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

M. Umair Tariq and Wesley J Moran

*Department of Chemistry, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, U.K.

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.

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.
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. After some experimentation with different 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. It is known that oligomeric ureas can adopt helical conformations, therefore we designed a small family of iodoarenes containing urea appendages (Fig. 2). In the event, 2-iodoaniline 15 was readily converted into isocyanate 14, by the literature procedure, 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, 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). 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.
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 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.

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.

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.

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 lead to higher yields of product but poorer levels of selectivity in hypervalent iodine mediated reactions. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArI</th>
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<th>T/°C</th>
<th>Yield %a</th>
<th>ee%</th>
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<tbody>
<tr>
<td>1</td>
<td>13a</td>
<td>McCN</td>
<td>20</td>
<td>&lt;5</td>
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</tr>
<tr>
<td>2</td>
<td>13b</td>
<td>McCN</td>
<td>20</td>
<td>&lt;5</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
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<td>MeCN</td>
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<tr>
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<td>(4 h), then 20</td>
<td>&lt;10</td>
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<tr>
<td>5</td>
<td>16b</td>
<td>3:1 CHCl₃/MeOH</td>
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<td>(6 h), then 20</td>
<td>&lt;10</td>
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<tr>
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<td>-</td>
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<tr>
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<td>68 (41)b</td>
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<td>8</td>
<td>16e</td>
<td>HFIP</td>
<td>40</td>
<td>25 (14)b</td>
<td>4</td>
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<td>16e</td>
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<tr>
<td>16</td>
<td>29</td>
<td>McCN</td>
<td>20</td>
<td>56 (46)b</td>
<td>2</td>
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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.

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(VIII)-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 P254 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-2H,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-CBPA (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, 126.7, 120.7, 125.7, 123.7, 86.6, 69.8; HRMS [M+H⁺] m/z calc’d for C₂₃H₂₈N₂O 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. The product was washed with hexane 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 ⁰C; IR 3301, 2951, 2868, 1737, 1641, 1573, 1557, 1519, 1463, 1337, 1273, 1255, 1205, 1155, 1016 cm⁻¹; ¹H NMR (DMSO-d₆, 400 MHz) 6.84-7.8 (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), 4.24-4.21 (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-d₆, 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 C₁₇H₁₇NO₃, 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 ⁰C; IR 3299, 3060, 2979, 2650, 2498, 1720, 1633, 1556, 1512, 1463, 1452, 1432, 1318, 1291, 1221, 1164, 1097 cm⁻¹; ¹H NMR (DMSO-d₆, 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-d₆, 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 C₁₉H₁₆N₂O₄, 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
3.5. Preparation of bisureas 16

To a solution of 2-iodo-1,3-diisocyanobenzene 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 until TLC analysis showed completion of the reaction. Then, the reaction mixture was concentrated under reduced pressure and the residue was 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-hydroxyprop-2-yl)urea) (16a)

White solid. (0.50 g, 81%). M.p. 249-250 °C; IR 3217, 3391 bis(3-iodo)phenylene)bis(3-(1R,2S)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)urea) (16e)

Off-white solid (0.52 g, 63%). M.p. 247-248 °C; IR 3318, 3240, 2912, 1682, 1632, 1540, 1465, 1400, 1359, 1231, 1142, 1047 cm⁻¹; ¹H NMR (DMSO-d⁶, 400 MHz) 8.09 (s, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.29-7.18 (m, 1H), 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), 2.82 (d, J = 16.1 Hz, 2H); ¹³C NMR (DMSO-d⁶, 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 calcd for C₃₀H₂₃N₅O₄ 585.0933, found 585.089. 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, 2992, 2930, 2873, 2355, 1633, 1556, 1463, 1410, 1274, 1223, 1074, 1018 cm⁻¹; ¹H NMR (DMSO-d⁶, 400 MHz) 7.62 (m, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.13 (t, J = 8.1 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 4.76 (m, 2H), 3.53 (m, 1H), 3.03 (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-d⁶, 100 MHz) 155.0, 141.3, 127.8, 117.1, 89.7, 63.0, 52.5, 24.2, 10.5; HRMS [M+H⁺] m/z calcd for C₂₃H₂₀N₅O₂ 465.0993, found 465.099. 3.5.3. 1,1’-((2-iodo-1,3-phenylene)bis(3-((S)-1-hydroxy-3-phenylprop-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-d⁶, 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 (brs, 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-d⁶, 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 calcd for C₂₈H₂₄N₅O₄ 598.1306, found 589.1321. 3.5.4. 1,1’-((2-iodo-1,3-phenylene)bis(3-((1S,2R)-1-hydroxy-2-1,2-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 cm⁻¹; ¹H NMR (DMSO-d⁶, 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-d⁶, 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 calcd for C₃₅H₃₆N₅O₄ 835.2474, found 835.2468. 3.5.5. 1,1’-((2-iodo-1,3-phenylene)bis(3-((1R,2S)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)urea) (16e)

To a solution of 2-iodo-1,3-diisocyanobenzene 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 (20 mL 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, 1018 cm⁻¹; ¹H NMR (DMSO-d₆, 400 MHz) 9.06 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 4.56 (t, J = 7.0 Hz, 6H), 1.67-1.59 (m, 4H), 0.79 (t, J = 7.0 Hz, 6H); ¹³C NMR (DMSO-d₆, 100 MHz) 157.0, 154.2, 144.5, 140.6, 138.2, 129.3, 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]+ ml/z calc’d for CsH₃I₂N₂NaO₆ 933.2807, found 933.2813.

Acknowledgments

We thank the University of Huddersfield for funding (fee-waiver scholarship to MUT). We thank Mirdyal Das (University of Huddersfield) for the preparation of iodoarene 1a.

References and notes


Appendix A. Supplementary Material

Supplementary data to this article can be found online at