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Chemoselective Oxidative Spiroetherification and Spiroamination of Arenols Using I⁺/Oxone Catalysis

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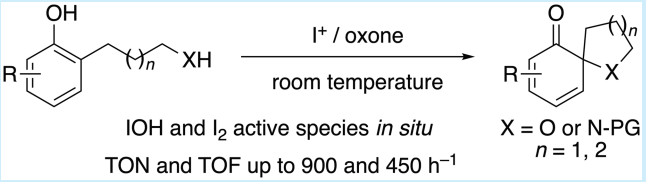
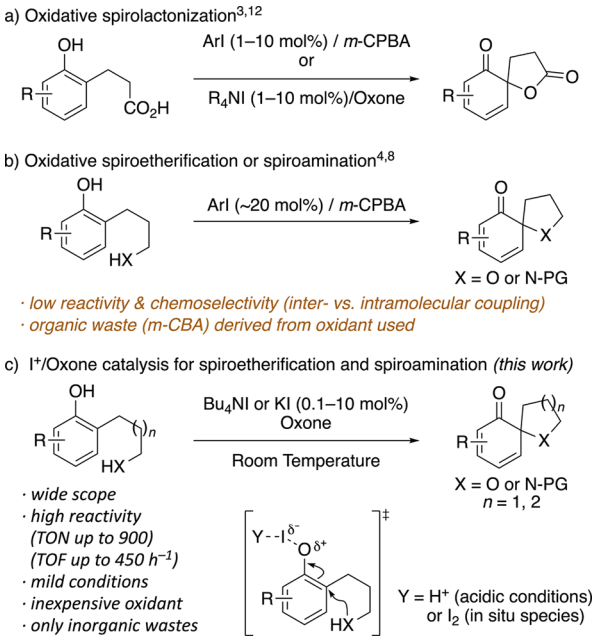
Supporting Information

ABSTRACT: We developed a chemoselective oxidative dearomative spiroetherification and spiroamination of arenols using I⁺/oxone catalysis. The intramolecular dearomative C–O and C–N couplings proceeded much more efficiently under slightly acidic conditions to give the corresponding spiro adducts in higher yields compared with previous methods using transition metal or hypervalent iodine catalysts. Control experiments suggested that both hypoiodous acid and iodine might be active species for these reactions.



Oxidative dearomatization reactions are found in the biosynthesis of many biologically active compounds in nature.[1] In chemical synthesis, many oxidative methods mediated by mainly transition metal or hypervalent iodine compounds have been developed for the dearomatization of arenols.[2] In this context, dearomative spirolactonization of arenols tethered to a carboxyl group as an intramolecular nucleophile have been developed using iodine-based catalysis (Scheme 1a).[3] Compared with spirolactonization, oxidative spiroetherification of arenols tethered to a hydroxy group and spiroamination of arenols tethered to a secondary amido group have been less explored,[2,4] despite their usefulness for the synthesis of core structures of many biologically important compounds.[5] Conventionally, these reactions were best performed using hypervalent iodine compounds as stoichiometric oxidants under acidic conditions.[4] Recently, the oxidative cyclization of arenols under stoichiometric ($R_4N^+[Br_3]^-/K_2CO_3$)[6] or catalytic (10 mol % $RuCl_3$/$KBrO_3$)[7] conditions has also been reported. On the other hand, Ciufolini and colleagues developed hypervalent iodine-catalyzed enantioselective oxidative spiroetherification and spiroamination reactions as a transition-metal-free method using *m*-chloroperoxybenzoic acid (*m*-CPBA) as an organic oxidant (Scheme 1b).[8] However, the substrate scope seemed to be limited to 1- and 2-naphthols, and more importantly, the chemical yield of the cyclic products was moderate because of undesired competitive reactions, including intermolecular coupling with *m*-chlorobenzoic acid (*m*-CBA), which was generated from the oxidant used, due to the lower reactivity of alcohols and amides compared with carboxylic acids as intramolecular nucleophiles.

Scheme 1. Oxidative Dearomative Cyclization of Arenol Derivatives Using Iodine-Based Catalysis



We recently reported the quaternary ammonium hypoiodite[9]-catalyzed dearomative spirolactonization of arenols using oxone,[10,11] a triple salt ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), as an environmentally benign, safe, and easy to handle inorganic oxidant (Scheme 1a).[12] Compared with our previous I⁺/(H_2O_2 or ROOH) systems,[13] high-performance catalysis could be realized under these slightly acidic conditions (the pK_a of $KHSO_4$ is 2.0[14]) (Scheme 1c). Here, we applied I⁺/oxone catalysis to the oxidative spiroetherification and spiroamination of arenols. We envisioned that chemoselective intramolecular oxidative coupling with alcohols or amide tethers might be achieved by acceleration of the reductive elimination of iodide via hydrogen-bonding interactions[15] under acidic conditions or halogen-bonding interactions with I_2,[16] a catalytic species

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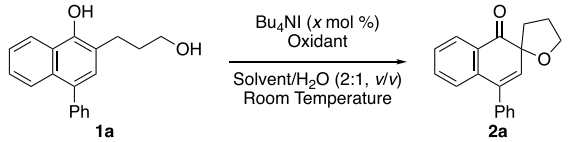
Org. Lett. XXXX, XXX, XXX–XXX

generated in situ,[12] to enhance the positive charge on the electrophilic partner (arenol), which might then be easily trapped by an intramolecular nucleophile. The dearomative C−O and C−N couplings proceeded much more efficiently (TON and TOF up to 900 and 450 h^{-1}, respectively) under mild conditions to give the corresponding spiro adducts in higher yields compared with previous methods using transition metal[7] or hypervalent iodine catalysts.[8]

We began our investigation using 1-naphthol **1a** as a model substrate for the oxidative spiroetherification reaction (Table 1).[17] First, we investigated the oxidant in the presence of 10 mol % tetrabutylammonium iodide as a catalyst in toluene−water biphasic solvents at room temperature. Because the substrate is highly reactive toward oxidation,[3c,12] **1a** was consumed with the use of either hydrogen peroxide, alkyl hydroperoxides, or *m*-CPBA; however, this gave complex mixtures of several unidentified and oligomeric products along with the desired spiroether **2a** in less than 10% yield (entries 1−4). In sharp contrast, not only high reactivity toward oxidative dearomatization, as in our spirolactonization,[12] but also high chemoselectivity for the desired intramolecular cyclization could be achieved by I^+/oxone catalysis under acidic conditions. Indeed, clean oxidation of **1a** using oxone proceeded smoothly to give spiroether **2a** in 85% yield (entry 5). In view of the beneficial effects of acidity on the reactivity and especially the chemoselectivity, the oxidation of **1a** with hydrogen peroxide or TBHP was re-examined under acidic conditions in the presence of $KHSO_4$ as an additive. Although the chemoselectivity of both reactions was improved, the oxidative conversion of **1a** was remarkably decreased because of the competitive acceleration of nonproductive pathways as in spirolactonization reactions (entries 6 and 7).[9a,b,18] These results suggested that undesired side reactions might be suppressed under acidic conditions. Interestingly, in contrast to spirolactonization,[12] oxidative spiroetherification of **1a** proceeded under nonaqueous conditions in which oxone was not dissolved, although a longer time was required (entry 8). Organic solvents were screened briefly under biphasic conditions (entries 9−13), which revealed that an extremely rapid reaction was observed in acetonitrile (entry 13). Additionally, spiroetherification of **1a** proceeded smoothly even at low catalyst loading (0.1 mol %, TON = 900) with the use of an almost equimolar amount of oxone (1.2 equiv of $KHSO_5$ as a component of oxone) to give **2a** in 90% yield (entries 14 and 15). Moreover, inexpensive KI could also be used as a catalyst under identical conditions (entry 16). Finally, almost no oxidation reaction was observed at 2 h in the absence of catalyst (entry 17).

Next we investigated the oxidative dearomative spiroamination reaction using 1-naphthol **3a** tethered to a tosylamido group as a model substrate (Table 2).[17] The oxidation of **3a** using either hydrogen peroxide, alkyl hydroperoxides, or *m*-CPBA as an oxidant gave a much messier reaction than the spiroetherification of **1a**, which indicated that spiroamination is much more challenging than spiroetherification with respect to chemoselectivity (entries 1−4). In contrast, to our delight again, a chemoselective intramolecular dearomative cycloamination reaction proceeded using oxone as an oxidant, and the desired spiroamine **4a** was obtained in 82% yield (entry 5). In contrast to spiroetherification, toluene was optimal with respect to chemoselectivity (entries 6−10). Additionally, a sluggish reaction was observed with a low catalyst loading or with the use of KI instead of Bu_4NI (entries 11 and 12). On

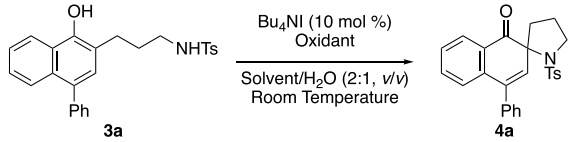
Table 1. Oxidative Spiroetherification of 1a[a]



entry	oxidant (equiv)	solvent	t (h)	conv. of **1a** (%)[b]	yield of **2a** (%)[b]
1	30% H_2O_2 (2)	toluene	24	45	8[c]
2	TBHP (2)	toluene	24	>95	<1[c]
3	CHP (2)	toluene	24	>95	<1[c]
4	*m*-CPBA (2)	toluene	1	>95	10[c]
5	oxone (1)	toluene	8	>95	85
6[d]	30% H_2O_2 (2)	toluene	24	10	7
7[d]	TBHP (2)	toluene	24	10	6
8	oxone (1)	toluene[e]	24	>95	88
9	oxone (1)	EtOAc	5	>95	86
10	oxone (1)	*t*-BuOMe	24	65	52
11	oxone (1)	CH_3NO_2	3	>95	89
12	oxone (1)	CH_2Cl_2	3	>95	90
13	oxone (1)	CH_3CN	0.3	>95	90
14[f,g]	oxone (0.6)	CH_3CN	0.5	>95	91[h]
15[i]	oxone (0.6)	CH_3CN	2	>95	90
16[j]	oxone (0.6)	CH_3CN	0.5	>95	91
17[k]	oxone (1)	CH_3CN	2	<1	<1

[a]Unless otherwise noted, the reactions were performed using **1a** (0.1 mmol) and Bu_4NI (10 mol %) in solvent (0.1 *M*)/H_2O (2:1). [b]Determined by ^1H NMR analysis. [c]A messy complex mixture was obtained. [d]$KHSO_4$ (2 equiv) was added. [e]In toluene (monophasic). [f]Bu_4NI (1 mol %). [g]**1a** (1 mmol) was used. [h]Isolated yield. [i]Bu_4NI (0.1 mol %). [j]KI (1 mol %). [k]In the absence of catalysts. For details, see the Supporting Information.

Table 2. Oxidative Spiroamination of 3a[a]



entry	oxidant (equiv)	solvent	t (h)	conv. of **3a** (%)[b]	yield of **4a** (%)[b]
1	30% H_2O_2 (2)	toluene	24	60	<1[c]
2	TBHP (2)	toluene	24	>95	<1[c]
3	CHP (2)	toluene	24	>95	<1[c]
4	*m*-CPBA (2)	toluene	1	>95	<1[c]
5	oxone (1)	toluene	3	>95	82[d]
6	oxone (1)	EtOAc	3	>95	70
7	oxone (1)	*t*-BuOMe	24	80	48
8	oxone (1)	CH_3NO_2	3	>95	48
9	oxone (1)	CH_2Cl_2	3	>95	58
10	oxone (1)	CH_3CN	3	>95	60
11[e]	oxone (1)	toluene	24	<10	<5
12[f]	oxone (0.6)	toluene	24	40	31
13	oxone (0.6)	toluene	3	>95	84

[a]Unless otherwise noted, the reactions were performed using Bu_4NI (10 mol %) in solvent (0.1 *M*)/H_2O (2:1). [b]Determined by ^1H NMR analysis. [c]A messy complex mixture was obtained. [d]Isolated yield. [e]Bu_4NI (1 mol %). [f]KI was used instead of Bu_4NI. For details, see the Supporting Information.

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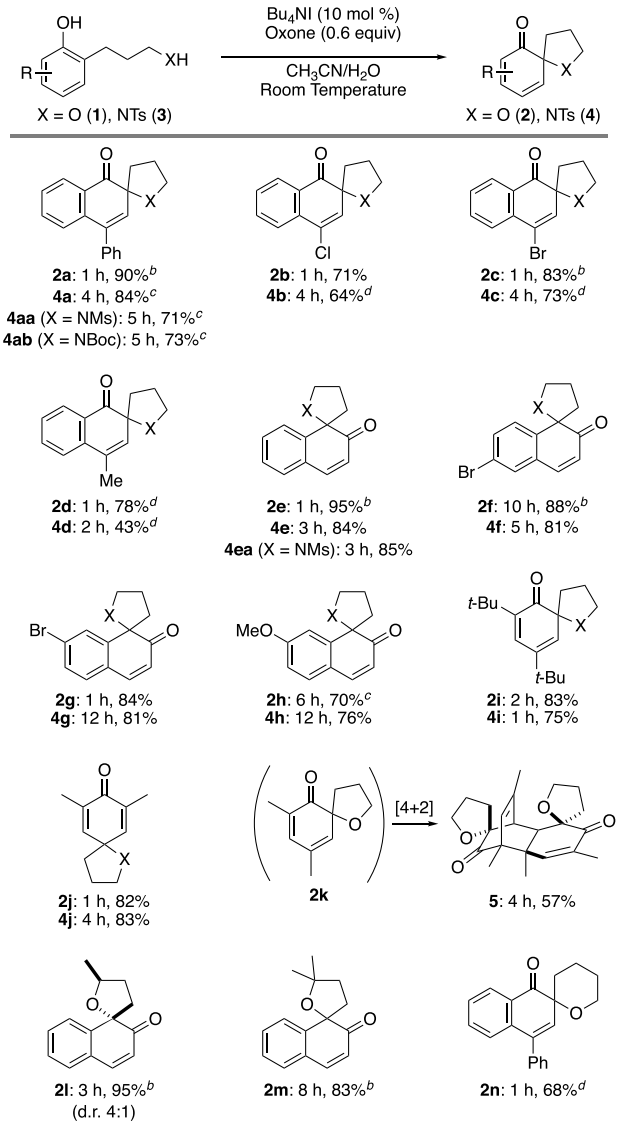
the other hand, the use of almost an equimolar amount of oxone (1.2 equiv of $KHSO_5$ as a component of oxone) was enough to complete the reaction to give **4a** in 84% yield (entry 13).

Several arenols **1** and **3**, including 1- and 2-naphthols and phenols, tethered to hydroxy or sulfonamido groups were examined for oxidative spiroetherification or spiroamination, respectively, under the optimized conditions (Scheme 2).

Scheme 2. Oxidative Spiroetherification and Spiroamination of Arenols 1 and 3[a]



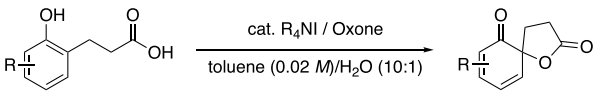
[a]Unless otherwise noted, the reactions were performed using Bu_4NI (10 mol %) and oxone (0.6 equiv) in CH_3CN/H_2O. [b]Bu_4NI (1 mol %). [c]In toluene/H_2O. [d]Oxone (1 equiv). For details, see the Supporting Information.

Notably, for most of the spiroamination reactions, CH_3CN was used as the organic solvent instead of toluene, which was the optimal solvent for model substrate **3a**, because of the low solubility of most arenols **3** in toluene. In general, as expected from the optimization studies shown in Tables 1 and 2, the spiroetherification reaction proceeded within a shorter reaction time even at low catalyst loadings. Both *o*- (**2a**–**h**) and *p*-spiroethers (**2i** and **2j**) as well as *o*- (**4a**–**h**) and *p*-spiroamines (**4i** and **4j**) could be synthesized from the common arenol core structures tethered to hydroxy or sulfonamido groups, respectively. Spiroether **2k** was too unstable to isolate, and [4 + 2]-dimerized to form the corresponding dimer **5** with perfect diastereoselectivity,[19] albeit in moderate yield. In contrast, the oxidation of **3k** afforded a complex mixture, and no desired spiroamine **4k** or its dimer was obtained. On the other hand, oxidative cyclization of secondary and tertiary alcohols **1l** and **1m** afforded the corresponding spiroethers **2l** and **2m** in good to excellent yields. Moderate diastereoselectivity (4:1 d.r.), as in previous methods,[7c] was observed for the oxidative cyclization of **1l**. Moreover, six-membered spiroether **2n** could also be synthesized in good yield from the oxidative cyclization of **1n**. Notably, beside the tosyl group as a protecting group for the amine tether, a methanesulfonyl (Ms) or *tert*-butyloxycarbonyl (Boc) group could also be used to afford the desired spiroamines **4aa** and **4ea** or **4ab**, respectively.

Some interesting features were observed in control experiments (Scheme 3). In our previous spirolactonization reactions using I^+/oxone catalysis, Raman analysis revealed the in situ generation of I_2 under acidic conditions but neither $[I_3]^-$ nor higher-valent species (Scheme 3a).[12] Although hypoiodous acid, which would be in equilibrium with hypoiodite, could not

Scheme 3. Control Experiments To Probe the Active Species

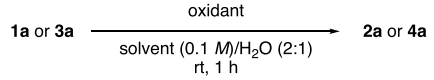
a) Oxidative spirolactonization (our previous work)[12]



Raman analysis: I^- —Oxone→ I_2 (*detected*); $[I_3]^-$, $[IO_3]^-$, $[IO_4]^-$ (*not detected*); IOH or $[IO]^-$ (*not detected (band overlap)*)

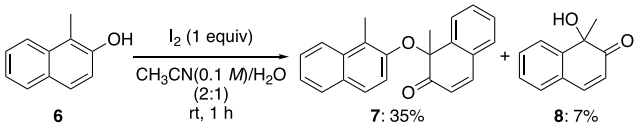
Control experiments: IOH *(active species)*, I_2 *(inert but dormant species)*

b) Control experiments for oxidative spiroetherification and spiroamination



entry	substrate	oxidant (equiv.)	solvent	product: yield (%)[a]
1	**1a**	I_2 (1), Bu_4NOH (2)	CH_3CN	**2a**: 55 (74)
2	**1a**	I_2 (1), K_2CO_3 (2)	toluene	**2a**: >95 (>95)
3	**1a**	Bu_4NI_3 (1)	CH_3CN	**2a**: <1 (<5)
4	**1a**	I_2 (1)	CH_3CN	**2a**: 35 (40)
5	**1a**	I_2 (1)	toluene (8 h)	**2a**: 33 (35)
6	**1a**	I_2 (1), AcOH (1)	toluene	**2a**: 30 (30)
7[b]	**1a**	I_2 (1)	toluene (24 h)	**2a**: <1 (<5)
8	**3a**	I_2 (1), Bu_4NOH (2)	toluene	**4a**: <5 (>95)
9	**3a**	I_2 (1), K_2CO_3 (2)	toluene	**4a**: >95 (>95)
10	**3a**	Bu_4NI_3 (1)	toluene	**4a**: <1 (<5)
11	**3a**	I_2 (1)	toluene	**4a**: 30 (30)

c) Oxidative dearomative dimerization of 1-methyl-2-naphthol (**6**)



[a]Conversions of the substrate (**1a** or **3a**) are shown in parentheses. [b]In toluene (0.02 *M*)/H_2O (10:1 v/v).

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Org. Lett. XXXX, XXX, XXX–XXX

be detected, probably because of band overlap with oxone, control experiments suggested that hypoiodous acid might be the active species and iodine might be an inert but dormant species under these optimized conditions for enantioselective oxidation (Scheme 3a).[12] On the basis of these findings, we performed stoichiometric control experiments for spiroetherification and spiroamination reactions (Scheme 3b). As in our previous spirolactonization reaction,[12] while the oxidation of both **1a** and **3a** proceeded using hypoiodite species generated in situ from I_2 and base additives[9b] (entries 1, 2, 8, and 9), no reactions were observed with the use of $Bu_4N^+[I_3]^-$ (entries 3 and 10).[20] Notably, compared with strong alkali conditions with Bu_4NOH, cleaner reactions were observed under mild basic conditions with K_2CO_3. In addition, the oxidation of **3a** was much messier than that of **1a** (entry 8 versus entry 1). These results were consistent with the catalytic reactions in that spiroamination is much more challenging than spiroetherification with respect to chemoselectivity (vide supra). On the other hand, both oxidative spiroetherification and spiroamination reactions proceeded with I_2 regardless of the solvent used (entries 4−6 and 11). These results suggested that both hypoiodous acid and iodine might be active species for spiroetherification and spiroamination reactions, which is consistent with the high-performance catalytic activity (TON and TOF up to 900 and 450 h^{-1}, respectively), especially for the spiroetherification reaction in acetonitrile. The low conversion of these stoichiometric reactions with I_2 might be attributed to the generation of $[I_3]^-$, an inert species, from the fast reaction of I_2 with I^-, which is generated as the reaction progresses.[21] In our previous work, oxidative spirolactonization reactions did not proceed with I_2 in toluene under diluted conditions, which was optimal for enantioselective reactions.[12] We reinvestigated spirolactonization reactions under the conditions used for spiroetherification. Interestingly, spirolactonization reactions also proceeded in toluene or especially in acetonitrile under concentrated conditions, but with diminished efficiency.[17] In addition, spiroetherification of **1a** did not proceed with I_2 under the diluted conditions used for spirolactonization reactions (entry 7). These results suggest that I_2 might be an active species for either spirolactonization, spiroetherification, or spiroamination reactions in polar solvents and/or under concentrated conditions. Nevertheless, to investigate the influence of the tether on the reaction with I_2, we performed an additional control experiment. Oxidation of 1-methyl-2-naphthol (**6**) using iodine in acetonitrile proceeded with similar efficiency as that of **1a** or **3a** to give dimer **7**[22] along with a small amount of *o*-quinol **8**[23] (Scheme 3c). These results suggested that the reaction of arenols with I_2 might not be accelerated by hydroxy or amido group tethers.

Since the generation of anionic species from alcohols or amides seems to be difficult under acidic conditions, these nucleophiles might react in neutral form followed by deprotonation. Indeed, in contrast to previous spirolactonization reactions,[12] we could not achieve any asymmetric induction in the present spiroetherification or spiroamination reactions with the use of chiral quaternary ammonium iodide catalysts, perhaps because no chiral ammonium alkoxides or amides were generated.[17]

In conclusion, we developed an oxidative dearomative spiroetherification and spiroamination of arenols using I^+/oxone catalysis. The chemoselective intramolecular dearomative C−O and C−N couplings proceeded much more efficiently under slightly acidic conditions to give the corresponding spiro adducts in higher yields compared with previous methods. Control experiments suggested that both hypoiodous acid and iodine might be active species for spiroetherification and spiroamination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04324.

Additional information, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX