Oxidation

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A Chiral Hypervalent Iodine(III) Reagent for Enantioselective Dearomatization of Phenols[**]

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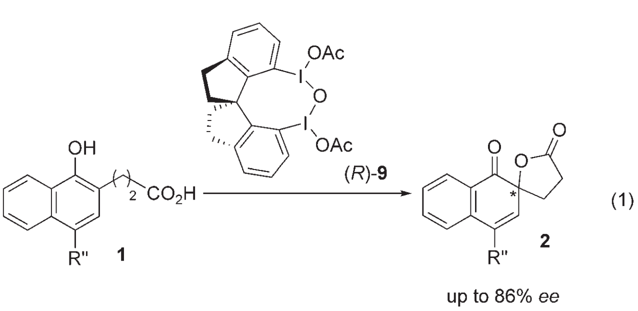
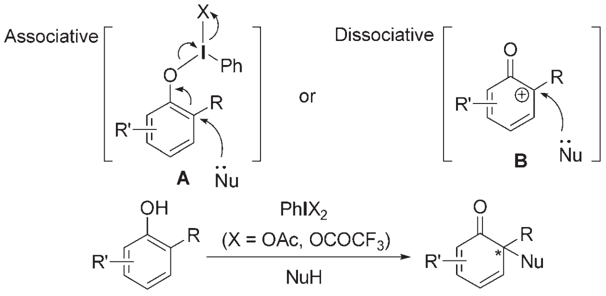
Asymmetric induction by hypervalent iodine reagent control is challenging work. Many efforts have been devoted to the design of new chiral reagents with the aim of achieving asymmetric oxidations with high stereoselectivities.[1] However, no effective chiral hypervalent iodine compounds have been reported thus far. We report herein a promising new chiral hypervalent iodine(III) reagent ((*R*)-**9**), having a rigid spirobiindane backbone, for the first enantioselective dearomatization of phenols [Eq. (1)]. The use of this chiral reagent also provides important mechanistic insights into the dearomatization processes of phenols induced by hypervalent iodine(III) reagents.



For the past two decades we have been engaged in hypervalent iodine(III)-induced oxidative dearomatizations of phenols, and applied the transformations to natural product syntheses.[2] Phenolic oxidations are pivotal steps frequently involved in the biosynthesis of naturally occurring products, which possess a variety of important biological activities.[3] Therefore, there exists a continuing interest in such transformations and hypervalent iodine(III) reagents can be particularly attractive organo-oxidants because of low-toxicity and because it is ecologically benign for applications in natural product syntheses.[4] The key intermediate in the reaction, phenoxy-λ^3-iodane species **A**, would be formed first by ligand transfer[5] of the phenolic oxygen atom to the iodine(III) center (Scheme 1). The oxidation to quinone or quinol variants (i.e. cyclohexadienones) is typically rationalized as proceeding by the attack of a nucleophile on intermediate **A** in an associative manner.[6] Alternatively, the oxidation could include discrete phenoxenium ions of type **B**, which are formed after dissociation of iodobenzene from intermediate **A**, and subsequent attack by the nucleophile to deliver the product; the mechanism was supported by both theoretical and experimental evidences. [7]



Scheme 1. The two postulated types of intermediates: **A** and **B**. R, R′ = alkyl or alkoxy.

Elucidation and control of the two distinct mechanisms would help in the construction of advanced oxidative transformations of phenols by hypervalent iodine reagents, which are attractive because of recent interest in clean, safe, and practical methods that avoid the use of toxic metal oxidants.[8] The possibility for asymmetric induction when using optically active iodine(III) compounds with suitable chiral environments is anticipated, especially from intermediates **A**. However, preliminary studies on the intermolecular reactions of phenols with nucleophiles led to the conclusion that there was no opportunity for such asymmetric induction by chiral reagent control because of the exclusive formation of phenoxenium ion **B** during the reaction.[7b,c] The intramolecular reactions have not yet been examined thus far.

In this study, we used intramolecular oxidative substitution of naphthol **1a** ([Eq. (1)] where $R'' = \text{H}$) as a model case since the resulting five-membered chiral spirolactone naph-

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thoquinol **2a**[9] ([Eq. (1)] where R'' = H) is amenable to isolation.[10] Under the assumption that fast attack of the internal carboxylic acid at the prochiral carbon center of an intermediate of type **A** would alter the course of the reaction mechanism to one that is concerted and more favorable, we examined the asymmetric reaction of **1a** by using a variety of reported optically active iodine(III) carboxylates, such as **3**–**5** (> 98% *ee*),[1b–d] in dichloromethane, which gave disappointing *ee* values (Figure 1).

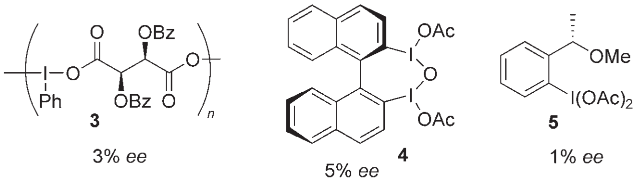


Figure 1. The enantioselectivities of **2a** obtained by the spirocyclization of **1a** with **3**–**5**. Bz = benzoyl. The *ee* values in the figure are those for the resulting oxidation product **2a**.

The above results imply the involvement of transition states that have certain chiral environments under the stated conditions despite their low enantiocontrol. Inspired by this evidence, intensive studies on the design of new chiral iodine(III) compounds were pursued in our laboratory. We hypothesized that one of the major reasons for the low enantioselectivities observed when using compounds **3**–**5** was the liberation of the chiral ligand (for **3**), or the formation of conformationally flexible iodoarenes (for **4** and **5**) during the last step of the reaction. On the basis of this hypothesis we introduced a rigid 1,1'-spirobiindane backbone;[11] the rigid structure was selected to maintain the chiral environment around the iodine(III) center throughout the reaction (Figure 2).

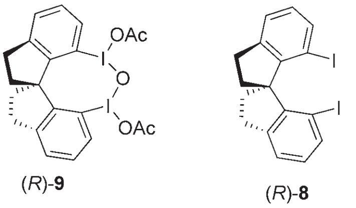
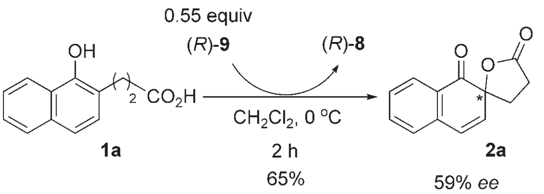


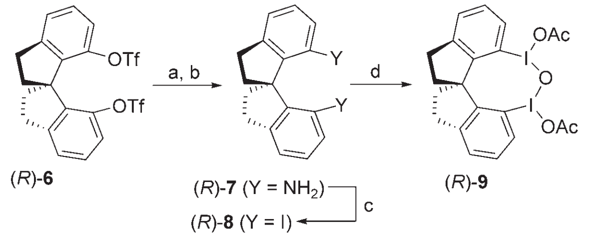
Figure 2. New chiral hypervalent iodine(III) reagent (*R*)-**9**.

Surprisingly, reaction of optically active (*R*)-**9** with naphthol **1a** under the same conditions significantly enhanced the selectivity to provide enantioenriched **2a** in a good yield [Eq. (2)].



(2)

The synthesis of newly developed iodine(III) compound (*R*)-**9** was accomplished from known triflate precursor (*R*)-**6**[11c] by using a four-step conversion sequence (Scheme 2). Thus, after introduction of the iodine atom by using conventional protocols to transform diamine **7**, treatment of corresponding (*R*)-**8** ($[\alpha]_D^{25} = +6.3°$ ($c = 0.93$, $CHCl_3$)) with Selectfluor in dilute $AcOH/CH_3CN$[12] afforded optically pure μ-oxo-bridged iodine(III) carboxylate (*R*)-**9** ($[\alpha]_D^{25} = +21.0°$ ($c = 1.09$, $CHCl_3$)); (*R*)-**9** is a white powder[13] that is stable in the refrigerator for several months if protected from light. The formation of **9** was confirmed by high resolution fast-atom bombardment mass spectroscopy measurements and NMR and IR spectroscopies. The ^1H NMR observation of (*R*)-**9** at 25 °C showed a single peak of for the two acetoxy groups and three different types of aromatic protons, all in accord with the fine symmetric structure of **9**.



Scheme 2. Preparation of new chiral iodine(III) compound (*R*)-**9**. Reagents and conditions: a) $Pd(OAc)_2$, BINAP, $BnNH_2$, Cs_2CO_3, toluene, 100 °C, 2 h; b) $Pd(OH)_2/C$, H_2 (1 atm), AcOEt/MeOH, 40 °C, 16 h (80% from (*R*)-**6**); c) $NaNO_2$, TFA, 0 °C, 30 min., then KI, RT→40 °C, 5 h, 52%; d) Selectfluor, $AcOH/CH_3CN$, RT, 12 h, 90%. BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl; TFA = trifluoroacetic acid; Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate.

One important mechanistic insight into the reaction has been identified by screening different solvents for the oxidation of **1a** with optically active (*R*)-**9** (Table 1). The *ee* values of **2a** obtained from the reactions were highly dependent on the solvent polarities. The results from using a series of noncoordinative solvent systems showed good correlation between the *ee* values and the E_T values[14] of the solvents (Table 1, entries 1–4). One possible explanation for the phenomenon is that there is participation of discrete cationic intermediates (**B** in Scheme 1) in the more polar

Table 1: Correlation of the solvent polarity and *ee* values for the reaction in [Eq. (2)].[a]

Entry	Solvent	$E_T(30)$[b] [kcal mol^{-1}]	*ee* [%]	*t* [h]	Yield [%]
1	CCl_4	32.5	70	2	47
2	$CHCl_3$	39.1	72	2	64
3	CH_2Cl_2	41.1	59	2	65
4	$ClCH_2CH_2Cl$	41.9	60	2	69
5	CH_3CN	46.0	20	2	50
6	$CH_3CN/AcOH$ (10:1)	46.5	16	2	77
7	$(CF_3)_2CHOH$	69.3	0	0.5	87

[a] The reactions were performed with 0.55 equiv (110 mol% iodine) of (*R*)-**9**. [b] Reported values from reference [14].

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solvents. In fact, the use of more polarizable solvents, such as CH_3CN, AcOH, and ultimately $(CF_3)_2CHOH$, produced increasingly inferior *ee* values as the E_T values increased (Table 1, entries 5–7).

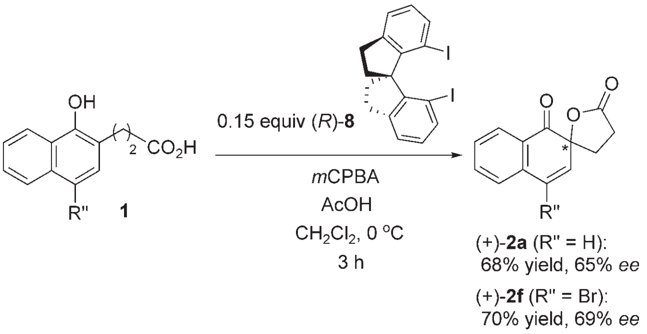
Finally, the selected examples of the reactions with the 4-alkoxy- and 4-alkylnaphthol derivatives **1** are listed in Table 2. A slightly better *ee* value was obtained at lower temperature (−50 °C; Table 2, entry 1). As expected from the ambident nature of reaction intermediates **A** and **B**, the presence of the electron-donating group in **1** reduced the *ee* value of product **2** even though it is located in a remote position (Table 2, entry 2). In contrast, alkylnaphthols **1c–e** were generally suitable for fully exerting the stereoselective ability of reagent (*R*)-**9** in the oxidations (Table 2, entries 3–5). The new reagent ((*R*)-**9**) showed high reactivity suitable for providing oxidation products **2** in good yields. The ability of reagent (*R*)-**9** to exert stereocontrol at the quaternary chiral carbon center in products **2** indicates that the present method is a powerful alternative to the previously reported oxidation methods of enol ethers for obtaining chiral α-hydroxy ketones.[15]

Table 2: Effect of the 4-substituents (R″) of **1** on the *ee* values for the reaction in [Eq. (1)].[a]

Entry	R″	Product	*ee* [%]	Yield [%]
1	H (**1a**)	(+)-**2a**	78	66
2	OMe (**1b**)	(±)-**2b**	0	30
3	Et (**1c**)	(+)-**2c**	81	83
4	Cy (**1d**)	(+)-**2d**	81	80
5	Bn (**1e**)	(+)-**2e**	86	86

[a] Performed with 0.55 equiv of (*R*)-**9** in chloroform at −50 °C for 2 h. Cy = cyclohexyl.

Although further explorations are required, catalytic use of chiral reagent (*R*)-**9** is possible by using the corresponding chiral iodoarene (*R*)-**8** and *m*-chloroperbenzoic acid (*m*CPBA) as a catalyst and co-oxidant, respectively (Scheme 3).[16,17] Thus, both phenol **1a** and functionalized **1f** (R″ = Br) afforded cyclization products **2a** and **2f**, respectively, with good enantioselectivities in the presence of catalytic amounts of (*R*)-**8** (0.15 equiv), *m*CPBA (1.3 equiv), and AcOH (1 equiv) in dichloromethane at 0 °C. After the completion of the reaction catalyst iodoarene (*R*)-**8** was easily recovered by using silica gel column chromatography. In this way, the use of our catalytic strategy for the phenolic oxidations makes the new chiral reagent (**9**) practical and versatile.



Scheme 3. Catalytic utilization of the new chiral reagent.

In summary, we have succeeded in the first enantioselective oxidative dearomatization of phenols to construct a chiral *ortho*-spirolactone structure under reagent control by the use of new chiral organoiodine(III) compound **9**. The reactions demonstrate the highest level of the asymmetric induction (c.a. 86% *ee*) in the field of iodine(III)-mediated transformations, and detailed investigations into the transition-state model of the present reaction will contribute to the theoretical design of more effective chiral reagents; understanding the reaction mechanism will enable the advance of phenolic oxidations in accord with the natural product syntheses.

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[1] a) T. Imamoto, H. Koto, *Chem. Lett.* **1986**, 967; b) D. G. Ray, G. F. Koser, *J. Org. Chem.* **1992**, *57*, 1607; c) U. H. Hirt, B. Spingler, T. Wirth, *J. Org. Chem.* **1998**, *63*, 7674; d) M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233; e) H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519; f) U. Ladziata, J. Carlson, V. V. Zhdankin, *Tetrahedron Lett.* **2006**, *47*, 6301; g) R. D. Richardson, T. K. Page, S. Altermann, S. M. Paradine, A. N. French, T. Wirth, *Synlett* **2007**, 538.

[2] a) Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem.* **1987**, *52*, 3927; b) Y. Kita, H. Tohma, K. Kikuchi, M. Inagaki, T. Yakura, *J. Org. Chem.* **1991**, *56*, 435; c) Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka, T. Yakura, *J. Am. Chem. Soc.* **1992**, *114*, 2175; d) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, *63*, 6625; e) H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, M. Egi, Y. Kita, *Angew. Chem.* **2002**, *114*, 358; *Angew. Chem. Int. Ed.* **2002**, *41*, 348.

[3] a) S. G. Humphries in *Biogenesis of Natural Products* (Ed.: P. Bernfeld), McMillan, New York, **1963**, p. 617; b) J. S. Swenton in *The Chemistry of Quinonoid Compounds*, *Vol. 2*, Part 2 (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1988**, p. 899; c) D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383; d) S. E. Bode, D. Drochner, M. Müller, *Angew. Chem.* **2007**, *119*, 6020; *Angew. Chem. Int. Ed.* **2007**, *46*, 5916.

[4] a) R. M. Moriarty, O. Prakash, *Org. React.* **2001**, *57*, 327; b) H. Tohma, Y. Kita in *Hypervalent Iodine Chemistry* (Ed.: T. Wirth), Springer, Berlin, **2003**, p. 209; c) A. Varvoglis, *Hypervalent Iodine in Organic Synthesis* Academic Press, San Diego, **1997**; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523.

[5] a) R. Bell, K. J. Morgan, *J. Chem. Soc.* **1960**, 1209; b) R. M. Moriarty, O. Prakash, M. P. Duncan, *Synthesis* **1985**, 943; c) R. M. Moriarty, O. Prakash, *Acc. Chem. Res.* **1986**, *19*, 244; d) A. Ozanne-Beaudenon, S. Quideau, *Angew. Chem.* **2005**, *117*, 7227; *Angew. Chem. Int. Ed.* **2005**, *44*, 7065.

[6] a) N. Lewis, P. Wallbank, *Synthesis* **1987**, 1103; b) R. Barret, M. Daudon, *Tetrahedron Lett.* **1990**, *31*, 4871; c) D. Mal, H. N. Roy, N. K. Hazra, S. Adhikari, *Tetrahedron* **1997**, *53*, 2177; d) S. Quideau, M. A. Looney, L. Pouysegu, *Org. Lett.* **1999**, *1*, 1651; e) S. Quideau, L. Pouységu, M. Oxoby, M. A. Looney, *Tetrahedron* **2001**, *57*, 319; f) J. L. Wood, J. K. Graeber, J. T. Njardarson, *Tetrahedron* **2003**, *59*, 8855.

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[7] a) A. Pelter, S. Elgendy, *Tetrahedron Lett.* **1988**, *29*, 677; b) L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, A. Pelter, *J. Chem. Soc. Perkin Trans. 1* **1999**, 379; c) A. Pelter, R. S. Ward, *Tetrahedron* **2001**, *57*, 273.

[8] Selected works for stereoselective dearomatization of phenols: a) L. H. Mejorado, C. Hoarau, T. R. R. Pettus, *Org. Lett.* **2004**, *6*, 1535; b) M. Murakata, K. Yamada, O. Hoshino, *J. Chem. Soc. Chem. Commun.* **1994**, 443; c) S. Quideau, I. Fabre, D. Deffieux, *Org. Lett.* **2004**, *6*, 4571; d) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404.

[9] Recent reports of natural product syntheses containing chiral *ortho*-spirolactone structures: a) T. Siu, C. D. Cox, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 5787; *Angew. Chem. Int. Ed.* **2003**, *42*, 5629; b) D. A. Henderson, P. N. Collier, G. Pave, P. Rzepa, A. J. P. White, J. N. Burrows, A. G. M. Barrett, *J. Org. Chem.* **2006**, *71*, 2434.

[10] In contrast, the cyclohexa-2,4-dienones obtained from the oxidation of phenols are generally quite reactive and are useful for subsequent transformations. See, references [3] and [4].

[11] The 1,1′-spirobiindane backbone has been introduced as an elegant ligand for transition metals in asymmetric syntheses: a) V. B. Birman, A. L. Rheingold, K. C. Lam, *Tetrahedron: Asymmetry* **1999**, *10*, 125; b) A. G. Hu, Y. Fu, J. H. Xie, H. Zhou, L. X. Wang, Q. L. Zhou, *Angew. Chem.* **2002**, *114*, 2454; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348; c) J. H. Xie, L. X. Wang, Y. Fu, S. F. Zhu, B. M. Fan, H. F. Duan, Q. L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404.

[12] C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961.

[13] Although (*R*)-**9** could be obtained by using *m*CPBA in AcOH/CH_2Cl_2, higher purity of (*R*)-**9** was obtained by the method using Selectfluor.

[14] a) C. Reichardt, *Angew. Chem.* **1979**, *91*, 119; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 98; b) C. Reichardt, *Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim, **1979**.

[15] a) K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 8463; b) A. Solladié-Cavallo, P. Lupattelli, L. Jierry, P. Bovicelli, F. Angeli, R. Antonioletti, A. Klein, *Tetrahedron Lett.* **2003**, *44*, 6523.

[16] a) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem.* **2005**, *117*, 6349; *Angew. Chem. Int. Ed.* **2005**, *44*, 6193; b) T. Dohi, A. Maruyama, Y. Minamitsuji, N. Takenaga, Y. Kita, *Chem. Commun.* **2007**, 1189.

[17] Reviews: a) T. Dohi, Y. Kita, *Kagaku* **2006**, *61*, 68; b) R. D. Richardson, T. Wirth, *Angew. Chem.* **2006**, *118*, 4510; *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.

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