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Asymmetric Kita spirolactonisation catalysed by anti-dimethanoanthracene-based iodoarenes

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Enantiopure C₂-symmetric iodoarenes based on the rigid all-carbon anti-dimethanoanthracene framework are shown to catalyse the asymmetric oxidative Kita spirolactonisation of propanoic acid-tethered 1-naphthols with significant levels of asymmetric induction of up to 67% ee.

The oxidative dearomatization of phenols is an efficient strategy for the rapid assembly of polycyclic structures frequently found in complex natural products. This transformation leads to reactive intermediates such as cyclohexadienones, capable of undergoing a host of follow up C-C and C-X bond forming reactions. Several asymmetric dearomatization reactions have been disclosed in recent years. Among these, the use of chiral hypervalent iodine reagents, either in stoichiometric amounts or generated in situ from catalytic amounts of chiral iodoarenes and stoichiometric oxidants, is promising, yet remains under-developed and challenging. Chiral hypervalent iodine reagents were employed by Birman and Quideau in the asymmetric ortho-hydroxylation of phenols to ortho-quinols, and recently by Harned in the asymmetric para-hydroxylation of phenols to para-quinols. These reports constitute intermolecular reactions between the substrate and the incoming nucleophile. Kita reported the first intramolecular iodoarene-catalysed asymmetric oxidative dearomatization of phenols. In the presence of stoichiometric amounts of mCPBA, the rigid spiroindane-based diiodoarene 1a was shown to catalyse the ortho-spirolactonisation of propanoic acid substituted 1-naphthols with moderate enantioselectivity, which could be improved significantly with the ortho-ethyl derivative 1b (Scheme 1). The in situ oxidation of 1 was proposed to form a μ-oxo-brided bis-α,2-iodane, postulated to be responsible for both high reactivity and enantioselectivity. Subsequently, Ishihara disclosed lactate-derived conformationally flexible C₂-symmetric iodoarenes, such as bisamide 2, capable of catalysing the asymmetric spirolactonisation of 1-naphthols with high levels of stereocontrol (Scheme 1). The amide tethers in 2 were found to be crucial for both high reactivity and enantioselectivity.

In the above systems, chirality transfer within the in situ formed iodine(III) naphtholate intermediates is proposed to be aided by a μ-oxo-bridge directed substrate pre-organisation in the former, or a hydrogen bonding stabilised chiral pocket in the latter. Such bonding or secondary interactions between the chiral aryl-iodane backbone and the iodine centre are common and often a desired feature of chiral hypervalent iodine reagents. However, significant asymmetric induction without such interactions is rare, especially under catalytic conditions.

We recently reported on the synthesis of a series of congested all-carbon aryl-iodanes based on the C₈₅-symmetric anti-dimethanoanthracene framework and demonstrated that, despite their encumbered nature, they mediated various functional group transfer reactions, including the ortho-hydroxylation of phenols. We now wish to report the synthesis of enantiopure iodoarene precursors, and disclose preliminary results from their application as catalysts in the asymmetric oxidative spirolactonisation of 1-naphthols.

Contrary to the above systems, chirality transfer from iodoarenes is solely dependent upon steric interactions with the rigid all-carbon anti-dimethanoanthracene backbone. Such a framework as a source of chirality is relatively unexplored, with most applications revolving around the use as asymmetric catalysts of anti-dimethanoanthracene containing Haltermann-type metalloctetraarylporphyrins. Our approach to iodoarene (-)-5a started from literature-known resolved aldehyde (+)-3. Catalytic hydrogenation gave toluene derivative (+)-4 in 99% yield which was iodinated using...
(diacetoxycarbonyl)benzene (DIB) and iodine to give optically pure iodoarene (−)-5a in 70% yield (Scheme 2).

Iodoarene (−)-5a was subjected, in the presence of 1.5 equivalents of mCPBA, to the catalytic spiro lactonisation of naphthol 6a. An initial experiment was conducted with 15 mol% of (−)-5a in dichloromethane at room temperature for 48 hours which, gratifyingly, gave spiro lactone 7a in 65% yield and an encouraging 39% ee (Table 1, entry 1). Lowering the temperature to −20 °C gave a lower yield of 29% with little effect on the enantioselectivity (entry 2). Having shown that (−)-5a can catalyse the spiro lactonisation of naphthol 6a in dichloromethane, we undertook a solvent screen to further optimise reaction conditions at 0 °C and a reaction time of 5 hours. Subjecting 6a to these conditions in dichloromethane delivered the product in a low 21% yield but with comparable ee (entry 2). The use of chloroform gave a higher yield of 36% with no effect on enantioselectivity (entry 4). Acetonitrile and nitromethane had a negative effect on both yield and enantioselectivity (entries 5 and 6), while ethereal solvents and toluene gave very low conversions (entries 7-9).

Having established that chloroform was superior to all other solvents tested, we proceeded to examine the substrate scope using 10 mol% of (−)-5a in chloroform, as well as chloroform-based solvent mixtures at −20 °C and a reaction time of 19 hours (Table 2).11 Examining the reaction of naphthol 6a under these conditions in a 2:1 mixture of CHCl₃/MeNO₂ or CHCl₃/TFE (trifluoroethanol) had no significant effect on enantioselectivity (entries 2 and 3). However, temperature and solvent effects were more pronounced with bromo-naphthol 6b. Running the reaction of 6b in chloroform at 0 °C produced spiro lactone (+)-(R)-7b in 64% yield and 40% ee, while reducing the temperature to −20 °C gave the product with a comparable yield but with a significantly higher enantiomeric excess of 60% (entries 4 vs 5). Gratifyingly, using the CHCl₃/MeNO₂ solvent mixture further improved the enantioselectivity to 67% ee (entry 6). The solvent effect with the chloro-naphthol 6c resembled that of naphthol 6a with the reaction in chloroform producing a markedly higher selectivity (42% ee) than reactions in solvent mixtures (entries 8-10). In contrast, substrate 6d gave the highest selectivity of 48% ee in the CHCl₃/TFE solvent mixture (entry 12). For naphthol 6e, the selectivity obtained in chloroform (57% ee) was dramatically higher than those in solvent mixtures (entry 14 vs entries 15 and 16). Overall, varying the solvent had no pronounced effect on yield but a notable effect on enantioselectivity, with each of the solvent systems tested performing best with a different substrate.

Given that iodoarene (−)-5a displayed moderate catalytic activity, we decided to examine electronically tuned analogues. We envisaged that decreasing the oxidation potential of iodoarene (−)-5a by introducing an electron-donating para-methoxy group would allow for a more efficient generation of the iodine(III) intermediate.20 Thus, iodoarene (−)-5b was synthesised from aldehyde (+)-3 by mCPBA oxidation to phenol (+)-8 followed by methylation to anisole derivative (+)-9. Subsequent iodination of (+)-9 proved to be problematic as neither the DIB/I₂ tandem, successfully employed for the iodination of (−)-5a, nor several other iodination procedures afforded (−)-5b. Ultimately, the iodination of (+)-9 was accomplished in 79% yield using NIS and catalytic amounts of trifluoroacetic acid in acetonitrile at room temperature (Scheme 3).

When subjecting 10 mol% of iodoarene (−)-5b to the spiro-

\[ \text{CHO} \rightarrow \text{OMe} \]
\[ \text{(+)-3} \rightarrow \text{(+)-9} \rightarrow \text{(-)-5b} \]

Scheme 3 (a) mCPBA, CH₂Cl₂, rt, 2 h, 73%; (b) NaOH, (MeO₂)SO₂THF, reflux, 4 h, 93%; (c) NIS, CF₃CO₂H (cat.), MeCN, rt, 12 h, 79%.
lactonisation of 6b in CHCl₃/MeNO₂, we were delighted to find that it proved more active than (−)-5a, affording (+)-7b in a good 82% yield, but with a lower enantioselectivity of 53% ee (Scheme 4).²¹

Our rationale for the observed preference to the spirulactone $R$ enantiomer is depicted in Figure 1. In accordance with DFT calculations by Harned on the iodine(III) phenolate intermediate in the para-hydroxylation of phenols, the transition state model places the equatorial anti-dimethanoanthracene partially eclipsed by the apical naphtholate ligand. Minimising steric interactions in this arrangement positions the naphtholate ligand preferentially above the methano rather the ethano bridge of the anti-dimethanoanthracene backbone, blocking the bottom face from nucleophilic attack.²² This leaves the top Re-face exposed towards C-O bond forming attack onto the naphtholate ipso carbon by the propanic acid side chain, leading to the formation of 7 with an $R$ configuration (Fig. 1).

![Scheme 4](image)

**Scheme 4** Spirolactonisation of 1-naphthol 6b with iodoarene (−)-5b

In conclusion, we have demonstrated that the rigid all-carbon $C_2$-symmetric iodoarene (−)-5a is capable of imparting significant levels of stereocontrol in the catalytic asymmetric Kita spirolactonisation of 1-naphthols 6. The activity of the catalyst was affected by electronic tuning of the position para to the iodo substituent, with methoxy-iodoarene (−)-5b displaying significantly enhanced activity. Given our working hypothesis for stereoselection, and the ready accessibility of sterically and electronically engineered anti-dimethanoanthracene analogues,²⁴ we anticipate that higher levels of stereocontrol might be attainable in this reaction. Efforts towards achieving this goal are underway and will be reported in due course.

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**Notes and references**

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data, including $^{1}H$ and $^{13}C$ spectra of all new compounds. See DOI: 10.1039/b000000xx

13. An iodoarene with modified amide tethers was recently reported to be a highly enantioselective catalyst in the asymmetric oxidative spirolactonisation of simple phenols: M. Uyanik, T. Yasui and K. Ishihara, Angew. Chem. Int. Ed., 2013, 52, 9215.
No reaction occurred when treating 6b with stoichiometric amounts of (±)-9-diacetoxyiodo-anti-dimethanoanthracene (see ref. 17) in chloroform at room temperature for 48 h.

An X-ray structure analysis of a diaryliodonium arenolate salt from our laboratory corroborates such an arrangement: S. J. Murray, H. Müller-Bunz and H. Ibrahim, unpublished results.

The relative steric size difference between the methano and ethano bridges is illustrated on hand of the X-ray structure of (±)-9-iodo-anti-dimethanoanthracene included in the ESI. CCDC 1040056 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.