## Hydrogen Bonding and Alcohol Effects in Asymmetric Hypervalent Iodine Catalysis: Enantioselective Oxidative Dearomatization of Phenols\*\*

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The enantioselective oxidative dearomatization of phenols and their analogues is a key reaction for the synthesis of several natural products.<sup>[1]</sup> Conventionally, enantioselective transition-metal catalysis has been used for these transformations.<sup>[1c-e]</sup> Recently, some research groups<sup>[2]</sup> have reported catalytic enantioselective oxidative dearomatization reactions using chiral hypervalent iodine compounds.<sup>[3]</sup> However, the catalytic activities and enantioselectivities are moderate, and the substrate scope of the oxidation reactions is limited to 1-naphthol derivatives. Herein, we describe the rationally designed chiral iodoarene 1, which is derived from chiral 2-aminoalcohol, as a chiral precatalyst for the first enantioselective catalytic oxidative dearomatization of phenol derivatives 3 to give the desired cyclohexadienone spirolactones **4** and the subsequent Diels–Alder adducts<sup>[4]</sup> **5** with high to excellent enantioselectivities (87-99% ee,



**Scheme 1.** Chiral organoiodine(III)-catalyzed enantioselective oxidative dearomatization of phenols and subsequent Diels–Alder reactions. m-CPBA = meta-chloroperoxybenzoic acid, L = ligand, Mes = mesityl.

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Scheme 1). Active iodine(III) species 2 would be generated in situ from  $C_2$ -symmetric and conformationally flexible chiral iodoarene 1 and *meta*-chloroperoxybenzoic acid (*m*-CPBA). We envisioned that a suitable chiral environment might be constructed around the iodine(III) center via intramolecular hydrogen bonding interactions between the acidic amido protons and the iodine(III) ligands (L).

A preliminary examination of  $1 \pmod{10}$  in the oxidative dearomatization of 2,4-di-tert-butylphenol derivative 3a with 1.2 equivalents of m-CPBA in chloroform gave cyclohexadienone 4a in 72% yield with 91% ee (Table 1, entry 1). However, the chemical yield and enantioselectivity of 4a were significantly reduced when the reaction was performed in distilled chloroform (entry 2). The commercial chloroform that we used (Nacalai Tesque Inc., Japan) contained a small amount (ca. 1 wt%) of ethanol as a stabilizer. Thus, we serendipitously found that both the chemical yield and enantioselectivity of 4a could be improved to the same level as in entry 1 by the addition of 10 equivalents of ethanol in distilled chloroform (entry 3). Next, alcohol additives and solvents were investigated in detail,<sup>[5]</sup> and the best result was obtained using 25 equivalents of methanol as an additive and dichloromethane as a solvent

Table 1: Oxidative dearomatization of 3 a.

tΒ	OH u tBu 3a	) CO <sub>2</sub> H	Precat. (10 mol%) -CPBA (1.2 equiv) solvent, additive -10 °C, 23 h	tBu tBu tBu tBu tBu tBu	) a
Entry	Precat.	Solvent	Additive (equiv)	Yield [%]	ee [%]
1	1	CHCl <sub>3</sub> <sup>[a]</sup>	-	72	91
2	1	CHCl <sub>3</sub> <sup>[b]</sup>	-	13	69
3	1	CHCl <sub>3</sub> <sup>[b]</sup>	EtOH (10)	74	91
4	1	$CH_2CI_2$	MeOH (25)	90	92
5	7	$CH_2Cl_2$	MeOH (25)	30	92
6	8	$CH_2Cl_2$	MeOH (25)	17	30
7	9	$CH_2Cl_2$	MeOH (25)	36	3
8	10	$CH_2Cl_2$	MeOH (25)	59	38

[a] Commercial chloroform (contains ca. 1 wt% of EtOH). [b] Distilled chloroform. For details, see the Supporting Information. Mes = mesityl.



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(entry 4). On the other hand, the use of bisamide 7,<sup>[2d]</sup> which we previously developed as a precatalyst for the Kita reaction of 1-naphthol derivatives, gave **4a** with high enantioselectivity, albeit in very low chemical yield (entry 5).<sup>[6]</sup> The use of other chiral iodoarenes, such as bis(tertiary amide) **8**, diester **9**, and monoamide **10**, gave **4a** in low yields and with low enantioselectivities (entries 5–8). These results suggested that the amido protons, as well as the C<sub>2</sub>-symmetric chirality in **1**, were essential for the present reaction.

In general, the oxidation of electron-deficient phenols is slower than that of electron-rich phenols.<sup>[1]</sup> In fact, **3b** was much less reactive than **3a** (Scheme 2 vs. Table 1).<sup>[7]</sup> After



**Scheme 2.** Oxidative dearomatization of **3b**. [a] Value in parentheses is after one recrystallization. HFIP=1,1,1,3,3,3-hexafluoro-2-propanol.

investigation,<sup>[5]</sup> we found that the reactivity was dramatically increased with the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)<sup>[8,9]</sup> instead of methanol as an additive, and **4b** was obtained in 84% yield with 87% *ee.* Importantly, enantiomerically pure (>99% *ee*) **4b** was obtained after a single recrystallization. Notably, not only the chemical yield, but also the enantioselectivity of **4b** dropped with the use of **7** (Scheme 2).

Cyclohexadienones are highly reactive for further chemical transformations, such as homo-dimerization and Diels– Alder reactions.<sup>[1,4]</sup> For example, after the oxidation of **3b** was complete, the addition of methyl vinyl ketone (**6A**) to the same flask gave the corresponding adduct **5bA** as a single diastereomer in 91 % yield with 87 % *ee* (Scheme 3).



Scheme 3. Oxidation of 3 b and subsequent Diels-Alder reaction.

Various phenols **3** were examined under optimized conditions (Scheme 4).<sup>[10]</sup> MeOH (Method I) and HFIP (Method II) were used as additives for the oxidation of electron-rich and electron-deficient phenols, respectively. Exceptionally, **3g** could be also efficiently oxidized in a mixture of dichloroethane and nitromethane.<sup>[5]</sup> Additionally, various dienophiles **6A–E** could be used for the subsequent reaction of **4** to give the corresponding products **5** as single diastereomers.<sup>[4,11]</sup> Thus, **4** and/or **5** could be obtained in high yields with excellent enantioselectivities (89–



**Scheme 4.** Scope of the enantioselective dearomatization and the subsequent Diels–Alder reactions. Methods, yields of isolated products and *ee* values are shown. Method I: **1** (10 mol%), *m*-CPBA (1.2 equiv), MeOH (25 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $-10^{\circ}$ C, 23 h; Method II: **1** (5 mol%), *m*-CPBA (1.2 equiv), HFIP (50 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $-20^{\circ}$ C, 18–24 h. [a] The reaction was performed with **3g** (1 mmol) using **1** (1 mol%) at  $-10^{\circ}$ C in DCE/MeNO<sub>2</sub>. [b] Optically pure products were obtained after a single recrystallization. For details, see the Supporting Information. DCE = 1,2-dichloroethane, Ts = *para*-toluenesulfonyl.

99% *ee*). The oxidation of **3a** (Table 1) and 3-substituted phenols **3c-f** ( $\mathbb{R}^4 \neq H$ ) gave the corresponding cyclohexadienones **4**, which did not easily react with a dienophile for steric reasons. In contrast, cyclohexadienones **4h-j** were too unstable to be isolated, and could be successively transformed into **5**. The oxidation of **3b** and **3g** gave **4b** and **4g**, respectively, which could also be easily reacted with **6** to give the corresponding products **5** (Schemes 2–4). Importantly, the catalyst loading of **1** could be reduced to 1 mol% without seriously reducing the chemical yield and enantioselectivity (**5gA**). The absolute configurations of **4** and **5** were determined based on X-ray crystal analysis of **4b**, **5gA**, and **5kA**.<sup>[5]</sup>

To gain insight into the present hypervalent iodine catalysis, iodosylarene diacetate 11 (OR=OCOMe) and



**Scheme 5.** a) Preparation of iodines **11** and **12**. Key NOE correlations are shown by blue arrows. b) X-ray crystal structures of **1** and **12** (top view). Hydrogen atoms, except for the amide protons, were omitted for clarity. C dark grey, H light grey, O red, N blue, I pink.

dimethoxide **12** (OR = OMe) were prepared by the oxidation of **1** and ligand exchange, respectively (Scheme 5 a).<sup>[5]</sup> Fortunately, we succeeded in obtaining single crystals, which were suitable for X-ray diffraction analysis of **1** and **12** (Scheme 5b).<sup>[5]</sup> The two intramolecular hydrogen-bonding interactions between the acidic amido protons and the methoxy ligands in **12** were clearly observed, and the folded geometry was confirmed. In contrast, the conformation of **1** was confirmed to be linear. The folding conformation of **11** and **12** in solution was also confirmed by nuclear Overhauser effect (NOE) analysis (Scheme 5 a).<sup>[6]</sup>

The proposed additive effect of methanol for the oxidation of electron-rich phenols is depicted in Scheme 6.<sup>[5]</sup> In the presence of excess amounts of methanol, methoxyphenoxy iodine(III) complex **14** might be generated from acyloxyphenoxy iodine(III) complex **13** through ligand exchange under equilibrium conditions. The oxidative cyclization reaction should enantioselectively occur to produce enantioenriched **4** 





**Scheme 6.** Proposed additive effect of methanol for the oxidation of electron-rich phenols. EDG = electron-donating group.

(Scheme 6, enantioselective path). In contrast, if the phenoxenium ion 15 is generated through dissociation of the iodoarene moiety ([Ar\*I(OCOR)]-) from 13, racemic 4 would be obtained (Scheme 6, racemic path).<sup>[12]</sup> Dissociative intermediate 15 might be preferentially generated in the oxidation of more electron-rich phenols, owing to stabilization of the cationic intermediates.<sup>[12]</sup> The generation of 15 might be suppressed by the formation of 14, as the leaving ability of a methoxy ligand would be inferior to that of a carboxylate ligand.<sup>[12]</sup> In fact, the enantioselectivities were significantly improved with the use of MeOH for the catalytic or stoichiometric<sup>[5]</sup> oxidation of electron-rich phenols (Table 1). Additionally, control experiments suggest that MeOH both accelerates the oxidation reaction, as a protic polar solvent, and improves the enantioselectivity, as a ligand of iodine(III).<sup>[5]</sup>

In summary, we have developed a novel, highly effective hypervalent organoiodine catalytic method for the highly enantioselective oxidative dearomatization of phenols. Intramolecular hydrogen bonding interactions and additional achiral alcohols play crucial roles in the enantioselectivity and turnover frequency (TOF) of hypervalent organoiodine catalysis. Thus, not only low catalyst loading (1–10 mol%), but also high enantioselectivity (up to >99% *ee*) could, for the first time, be achieved in the field of hypervalent organoiodine chemistry. Studies to elucidate the detailed mechanism are currently underway.

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- Selected recent reviews, see: a) "Sequential Reactions Initiated by Oxidative Dearomatization": S. K. Jackson, K.-L. Wu, T. R. R. Pettus in *Biomimetic Organic Synthesis* (Eds.: E. Poupon, B. Nay), Wiley-VCH, Weinheim, **2011**, chap. 20; b) C.-C. Liao, R. K. Peddinti, *Acc. Chem. Res.* **2002**, *35*, 856; c) S. Quideau, D. Deffieux, L. Pouységu, *Tetrahedron* **2010**, *66*, 2235; d) S. P. Roche, J. A. Porco, *Angew. Chem.* **2011**, *123*, 4154; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; e) A. Bartoli, F. Rodier, L. Commeiras, J.-L. Parrain, G. Chouraqui, *Nat. Prod. Rep.* **2011**, *28*, 763; f) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem.* **2012**, *124*, 12834; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662.
- [2] a) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, Angew. Chem. 2008, 120, 3847; Angew. Chem. Int. Ed. 2008, 47, 3787; b) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, J. Am. Chem. Soc. 2013, 135, 4558; c) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chenede, Angew. Chem. 2009, 121, 4675; Angew. Chem. Int. Ed. 2009, 48, 4605; d) M. Uyanik, T. Yasui, K. Ishihara, Angew. Chem. 2010, 122, 2221; Angew. Chem. Int. Ed. 2010, 49, 2175; e) M. Uyanik, T. Yasui, K. Ishihara, Tetrahedron 2010, 66, 5841.
- [3] For recent reviews, see: a) D. W. Lupton, M. Ngatimin, Aust. J. Chem. 2010, 63, 653; b) H. Liang, M. A. Ciufolini, Angew. Chem. 2011, 123, 12051; Angew. Chem. Int. Ed. 2011, 50, 11849; for selected recent examples, see: c) U. Ladziata, J. Carlson, V. V. Zhdankin, Tetrahedron Lett. 2006, 47, 6301; d) J. K. Boppisetti,

Angew. Chem. Int. Ed. 2013, 52, 9215-9218

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## Angewandte Communications

V. B. Birman, Org. Lett. 2009, 11, 1221; e) M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, Tetrahedron Lett. 2007, 48, 8691; f) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, Angew. Chem. 2010, 122, 7222; Angew. Chem. Int. Ed. 2010, 49, 7068; g) M. Fujita, M. Wakita, T. Sugimura, Chem. Commun. 2011, 47, 3983; h) C. Röben, J. A. Souto, Y, González, A. Lishchtnskyi, K. Muñiz, Angew. Chem. 2011, 123, 9650; Angew. Chem. Int. Ed. 2011, 50, 9478; i) U. Farid, T. Wirth, Angew. Chem. 2012, 124, 3518; Angew. Chem. Int. Ed. 2012, 51, 3462; for examples of chiral hypervalent iodine catalysts, see: j) S. M. Altermann, R. D. Richardson, T. K. Page, R. K. Schmidt, E. Holland, U. Mohammed, S. M. Paradine, A. N. French, C. Richter, A. M. Bahar, B. Witulski, T. Wirth, Eur. J. Org. Chem. 2008, 5315; k) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, Science 2010, 328, 1376; l) J. Yu, J. Cui, X.-S. Hou, S.-S. Liu, W.-C. Gao, S. Jiang, J. Tian, C. Zhang, Tetrahedron: Asymmetry 2011, 22, 2039; m) A. Rodríguez, W. J. Moran, Synthesis 2012, 1178; n) A.-A. Guilbault, B. Basdevant, V. Wanie, C. Y. Legault, J. Org. Chem. 2012, 77, 11283.

- [4] a) I. Drutu, J. T. Njardarson, J. L. Wood, Org. Lett. 2002, 4, 493; For representative examples of related Diels – Alder reactions of masked o-benzoquinones, see: b) H. Auksi, P. Yates, Can. J. Chem. 1981, 59, 2510; c) O. Arjona, R. Medel, J. Plumet, R. Herrera, H. A. Jiménez-Vázquez, J. Tamariz, J. Org. Chem. 2004, 69, 2348; d) J. Gagnepain, R. Méreau, D. Dejugnac, J.-M. Léger, F. Castet, D. Deffieux, L. Pouységu, S. Quideau, Tetrahedron 2007, 63, 6493; e) S.-Y. Luo, T.-J. Jang, J.-Y. Liu, C.-S. Chu, C.-C. Liao, S.-C. Hung, Angew. Chem. 2008, 120, 8202; Angew. Chem. Int. Ed. 2008, 47, 8082; f) S. R. Surasani, V. S. Rajora, N. Bodipati, R. K. Peddinti, Tetrahedron Lett. 2009, 50, 773; g) V. Singh, P. Bhalerao, S. M. Mobin, Tetrahedron Lett. 2010, 51, 3337.
- [5] For details, see the Supporting Information.

- [6] Additionally, oxidation of 3a with 7 in the absence of methanol gave only trace amount of 4a. These results can be explained by the fact that the oxidation of 7 to the corresponding iodine(III) and the consumption of iodine(III) were much slower than those of 1. For details, see the Supporting Information.
- [7] The pK<sub>a</sub> values of 4-bromo-3-methylphenol and 2,4-di-*tert*-butylphenol are 9.5 and 11.7, respectively. J. B. Quintana, R. Rodil, S. Muniategui-Lorenzo, P. López-Mahía, D. Prada-Rodríguez, J. Chromatogr. A 2007, 1174, 27.
- [8] T. Dohi, N. Yamaoka, Y. Kita, Tetrahedron 2010, 66, 5775.
- [9] The beneficial effect of HFIP on the reactivity of hypervalentorganoiodine-mediated reactions was investigated by Kita et al.<sup>[8]</sup> However, in accordance with the previous work of Kita<sup>[2a,b]</sup> and ourselves,<sup>[2d,e]</sup> the enantioselectivities were significantly lower for the oxidation of 1-naphthol derivatives in the presence of HFIP. In sharp contrast, HFIP did not reduce the enantioselectivities for the present oxidation of electron-deficient phenols. This can be explained by the dissociative path of electron-deficient phenols being disfavored under our conditions.
- [10] Unfortunately, the oxidation of unsubstituted phenols ( $R^1-R^4 = H$ ) was inefficient under the present conditions.
- [11] The perfect diastereoselectivities of the present Diels–Alder reactions are in agreement with earlier studies on related [4+2] cycloadditions of cyclohexadienones; see Refs. [1] and [4].
- [12] a) L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, A. Pelter, J. Chem. Soc. Perkin Trans. 1 1999, 379; b) A. Pelter, R. S. Ward, Tetrahedron 2001, 57, 273.
- [13] a) M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem.* 2006, 118, 8383; *Angew. Chem. Int. Ed.* 2006, 45, 8203; b) "Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis": M. Ochiai in *Topics in Current Chemistry, Vol.* 224 (Ed.: T. Wirth), Springer, Berlin, 2003, pp. 5–68.