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Chiral Iodine-Catalyzed Dearomatizative Spirocyclization for the Enantioselective Construction of an All-Carbon Stereogenic Center

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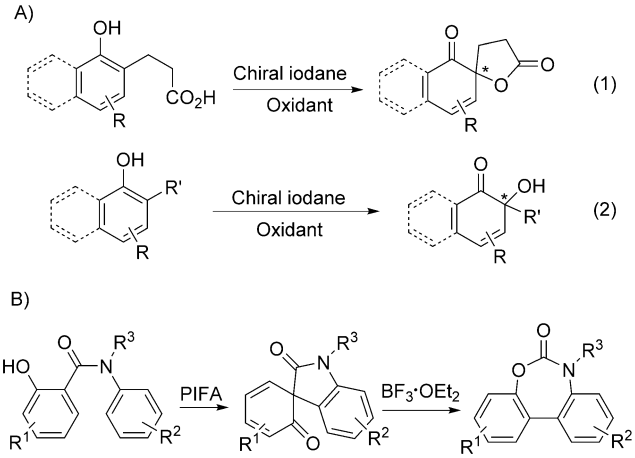
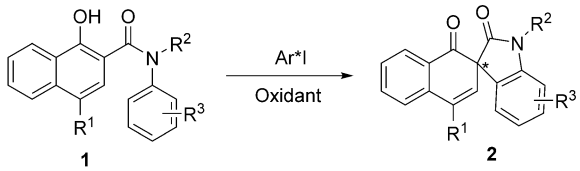
Abstract: The first enantioselective dearomatizative spirocyclization of 1-hydroxy-*N*-aryl-2-naphthamide derivatives has been accomplished by chiral organoiodine catalysis to stereoselectively create an all-carbon stereogenic center, providing a straightforward approach to access spirooxindole derivatives in good yields and with high to excellent levels of enantioselectivity. Chiral hypervalent phenyl-λ^3-iodanes generated in situ from the oxidation of the chiral phenyl iodine actually participate in the asymmetric oxidative dearomatizative spirocyclization reaction.

The enantioselective dearomatization of phenols and structurally relevant electronically rich aromatic molecules has emerged as a valuable platform for the construction of densely functionalized cyclic skeletons that hold great potential in the synthesis of structurally complicated molecules and has hence received increasing research interest.[1,2] Chiral hypervalent iodine compounds have been frequently exploited, either as reagents or catalysts, for the oxidative enantioselective functionalization and other transformations, owing to their privileged characteristics including their low toxicity, mild reaction conditions, and environmentally benign nature.[3–6] In particular, chiral hypervalent iodine species have been highly efficient organocatalysts for the enantioselective dearomatization of phenols, leading to various transformations that are otherwise hard to accomplish, benefiting from the fundamental contributions given by the groups of Kita, Ishihara, and others.[7] Specifically, notable progress has been made in asymmetric oxidative spirolactonization [Scheme 1 A, Eq. (1)] and hydroxylative phenol dearomatization [Scheme 1 A, Eq. (2)] catalyzed by chiral organoiodines. Very recently, Du, Zhao, and co-workers described a unique intramolecular metal-free oxidative aryl–aryl coupling, which was considered to proceed via a sequential hypervalent iodine-mediated phenol dearomatization and Lewis acid-catalyzed rearrangement (Scheme 1 B).[8]



Scheme 1. Previously reported phenol dearomatization reactions with hypervalent iodines: A) Asymmetric dearomatization of phenols catalyzed by chiral hypervalent iodine;[7] B) oxidative coupling via hypervalent iodine-mediated dearomatization. PIFA = phenyliodine(III) bis(trifluoroacetate).[8]

However, enantioselective construction of an all-carbon spiro-stereogenic center has long been considered a daunting challenge for organic synthesis[9] and, therefore, the creation of new efficient and green protocols to ultimately get this goal will be of great synthetic value. The asymmetric dearomatization of phenol derivatives of type **1** to generate all-carbon spiro-stereogenic center (Scheme 2), however, has, to our knowledge, not been documented to date. Herein, we report the first enantioselective dearomatizative spirocyclization of 1-hydroxy-*N*-aryl-2-naphthamide derivatives enabled by chiral organoiodine catalysis, to directly generate spirooxindole derivatives in good yields and with high enantioselectivity.



Scheme 2. Asymmetric oxidative spirocyclization: Enantioselective generation of all-carbon spiro-stereogenic center (reported herein).

The initial studies commenced with an oxidative spirocyclization of 1-hydroxy-*N*-methyl-*N*-(2-naphthalenyl)-2-naphthamide (**1a**) catalyzed by **3a** in the presence of 3-chloroperoxy-

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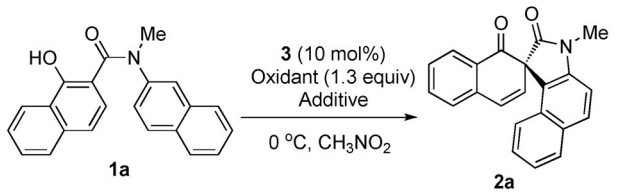
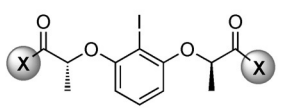
Table 1. Optimization of reaction conditions.





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3a: X = NHMes
3b: X = NHPh
3c: X = NH(3,5-$(CF_3)_2C_6H_3$)
3d: X = NH(3,4,5-$F_3C_6H_2$)
3e: X = NH(3,4,5-$(OMe)_3C_6H_2$)
3f: X = NEt_2

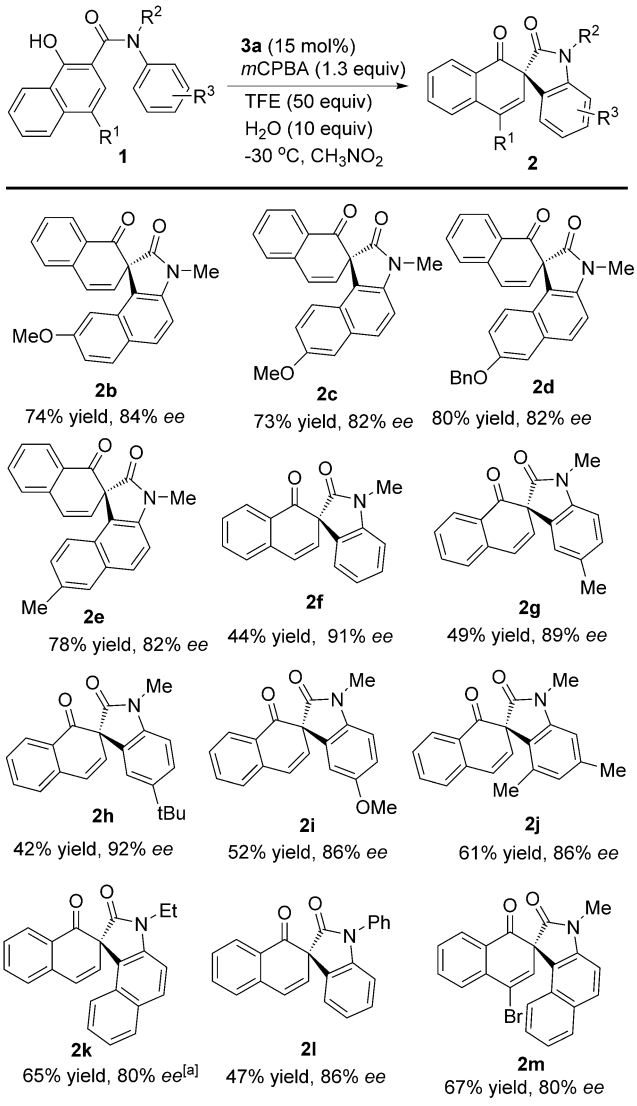
Entry	3	Oxidant	Additive (equiv)	Yield [%][b]	*ee* [%][c]
1	**3a**	*m*CPBA	TFA (2)	64	10
2	**3a**	*m*CPBA	–	30	42
3	**3a**	*m*CPBA	HFIP (50)	47	44
4	**3a**	*m*CPBA	TFE (50)	48	50
5	**3a**	CH_3CO_3H	TFE (50)	–[d]	–
6	**3a**	TBHP	TFE (50)	–[d]	–
7	**3a**	BPO	TFE (50)	–[d]	–
8	**3b**	*m*CPBA	TFE (50)	34	41
9	**3c**	*m*CPBA	TFE (50)	39	−5
10	**3d**	*m*CPBA	TFE (50)	41	15
11	**3e**	*m*CPBA	TFE (50)	24	51
12	**3f**	*m*CPBA	TFE (50)	46	47
13[e]	**3a**	*m*CPBA	TFE (50)	44	31
14[f]	**3a**	*m*CPBA	TFE (50)	51	71
15[f]	**3a**	*m*CPBA	TFE (50) + H_2O (10)	74	84
16[g]	**3a**	*m*CPBA	TFE (50) + H_2O (10)	72	87

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale (**1a**); [b] yield of the isolated product; [c] *ee* values determined by HPLC analysis; [d] no target product; [e] at room temperature; [f] $T = -30\,^{\circ}C$; [g] 15 mol% of **3a** was used, $T = -30\,^{\circ}C$. *m*CPBA = 3-chloroperoxybenzoic acid; TFA = trifluoroacetic acid; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = trifluoroethanol; TBHP = *tert*-butyl hydrogen peroxide; BPO = benzoyl peroxide.

benzoic acid (*m*CPBA, 1.3 equiv) and trifluoroacetic acid (2.0 equiv) in CH_3NO_2 at 0 °C (Table 1). As anticipated, the reaction proceeded smoothly to generate the desired product, (*S*)-3-methyl-1′*H*-spiro[benzo[*e*]indole-1,2′-naphthalene]-1′,2(3*H*)-dione (**2a**) in a good yield of 64%, but with a rather poor enantioselectivity of 10% *ee* (Table 1, entry 1). Previously, Ishihara and co-workers indicated that the presence of alcohol additives was able to significantly enhance the enantioselectivity of the chiral organoiodine-catalyzed dearomatization reactions.[7e] Thus, we also investigated the effect of alcohol additives on the reaction performance and identified that the presence of 50 equivalents of trifluoroethanol (TFE) permitted the reaction to give the best results in terms of both chemical yield and enantiomeric excess under the otherwise identical conditions (Table 1, entries 3 and 4). Since external oxidants exerted a notable effect on the reactions of this type,[4c] a variety of organic oxidants were subsequently investigated. Indeed, the oxidants played a dominant role in the reactivity in this case. For instance, other common oxidants, including CH_3CO_3H, *t*BuOOH, and benzoyl peroxide (BPO), failed to oxidize the substrate **1a** into the desired product **2a** (Table 1, entries 5–7). Under the preliminarily optimized conditions, a serious of chiral iodoarenes were next evaluated. The *N*-aryl substituents of the catalyst **3** evidently had considerable impact on either the chemical yield or enantioselectivity. The presence of electron-deficient *N*-aryl groups turned out to be deleterious to the stereoselectivity (Table 1, entries 9 and 10). In contrast, the installation of electronically rich *N*-aryl substituents to the catalysts **3** was seemingly beneficial to the stereochemical control (Table 1, entries 4 and 11 vs. 8–10). Although the catalyst **3e** was able to provide the highest levels of enantioselectivity (51% *ee*), a much lower yield was obtained in comparison with other relatively promising chiral iodine catalysts (Table 1, entry 11 vs. 4 and 8). The tertiary amide-based chiral iodine catalyst **3f**, which was found to be superior to secondary amide-derived ones in controlling the enantioselectivity of direct C–H/C–H oxidative coupling reaction of N^1,N^3-diphenylmalonamides,[4c] gave a slightly diminished yield and enantioselectivity in comparison with the reaction catalyzed by **3a** (Table 1, entry 12 vs. 4).

With the optimal chiral iodoarene catalyst **3a** in hand, we then investigated other reaction parameters to further optimize the conditions. In fact, the enantioselectivity is highly sensitive to the reaction temperature. For instance, a much diminished enantiomeric excess was obtained when the reaction was conducted at room temperature (Table 1, entry 13) whereas a significantly improved enantioselectivity was obtained upon carrying out the reaction at −30 °C (entry 14). The groups of Ochiai and Harned both found that the presence of water was able to improve the yields of some oxidative coupling reactions catalyzed by organoiodines.[10] Inspired by these findings, we systematically investigated whether water exerts an effect on the reaction performance (see the Supporting Information for details). Interestingly, the presence of water (10 equiv) not only resulted in a much higher yield, but also a dramatically improved enantioselectivity (Table 1, entry 15). Furthermore, increasing the catalyst loading to 15 mol% led to a slightly greater enantioselectivity (entry 16, 72% yield, 87% *ee*).

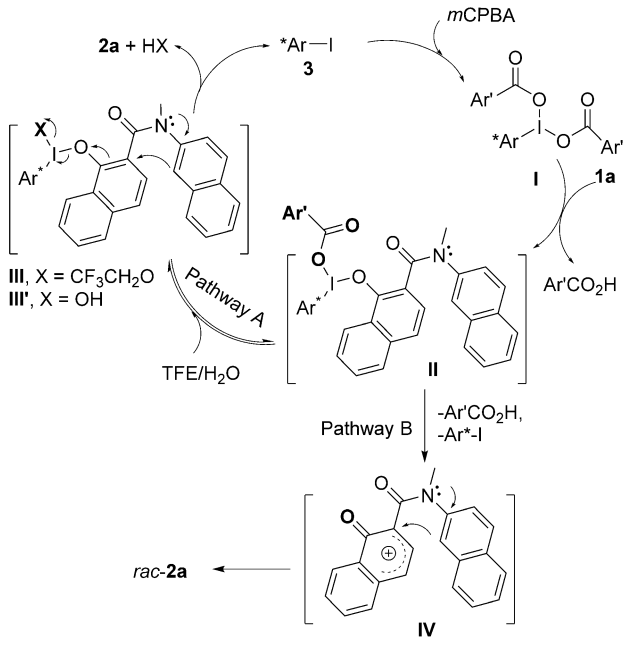
Under the optimized conditions, the generality of the asymmetric oxidative spirocyclization reaction for different substrates was explored (Scheme 3). All *N*-methyl-*N*-(2-naphthyl)-2-naphthamide substrates **1b–e** underwent clean oxidative spirocyclization reactions to generate **2b–e** in high yields ranging from 73% to 80% and with good levels of enantioselectivity (82–84% *ee*). Steric features and the substitution pattern of the substituents on the *N*-(2-naphthyl) moiety had little effect on the reaction performance. In contrast, for *N*-methyl-*N*-(phenyl)-2-naphthamide substrates **1f–j**, both the reaction conversion and stereoselectivity were highly sensitive to substituents on the *N*-phenyl group. In general, higher levels of enantioselectivity but diminished yields were provided by these substrates in comparison with the *N*-methyl, *N*-(2-naphthyl)-2-naphthamide substrates (**2b–e** *vs* **2f–j**). In particular, excellent enantioselectivities of 91 and 92% *ee* were observed for **2f** and **2h**, respectively. Additionally, changing *N*-methyl to either *N*-ethyl or *N*-phenyl was also tolerated to give the desired products in good to moderate yields and with high enantioselectivities, as



Scheme 3. Substrate scope of the asymmetric spirocyclization reaction. [a] 5 equivalents of H_2O were used.

exemplified by **2k** and **2l**. The installation of a substituent at the 4-position of the naphthamide moiety was well tolerated to undergo the desired reaction in a fairly good yield and with high stereoselectivity, as shown for **2m**. The absolute configuration of **2a** was assigned to be *S* by X-ray crystallographic analysis of the single crystal. The configurations of the other products were assigned by analogy.[11]

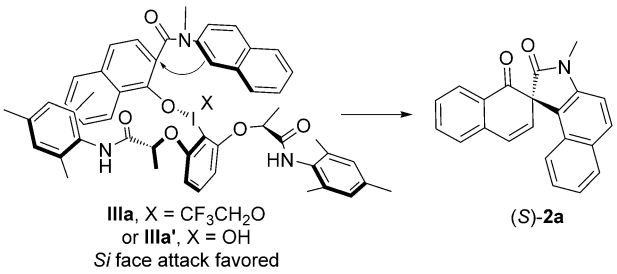
As reported previously,[4,10] the chiral aryl iodine **3** was proposed to be oxidized into a hypervalent phenyl-λ^3-iodane **I** by *m*CPBA (see proposed mechanism, Scheme 4). Subsequent substitution of **I** with the hydroxy group of **1a** then yields a chiral iodo-enol type intermediate **II**. Based on Ishihara's hypothesis,[7e] the intermediate **II** would be able to undergo a ligand exchange with trifluoroethanol or water to generate an associative intermediate **III** or **III′** (Scheme 4, Pathway A), either of which would undergo an intramolecular S_N2'-like Friedel–Crafts substitution[4c,7a–c,e] to give the product and to release the chiral iodobenzene **3**. Alternatively, a dissociative in-



Scheme 4. Proposed reaction mechanism.

termediate **IV** could also be possibly generated from **II** (Scheme 4, Pathway B), leading to the generation of racemic **2a**. Because 2,2,2-trifluoroethoxy and hydroxy are both less active leaving groups than carboxylate, the presence of large excess amounts of TFE and water would facilitate the favorable formation of **III** and thereby inhibit the generation of **IV** to result in better stereochemical control.

Since the *Re* face of the naphthamide moiety in either intermediate **IIIa** or **IIIa′** was blocked by one of the bulky *N*-phenyl amides, the *Si* face was open for the nucleophilic attack of the *N*-naphthyl moiety in a *syn*-addition–elimination manner, to therefore allow for the favorable generation of (*S*)-**2a** (Scheme 5).



Scheme 5. The intermediate to explain the stereochemistry.

In conclusion, we have established the first highly enantioselective dearomatizative spirocyclization of 1-hydroxy-*N*-aryl-2-naphthamide derivatives by virtue of chiral iodine catalysis, enabling the direct synthesis of optically spirooxindoles and their analogues through intramolecular SN_2'-like Friedel–Crafts substitution. Chiral hypervalent phenyl-λ^3-iodanes generated in situ from the oxidation of the chiral phenyl iodine species

were involved in the oxidative dearomatizative spirocyclization reaction. More importantly, the findings suggest that chiral aryl iodine catalysis holds great potential in the creation of new stereoselective transformations by the activation of aromatic systems. Further studies of asymmetric dearomatization of other phenol derivatives catalyzed by chiral organoiodines for the synthesis of structurally complex optically active skeletons are currently in progress.

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Keywords: asymmetric catalysis · dearomatization · hypervalent iodine · organocatalysis · spirooxindoles

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[11] CCDC 1043239 [(*S*)-**2a**] contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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