

Design and synthesis of chiral urea-derived iodoarenes and their assessment in the enantioselective dearomatizing cyclization of a naphthyl amide

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ABSTRACT

A novel family of urea-derived chiral iodoarenes was designed and synthesized for use in enantioselective iodine(I/III) catalysis. Their preparation required the development of a bidirectional synthetic strategy. These new chiral iodoarenes were assessed as catalysts in the dearomatizing cyclization of a naphthyl amide and provided moderate yields of product in some cases with low enantioselectivities.

1. Introduction

Enantioselective reactions mediated or catalyzed by chiral hypervalent iodine reagents or chiral iodoarene precatalysts have attracted significant attention over the past decade.¹ In this regard, a variety of chiral iodoarene backbones have been reported; however, the most successful, and most reported, framework is the bislactate ethers **1** and **2** reported independently by Fujita and Ishihara (Fig. 1).^{2,3} A number of modifications of this skeleton have been investigated,⁴ as each new application often requires a new derivative for optimal results. Other reported chiral iodoarenes include Zhang's spirobiindane derivative **3**,⁵ Quideau's helicene **4**,⁶ Maruoka's indane **5**,⁷ Ibrahim's dimethanoanthracene **6**,⁸ and Moran's pseudoephedrine derivative **7**.⁹ More recently, Nachtsheim reported his second generation triazole catalyst **8** which appears to yield superior selectivities in a range of enantioselective oxidation reactions.¹⁰ It is clear that, as in other areas of enantioselective catalysis, there is no panacea and the investigation of new chiral iodoarenes and hypervalent iodine reagents is still of interest and importance.

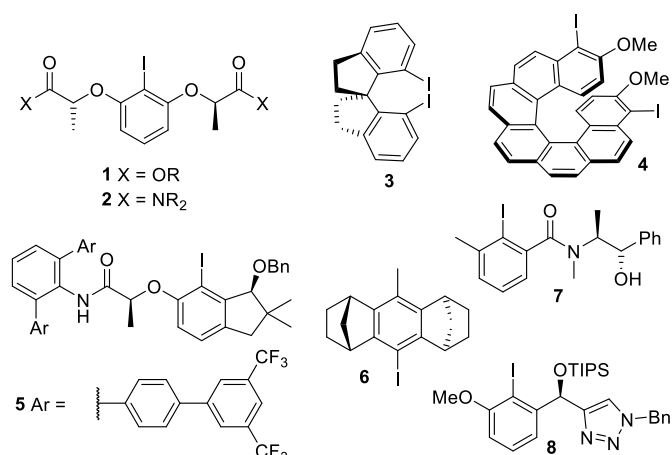
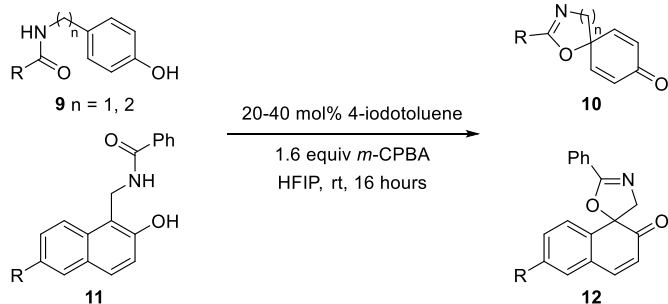


Fig. 1. Examples of chiral iodoarenes

We recently reported the dearomatizing cyclization of phenols and naphthols with pendent amides catalyzed by iodoarenes (Scheme 1).¹¹ We envisaged that the use of chiral iodoarene precatalysts would enable the enantioselective cyclization of the naphthols.

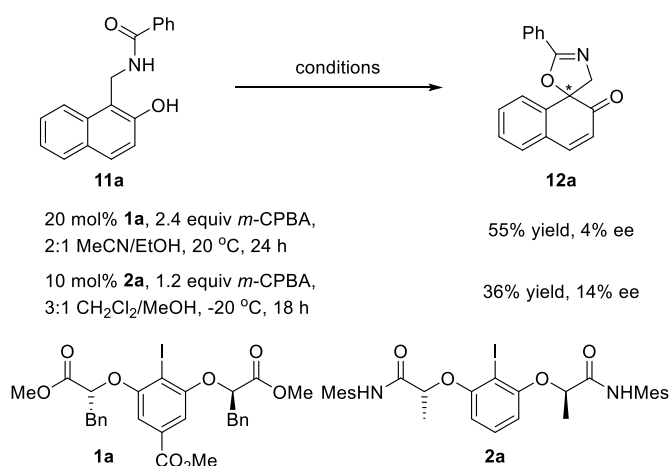
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Scheme 1. Dearomatizing cyclization of phenols and naphthols bearing pendent amides

2. Results and Discussion

At the outset of the project we tested the efficacy of the known iodoarenes **1a** and **2a** on their ability to catalyze the dearomatizing cyclization of naphthol **11a**.¹² After some experimentation with different we did weeyes solvents and temperature, the best selectivity observed with **1a** was 4% ee and with **2a** was 14% ee (Scheme 2). These preliminary observations suggested that the reaction could be rendered enantioselective but that an alternative catalyst structure would probably be required for high levels of enantioinduction.



Scheme 2. Initial attempts at the dearomatizing cyclization of naphthyl amide **11a**

At this juncture we wished to design a new family of chiral iodoarenes for use in iodine(I/III) catalysis and investigate their efficacy in the enantioselective dearomatizing cyclization of naphthols. Specifically, we aimed to prepare novel iodoarenes that could potentially form helical structures in solution in a similar manner to lactates **1** and **2**, as shown by Muñiz.¹³ It is known that oligomeric ureas can adopt helical conformations,^{14,15} therefore we designed a small family of iodoarenes containing urea appendages (Fig. 2).¹⁶ It was anticipated that ureas **13** would be readily prepared from the isocyanate **14**, itself derived from 2-iodoaniline **15**. In a similar manner, the C₂ symmetric bisureas **16** would be obtained from isocyanates **18**, which could be prepared from bisanilines **18** or dicarboxylic acids **19**. We knew that these ureas would not display helicity, as a chain of at least four ureas would be required, but this was our starting point.

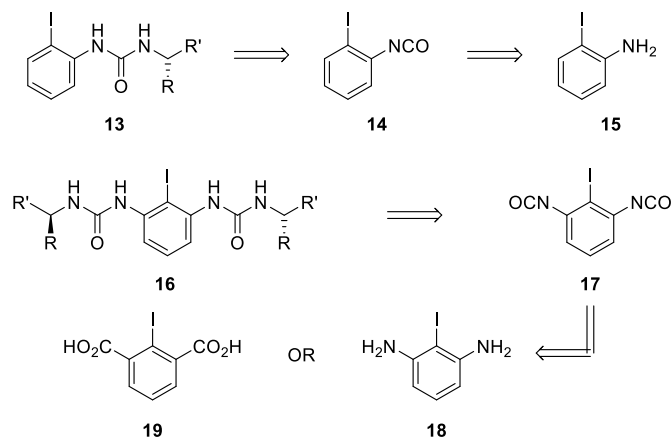
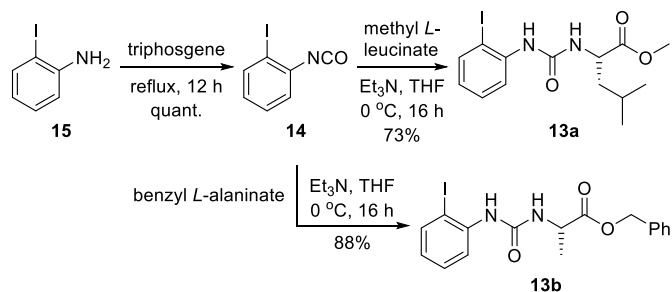


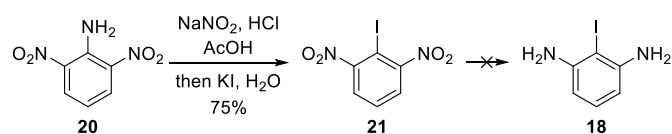
Fig. 2. Retrosynthesis of novel chiral iodoarenes **13** and **16** containing urea appendages

In the event, 2-iodoaniline **15** was readily converted into isocyanate **14**, by the literature procedure,¹⁷ and this was efficiently transformed into ureas **13a** and **13b** in very good yields under typical reaction conditions (Scheme 3).



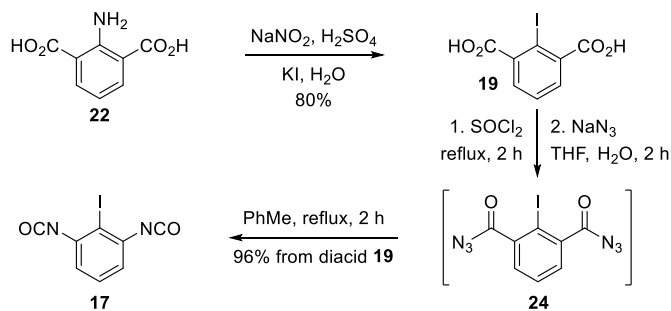
Scheme 3. Preparation of ureas **13a** and **13b**

Delighted by this success, we endeavored to prepare bisaniline **18** by an identical, but two-directional, two-step protocol starting from commercially available 2,6-dinitroaniline **20** (Scheme 4). Initial conversion of the amino group to an iodide through diazotization proceeded to give **21** in good yield,¹⁸ however subsequent attempts to reduce the two nitro groups were unsuccessful. Treatment with Fe powder (under a variety of conditions), H₂ gas or hydrazine over Pd on charcoal, and trichlorosilane were all ineffective. In all cases studied, partial reductions and/or side reactions including deiodination were observed.



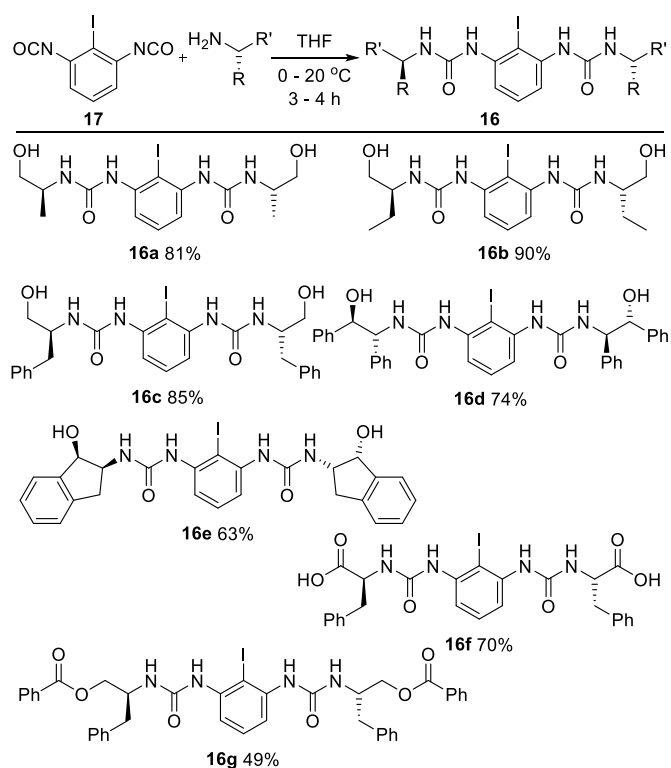
Scheme 4. Initial attempts to prepare bisaniline **18**

Accordingly, we turned our attention to the second route starting from 2-aminoisophthalic acid **22**; this was converted readily into iodide **19** in 80% yield (Scheme 5).¹⁹ Conversion of the carboxylic acid directly to the isocyanate **17** using diphenylphosphoroyl azide was unsuccessful; however, successive conversion to the acid chloride and the azide **24** led to the isocyanate **17** in quantitative yield by a Curtius rearrangement.



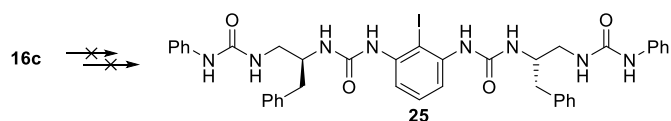
Scheme 5. Successful route to bisisocyanate **17**

With the isocyanate **17** in hand, a variety of bisureas were prepared by addition of amines in THF (Scheme 6). A range of amino alcohols or secondary alcohols were used to generate ureas **16a-16e**, which carry primary or secondary alcohols apparently ready for further derivatization. **16f** has terminal carboxylic acid groups prone for further functionalization. Finally, **16g** is the benzoyl ester of **16c**, although it was prepared by the coupling reaction shown rather than esterification.



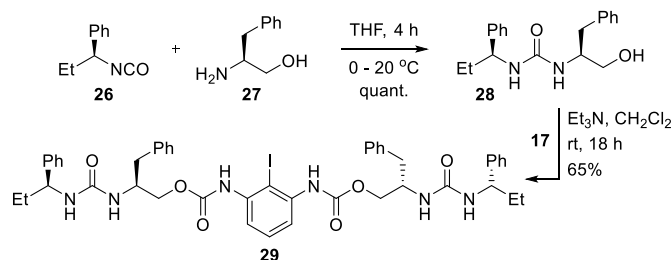
Scheme 6. Preparation of bisureas **16**

Attempts to convert bisurea **16c** into tetraurea **25** via conversion of the primary alcohols into tosylates or primary amines were unsuccessful (Scheme 7). In both cases, mixtures of unknown compounds were formed. Similarly, attempts to convert the carboxylic acids in **16f** into amides via acid chloride formation were unproductive. These ureas **16a-f** exhibit low solubility in organic solvents, which could explain the difficulties faced in their synthetic manipulation.



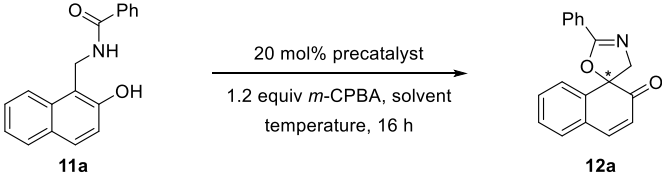
Scheme 7. Unsuccessful attempts to prepare tetraurea **25**

Next, we prepared alcohol **28**, which contained a urea functionality, and coupled this with bisisocyanate **17** (Scheme 8). The desired product **29**, which contained two urethanes and two ureas, was isolated in good yield.



Scheme 8. Preparation of mixed urethane-urea **29**

The ability of these 10 novel urea-containing chiral iodoarenes to effect the enantioselective dearomatizing cyclization of naphthyl amide **11a** was investigated (Table 1). A subset of the experiments undertaken are presented but it can be seen that products were typically obtained in low yields, and that they could not be purified sufficiently for HPLC analysis. Using iodoarene **16c** did lead to pure samples of **12a** being isolated, however selectivity was very low (entries 7-9). Using polar solvents like EtOH, MeOH and HFIP often leads to higher yields of product but poorer levels of selectivity in hypervalent iodine mediated reactions.^{9,20} The highest yield of product was obtained with precatalyst **29**, but the selectivity was just 2% ee. It is likely that the active catalytic species, i.e. the iodine(III) compounds, are even more sparingly soluble than the parent iodoarenes, which could explain their low reactivities.

Table 1. Efficacy of novel urea-based iodoarenes in the dearomatizing cyclization of naphthyl amide **11a**


Entry	ArI	Solvent	T/°C	Yield % ^a	% ee ^c
1	13a	MeCN	20	<5	-
2	13b	MeCN	20	<20	-
3	16a	MeCN	-20 (4 h), then 20	<30	-
4	16b	MeCN	-20 (4 h), then 20	<10	-
5	16b	3:1 CH ₂ Cl ₂ /MeOH	-78 (6 h), then 20	<10	-
6	16c	MeCN	20	<5	-
7	16c	2:1 MeCN/EtOH	20	68 (41) ^b	1
8	16c	HFIP	40	25 (14) ^b	4
9	16c	3:1 CH ₂ Cl ₂ /MeOH	-78 (6 h), then 20	(30) ^b	3
10	16d	MeCN	-20 (4 h), then 20	<10	-
11	16e	MeOH	20	<5	-
12	16e	3:1 CH ₂ Cl ₂ /MeOH	-78 (6 h), then 20	<5	-
13	16f	MeCN	20	<5	-
14	16g	CH ₂ Cl ₂	-78 (6 h), then 20	<10	-
15	16g	HFIP	40	<36	-
16	29	MeCN	20	56 (46) ^b	2

^a Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^b Yield of pure isolated compound. ^c Determined by chiral HPLC analysis.

In summary, we have developed a synthetic route into urea-based chiral iodoarenes. In particular, a two-directional strategy to symmetrical bisureas has been revealed. Some of these compounds can effectively catalyze the dearomatizing cyclization of a naphthyl amide. Unfortunately, these precatalysts were not effective in delivering the dearomatizing cyclization products in high enantioselectivities, but they may be useful in other iodine(I/III)-catalyzed processes.

3. Experimental section

3.1. General

Infrared (IR) spectra were recorded on a Nicolet 380, equipped with a diamond probe ATR attachment. Low and high resolution mass spectra (*m/z*) were obtained in the electrospray (ESI) mode. Melting points (uncorrected) were measured on a Stuart SMP10 apparatus. All reagents and solvents were used without further purification except THF (dried over 3 Å MS and then distilled over Na/benzophenone under N₂). The reactions were monitored by thin layer chromatography (TLC) using F254 pre-coated silica gel

plates. Spots were visualized with UV, KMnO₄ stain or vanillin stain. Flash chromatography was performed with 35-70 μm, 60 Å silica gel.

3.2. Synthesis of 2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-one (**12a**)

To a solution of amide **11a** (1 equiv) in anhydrous solvent (0.030 M) at room temperature (or below) was added *m*-CPBA (2.2 equiv) and iodoarene catalyst (0.1 or 0.2 equiv). The reaction mixture was stirred for 16 h and then quenched with a saturated solution of NaHCO₃. The organic layer was extracted with ethyl acetate (three times), dried over MgSO₄, filtered and concentrated under vacuum. The resulting residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to afford **12a** as a pale yellow oil. IR (thin film) 3160, 3053, 2869, 1715, 1673, 1652, 1603, 1569, 1547, 1367, 1338, 1283, 770 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) 8.08-8.06 (m, 2H), 7.56-7.35 (m, 8H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H); ¹³C NMR (CDCl₃ 100 MHz) 197.8, 164.3, 145.8, 142.3, 132.0, 131.0, 129.7, 129.0, 128.9, 128.8, 128.6, 127.0, 125.7, 123.7, 86.6, 69.8; HRMS [M+H]⁺ *m/z* calc'd for C₁₈H₁₄NO₂ requires 276.1019, found 276.1019. HPLC: Chiralpak IB, 254 nm, hexane/IPA gradient (100:0 to 90:10 over 35 min), 1 mL/min, retention times 12.9 & 15.1 minutes.

3.3. Preparation of ureas **13**

To the solution of 1-iodo-2-isocyanatobenzene **14** (0.50 g, 2.0 mmol, 1 equiv) in THF (30 mL) at 0 °C was added a solution of amino ester (2.2 mmol, 1.1 equiv) and triethylamine (0.57 mL, 4.1 mmol, 2.0 equiv) in THF (10 mL) dropwise. Then, the ice bath was removed and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure was washed with hexanes multiple times. Recrystallization either with dichloromethane/ethyl acetate or ethanol provided the urea **13**.

3.3.1. Methyl ((2-iodophenyl)carbamoyl)-L-leucinate (**13a**)

Yellow solid (0.58 g, 73%). M.p. 158-160 °C; IR 3301, 2951, 2868, 1737, 1641, 1573, 1557, 1519, 1463, 1433, 1367, 1273, 1255, 1205, 1155, 1016 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) 7.84-7.78 (m, 2H), 7.72 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 4.26-4.21 (m, 1H), 3.65 (s, 3H), 1.73-1.66 (m, 1H), 1.58 (t, *J* = 7.3 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 100 MHz) 173.7, 154.7, 140.3, 138.9, 128.5, 124.3, 122.0, 90.0, 51.8, 51.0, 40.6, 24.3, 22.7, 21.5; HRMS [M+H]⁺ *m/z* calc'd for C₁₄H₂₀IN₂O₃ 391.0513, found 391.0510.

3.3.2. Benzyl ((2-iodophenyl)carbamoyl)-L-alaninate (**13b**)

Pale yellow solid (0.37 g, 88%). M.p. 161-163 °C; IR 3299, 3060, 2979, 2605, 2498, 1720, 1633, 1556, 1512, 1463, 1452, 1432, 1318, 1291, 1221, 1164, 1097 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) 7.84-7.79 (m, 2H), 7.74 (s, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.39-7.27 (m, 6H), 6.77 (t, *J* = 7.4 Hz, 1H), 5.20-5.11 (m, 2H), 4.33-4.24 (m, 1H), 1.35 (d, *J* = 7.4 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 100 MHz) 173.2, 154.5, 140.3, 138.9, 136.1, 128.5, 128.5, 128.0, 127.7, 124.4, 122.1, 90.1, 65.9, 48.5, 17.6; HRMS [M+H]⁺ *m/z* calc'd for C₁₇H₁₈IN₂O₃ 425.0357, found 425.0359.

3.4. Preparation of 2-iodo-1,3-diisocyanatobenzene **17**

A solution of 2-iodoisophthalic acid **19** (1.5 g, 5.1 mmol) in thionyl chloride (40 mL) was heated to reflux for 2 h then concentrated under reduced pressure to afford 2-iodoisophthaloyl chloride. This crude mixture was dissolved in THF (15 mL), cooled to 0 °C and NaN₃ (2.2 g, 34 mmol) dissolved in water (8

mL) was added. After 2 h, the reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL) solution and extracted with toluene (30 mL). This was dried over MgSO₄ and evaporated to half under reduced pressure to give a toluene solution of 2-iodoisophthaloyl diazide **24**. Without further purification, the crude mixture was heated at reflux for 2 hours and then concentrated to ~3 mL to afford **17** as a light brown solution (1.42 g, 96% – determined by NMR). The progress of the reaction was monitored by IR. IR 3370, 3024, 2251, 2141, 1723, 1573, 1494, 1396, 1214, 781, 728 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) 7.20-7.30 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) 138.2, 130.0, 129.8, 122.2, 97.2; HRMS [M-CO+3H]⁺ *m/z* calc'd for C₇H₆IN₂O 260.9519, found 260.9516.

3.5. Preparation of bisureas **16**

To a solution of 2-iodo-1,3-diisocyanatobenzene **17** (0.70 mL, 4.3 mmol, 1 equiv) in THF (60 mL) at 0 °C was added dropwise a solution of amine (1.5 g, 9.5 mmol, 2.2 equiv) in THF (10 mL). The ice bath was removed and the reaction mixture was stirred for 3-4 hours or until TLC analysis showed completion of the reaction. Then, the reaction mixture was concentrated under reduced pressure and the residue washed with hexanes multiple times. Recrystallization from ethyl acetate and ethanol provided the bisurea **16**. Typically, solvents could not be completely removed from these compounds.

3.5.1. 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxypropan-2-yl)urea) (**16a**)

White solid. (0.50 g, 81%). M.p. 249-250 °C; IR 3284, 2980, 2851, 1632, 1162, 1035 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.60 (s, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 4.77 (br s, 2H), 3.70-3.65 (m, 2H), 3.42-3.28 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 6H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 154.7, 141.2, 127.8, 117.1, 89.3, 64.8, 47.0, 17.8; HRMS [M+H]⁺ *m/z* calc'd for C₁₄H₂₂IN₄O₄ 437.0680, found 437.0698.

3.5.2. 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxybutan-2-yl)urea) (**16b**)

Pale yellow solid (0.60 g, 90%). M.p. 252-254 °C; IR 3290, 2962, 2930, 2873, 2355, 1633, 1556, 1463, 1410, 1274, 1223, 1074, 1018 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.62 (s, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.72 (br s, 2H), 3.56-3.42 (m, 4H), 3.35-3.32 (m, 2H), 1.64-1.54 (m, 2H), 1.43-1.31 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 155.0, 141.3, 127.8, 117.1, 89.3, 63.0, 52.5, 24.2, 10.5; HRMS [M+H]⁺ *m/z* calc'd for C₁₆H₂₆IN₄O₄ 465.0993, found 465.0990.

3.5.3. 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxy-3-phenylpropan-2-yl)urea) (**16c**)

Yellow solid (1.7 g, 85%). M.p. 265-266 °C; IR 3297, 3024, 2919, 1634, 1548, 1465, 1271 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.64 (s, 2H), 7.32-7.20 (m, 12H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 4.90 (br s, 2H), 3.85-3.78 (m, 2H), 3.43-3.32 (m, 4H), 2.91-2.81 (m, 2H), 2.73-2.65 (m, 2H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 154.7, 141.2, 139.2, 129.3, 128.2, 127.7, 125.9, 117.2, 89.5, 62.4, 52.8, 37.3; HRMS [M+H]⁺ *m/z* calc'd for C₂₆H₃₀IN₄O₄ 589.1306, found 589.1321.

3.5.4. 1,1'-(2-iodo-1,3-phenylene)bis(3-((*1S,2R*)-2-hydroxy-1,2-diphenylethyl)urea) (**16d**)

White solid (370 mg, 74%). M.p. 221-223 °C; IR 3343, 3213, 2981, 1647, 1587, 1556, 1503, 1465, 1396, 1276, 1231, 1068, 1047 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.98 (s, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 4H), 7.42 (d, *J* = 7.4 Hz, 4H), 7.36-7.32 (m, 8H), 7.26-7.20 (m, 4H), 7.07-7.06 (m, 2H), 6.99-6.93 (m, 1H), 5.67 (d, *J* = 4.1 Hz, 2H), 4.90-4.83 (m, 4H); ¹³C

NMR (DMSO-*d*⁶, 100 MHz) 154.7, 143.7, 142.8, 141.1, 127.8, 127.6, 127.4, 127.1, 126.8, 126.6, 126.4, 117.6, 90.0, 75.6, 59.1; HRMS [M+Na]⁺ *m/z* calc'd for C₃₆H₃₃IN₄O₄Na 735.1439, found 735.1441.

3.5.5. 1,1'-(2-iodo-1,3-phenylene)bis(3-((*1R,2S*)-1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)urea) (**16e**)

Off-white solid (0.52 g, 63%). M.p. 247-248 °C; IR 3318, 3240, 2912, 1682, 1632, 1550, 1465, 1400, 1359, 1231, 1142, 1047 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 8.09 (s, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29-7.18 (m, 11H), 5.23 (d, *J* = 4.1 Hz, 2H), 5.11 (dd, *J* = 8.7, 4.9 Hz, 2H), 4.47 (q, *J* = 4.5 Hz, 2H), 3.07 (dd, *J* = 16.2, 4.6 Hz, 2H), 2.81 (d, *J* = 16.1 Hz, 2H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 155.5, 143.2, 141.4, 140.5, 127.8, 127.1, 126.3, 124.9, 124.1, 118.3, 90.9, 72.3, 57.6; HRMS [M+H]⁺ *m/z* calc'd for C₂₆H₂₆IN₄O₄ 585.0993, found 585.0989.

3.5.6. (2*S,2'S*)-2,2'-(((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl)bis(3-phenylpropanoic acid) (**16f**)

Pale-yellow solid (0.76 g, 70%). M.p. 227-229 °C; IR 3217, 3025, 2890, 1714, 1638, 1547, 1494, 1464, 1407, 1275, 1214, 1075 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.88 (s, 2H), 7.33-7.21 (m, 16H), 7.15-7.11 (m, 1H), 4.48-4.40 (m, 2H), 3.14-3.07 (m, 2H), 2.98-2.90 (m, 2H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 173.5, 154.6, 141.0, 137.3, 136.6, 129.5, 128.5, 126.5, 117.8, 90.1, 54.0, 37.6; HRMS: [M+H]⁺ *m/z* calc'd for C₂₆H₂₆IN₄O₆ 617.0892, found 617.0898.

3.5.7. (2*S,2'S*)-(((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl)bis(3-phenylpropane-2,1-diyl) dibenzoate (**16g**)

Yellow solid (120 mg, 49%). M.p. 230-232 °C; IR 3288, 3064, 2923, 2852, 1716, 1641, 1538 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 8.05-8.02 (m, 4H), 7.70-7.66 (m, 2H), 7.57-7.52 (m, 4H), 7.41-7.37 (m, 2H), 7.33-7.30 (m, 10H), 7.26-7.21 (m, 4H), 7.14-7.08 (m, 1H), 4.36-4.17 (m, 6H), 2.99-2.84 (m, 4H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 165.7, 154.7, 149.2, 138.2, 133.5, 129.7, 129.4, 129.2, 128.8, 128.4, 128.0, 126.3, 119.3, 87.9, 66.1, 49.8, 37.4; HRMS [M+H]⁺ *m/z* calc'd for C₄₀H₃₈IN₄O₆ 797.1831, found 797.1835.

3.6. Preparation of 1-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-3-((*S*)-1-phenylpropyl)urea **28**

To a solution of (*S*)-(1-isocyanatopropyl)benzene **26** (0.50 g, 3.1 mmol, 1 equiv) in THF (40 mL) at 0 °C was added dropwise a solution of amine **27** (0.52 g, 3.4 mmol, 1.1 equiv) in THF (10 mL). The ice bath was removed and the reaction mixture was stirred for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was washed with hexanes multiple times and then purified by flash chromatography (silica gel; 1:1 petroleum ether/EtOAc) to provide **28** as a white solid (1.0 g, 99%). M.p. 130-131 °C; IR 3336, 3026, 2927, 2356, 2341, 1610, 1586, 1565, 1493, 1449, 1380, 1253, 1073, 1046 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 7.32-7.14 (m, 10H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.79 (d, *J* = 8.6 Hz, 1H), 4.83 (br s, 1H), 4.50 (q, *J* = 7.3 Hz, 1H), 3.71-3.67 (m, 1H), 3.35-3.25 (m, 2H), 2.80-2.75 (m, 1H), 2.62-2.57 (m, 1H), 1.67-1.53 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 157.2, 144.6, 139.2, 129.2, 128.1, 128.1, 126.2, 62.5, 54.3, 52.4, 37.2, 30.0, 10.6; HRMS [M+H]⁺ *m/z* calc'd for C₁₉H₂₅N₂O₂ 313.1911, found 313.1909.

3.7. Preparation of bis((*S*)-3-phenyl-2-(3-((*S*)-1-phenylpropyl)ureido)propyl)(2-iodo-1,3-phenylene)dicarbamate **29**

2-Iodo-1,3-diisocyanatobenzene **17** (350 mg, 1.2 mmol, 1 equiv – as a solution in toluene) and triethylamine (0.37 mL, 2.7 mmol,

2.2 equiv) were dissolved in dichloromethane (30 mL) and cooled to 0 °C under N₂. Urea **28** (0.75 g, 2.4 mmol, 2.2 equiv) was dissolved in dichloromethane (20 mL) in a separate flask and added to the first solution dropwise over 10 minutes. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was quenched with 1 N HCl (20 mL) and extracted with EtOAc (20 mL x 3), dried over MgSO₄ and concentrated under reduced pressure. Recrystallization from CH₂Cl₂/EtOAc afforded **29** as a dark brown solid (0.73 g, 65%). M.p. 249-251 °C; IR 3270, 3026, 2961, 1702, 1633, 1584, 1519, 1461, 1398, 1202, 1109, 1109, 1018 cm⁻¹; ¹H NMR (DMSO-*d*⁶, 400 MHz) 9.01 (s, 2H), 7.32-7.17 (m, 23H), 6.43 (d, *J* = 8.0 Hz, 2H), 5.86 (d, *J* = 8.0 Hz, 2H), 4.56-4.49 (m, 2H), 4.02-3.95 (m, 6H), 2.83-2.70 (m, 4H), 1.67-1.59 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (DMSO-*d*⁶, 100 MHz) 157.0, 154.2, 144.5, 140.6, 138.2, 129.3, 128.5, 128.5, 128.1, 126.4, 126.2, 83.2, 65.8, 54.4, 49.8, 37.3, 29.9, 10.7; HRMS [M+Na]⁺ *m/z* calc'd for C₄₆H₅₁IN₆NaO₆ 933.2807, found 933.2813.

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References and notes

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Appendix A. Supplementary Material

Supplementary data to this article can be found online at