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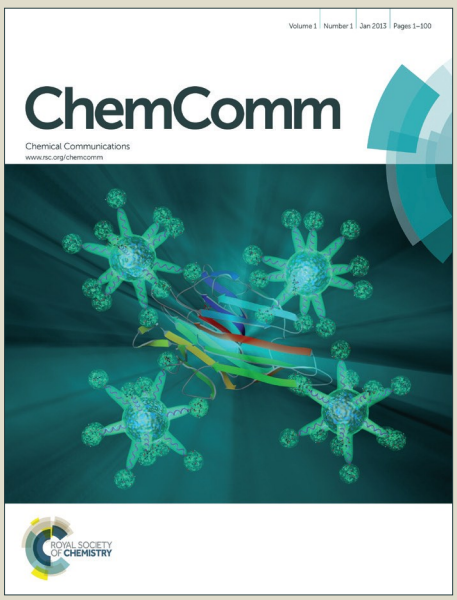

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ARTICLE TYPE

Asymmetric Kita spirolactonisation catalysed by *anti*-dimethanoanthracene-based iodoarenes

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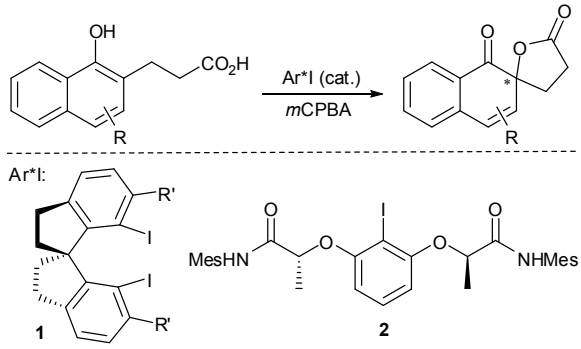
Enantiopure C_2-symmetric iodoarenes based on the rigid all-carbon *anti*-dimethanoanthracene framework are shown to catalyse the asymmetric oxidative Kita spirolactonisation of propanoic acid-tethered 1-naphthols with significant levels of asymmetric induction of up to 67% ee.

The oxidative dearomatisation of phenols is an efficient strategy for the rapid assembly of polycyclic structures frequently found in complex natural products.[1] 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.[1,2] Several asymmetric dearomatisation reactions have been disclosed in recent years.[3] 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,[4] yet remains under-developed and challenging.[5] Chiral hypervalent iodine reagents were employed by Birman[6] and Quideau[7] in the asymmetric *ortho*-hydroxylation of phenols to *ortho*-quinols, and recently by Harned in the asymmetric *para*-hydroxylation of phenols to *para*-quinols.[8] These reports constitute intermolecular reactions between the substrate and the incoming nucleophile. Kita reported the first intramolecular iodoarene-catalysed asymmetric oxidative dearomatisation of phenols.[9] In the presence of stoichiomeric amounts of *m*CPBA, the rigid spirobiindane-based diiodoarene **1a** was shown to catalyse the *ortho*-spirolactonisaton of propanoic acid substituted 1-naphthols with moderate enantioselectivity,[9a] which could be improved significantly with the *ortho*-ethyl derivative **1b** (Scheme 1).[9b] The *in situ* oxidation of **1** was proposed to form a μ-oxo-bridged bis-λ^3-iodane, postulated to be responsible for both high reactivity[10] and enantioselectivity.[9b] Subsequently, Ishihara disclosed lactate-derived conformationally flexible C_2-symmetric iodoarenes, such as bisamide **2**, capable of catalysing the asymmetric spirolactonisation of 1-naphthols with high levels of stereocontrol (Scheme 1).[11,12] The amide tethers in **2** were found to be crucial for both high reactivity and enantioselectivity.[13]



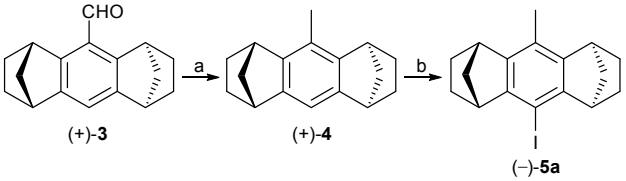
Scheme 1 Asymmetric spirolactonisation of 1-naphthols catalysed by Kita's diiodoarene **1** (**1a**: R' = H, **1b**: R' = Et) and Ishihara's iodoarene **2**

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,[9b] or a hydrogen bonding stabilised chiral pocket in the latter.[11a,13] 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.[14] However, significant asymmetric induction without such interactions is rare,[15] especially under catalytic conditions.[16]

We recently reported on the synthesis of a series of congested all-carbon aryl-iodanes based on the C_{2h}-symmetric *anti*-dimethanoanthracene framework and demonstrated that, despite their encumbered nature, they mediated various functional group transfer reactions, including the *ortho*-hydroxylation of phenols.[17] We now wish to report the synthesis of enantiopure iodoarene precursor analogues **5**, and disclose preliminary results from their application as catalysts in the asymmetric oxidative spirolactonisation of 1-naphthols.

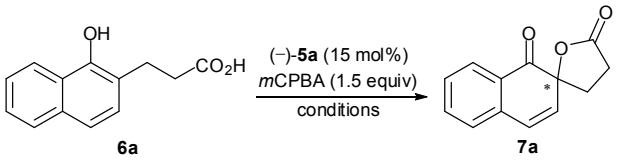
Contrary to the above systems, chirality transfer from iodoarenes **5** is solely dependent upon steric interactions with the rigid all-carbon *anti*-dimethanoanthracene backbone. Such a framework as a source of chirality is relatively unexplored, with most applications revolving around the use as asymmetric catalysts of *anti*-dimethanoanthracene containing Halterman-type metallotetraarylporphyrins.[18,19]

Our approach to iodoarene (−)-**5a** started from literature-known resolved aldehyde (+)-**3**.[18] Catalytic hydrogenation gave toluene derivative (+)-**4** in 99% yield which was iodinated using



Scheme 2 (a) H_2 (50 bar), 10% Pd/C, EtOAc, rt, 12 h, 99%; (b) DIB, I_2, EtOAc, rt, 12 h, 70%.

Table 1 Screening of reaction conditions using (–)-**5a** as catalyst[a]



6a **7a**

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	CH_2Cl_2	25	48	65	39
2	CH_2Cl_2	–20	48	29	37
3	CH_2Cl_2	0	5	21	40
4	$CHCl_3$	0	5	36	40
5	MeCN	0	5	35	29
6	$MeNO_2$	0	5	16	38
7	THF	0	5	<5	n.d.
8	Et_2O	0	5	<5	n.d.
9	Toluene	0	5	<5	n.d.

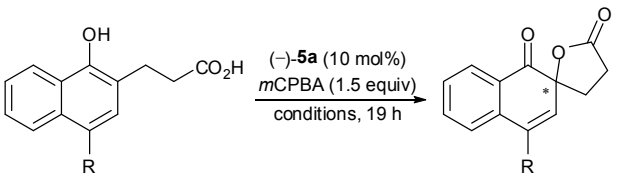
[a] Reaction conditions: **6a** (0.5 mmol), solvent (4 mL, 0.13 M). [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on chiral stationary phase.

(diacetoxyiodo)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 *m*CPBA, to the catalytic spirolactonisation of naphthol **6a**. An initial experiment was conducted with 15 mol% of (–)-**5a** in dichloromethane at room temperature for 48 hours which, gratifyingly, gave spirolactone **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 spirolactonisation 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 mixture systems 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 $CHCl_3/MeNO_2$ or $CHCl_3$/TFE (trifluoroethanol) had no significant effect on enantioseletivity (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 spirolactone (+)-(*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 $CHCl_3/MeNO_2$ 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

Table 2 Scope of the spirolactionisation reaction using (–)-**5a** as catalyst[a]



6 **7**

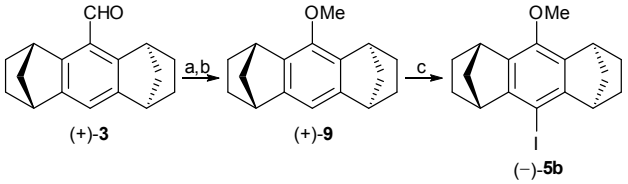
Entry	R	Solvent	Temp (°C)	Yield[b] (%)	Ee[c] (%)
1[d]	H (**6a**)	$CHCl_3$	0	36	40 (+)
2		$CHCl_3/MeNO_2$ (2:1)	–20	44	39 (+)
3		$CHCl_3$/TFE (2:1)	–20	38	37 (+)
4	Br (**6b**)	$CHCl_3$	0	64	40 (+)
5		$CHCl_3$	–20	61	60 (+)
6		$CHCl_3/MeNO_2$ (2:1)	–20	63	67 (+)
7		$CHCl_3$/TFE (2:1)	–20	58	40 (+)
8	Cl (**6c**)	$CHCl_3$	–20	57	42 (+)
9		$CHCl_3/MeNO_2$ (2:1)	–20	59	31 (+)
10		$CHCl_3$/TFE (2:1)	–20	60	33 (+)
11	CN (**6d**)	$CHCl_3$	–20	47	41 (+)
12		$CHCl_3/MeNO_2$ (2:1)	–20	32	23 (+)
13		$CHCl_3$/TFE (2:1)	–20	44	48 (+)
14	Ph (**6e**)	$CHCl_3$	–20	62	57 (+)
15		$CHCl_3/MeNO_2$ (2:1)	–20	58	24 (+)
16		$CHCl_3$/TFE (2:1)	–20	65	18 (+)
17[e]		$CHCl_3$/TFE (2:1)	–20	60	19 (+)

[a] Reaction conditions: **6** (0.5 mmol), solvent (4 mL, 0.13 M). [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on chiral stationary phase. [d] From Table 1, entry 4. [e] 0.02 M.

selectivity of 48% ee in the $CHCl_3$/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.

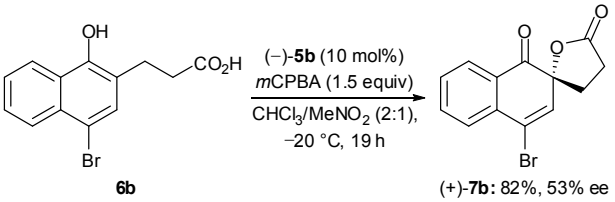
Given that iodoarene (–)-**5a** displayed moderate catalytic activity, we decided to examine electronically tuned analogues. We envisaged that decreasing the oxidation potential of iodoarene (–)-**5a** by introducing a electron-donating *para*-methoxy group would allow for a more efficient generation of the iodine(III) intermediate.[20] Thus, iodoarene (–)-**5b** was synthesised from aldehyde (+)-**3** by *m*CPBA oxidation to phenol (+)-**8** followed by methylation to anisol derivative (+)-**9**. Subsequent iodination of (+)-**9** proved to be problematic as neither the DIB/I_2 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-



(+)-**3** (+)-**9** (–)-**5b**

Scheme 3 (a) *m*CPBA, CH_2Cl_2, rt, 2 h, 73%; (b) NaOH, $(MeO)_2SO_2$, THF, reflux, 4 h, 93%; (c) NIS, CF_3CO_2H (cat.), MeCN, rt, 12 h, 79%.



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

lactonisation of **6b** in $CHCl_3/MeNO_2$, 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 spirolactone *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,[8] our transition state model places the equatorial *anti*-dimethanoanthracene partially eclipsed by the apical naphtholate ligand.[22] Minimising steric interactions in this arrangement positions the naphtholate ligand preferentially above the methano rather the ethano bridge of the *anti*-dimethanoanthrace backbone, blocking the bottom face from nucleophilic attack.[23] This leaves the top *Re*-face exposed towards C-O bond forming attack onto the naphtholate *ipso* carbon by the propanoic acid side chain, leading to the formation of **7** with an *R* configuration (Fig. 1).

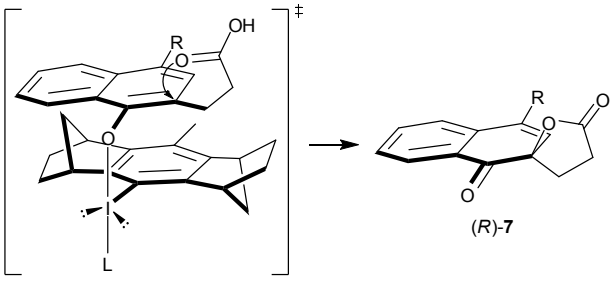


Fig. 1 Rationale for the observed enantioface selection in the spirolactonisation of 1-naphthols **6** (L = OR)

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 ^1H and ^{13}C spectra of all new compounds. See DOI: 10.1039/b000000x/

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