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Synthesis and oxidative reactivity of new chiral hypervalent iodine(V) reagents based on (*S*)-proline

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Abstract—Design and preparation of two chiral pseudo-benziodoxazine derivatives based on inexpensive and readily available (*S*)-proline have been carried out. The evaluation of these new reagents as stereoselective oxidizing agents toward a racemic alcohol, *meso*-diol, and sulfide was performed. Moderate enantioselectivities in a range of 29–41% have been achieved.

Hypervalent iodine(V) compounds, both cyclic[1] and pseudo-cyclic,[2] have found a broad application in organic synthesis as mild and selective reagents for the oxidation of alcohols to carbonyl compounds along with a series of other synthetically useful oxidative transformations.[3] Taking into account spectacular advancements in the field of asymmetric synthesis,[4] there is a vital need to develop chiral hypervalent iodine oxidants which will allow to obtain products with high enantiomeric excess. Very few chiral iodine(III) compounds have been reported,[5a–j] among them iodo(III)binaphthyls **1** and iodosylarene derivatives **2** and **3** with chiral moiety fixed *ortho*- to the hypervalent iodine center (Fig. 1). An advanced protocol for asymmetric oxidation of sulfides to sulfoxides employing $PhIO_2$ and chiral tartaric acid derivatives represents just a single successful example of utilizing iodine(V) chemistry for chiral oxidations of organic substrates.[5k,l]

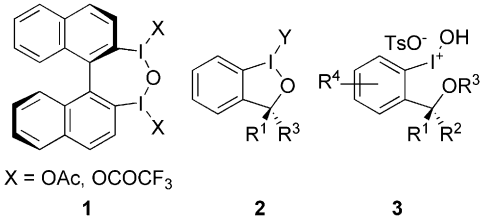

Figure 1. Chiral organoiodine reagents.

Recently, we have reported on the preparation and oxidative properties of *N*-(2-iodyl-phenyl)-acylamides (NIPAs) **4**, which are soluble and stable IBX analogs having pseudo benziodoxazine structure (Fig. 2).[6a] These investigations, being a logical continuation of our previous work on IBX amides,[2c] revealed that compounds **4** are able to oxidize either alcohols or sulfides, with the reactivity depending largely on the substitution pattern on amide group adjacent to the iodyl moiety. The synthesis of polymer supported NIPA reagent has been reported as well.[6b]

NIPA compounds **4** seem to be a good starting point for the design of a chiral pentavalent iodine oxidant. Indeed, preparative advantages are notable: the reactions can be performed under an aerobic atmosphere with solvents of regular grade. NIPA compounds are inexpensive and they are more stable than enzymes or other bioorganic catalysts. Also, NIPAs can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogs, and thus show promising adaptability to high throughput screening

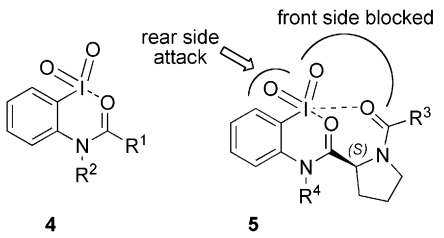

Figure 2. Design of a chiral NIPA reagent.

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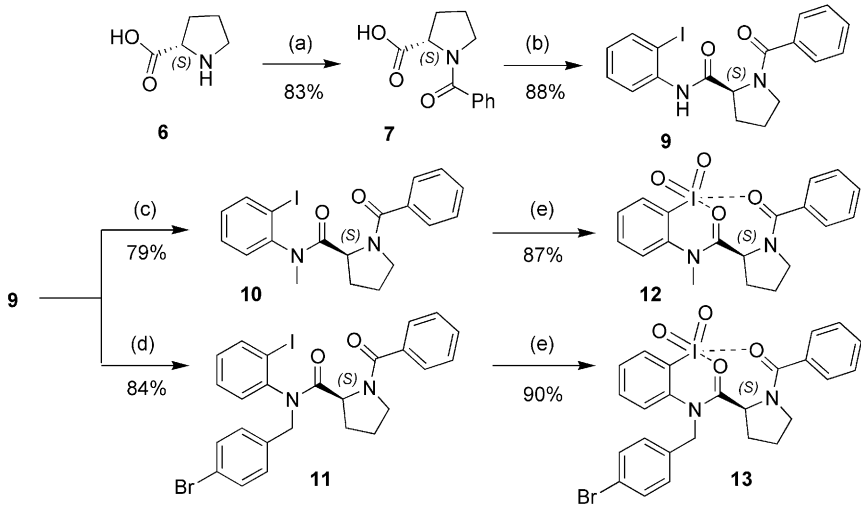
and process chemistry. In addition to these points, NIPA structure **4** is easy to modify, which allows broad opportunities for chiral auxiliary design. Here we present facile syntheses of chiral *N*-(2-iodyl-phenyl)-acylamides and evaluate their enantioselectivity using kinetic resolution of a racemic alcohol, and oxidation of a *meso*-diol and sulfide.

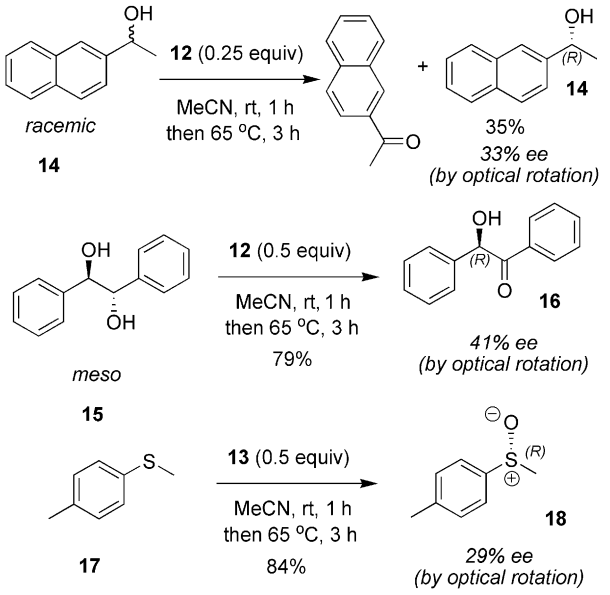
To initiate the synthesis of chiral NIPA derivative, we decided upon taking natural amino acid as an asymmetric controller. The key feature in NIPA structure **4** is the amide bond formed by 2-iodoaniline **8** and a carboxylic acid. Since amino acids possess carboxylic functionality attached to the asymmetric center, this type of structure is ideal as a carboxylic acid component. We expect chiral information to be transferred from the amino acid residue to the transition state, leading to chiral discrimination during oxidation. (*S*)-Proline **6** occupies a special position in a series of natural amino acids. This fact is due to a compact and rigid pyrrolidine ring in the core of this chiral molecule. This rigid structure helps to promote the formation of highly organized transition states, and thus to achieve exceptional enantioselectivities.[7] Taking into account this outstanding properties of (*S*)-proline, we decided to use this cheap natural amino acid as an asymmetric portion of the NIPA compound. The reactive amino group of (*S*)-proline was blocked via conversion to an amide functionality. Coupling this portion with aromatic aniline **8** yields the target structure of chiral NIPA **5** (Fig. 2). We speculate that amide oxygen in structure **5** could also participate in the pseudo-bonding with IO_2 group, thus forming additional pseudo 7-membered ring (Fig. 2). This coordination could possibly block the front side of IO_2 moiety, thus allowing alcohol coordination only from the rear side. This will actually lead to the chiral environment near iodyl group, and hopefully will result in enantioselective oxidations.

We decided on benzoylamide group ($R^3 = Ph$) at the proline portion of structure **5**, as well as *N*-methyl and *N*-4-Br-benzyl amides ($R^4 = Me$, 4-$BrC_6H_4CH_2$) at the 2-iodoaniline moiety (Fig. 2). As it was previously shown, *N*-methyl NIPAs are selective toward alcohol oxidation, while *N*-benzyl derivatives can oxidize sulfides to sulfoxides.[6a] Synthesis of chiral NIPAs **12** and **13** was accomplished starting from (*S*)-proline **6** (Scheme 1). Compound **6** was acylated with benzoyl chloride under standard Schotten–Baumann conditions.[8] Obtained (*S*)-benzoylproline **7** was then coupled with 2-iodoaniline **8** using Steglich reaction[9] to give monovalent iodine precursor **9**[10] in good yield and without epimerization. Compound **9** was alkylated using standard protocol affording substituted amides **10** and **11** in good yields.[10] Finally, oxidation with 3,3-dimethyldioxirane afforded target compounds **12** and **13** as snow-white solids (Scheme 1).[10]

The enantioselective oxidative properties of NIPA **12** were evaluated using the kinetic resolution of racemic 1-(naphthalen-2-yl)ethanol **14** (Scheme 2). The oxidation was performed in MeCN first at room temperature (rt) for 1 h, and then at 65 °C for 3 h.[11] This specific temperature sequence was used since the initial alcohol coordination to IO_2 group proceeds quickly at rt (NMR evidence), but the decomposition of intermediate alkoxyiodane requires higher temperatures. Apparently, lower temperatures favor stereoselective coordination, and thus we are performing this protocol stepwise to increase stereoselectivity. The amount of NIPA oxidant used was lower then the stoichiometric amount (NIPA transfers two oxygen atoms to the substrate; 0.25 equiv of chiral oxidant **12** taken). Upon reaction completion, the remaining alcohol **14** was separated from ketone product, and optical rotation of alcohol **14** was measured. If compound **12** exhibits enantioselectivity, then two enantiomers of alcohol **14** will be oxidized in a different rate, and the remaining alcohol mixture will be enriched with one isomer, which reacts slower. Indeed, based on optical rotation, the remaining alcohol was enriched with (*R*)-isomer with a reasonable 33% ee.[12a]



Scheme 1. Reagents and conditions: (a) BzCl (1.25 equiv), NaOH (2.5 equiv), H_2O, 0 °C, 30 min; (b) 2-iodoaniline **8** (1.0 equiv), DIC (1.0 equiv), DMAP (0.1 equiv), CH_2Cl_2–DMF, 0 °C, 5 min then rt, 3 h; (c) (i) NaH (1.25 equiv), DMF, 0 °C; (ii) MeI (1.5 equiv), 0 °C–rt, 3 h; (d) (i) NaH (1.25 equiv), DMF, 0 °C; (ii) 1-bromo-4-(bromomethyl)benzene (1.5 equiv), 0 °C–rt, 3 h; (e) 3,3-dimethyldioxirane (3.0 equiv, 0.1 M in acetone), CH_2Cl_2–acetone, 0 °C–rt, 3 h.



Scheme 2. Evaluation of chiral NIPA **12** and **13** enantioselectivity.

Similarly, chiral NIPA **12** was evaluated by oxidation of *meso*-diol **15** under the same reaction conditions.[11] This oxidation led to (*R*)-hydroxyketone **16** with a moderate 41% ee (Scheme 2).[12b] Asymmetric oxidation of methyl(*p*-tolyl)sulfane **17** with oxidant **13** gave (*R*)-sulfoxide **18** with good chemical yield and moderate enantioselectivity (Scheme 2).[12c]

These results indicate that compounds **12** and **13** represent promising lead structures for the design of chiral oxidants based on pseudo-benziodoxazine scaffold. Further optimization efforts could include modifications of amide nitrogen to enhance solubility, and introducing electron-accepting groups (preferably CF_3) to the aromatic ring. This modification would decrease the electron density on IO_2 group and, consequently, would increase the reactivity toward alcohol and sulfur oxidation. Enhanced reactivity will allow decreasing the reaction temperature, which will probably lead to higher % ee values. A careful consideration of reaction conditions also could help increasing enantioselectivity. These further investigations are ongoing and will be reported in due course.

In conclusion, we have designed and prepared chiral NIPA derivatives **12** and **13** based on cheap and readily available (*S*)-proline. The initial design concept suggested that iodylarenes **12**, **13** would act as asymmetric oxidants, which was subsequently shown by performing kinetic resolution experiment and asymmetric oxidations. Moderate % ee values were obtained; further structure optimization will be performed hopefully leading to highly efficient chiral oxidants.

Acknowledgments

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10. Compound **9**: Mp 126–127 °C; $[\alpha]_D^{25}$ −106.3 (*c* 1.0, MeOH); IR υ_{max} (NaCl) cm^{-1} 3256, 1693, 1613, 1564, 1508, 1400, 1282, 1171, 1139, 1009, 790, 766, 733, 693, 664; ^1H NMR (500 MHz, $CDCl_3$): δ 8.80 (br s, 1H), 8.18 (dd, $^3J = 6.9$ Hz, $^4J = 1.2$ Hz, 1H), 7.78 (dd, $^3J = 6.6$ Hz, $^4J = 1.5$ Hz, 1H), 7.62 (m, 2H), 7.43 (m, 3H), 7.34 (td, $^3J = 7.5$ Hz, $^4J = 1.2$ Hz, 1H), 6.85 (td, $^3J = 7.5$ Hz, $^4J = 1.2$ Hz, 1H), 5.02 (t, $^3J = 4.8$ Hz, 1H), 3.63 (m, 2H),

2.49 (m, 1H), 2.12 (m, 2H), 1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 169.5, 138.9, 138.4, 135.8, 130.5, 129.0, 128.4, 127.4, 126.2, 122.8, 90.6, 61.1, 50.6, 27.8, 25.5; APCI-MS: m/z (%) 420.64 (100) $[M]^+$. Compound **10**: Mp 200–201 °C; $[\alpha]_D^{25}$ +135.8 (c 1.0, MeOH); IR υ_{max} (NaCl) cm^{-1} 2959, 1664, 1626, 1467, 1419, 1382, 1272, 1113, 1056, 1019, 777, 743, 725, 701, 653; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, $^3J = 6.5$ Hz, $^4J = 1.5$ Hz, 1H), 7.93 (dd, $^3J = 6.6$ Hz, $^4J = 1.1$ Hz, 1H), 7.57 (m, 2H), 7.50 (td, $^3J = 7.5$ Hz, $^4J = 1.0$ Hz, 1H), 7.40 (m, 3H), 7.10 (td, $^3J = 7.5$ Hz, $^4J = 1.1$ Hz, 1H), 4.42 (t, $^3J = 7.4$ Hz, 1H), 3.69 (m, 1H), 3.47 (m, 1H), 3.25 (s, 3H), 2.17 (m, 1H), 2.07 (m, 2H), 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 169.2, 145.7, 139.7, 136.4, 130.9, 130.1, 130.0, 129.9, 128.1, 127.3, 98.8, 57.4, 50.4, 36.5, 30.1, 25.7; APCI-MS: m/z (%) 434.54 (11) $[M]^+$. Compound **11**: Mp 115–116 °C; $[\alpha]_D^{25}$ +84.5 (c 1.0, MeOH); IR υ_{max} (NaCl) cm^{-1} 2970, 1672, 1650, 1615, 1572, 1470, 1422, 1395, 1271, 1245, 1202, 1075, 1011, 787, 776, 723; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, $^3J = 7.5$ Hz, $^4J = 1.5$ Hz, 1H), 7.59 (m, 2H), 7.51 (dd, $^3J = 6.5$ Hz,$^4J = 1.5$ Hz, 1H), 7.49 (m, 5H), 7.31 (td, $^3J = 8.0$ Hz, $^4J = 1.5$ Hz, 1H), 7.19 (m, 2H), 7.07 (td, $^3J = 8.0$ Hz, $^4J = 1.5$ Hz, 1H), 5.76 (d, $^1J = 15.0$ Hz, 1H), 4.41 (t, $^3J = 7.5$ Hz, 1H), 4.02 (d, $^1J = 15.0$ Hz, 1H), 3.72 (m, 1H), 3.50 (m, 1H), 2.23 (m, 1H), 2.11 (m, 2H), 1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 169.2, 143.0, 139.8, 136.4, 135.3, 132.7, 131.6, 131.5, 131.1, 130.6, 130.1, 129.5, 128.2, 127.3, 121.3, 99.3, 57.6, 51.3, 50.4, 30.1, 25.8; APCI-MS: m/z (%) 588.36 (34) $[M]^+$. Compound **12**: Mixture of rotamers; Mp 167–169 °C; $[\alpha]_D^{25}$ −139.6 (c 1.0, MeOH); IR υ_{max} (NaCl) cm^{-1} 2975, 1618, 1567, 1409, 1323, 1245, 1164, 1113, 1024, 777, 723; ^{1}H NMR (500 MHz, CD_3OD): δ 7.28–8.23 (m, 9H), 4.34 (t, $^3J = 7.2$ Hz, 1H), 3.77–3.31 (m, 5H), 2.49–1.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 174.9, 171.8, 171.0, 151.0, 146.6, 142.9, 142.2, 138.4, 137.3, 136.9, 135.9, 134.9, 134.7, 131.9, 131.8, 131.7, 131.3, 129.8, 129.7, 129.6, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 126.0, 125.3, 60.3, 59.8, 51.9, 51.8, 39.7, 39.6, 30.6, 28.8, 26.8, 26.5; APCI-MS: m/z (%) 466.64 (28) $[M]^+$. Compound **13**: Mixture of rotamers; Mp 157–159 °C; $[\alpha]_D^{25}$ −13.7 (c 1.0, MeOH); IR υ_{max} (NaCl) cm^{-1} 2949, 1675, 1613, 1575, 1422, 1204, 1067, 1005, 777, 726; ^{1}H NMR (500 MHz, CD_3OD): δ 6.95–8.25 (m, 13H), 5.50 (d, $^1J = 15.0$ Hz, 1H), 4.54 (d, $^1J = 15.0$ Hz, 1H), 4.25 (t, $^3J = 7.5$ Hz, 1H), 3.75–3.50 (m, 2H), 2.51–1.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 174.8, 172.0, 171.0, 151.6, 140.4, 137.4, 136.7, 135.3, 133.3, 133.2, 132.7, 132.4, 132.3, 132.0, 130.8, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 123.5, 122.8, 60.6, 60.4, 55.2, 54.5, 51.9, 30.8, 30.7, 29.1, 26.9, 26.5; APCI-MS: m/z (%) 620.64 (68) $[M]^+$.

11. *General procedure for oxidation with amides* **12** *and* **13**. To a stirred solution of an alcohol (1.0 mmol) or a sulfide (1.0 mmol) in 2.0 ml of dry MeCN was added chiral oxidant **12** or **13** (0.25 mmol or 0.50 mmol), and the reaction mixture was stirred at rt for 1 h, and at 65 °C for 3 h. Then, the organic solvent was removed under reduced pressure and the residue was separated by flash chromatography (hexanes/EtOAc or hexanes/$CHCl_3$) to give the product. Optical rotation of the obtained sample was determined and the % ee was calculated.
12. For **14**: 33% ee based on measured $[\alpha]_D^{25}$ +14.1 (c 0.5, EtOH); lit.: $[\alpha]_D^{25}$ +41.2 (c 0.5, EtOH; 95% ee (R)) (a) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Willsa, M. *Org. Lett.* **2005**, *24*, 5489; For **16**: 41% ee based on measured $[\alpha]_D^{25}$ −66.0 (c 1.0, MeOH); lit.: $[\alpha]_D^{25}$ −65 (c 1.0, MeOH; 40% ee (R)) (b) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025; For **18**: 29% ee based on measured $[\alpha]_D^{25}$ +44.1 (c 1.2, EtOH); lit.: $[\alpha]_D^{25}$ +151 (c 1.2, EtOH; 100% ee (R)) (c) Puchot, C.; Samuel, O.; Duach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J . Am. Chem. Soc.* **1986**, *108*, 2353.