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Asymmetric Oxidation of *o*-Alkylphenols with Chiral 2-(*o*-Iodoxyphenyl)-oxazolines

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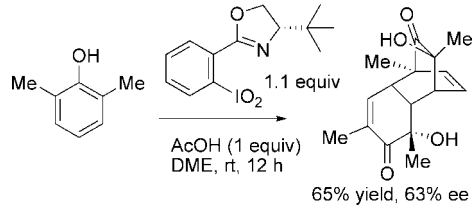
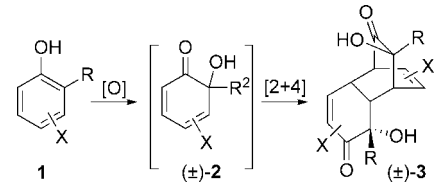
ABSTRACT



A new class of chiral iodine(V) derivatives has been prepared. These compounds have been found to transform *ortho*-alkylphenols into *ortho*-quinol Diels−Alder dimers with significant levels of asymmetric induction.

A reaction of *o*-alkylphenols **1** with achiral oxidants, such as sodium periodate **4**,[1] benzeneseleninic anhydride **5**,[2] and *o*-iodoxybenzoic acid (IBX) **6**,[3] produces *o*-quinols **2**, which dimerize spontaneously via a regio- and stereoselective intermolecular Diels−Alder reaction to give tricyclic products **3** (Scheme 1, Figure 1). The overall process is remarkable for the rapid increase in molecular complexity achieved in a single preparative step. Until a few years ago, enantioselective oxidative dearomatization of phenols remained unknown. In 2005, Porco et al. published a highly enantioselective oxidation of resorcinols with stoichiometric amounts of copper−spartein−dioxygen complex **7**.[4a] In 2008, they extended this process to *o*-alkylphenols producing *o*-quinol dimers with 99% ee's.[4b] The same year, Kita et al. developed a related process—asymmetric *ortho*-acetoxylation—using spirocyclic iodine(III) derivative **8**.[5]

Scheme 1. Transformation of *o*-Alkylphenols into *o*-Quinol Dimers



Prompted by these reports, we disclose the results of our recent studies in this area.

In connection with a total synthesis project, we sought to find new types of chiral oxidants capable of converting *o*-alkylphenols into *o*-quinol dimers in an enantioselective fashion. Inspired by the success of IBX in the racemic variant of this reaction,[3] we decided to explore the potential of chiral organoiodine(V) compounds. Although *ortho*-substituted iodoxybenzene derivatives, such as IBX **6**[6] and Dess-Martin periodinane,[7] are widely used in organic synthesis,[8] the utility of their chiral analogues remains relatively little explored. Chiral derivatives of IBX amide (**9**)[9] and iodoxybenzene

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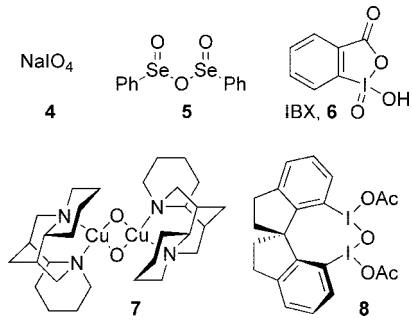


Figure 1. Reagents for oxidative dearomatization of *o*-alkylphenols.

(**10**)[10] (Figure 2) were synthesized and investigated by Zhdankin et al. The latter showed moderate levels of enantioselectivity in the oxidation of benzylic alcohols and thioanisole.

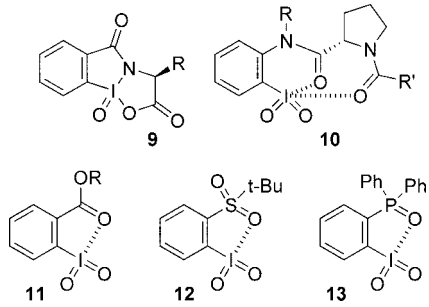
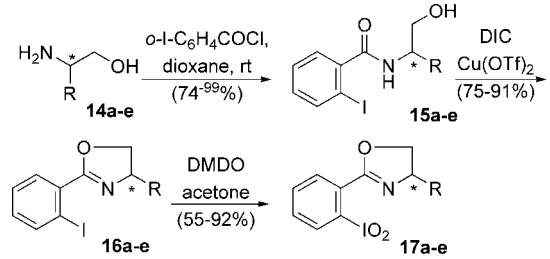


Figure 2. *o*-Substituted iodoxybenzene derivatives.

Iodoxybenzene derivatives *ortho*-substituted with a carbonyl, sulfonyl, or phosphonyl group, e.g., **10**−**13**, are known to form pseudocyclic structures in which the iodine forms a captodative bond with the adjacent oxygen atom.[11] Surprisingly, there have been no reports of the analogous iodoxybenzene derivatives with a *neutral* nitrogen ligand at the *ortho*-position. Given the ubiquitous use of oxazolines as chiral ligands for Lewis acids,[12] we decided to investigate the preparation and properties of chiral 2-(*o*-iodoxyphenyl)-oxazolines, abbreviated as CIPOs (cf. **17**, Scheme 2).

Scheme 2. Synthesis of Chiral 2-(*o*-Iodoxyphenyl)-oxazolines



a: R = *i*-Pr *(S)* **b:** R = *t*-Bu *(S)* **c:** R = Ph *(R)*
d: R = $PhCH_2$ *(R)* **e:** R = Ph_2CH *(R)*

Several 2-(*o*-iodophenyl)-oxazolines **16a**−**e** were prepared starting from chiral 2-amino alcohols **14a**−**e** following known general protocols.[13] Their oxidation with dimethyldioxirane[11a,14] yielded the desired CIPOs in moderate to good yields after chromatographic purification. The new compounds were obtained as white microcrystalline powders soluble in most organic solvents. The presence of the iodoxy group was evidenced by the diagnostic I═O stretches in IR (700−775 cm^{-1} region) and the chemical shifts of the *ipso*-carbon (149 ppm) and the *ortho*-proton (8.3 ppm) in NMR.[11] All attempts to grow X-ray quality crystals of CIPOs have so far proved unsuccessful. Thus, the existence of a captodative bond between the oxazoline nitrogen and the iodoxy group cannot be ascertained at this point.

To our delight, reaction of 0.6 equiv of *i*-Pr-CIPO **17a** with 1 equiv of 2,6-dimethylphenol **1a** in chloroform produced the desired *o*-quinol dimer **3a** with an encouraging level of enantioselectivity (Table 1, entry 1). Notably, Porco's enantioselective oxidation method was reported to be unsuccessful in the case of this substrate.[4b]

However, the reaction stopped at low conversions. Mindful of Barton's report on activation of the unsubstituted iodoxybenzene by trichloroacetic acid,[15] we investigated the effect of acid promoters (entries 2−5). Stoichiometric amounts of acetic acid were found to improve the reaction rate, whereas trifluoroacetic acid led to decomposition. Several solvents were screened next (entries 6−10). DME (1,2-dimethoxyethane) proved to be optimal giving **3a** in 51% yield and 55% ee (entry 10). Again, addition of acetic acid was confirmed to be beneficial in this solvent (entries 10−12). At this point, all other available CIPOs were examined

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Table 1. Oxidation of 2,6-Dimethylphenol **1a** with CIPOs[a]

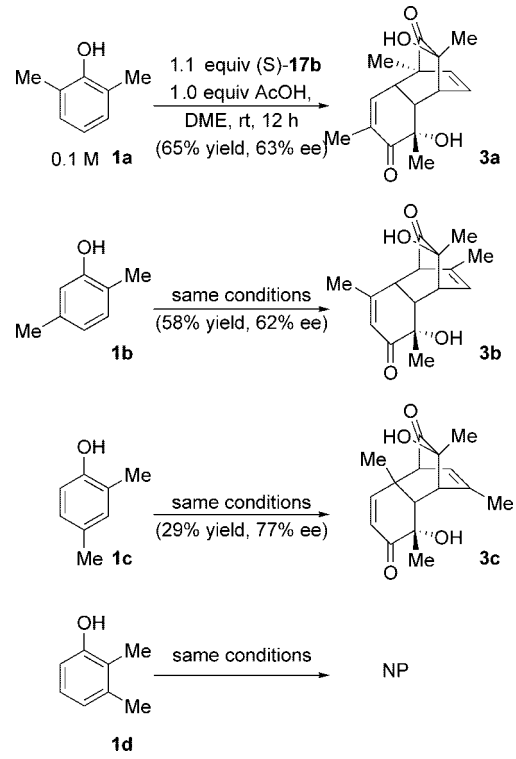
entry	oxidant	solvent	additive (equiv)	% yield[b]	% ee
1	**17a**	$CHCl_3$	none	29	30
2	**17a**	$CHCl_3$	AcOH (0.25)	40	33
3	**17a**	$CHCl_3$	AcOH (1.0)	47	36
4	**17a**	$CHCl_3$	AcOH (3.0)	14	38
5	**17a**	$CHCl_3$	TFA (1.0)	dec	ND
6	**17a**	PhMe	AcOH (1.0)	43	53
7	**17a**	MeCN	AcOH (1.0)	51	43
8	**17a**	CF_3CH_2OH	AcOH (1.0)	58	17
9	**17a**	THF	AcOH (1.0)	36	56
10	**17a**	DME	AcOH (1.0)	51	55
11	**17a**	DME	none	29	55
12	**17a**	DME	AcOH (0.25)	43	56
13	**17b**	DME	AcOH (1.0)	43	65
14	**17c**	DME	AcOH (1.0)	36	46
15	**17d**	DME	AcOH (1.0)	36	24
16	**17e**	DME	AcOH (1.0)	36	32
17	**17b**	DME	AcOH (1.0)	26(64)[c]	62
18	**17b**	DME	AcOH (1.0)	65[d]	63

[a] Conditions: 0.10 mmol 2,6-dimethylphenol **1a**, 0.060 mmol CIPO **17a**−**e**, 0.2 mL of solvent, rt, 12 h, unless noted otherwise. [b] Yields are based on **1a**, unless noted otherwise. [c] 0.10 mmol **1a** and 0.040 mmol **17b** were used. The yield shown in parentheses is based on **17b**. [d] 0.10 mmol **1a** and 0.11 mmol **17b** were used.

(entries 13−16). Only *t*-Bu-CIPO **17b** displayed enhanced enantioselectivity compared to *i*-Pr-CIPO **17a** and was therefore selected for further experimentation. The stoichiometry of the reaction with respect to the oxidant was initially uncertain, since in principle either one or both of the oxygen atoms of the iodoxy group could be utilized. An experiment with 2.5 equiv of the substrate with respect to the oxidant confirmed that only one oxygen atom is utilized in the desired oxidation (entry 17). Accordingly, increasing the amount of the oxidant from 0.6 to 1.1 equiv improved the yield of the dimer based on the substrate to 65% (entry 18). The rest of the starting material was mostly consumed by unidentified side reactions. The fate of the second oxygen atom of the iodoxy group remains unclear at this point. Only the fully reduced compounds, oxazoline **16b** (54%) and amide **15b** (19%), could be isolated after the reaction in entry 13.

Application of the optimized set of conditions to other dimethylphenols was investigated next. 2,5-Isomer **1b** produced the dimer (**3b**) with almost the same yield and enantioselectivity as **3a** (Scheme 3). Oxidation of 2,4-dimethylphenol **1c** attained 77% ee—the highest value observed in this study—albeit in a more modest yield. No dimer could be isolated from the reaction of 2,3-dimethylphenol **1d**, which is consistent with previous reports.[3c,4b] The absolute configurations of **3b** and **3c** were deduced from their signs of optical rotation.[4b] The configuration of **3a** was assigned by analogy.

Scheme 3. Asymmetric Oxidation of Isomeric Dimethylphenols with *t*-Bu-CIPO **17b**



In conclusion, we have synthesized the first examples of iodoxybenzene derivatives with chiral oxazoline groups at the *ortho*-position and applied them to the enantioselective oxidation of phenols. Although the ee values remain moderate at this point, our results demonstrate the potential of the new class of chiral hypervalent iodine compounds in asymmetric synthesis. Further studies in this direction will be reported in due course.

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Note Added after ASAP Publication. Scheme 3 contained errors in the version published ASAP February 20, 2009; the corrected version published February 25, 2009.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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