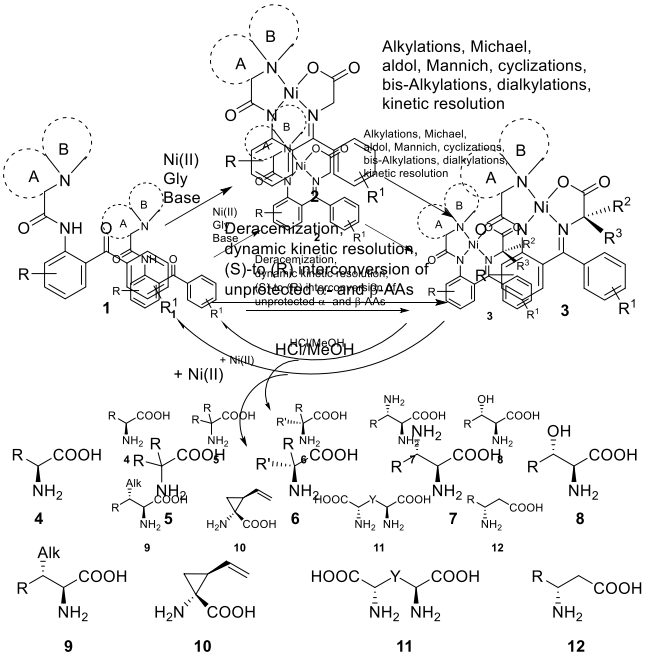
ABSTRACT: An advanced process for large scale (500 g) preparation of a (3*Z*,5*Z*)-2,7-dihydro-1*H*-azepine-derived chiral tridentate ligand (Hamari ligand), widely used for asymmetric synthesis of tailor-made α-amino acids via the corresponding glycine Schiff base Ni(II) complex, is disclosed. The process includes amidation, bis-alkylation, and precipitation/purification of the target compound by TFA as a counterion.

KEYWORDS: *Chiral tridentate ligands, binaphthyl, axial chirality, asymmetric synthesis, tailor-made amino acids*

INTRODUCTION

Amino acids (AAs) are among a few biologically privileged molecules principally involved in basic aspects of the phenomenon of life. From the early days of emerging chemistry sciences AAs played a major role in the development of organic, bio-organic, medicinal, and pharmaceutical fields, shaping the contemporary healthcare industry.[1] In fact, over past two decades, tailor-made α-AAs[2] became essential structural features of numerous modern pharmaceutical drugs and medicinal formulations.[3] The use of tailor-made α-AA residues in bioactive compounds design provides a convenient and reliable means for the 3D positioning of pharmacophoric groups with reasonable accuracy, thereby facilitating the targeted desired peptide−receptor interactions.[4,5] One of the most recent, emerging areas of tailor-made AAs applications is the biological-containment strategy in the produced genetically modified organisms.[6] Consequently, interest in asymmetric synthesis of tailor-made amino acids[7] and their analogs, such as fluorine-containing,[8] amino sulfonic[9] and phosphonic[10] acids, is at an all-time high, focusing on novel structural motifs, functions, and properties. Our long-standing interests in the development of general methods for asymmetric synthesis of various tailor-made AAs include fluorine-[11] and phosphorus-containing,[12] sterically constrained[13] derivatives, as well as nonlinear chiroptical properties of AA, such as self-disproportionation of enantiomers.[14] In particular, we were actively contributing to the advancement of the chemistry of Ni(II) complexes of AA Schiff bases[4d,7d,e,8b] as a general approach for preparation of tailor-made AAs in enantiomerically pure form (Scheme 1).

Scheme 1. General Methodology for Asymmetric Synthesis of α- and β-AAs via Ni(II) Complexes of Schiff Bases



As shown in Scheme 1, generically represented tridentate ligands (*S*)- or (*R*)-**1** are reacted with glycine and a source of Ni(II) ions to produce Schiff base complex **2**, serving as a versatile chiral nucleophilic glycine equivalent. Square-planar Ni(II) complex **2** readily reacts with various electrophilic reagents to afford products **3** with usually high chemical yields

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and diastereoselectivity. Commonly used reaction types include, but are not limited to, alkyl halide alkylations[15] and Michael,[16] aldol,[17] and Mannich[18] addition reactions. This method can be used for the preparation of common-type α-AAs **4**, sym-**5**,[19] or chiral quaternary α-AAs **6**,[20] α-functionalized **7** and **8**, and α-alkyl-substituted derivatives **9**. More structurally complex AAs, such as (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid **10**[21] or bis-α-AAs of type **11**,[22] can also be readily constructed using this methodology. Furthermore, ligands **1** can be directly reacted with unprotected AAs to perform deracemization, dynamic kinetic resolution, or (*S*)-to (*R*) interconversion of unprotected α-**4**[23] and β-**12** AAs.[24] Intermediate products **3** can be disassembled under operationally convenient conditions to release target AAs **4**−**12** along with recycling of the chiral tridentate ligands **1**.

Most recently, using the modular approach[25] for the design of chiral tridentate ligands, we developed a series of new ligands, represented by types **13**−**16** (Figure 1). As was shown

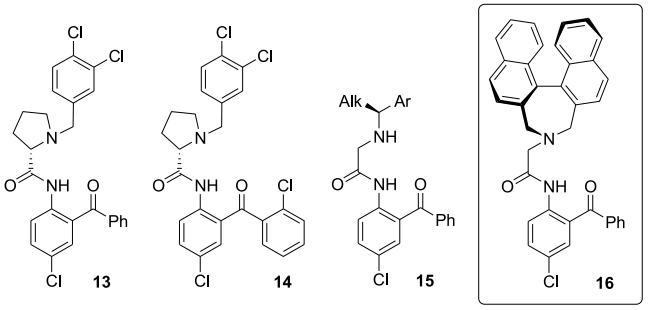


Figure 1. New structural types of chiral tridentate ligands **13**−**16**.

in recent work,[24] the aromatic chlorine on the benzophenone moiety is of great importance for the stereocontrolling properties of these ligands. Proline and chiral secondary amine derived ligands **13**,[26] **14**,[27] and **15**,[28] respectively, perform quite well for most of the homologation reactions, yet they are susceptible to partial racemization under strongly basic reaction conditions. Therefore, the design and development of axially chiral ligand **16**, the Hamari ligand, was considered as a major innovation in this field.

In fact, Hamari ligand **16** was shown to induce a synthetically useful level of stereoselectivity in several reaction types, such as dynamic kinetic resolution and (*S*)/(*R*)-interconversion of unprotected α-AA,[29a,c,30] and alkylation of the corresponding Ni(II) complex of a glycine Schiff base.[21b,29b,30] In particular, ligand **16** worked exceptionally well for the development of large-scale production of enantiomerically enriched (>95% ee) naphthyl alanine (Scheme 2) via alkylation of the corresponding glycine complex, followed by thermodynamic equilibration of the products.[30]

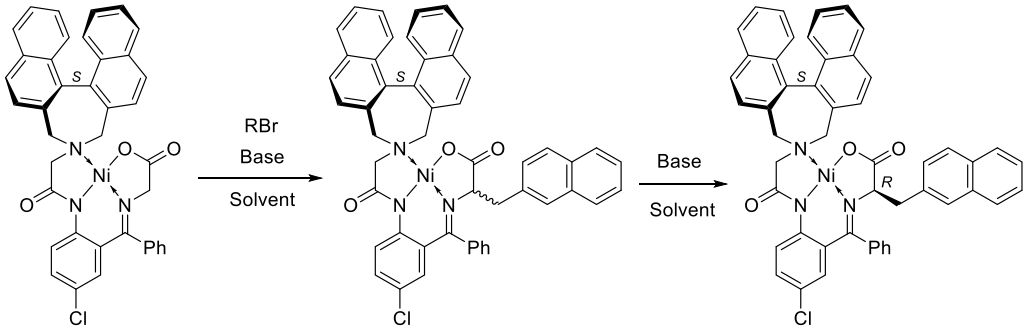
However, the most important structural advance realized with the development of Hamari ligand **16** is the chemically stable axial chirality allowing nearly complete recovery of the stereochemically intact chiral source. Thus, any noticeable racemization of ligand **16** would require rather extreme thermal conditions which are practically outside of the realm of chemical synthesis. In this work we report an economical synthesis of Hamari ligand **16** which was implemented on 500 g scale and showed high reproducibility and process reliability and can be recommended for the production of this highly valuable compound.

RESULTS AND DISCUSSION

Originally, the synthesis of Hamari ligand **16** was carried out using the following reaction sequence (Scheme 3):[30] (i) preparation of bis-bromide **17** from commercially available 1,1′-bi-2-naphthol, (ii) formation of azepine **18** by bis-alkylation of allyl amine with bis-bromide **17** and removal of the allyl group to give **19**, (iii) alkylation of **19** by amino benzophenone derivative **20**. This process has some disadvantages such as a multistep reaction sequence and the necessity for silica gel column purifications, rendering this approach rather unattractive for large scale manufacturing. In order to develop a more economically feasible approach, we considered the possibility of preparation of the target Hamari ligand **16** by the reaction of bis-bromide **17** with specially designed compound **21**, derived from glycine and *o*-amino-benzophenone.

The first objective of this study was the synthesis of requisite glycine-amide **21** (Scheme 4). As shown in Table 1, under the commonly used conditions for similar amidation reactions, using EDC/HOBt/Et_3N (entry 1) or oxalyl chloride/Et_3N (entry 2) at ambient temperature, the reaction between **22** and **23** did not occur. Application of more active condensing reagent BOP-Cl (entry 3) allowed for preparation of amide **24**, however, with only a 25% chemical yield. The use of isobutyl chloroformate (entry 4) gave a rather similar reaction outcome. Some noticeable improvement was observed in the reaction facilitated by TBTU/Et_3N, allowing isolation of amide **24** in 65% yield (entry 5). More successful results were obtained with application of pivaloyl chloride, as a condensing reagent, and 2,6-lutidine, as a base. Thus, the reaction performed in toluene afforded amide **24** in 70% yield (entry

Scheme 2. Alkylation and Thermodynamic Equilibration Steps in the Production of Naphthyl Alanine



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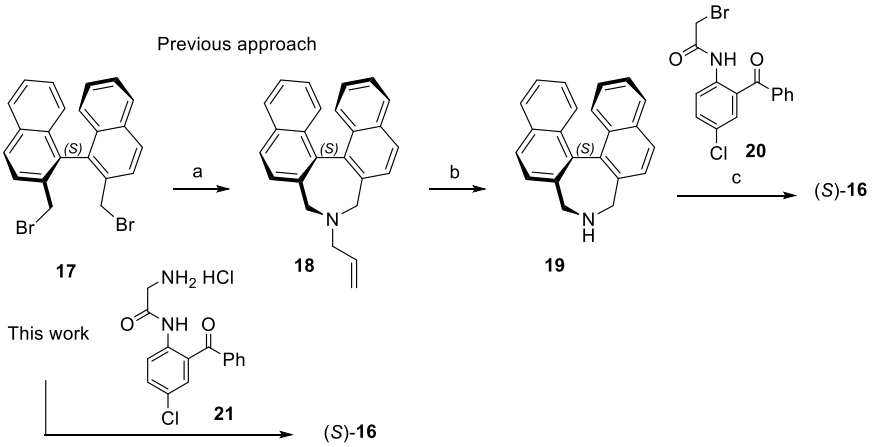
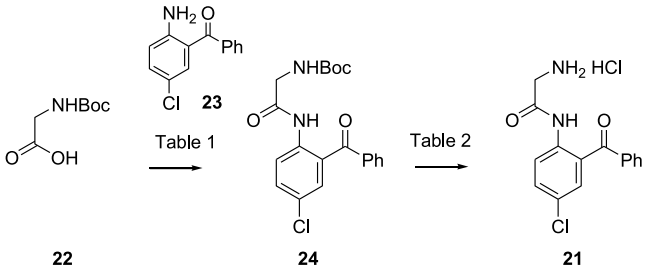
Scheme 3. Reported Synthesis of Hamari Ligand 16 and Our New Strategy Reported in the Present Work[a]



[a](a) Yield 86%. (b) Yield 67%. (c) Yield quant.; total yield 57% (3 steps).

Scheme 4. Preparation of Glycinamide Hydrochloride 21



6). Finally, we determined that increasing the reaction temperature to 50 °C allowed for isolation of product **24** with appreciable 92% chemical yield (entry 7).

Our next goal was to find appropriate conditions for removal of the Boc-protecting group in **24**; the results are summarized in Table 2. First, amide **24** was treated with hydrogen chloride in 1,4-dioxane (warning: carcinogenic properties) followed by trituration with *n*-heptane. This procedure afforded amide hydrochloride **21** in 60% yield (Table 2, entry 1). However, from the viewpoint of a large-scale production, 1,4-dioxane is a rather unsuitable solvent due to its suspected carcinogenic properties. In addition, the selection of a proper solvent was found to be a crucial issue for performing the deprotection with acceptable overall yields and operational convenience. Interestingly, the use of concentrated aqueous hydrochloric acid did not afford the desired glycinamide hydrochloride **21** (entry 2). Trifluoroacetic acid also did not give the expected glycinamide as the corresponding TFA salt, using 2-propanol as a solvent (entry 3). Eventually, it was found that HCl in ethyl acetate was a good reagent for this deprotection step (entry 4). Furthermore, an elevated temperature and use of an excess amount of HCl further improved the yield of **21** to 95% (entry 5). Glycinamide hydrochloride **21** showed low solubility in ethyl acetate, and that was a big advantage for precipitation of the corresponding salt without using auxiliary solvents after the deprotection. Reproducibility of this step was determined by the experiment using 75 g of the starting material (yield 90%). Moreover, repeating this procedure without isolation of intermediate **24** gave glycinamide hydrochloride **21** in 84% yield using only precipitation and filtration techniques.

Next, we focused on optimizing the process for preparation of bis-bromide **17**, using the literature method as a starting point (Scheme 5).[31] Commercially available enantiomerically pure binaphthol **25** was converted to bis-methyl intermediate **27** via triflation of the hydroxy group, followed by Kumada coupling of **26** with a Grignard reagent. Subsequent bromination of **27** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in ethyl acetate successfully afforded bis-bromide **17**. The literature method, used for bromination *N*-bromosuccinimide (NBS) and AIBN in cyclohexane, gave **17** in 54% yield.[31] By contrast, our procedure reliably affords a 71% yield from bis-methyl compound **27**.

The key step in this study, bis-alkylation of glycine-amide hydrochloride **21** with bis-bromide **17** (Scheme 6), was derived from our previous experience with the bis-alkylation of allylamine.[31] However, considering that the reaction conditions used gave only a moderate yield (62%) of the target product [allylamine (1.7 equiv), NEt_3 (3.0 equiv), 65 °C in tetrahydrofuran] there was a need for significant optimizations. Thus, in order to obtain Hamari ligand **16** with high

Table 1. Screening of the Reaction Conditions for *N*-Boc-amide 24 Formation

entry	base (1.0 equiv)	reagent (1.0 equiv)	solvent (6 volumes)	temp (°C)	time (h)	yield (%)
1	NEt_3	EDC/HOBt	DCM	rt[a]	6	0
2	NEt_3	$(COCl)_2$/DMF	DCM	5 to rt[a]	6	0
3	NEt_3	BOP-Cl	DCM	rt[a]	6	25
4	NEt_3	isobutyl chloroformate	DCM	5 to rt[a]	6	23
5	NEt_3	TBTU	DMF	rt[a]	6	65
6	2,6-Lutidine	pivaloyl chloride	toluene	rt[a]	6	70
7	2,6-Lutidine	pivaloyl chloride	toluene	50	6	92

[a]USP CRT 20−25 °C.

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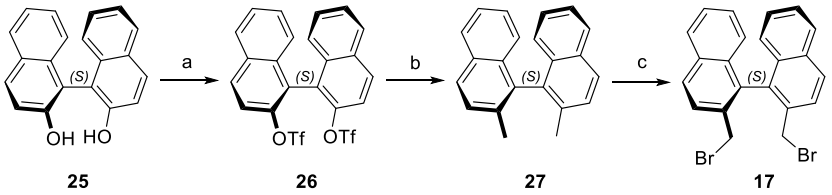
Table 2. Removal of *N*-Boc in 24

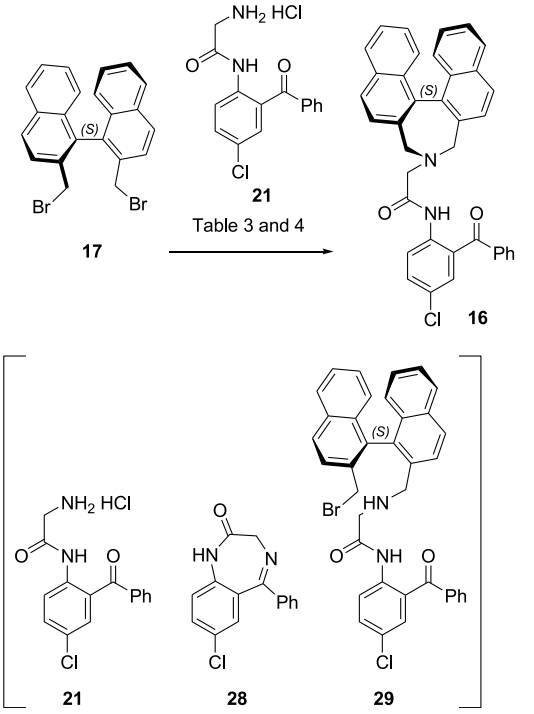
entry	**24** (50 mg, equiv)	solvent	reagent	equivalents	temp (°C)	time (h)	yield (%)
1	1	2-propanol	hydrogen chloride/dioxane	2	rt	5	60
2	1	2-propanol	37% HCl	2	rt	5	0
3	1	2-propanol	TFA	2	rt	5	0
4	1	–	hydrogen chloride/AcOEt	2	rt	5	70
5	1	–	hydrogen chloride/AcOEt	6	60	5	95

Scheme 5. Synthesis of Bis-bromide 17 from Binaphthol 25[a]



[a](a) **25** (112 g), Tf_2O (2.5 equiv), pyridine (4.0 equiv) in toluene (789 mL), yield 93%. (b) **26** (192 g), $NiCl_2(DPPP)_2$ (0.05 equiv), MeMgI (3 equiv) in MTBE (1500 mL), yield quant. (c) **27** (132 g), 1,3-dibromo-5,5-dimethylhydantoin (1.1 equiv), (AIBN) (3.84 g, 23 mmol) in ethyl acetate (40 mL), yield 71%.

Scheme 6. Bis-alkylation Step; Products and Impurities



conversion and low impurity, further studies were also needed, including the purification procedure. After screening for a suitable base and solvents, a biphasic system of isopropyl acetate and aqueous solution of sodium carbonate showed a low impurity profile on TLC. As a next step, experimental designing was carried out by using statistical software package to optimize the quantities of base, solvents, and temperature. The trend obtained is presented in Table 3. The response was evaluated by the HPLC area% of the reaction mixture. Following this trend the bis-alkylation procedure was optimized to obtain better reaction conditions to achieve high conversion and low impurities (high amount of base, low volume of isopropyl acetate, 6 volumes of water, 1.1 equiv of glycinamide hydrochloride **21**).

Table 3. Stoichiometric Ratios Used in the Process Optimization

factor unit	Na_2CO_3 (equiv)	isopropyl acetate (volumes)	H_2O (volumes)	temp (°C)	**21** (equiv)
lowest	2	**4**	0	65	1.1
	4	7	**6**	**78**	1.3
highest	**6**	10	10	85	1.5

The next objective of this research was optimization of the purification procedure for isolation of Hamari ligand **16** of adequate chemical purity to be used for general asymmetric synthesis of tailor-made AAs. First of all, we identified all major impurities found in the reaction mixture of the bis-alkylation step. As presented in Scheme 6, the following impurities were found: Schiff base **28**, monoalkylated compound **29**, and unreacted starting material **21**. The chemical origin of compounds **28** and **29** is easy to explain, and they can be considered as somewhat expected impurities. Basic and the less lipophilic compounds **21** and **28**, after the in situ hydrolysis of the Schiff base function, were easily transferred from the organic to aqueous phase by an extraction with aqueous sulfuric acid. However, target Hamari ligand **16** and monoalkylated compound **29**, possessing structural similarity and a quite lipophilic bis-naphthyl moiety, were found to be difficult to separate. Nonetheless, we found that ligand **16** can be successfully precipitated by addition of some acids as a counterion (hydrochloric acid, sulfuric acid, phosphoric acid, etc.; Table 4), but from the viewpoint of the ability to purge impurities, trifluoroacetic acid (TFA) was the acid of choice (Table 4, entry 6).

As shown in Table 4, the TFA salt of Hamari ligand **16** was obtained in sufficiently high purity (entry 6). Nevertheless, we devise an additional purification step using reprecipitation by ethanol and water. Thus, starting from 160 g of bis-bromide **17**, we repeated each step of the process with acceptable reproducibility allowing the preparation of Hamari ligand **16** as the TFA salt with high purity and chemical yield (HPLC purity 99%, yield 79%).

As the final objective for this study, the discussed above procedure was used for 500 g synthesis of (*S*)-**16** or (*R*)-**16** starting from **21** and (*S*)-**17** or (*R*)-**17**, which was

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Table 4. Precipitation Screening of 16 by Acids in MTBE

entry	acids (1.5 equiv)	yield (%)	**28** (area %)	**16**·HX (area %)	**29** (area%)
initial	–	–	11	82	6
1	conc. HCl	quant	7	85	7
2	HCl in EtOAc	quant	6	86	7
3	H_2SO_4	quant	7	87	5
4	MsOH	0	–	–	–
5	TsOH	77	7	87	5
6	TFA	98	1	95	3
7	AcOH	0	–	–	–
8	H_3PO_4	73	3	93	3
9	citric acid	38	55	35	8
10	HCO_2H	0	–	–	–
11	hydrobromic acid	80	7	88	4

accomplished with high reproducibility of each step as well as the overall method.

CONCLUSIONS

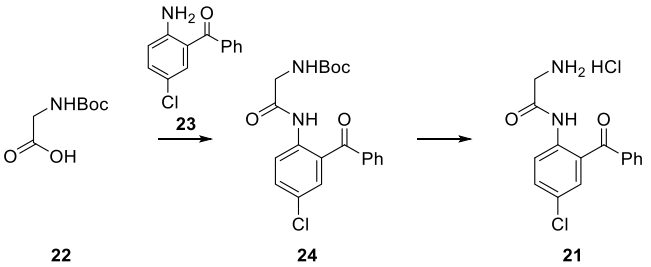
In summary, we developed a short, operationally convenient, and scalable synthetic process for preparation of Hamari ligand **16**, reliably reproducible on, at least, 500 g scale. Target product **16** was prepared, as a TFA salt, from commercially available (*R*)- and (*S*)-binaphthols in basically one key step involving bis-alkylation reaction and using a specially designed amide derived from glycine and *o*-amino-benzophenone. Our developed process is significantly advanced as compared with the literature precedents. The exciting potential of Hamari ligand **16** for general asymmetric synthesis of tailor-made AAs is currently under active investigation in our research laboratories, and results will be reported in a due course.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. All solvents and reagents were obtained from commercial sources and were used without further purification. Temperatures of reactions were monitored by using an internal thermocouple with a J-Kem temperature controller. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained using a Bruker AVACE III HD magnet and Bruker Topspin 3.5 software. Chemical shifts (ppm) are reported relative to tetramethylsilane for ^{1}H NMR spectra, signals for ^{13}C NMR spectra are reported relative to $CDCl_3$ (δ = 77.0 ppm) or DMSO-d_6 (δ = 39.5 ppm), and signals for ^{19}F NMR spectra are reported relative to trifluoroacetic acid (δ = 77.0 ppm). The letters s, d, t, q, m, and br. represent singlet, doublet, triplet, quartet, multiplet, and broad, respectively. High-resolution mass spectra (HRMS) were recorded with a UPLC/Xevo G2-XS Q-Tof (Waters Corporation, Wilmslow, UK). All reactions were monitored with an Agilent 1100 Series LC 61556A ESI-MSD system with the column temperature at 30 °C. The injection volume was 5 μL for all LC methods. UV detection utilized wavelengths of 210 and 254 nm. Method 1 used a Phenomenex Kinetex 2.6 μm XB-C18 100A, 4.6 mm × 100 mm column at a flow rate of 0.8 mL/min and a mobile phase comprised of solvents A (water with 0.1% trifluoroacetic acid) and B (acetonitrile): 25−70% B from 0−4 min, 70−90% B from 4−9 min, 90−95% B from 9−13 min, then held at 95% B for 4 min.

Method 2, a method for chiral analyses, used a Daicel CHIRALPAK IE 5 μm, 4.6 mm ID × 150 mm column and methanol as the mobile phase, with the flow rate as 0.5 mL/min at 10 °C. The retention times for (*S*)-**16** and (*R*)-**16** were 9.9 and 10.7 min, respectively. Polarimetry was carried out on a PerkinElmer model 341 Polarimeter with a standard cell. The apparent pH was measured using MColorpHast Universal Indicator pH indicator strips (EMD Millipore Corporation).

*2-Amino-N-(2-benzoyl-4-chlorophenyl) Acetamide Hydrochloride (**21**).* A 2 L round-bottom flask was fitted with



22 **24** **21**

an internal K-type thermocouple, J-Kem Apollo temperature controller, nitrogen gas inlet, outlet gas bubbler, and a mechanical stirring shaft with a 4 $^1/_4$" semispherical Teflon blade and heating mantle. The reactor was charged with Boc-glycine **22** (73.9 g, 422 mmol), 2,6-lutidine (67.8 g, 633 mmol), and toluene (739 mL). The resulting suspension was stirred to dissolve for 0.5 h at room temperature. The internal temperature was cooled down to 4 °C, and pivaloyl chloride (52.8 g, 438 mmol) was added dropwise to the reaction mixture below 10 °C. After stirring for 2 h at room temperature, 2-amino-5-chlorobenzophenone **23** (75.2 g, 325 mmol) was added in one portion and the mixture was heated to 50−55 °C and stirred for 4 h. The internal temperature was adjusted to 30−40 °C, and water (300 mL) was added. The mixture was cooled to room temperature and stirred for 10 min. The organic layer was washed with 5% citric acid (2 × 200 mL), 0.5 N sodium hydroxide (3 × 100 mL), and brine (2 × 200 mL), dried (anhydrous sodium sulfate, 15 g), and concentrated in vacuo to afford a yellow viscous oil (500 g). Ethyl acetate (400 mL) was added to the residual oil and concentrated in vacuo. Addition of ethyl acetate (400 mL) and concentration were repeated twice. Hydrogen chloride (1 N) in ethyl acetate (1900 mL) was added to the residual oil, and the solution was heated slowly to 60−65 °C. The solution was cooled down to 10−20 °C and stirred for 6 h at 10−20 °C. The resulting solids were collected by filtration and dried in a vacuum oven at 30−60 °C for 24 h to afford the product as a light-yellow solid (88.2 g, 84% yield for 2 steps). Mp 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.98 (2H, br s, $COCH_2$), 7.38 (1H, d, J = 2.5 Hz, ArH), 7.52−7.57 (2H, m, ArH), 7.58 (1H, d, J = 8.6 Hz, ArH), 7.68 (1H, ddt, J = 7.8, 7.0, 1.3 Hz, ArH), 7.69 (1H, dd, J = 8.6, 2.5 Hz, ArH), 7.73−7.76 (1H, m, ArH), 7.74 (1H, d, J = 8.6 Hz, ArH), 8.23 (3H, br s, NH_3^+), 11.01 (1H, br s, ArNH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 40.4 (CH_2), 125.7 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.9 (ArCH), 131.3 (ArCH), 133.2 (ArCH), 133.3 (quaternary ArC), 133.7 (quaternary ArC), 136.2 (quaternary ArC), 165.0 (amide CO), 193.1 (ketone CO).

Boc-2-amino-*N*-(2-benzoyl-4-chlorophenyl) acetamide (**24**): Mp 143.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s, CMe_3), 3.98 (2H, br d, J = 5.6 Hz, $COCH_2$), 5.33 (1H, br t-like, N*H*Boc), 7.48−7.54 (4H, m, ArH), 7.63 (1H, ddt, J = 8.0, 6.8, 1.3 Hz, ArH), 7.67−7.71 (2H, m, ArH), 8.63 (1H, d, J

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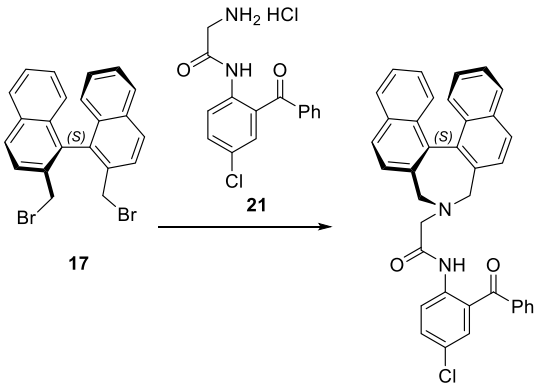
= 9.4 Hz, ArH), 11.14 (1H, br s, ArNH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.3 (CMe_3), 45.3 (CH_2), 80.6 (CMe_3), 122.9 (ArCH), 124.9 (quaternary ArC), 127.6 (quaternary ArC), 128.5 (ArCH), 129.9 (ArCH), 132.6 (ArCH), 132.9 (ArCH), 133.9 (ArCH), 137.7 (quaternary ArC), 138.3 (quaternary ArC), 155.9 (carbamate CO), 168.8 (amide CO), 197.9 (ketone CO). HRMS (TOF/pos): calcd for $C_{20}H_{21}ClN_2O_4Na$ $[M + Na]^+$ 411.1088, found 411.1086. (Crude **24** was purified by trituration with hexane in another experiment.)

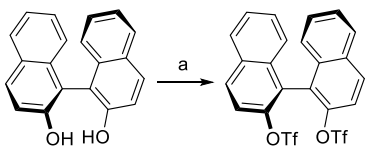
*(S)-N-(2-Benzoyl-4-chlorophenyl)-2-(3,5-dihydro-4H-dinaphtho[2,1-c:1′,2′-e]azepin-4-yl)acetamide Trifluoroacetic Acid ((S)-**16**).* A 10 L round-bottom flask was fitted with an



internal K-type thermocouple, J-Kem Apollo temperature controller, mechanical stirring shaft with a 4 $^1/_4$" semispherical Teflon blade, and heating mantle. The reactor was charged with (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (*S*)-**17** (435 g, 998 mmol), 2-amino-*N*-(2-benzoyl-4-chlorophenyl) acetamide **21** (370 g, 1.14 mol), and isopropyl acetate (1.74 L). Water (2.61 L) and sodium carbonate (628 g, 5.93 mol) were added, and the reactor was heated to 77−78 °C by applying external heating. After the internal temperature was maintained at 77 to 78 °C for 22 h, **21** (16.1 g, 49.5 mmol) was added to complete the reaction. Stirring was further continued at 77 to 78 °C for 6.5 h until HPLC showed completion of the reaction. The heating mantle was removed to allow the internal temperature to reach 30 to 35 °C. The layers were separated, and the aqueous layer was removed. Methyl acetate (7 L) was added to the organic layer. (Methyl acetate was added to improve phase separation by former solubility results.) The organic layer was washed with a 2 N solution of sulfuric acid in water (2.78 L) 5 times, 5% sodium bicarbonate (2.6 L) 3 times, and brine (2.6 L) twice at 30 to 35 °C. The organic layer was dried (anhydrous sodium sulfate, 160 g) and concentrated in vacuo. Solvent was exchanged by addition and concentration using MTBE (650 mL) 3 times. MTBE (6.9 L) was added into the residue, and the mixture was dissolved completely by agitation and warmed to 40 to 45 °C. The temperature was adjusted to 30 to 35 °C, and trifluoroacetic acid (225 g, 1.97 mol) was added at the same temperature. The mixture was cooled down to 25 °C and stirred for 1 h. For crystallization the mixture was cooled to 5 °C and further stirred for 7 h. Crystalline solids were collected by filtration, washed with MTBE (1.3 L), and dried in a vacuum oven at 45 °C for 4 days under a stream of dry nitrogen to afford the product as a pale-yellow solid (630 g, 93% yield). Ethanol (2.52 L) was added to dissolve the crude (*S*)-**16** by agitation at 35 to 40 °C. Water (1.26 L) was added into the solution dropwise at 35 to 40 °C. The temperature was cooled gradually to room temperature to effect recrystallization for 1 h. The mixture was agitated for 6 h at 5 °C. Crystalline solids were collected by filtration and dried in vacuum oven at 45 °C for 4 days to afford the product as a pale-yellow powder (570 g, 90% yield). Mp 143.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63−3.73 (2H, br, NCH_2), 3.78 and 3.86 (1H each, ABq, J = 14.6 Hz, $COCH_2$), 4.41 (2H, d, J = 12.1 Hz, NCH_2), 7.32 (2H, ddd, J = 6.8, 6.7, 1.2 Hz, ArH), 7.42−7.49 (6H, m, ArH), 7.53−7.61 (3H, m, ArH), 7.64 (2H, d, J = 8.3 Hz, ArH), 7.75−7.79 (2H, m, ArH), 7.97−8.00 (3H, m, ArH), 8.03 (2H, d, J = 8.3 Hz, ArH), 11.21 (1H, br s, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 54.5 (CH_2), 56.2 (CH_2), 116.3 (weak signal, q, J = 292.0 Hz, CF_3), 124.6 (ArCH), 126.8 (ArCH), 127.0 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 129.3 (quaternary ArC), 129.7 (quaternary ArC), 130.0 (ArCH), 130.1 (ArCH), 131.2 (ArCH), 132.8 (ArCH), 133.2 (ArCH), 134.2 (quaternary ArC), 135.3 (quaternary ArC), 135.9 (quaternary ArC), 136.8 (quaternary ArC), 162.9 (weak signal, q, J = 36.3 Hz, $COCF_3$), 163.2 (amide CO), 196.2 (ketone CO). ^{19}F-NMR (376.5 MHz, $CDCl_3$): δ −76.4 (s). HRMS (TOF/pos): Calcd for $C_{37}H_{28}ClN_2O_2$ $[M + H]^+$ 567.1839, found. 567.1870. $[\alpha]^{20}_D$ = +117.1° (c = 1.0, MeOH).

(*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-2-(3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′*e*]azepin-4-yl)acetamide trifluoroacetic acid ((*R*)-**16**) was prepared in the identical manner and had identical analytical properties to those given here (548 g, 78.8% yield). Mp 139.2 °C. HRMS (TOF/pos): calcd for $C_{37}H_{28}ClN_2O_2$ $[M + H]^+$ 567.1839, found 567.1972. $[\alpha]^{20}_D$ = −115.4° (c = 1.0, MeOH).

*(S)-[1,1′-Binaphthalene]-2,2′-diyl Bis(trifluoromethanesulfonate) ((S)-**26**).* A 5 L round-bottom flask was fitted with



an internal K-type thermocouple, J-Kem Apollo temperature controller, and a mechanical stirring shaft with 4 $^1/_4$" semispherical Teflon blade. The reactor was charged with (*S*)-(+)-1,1′-bi-2-naphthol (*S*)-**25** (113 g, 394 mmol) and toluene (789 mL) as a solvent. Pyridine (126 mL) was added and stirred for 0.5 h at room temperature. The internal temperature was adjusted to 5 °C within 1 h. Trifluoromethanesulfonic anhydride (166 mL, 984 mmol) was charged dropwise over 1.5 h below 10 °C. The solution was stirred for 19 h at 25 °C. Toluene (563 mL) and water (563 mL) were added, and the internal temperature was adjusted to 4 °C using an ice/water bath. Concentrated aqueous hydrochloric acid (172 mL) was charged while maintaining the internal temperature below 10 °C. The layers were separated. The organic layer was washed with water (2 × 563 mL) and brine (563 mL), dried (anhydrous sodium sulfate, 100 g), and concentrated in vacuo to afford a brown viscous oil. 2% MTBE in *n*-heptane (1080 mL) was added and concentrated in vacuo. 2% MTBE in *n*-heptane (1180 mL) was charged again and stirred for 18 h at room temperature. The resulting solids were collected by filtration and washed with *n*-heptane (100 mL).

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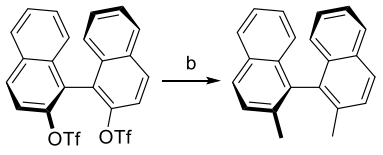
Mother liquor was collected and repeated with addition of 2% MTBE in *n*-heptane to collect the solid by filtration, yielding a second and third crop. The third crop was discarded due to impurities. The first and second crops were combined and dried in a vacuum oven at 28 °C for 48 h to afford the product as a light yellow to white solid (194 g, 89% yield).

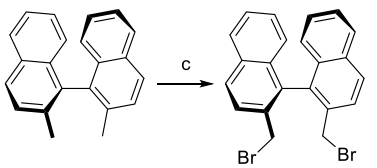
*(S)-2,2′-Dimethyl-1,1′-binaphthalene ((S)-**27**).* A 5 L round-bottom flask was fitted with an internal K-type



26 **27**

thermocouple, J-Kem Apollo temperature controller, nitrogen gas inlet, outlet gas bubbler, and a mechanical stirring shaft with a 4 $^{1}/_{4}$" semispherical Teflon blade and heating mantle. The reactor was charged with magnesium turnings (25.5 g, 1.05 mol) and MTBE (269 mL). Two pieces of iodine were added as activator for initiation of the Grignard reaction, and the mixture was stirred for 5 min until a color change to a brownish color. The solution (10 mL) of iodomethane (65.3 mL) dissolved in MTBE (153 mL) was added into the reaction vessel dropwise and stirred for 15 min. After the initiation of the Grignard reaction, the remainder of the iodomethane solution was charged into the reaction vessel dropwise while maintaining a gentle reflux without applying an external heating source. Then the internal temperature was adjusted at reflux by applying external heat via heating mantle and stirred for 30 min. The internal temperature was cooled to 50 °C, and {1,3-bis(diphenylphosphino)propane} nickel(II) chloride [$NiCl_2$(dppp)] (9.47 g, 17.5 mmol) was added into the reaction vessel in one portion. The internal temperature was adjusted at reflux rapidly by applying external heat, and the solution of (*S*)-[1,1′-binaphthalene]-2,2′-diyl bis(trifluoromethanesulfonate) (*S*)-**26** (192 g, 1.05 mol) dissolved in MTBE (1160 mL) was added dropwise at 55 °C with gentle reflux. The reaction mixture was further stirred for 45 min. The internal temperature was cooled to room temperature and stirred for 18 h. The internal temperature was adjusted to 4 °C, and 3 N hydrochloric acid (774 mL) was added below 10 °C. Toluene (744 mL) was added into the reaction mixture and stirred for 18 h at room temperature. The layers were separated. The organic layer was washed with water (2 × 800 mL), 10% sodium thiosulfate solution (400 mL), and brine (300 mL), dried (anhydrous sodium sulfate, 100 g), and concentrated in vacuo to afford a brown viscous oil (110 g). The crude product was purified by a silica gel (700 g) glass filter funnel by eluting 10−20% MTBE in *n*-heptane. The purified product was obtained as a light-yellow solid (98.2 g, 99% yield)

*(S)-2,2′-Bis(bromomethyl)-1,1′-binaphthalene ((S)-**17**).* A 2 L round-bottom flask was fitted with an internal K-type



27 **17**

thermocouple, J-Kem Apollo temperature controller, nitrogen gas inlet, outlet gas bubbler, and a mechanical stirring shaft with a 1 $^{3}/_{4}$" semispherical Teflon blade and heating mantle. The reactor was charged with (*S*)-2,2′-dimethyl-1,1′-binaphthalene (*S*)-**27** (132 g, 467 mmol) and ethyl acetate (528 mL). The resulting suspension was stirred. 1,3-Dibromo-5,5′-dimethylhydantoin (DBDMH) (147 g, 514 mmol) was added, and the mixture was stirred for 15 min at room temperature. Azobis(isobutyronitrile) (AIBN) (3.84 g, 23 mmol) was added followed by heating to 65 °C and stirring for 3.5 h. The internal temperature was cooled down to 25 °C, and water (528 mL) was added. The reaction mixture was stirred for 18 h at room temperature and cooled down to 1.5 °C over 1 h. The solids were collected by filtration, washed with water (200 mL), cold isopropyl acetate (75 mL), again with water (300 mL), and cold isopropyl acetate (100 mL) due to an orange color that remained in the filter cake. The solid was dried for 2 h to afford the product as a white to off-white powder (first crop, 122 g, 59% yield). Mother liquor from the above filtration was separated, and the aqueous layer was extracted with ethyl acetate (400 mL). The organic layer was washed with water (400 mL) and brine (2 × 260 mL), dried (anhydrous sodium sulfate, 70 g), and concentrated in vacuo to afford a brown oil (120 g). Isopropyl acetate (120 mL) was added and stirred for 18 h at room temperature. The internal temperature was cooled to 4 °C and stirred for 1.5 h for precipitation. The solids were collected by filtration and washed with cold isopropyl acetate until all orange color has been removed. The solids were dried for 2 h to afford the product as an off-white solid (27.6 g, 13% yield). Isopropyl acetate (28 mL) was added to the solids and stirred for 1.5 h at 4 °C. The solids were collected by filtration and washed with cold isopropyl acetate until all of the orange color had been removed. The solids were dried for 2 h to afford the product as off-white solids (second crop, 25.5 g, 12% yield). $[\alpha]^{20}_{D}$ = −173.1° (*c* = 1.0, $CHCl_3$).

(*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene ((*R*)-**17**) was prepared in the identical manner and had identical analytical properties to those given here. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (4H, s, 2 × CH_2), 7.07 (2H, dd, *J* = 8.4, 0.8 Hz, ArH), 7.27 (2H, ddd, *J* = 8.4, 6.8, 1.2 Hz, ArH), 7.48 (2H, ddd, *J* = 8.2, 6.8, 1.2 Hz, ArH), 7.74 (2H, d, *J* = 8.6 Hz, ArH), 7.92 (2H, d, *J* = 8.2 Hz, ArH), 8.02 (2H, d, *J* = 8.6 Hz, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.6 (CH_2), 126.80 (ArCH), 126.82 (ArCH), 126.84 (ArCH), 127.7 (ArCH), 128.0 (ArCH), 129.4 (ArCH), 132.5 (quaternary ArC), 133.3 (quaternary ArC), 134.1 (quaternary ArC), 134.2 (quaternary ArC). $[\alpha]^{20}_{D}$ = +173.8° (*c* = 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00406.

Experimental procedures, full spectroscopic data for new compounds, copies of ^{1}H, ^{13}C, ^{19}F NMR, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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