Hypervalent Compounds

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Enantioselective Kita Oxidative Spirolactonization Catalyzed by In Situ Generated Chiral Hypervalent Iodine(III) Species**

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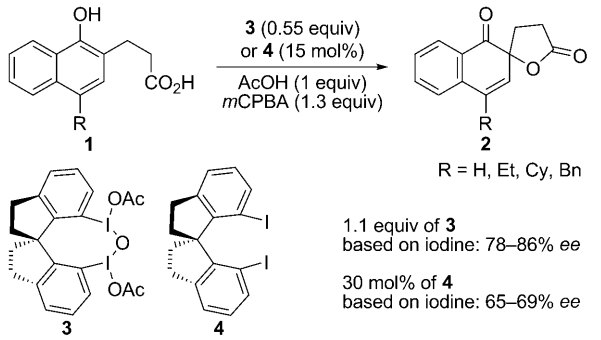
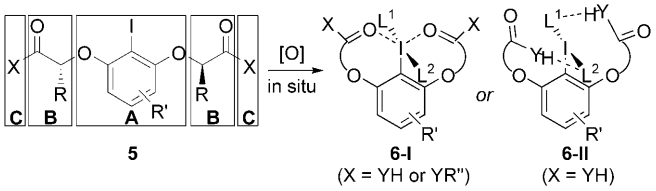
The development of enantioselective oxidative reactions catalyzed by chiral hypervalent iodine[1–4] is one of the most challenging areas in asymmetric organocatalysis. Recently, Kita and co-workers reported the enantioselective oxidative de-aromatization of 1-naphthol derivatives (**1**) into spirolactones **2** with high enantioselectivities (up to 86% *ee*) using stoichiometric chiral iodine(III) reagent **3**, which has a conformationally rigid 1,1-spiroindanone backbone (Scheme 1).[4] They also reported the catalytic use of **3** (30 mol% based on iodine), which was generated in situ from **4** and *m*CPBA in the presence of acetic acid, although the enantioselectivity was reduced to 69% *ee*.[4]



Scheme 1. Enantioselective oxidative spirolactonization of 1-naphthols (**1**) reported by Kita and co-workers.[4] Bn = benzyl, Cy = cyclohexyl, *m*CPBA = *m*-chloroperoxybenzoic acid.

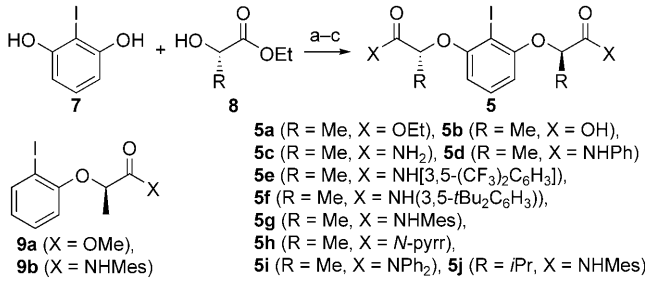
Recently, we reported the iodosylarene(III)-catalyzed oxidative lactonization reaction of ketocarboxylic acids with *m*CPBA [5a] which was analogous to the catalytic spirolactonization reported by Kita and co-workers.[4] Herein, we report the use of conformationally flexible C_2-symmetric chiral iodoarene **5g** (see Scheme 3) as a more effective precatalyst for the enantioselective Kita oxidative spirolactonization reaction. Iodine(III) catalyst **6g**, which is generated in situ from **5g** and *m*CPBA, tolerates a broader range of substrates and affords higher enantioselectivities (up to 92% *ee*) than Kita's previous work.[4] To the best of our knowledge, this catalytic system provides the highest asymmetric induction of all chiral hypervalent-iodine-catalyzed enantioselective oxidative reactions that have been reported to date.[2–4]

C_2-Symmetric chiral iodoarene **5** consists of three units: an iodoaryl moiety (**A**), chiral linkers (**B**), and subfunctional groups (**C**; Scheme 2). These units can be easily combined to afford a wide variety of chiral iodoarenes **5**. Iodosylarenes **6**, generated in situ from iodoarenes **5**, are thought to have intramolecular n–σ* interactions between the electron-deficient iodine(III) center (σ* orbital of C–I) of **A** and the Lewis basic group of **C** (lone pair of electrons (n)), such as carbonyl groups (**6-I**).[1,6] Alternatively, intramolecular hydrogen-bonding interactions between the acidic hydrogen of **C**, C(O)Y–H, and the iodine(III) ligand (L, such as an acetoxy group) might also be generated (**6-II**). We envisioned that a suitable chiral environment might be constructed around the iodine(III) center of **6** through such intramolecular interactions.



Scheme 2. Design of conformationally flexible iodoarene **5** (precatalyst) and iodosylarene **6** (catalyst).

The Mitsunobu reaction of 2-iodoresorcinol (**7**)[7] with (−)-ethyl lactate (**8**, R = Me) gave C_2-symmetric chiral iodoarene **5a** in 90% yield (Scheme 3). Hydrolysis of **5a**



Scheme 3. Synthesis of chiral iodoarenes **5** and **9**. Conditions: a) **7**, **8**, DIAD, PPh_3, 90% (**5b**); b) NaOH, 99% (**5a**); c) $SOCl_2$, then R^1R^2NH, 37–90% (**5c–j**). DIAD = diisopropyl azodicarboxylate. Mes = mesityl (2,4,6-trimethylphenyl), pyrr = *N*-pyrrolidinyl.

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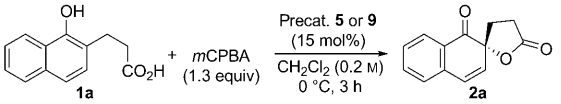
gave **5b** in quantitative yield without epimerization. Treatment of **5b** with thionyl chloride followed by several amines gave the corresponding amides **5c–i** in good yields. Compounds **5j**, **9a**,[2g] and **9b** were also prepared in a similar manner.

Next, a series of chiral iodoarenes were examined for their use as precatalysts for the enantioselective oxidative spirolactonization of **1a** into spirolactone **2a**, in the presence of *m*CPBA as a cooxidant under conditions described by Kita (Table 1).[4] The use of diester **5a** and dicarboxylic acid **5b**

Table 1: Precatalyst screening for the oxidative spirolactonization of **1a**.[8]



Entry	Precat.	Yield [%][a]	*ee* [%]	Entry	Precat.	Yield [%][a]	*ee* [%]
1	**5a**	27	23	9	**5i**	39	52
2	**5b**	26	43	10	**5j**	70	83
3	**5c**	40	70	11	**9a**	24	13
4	**5d**	25	77	12	**9b**	42	32
5	**5e**	53	75	13[b]	**5g**	56	88
6	**5f**	36	84	14[c]	**5g**	75	90
7	**5g**	64	82	15[d]	**5g**	82	85
8	**5h**	37	51	16[e]	**5g**	55	92

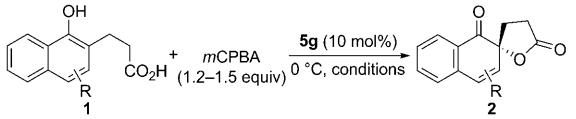
[a] Yield of isolated **2a**. [b] In CH_2Cl_2 (0.02 M), 0 °C, 5 h. [c] In CH_2Cl_2 (0.02 M), −20 °C, 48 h. [d] In CH_3NO_2 (0.02 M), 0 °C, 5 h. [e] In $CHCl_3$ (0.02 M), −20 °C, 48 h.

gave **2a** in 23% *ee* and 43% *ee*, respectively (Table 1, entries 1 and 2). In contrast, the use of bis(primary amide) **5c** gave **2a** in 70% *ee* (Table 1, entry 3), and the use of bis(*N*-aryl amide) compounds **5d–g** further increased the enantioselectivity (Table 1, entries 4–7). Bis(*N*-mesityl amide) **5g** as a precatalyst had the highest combination of activity and enantioselectivity (64% yield, 82% *ee*; Table 1, entry 7). Tertiary amides, such as **5h** and **5i**, gave moderate enantioselectivities (Table 1, entries 8 and 9). Bis(*N*-mesityl amide) **5j**, which has an *i*Pr group on the chiral linker (**B**) also gave high enantioselectivity and high catalytic activity, comparable to **5g** (Table 1, entry 10). However, monosubstituted iodoarenes, such as monoester **9a**[2g] and mono(*N*-mesityl amide) **9b**, gave low enantioselectivities (Table 1, entries 11 and 12). Therefore, the C_2-symmetric chirality in **6** seems to be essential for inducing high enantioselectivities in this oxidative spirolactonization reaction.

Next, we optimized the reaction conditions for **5g** (Table 1, entries 13–16). The enantioselectivity was enhanced at lower temperatures or under diluted conditions (Table 1, entries 13 and 14). Notably, good or high enantioselectivities were observed regardless of the polarity of the solvent.[8] In particular, **2a** was obtained in 82% yield with 85% *ee* in nitromethane (Table 1, entry 15); the highest enantioselectivity (92% *ee*) was observed in chloroform (Table 1, entry 16).

To explore the generality and the substrate scope of this spirolactonization procedure, several 1-naphthol derivatives **1** were prepared[8] and treated with **5g** (10 mol%) and *m*CPBA (1.2–1.5 equiv) under the optimized conditions (Table 2). The oxidation of 4-substituted naphthol derivatives **1b–1g** gave the corresponding spirolactones **2b–2g** in good to high yields

Table 2: Scope and limitations of the spirolactonization reaction.[8]



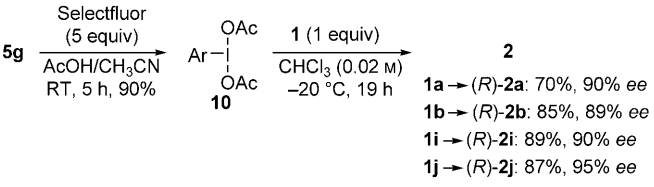
Entry	**2** (R)	Conditions	Yield [%][a]	*ee* [%]
1	**2b** (4-Me)	$CHCl_3/CH_3NO_2$,[b] 17 h	59	84
2	**2c** (4-Cl)	$CHCl_3$, 30 h	72	90
3	**2d** (4-Br)	$CHCl_3$, 16 h	67	85 (98)[c]
4	**2e** (4-Ph)	$CHCl_3$, 27 h	62	87 (98)[c]
5	**2f** (4-COPh)[d]	$CHCl_3/CH_3NO_2$,[b] 16 h	94	83 (>99)[c]
6	**2g** (4-COAr)[e]	$CHCl_3/CH_3NO_2$,[b] 30 h	92	84
7	**2h** (4-OMe)	$CHCl_3/CH_3NO_2$,[b] 7 h	28	0
8	**2i** (6-OMe)	$CHCl_3/CH_3NO_2$,[b] 18 h	40	87
9	**2j** (3-OMe)	$CHCl_3/CH_3NO_2$,[b] 24 h	3	88

[a] Yield of isolated **2**. [b] $CHCl_3/CH_3NO_2$ (2:1, v/v). [c] After a single recrystallization. [d] Compound **2f** was obtained in 67% yield and 91% *ee* under conditions: $CHCl_3$, 0 °C, 27 h. [e] Ar = 4-BrC_6H_4.

with high enantioselectivities (Table 2, entries 1–6). Importantly, nearly enantiomerically pure products **2d–2f** were obtained after a single recrystallization (≥98% *ee*, Table 2, entries 3–5). The absolute configuration of **2** was determined to be *R* from X-ray crystallographic analysis of **2f** (>99% *ee*; Table 2, entry 5).[8] Notably, oxidation of 4-benzoylnaphthol derivative **1f** gave **2f** in 94% yield and 83% *ee* (Table 2, entry 5). In sharp contrast to the report by Kita and coworkers, **3** afforded racemic **2f**.[4b] Although the oxidation of 4-methoxynaphthol derivative **1h** gave racemic **2h** (Table 2, entry 7), as did Kita's reagent **3**,[4] **5g** gave **2i** in 87% *ee*, for the oxidation of 6-methoxnaphthol derivative **1i** (Table 2, entry 8). Unfortunately, the 3-methoxynaphthol derivative **1j** gave **2j** in very low yield (Table 2, entry 9).

Iodosylarene diacetate **10**, which is analogous to **6g**, was isolated during the oxidation of **5g** with Selectfluor.[4] Treatment of **1a** with 1 equivalent of **10** in chloroform (0.02 M) at −20 °C gave (*R*)-**2a** in 90% *ee* (Scheme 4; cf. Table 1, entry 16). Thus, the iodine(III) compound that is generated in situ from **5** should be the actual oxidant in the spirolactonization reaction. Furthermore, the stoichiometric oxidations of **1b** and **1i** gave (*R*)-**2b** and (*R*)-**2i** in high yields and high enantioselectivities. Fortunately, (*R*)-**2j** was obtained in 87% yield and 95% *ee* from the stoichiometric oxidation of **1j**.

In summary, we have demonstrated the rational design of a conformationally flexible iodosylarene **6g** as a chiral



Scheme 4. Stoichiometric oxidation of **1** with iodosylarene **10**.

catalyst based on secondary n–σ* or hydrogen-bonding interactions for the enantioselective Kita oxidative spirolactonization.[9] We hope that precatalysts for other enantioselective oxidative transformations will be found from tuning the structure of the iodoarene precatalyst **5**. Studies to elucidate the mechanistic details are underway.

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[6] We do not yet have any experimental evidence for the nonbonding interactions between the iodine(III) center and functional groups in **6**. However, there are many reports on the intra- or intermolecular secondary interactions of I^{III} and I^{V}. For selected examples, see: a) V. V. Zhdankin, A. E. Koposov, J. T. Smart, *J. Am. Chem. Soc.* **2001**, *123*, 4095; b) M. Ochiai, *Coord. Chem. Rev.* **2006**, *250*, 2771, and the references therein.

[7] **7** was easily prepared from resorcinol, see: S. Tsujiyama, K. Suzuki, D. B. Guthrie, H. M. Gibney, D. P. Curran, *Org. Synth.* **2007**, *84*, 272.

[8] For details, see the Supporting Information.

[9] We also examined the spirolactonization reactions of simple phenol derivatives. Unfortunately, no sufficient results were observed under our present conditions. The desired spirolactones were obtained in very low yield (< 5%) as well as dimerization products and other side-products.

