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Ruthenium(VIII)-Catalyzed *ipso*-Dearomative Spiro-Etherification and Spiro-Amidation of Phenols

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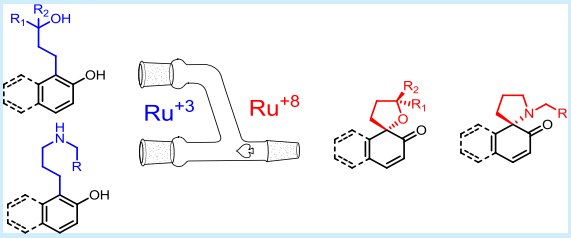
Supporting Information

ABSTRACT: An open air ruthenium(VIII)-catalyzed oxidative spiro-etherification as well as spiro-amidation of phenols has been performed. The transformation works satisfactorily with both phenols and naphthols and thus exhibits a wide range of flexibility. The catalysis is performed in open air at room temperature with a yield of ≤95%.



Dearomatization of arenes has been an important chemical transformation, providing easy access to the alicyclic framework found in biologically and pharmacologically active compounds.[1] Phenols and naphthols are readily available chemical feedstocks for organic synthesis.[2] Thus, catalytic dearomatization of these arenols through C−heteroatom bond-formation processes is a desired synthetic route for accessing complex organic molecular targets.[3] Efficient construction of spirocyclic frameworks has been an important challenge because of their presence in biologically active natural products and pharmaceuticals. Among the various spirocycles, spiro-oxacyclohexadienones and spiro-azacyclohexadienones are the primary targets.[4] Extensive efforts were focused on the development of efficient methods based on hypervalent iodine reagents,[5] *ipso*-halocyclization,[6] radical cyclization,[7] arene−Ru complex-mediated dearomatization,[8] and Cu-catalyzed oxygenation of R-*azido*-*N*-arylamides.[9]

The past decade has seen the prominent development of hypervalent iodine catalysts being exhaustively employed in such dearomatization reactions. Some important reports included the catalytic intramolecular spirolactonization by Ishihara[10] and Kita.[11] A quite generalized, tribromide-mediated spiro-oxacyclization was reported by our group.[12] Reterosynthetically, it is envisaged that a preferred *ipso*-attack of a tethered chain in a phenol can deliver spirocyclization that proceeds via oxidative dearomatization. It would be inspiring if the desired catalysis were an open air transformation.

Transition metal-catalyzed protocols have been limited mainly to spiro-carbon cyclizations.[9] Katsuki's spiro-etherification employing the Fe−Salan catalyst has been a direct way to spiro-oxacylizations. Although the reaction is carried out in open air, the required temperature is 90 °C.[13] A recent report by Vadola delineates a gold-catalyzed synthesis of spiroamides that proceeds through a dearomative alkyne insertion; however, the temperature required for the successful reaction was 80 °C, and $Ag(OTf)_2$ was employed as an activator with moderate yields ranging from 35% to 80%.[14]

Herein, we report the Ru(VIII)-catalyzed synthesis of spiro-azacycles and spiro-oxacycles employing oxidative dearomatization as the key step from easily available naphthols and phenols (Figure 1).

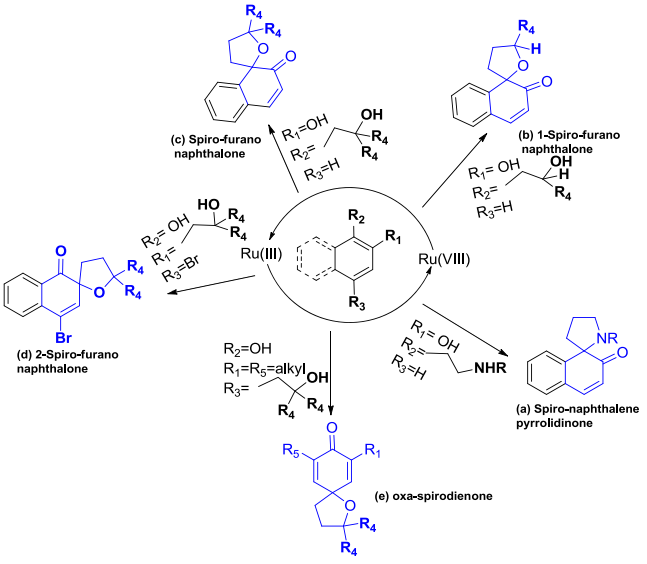


Figure 1. Ru(VIII)-catalyzed dearomative spiro-etherification and spiro-amidation.

Our initial investigation started with 1-(3-ethyl-3-hydroxypentyl)naphthalen-2-ol (**xxi**). The substrate (**xxi**) was treated with $RuCl_3 \cdot 3H_2O$ in the presence of K_2CO_3 as a base and $KBrO_3$ as a co-oxidant along with phenyl trimethylammonium iodide (PTAI) as the additive at room temperature that delivered a 10% yield of the desired spiroether (Table 1, i).

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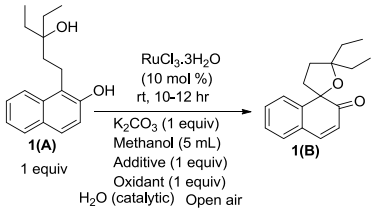
Table 1. Results of Optimization



	ammonium salt (additive)	oxidant	yield (%)
i[a]	phenyl trimethylammonium iodide	$KBrO_3$	10
ii[a]	tetrabutyl ammonium fluoride (TBAF)	*m*-CPBA	no reaction
iii[a]	TBAF	Na_2O_2	no reaction
iv[a]	TBAF	Oxone	no reaction
v[a]	tetrapropyl ammonium hydroxide (TPAH)	$KBrO_3$	60
vi[a]	TBAF	$KBrO_3$	95
vii[a]	benzyl triethylammonium chloride (BTEACl)	$KBrO_3$	93
viii[b]	TBAF	$KBrO_3$ (10 mol %)	10
ix[c]	BTEACl	$KBrO_3$	no reaction

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), additive (10 mol %), and 1 equiv of oxidant. [b]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), additive (10 mol %), and 10 mol % oxidant. [c]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, additive (1 equiv), and $KBrO_3$ (1 equiv). The reaction was carried out in the absence of $RuCl_3{\cdot}3H_2O$. The yield was determined after chromatographic separation.

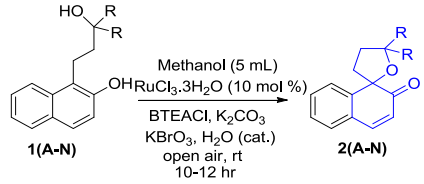
Methanol was used as the solvent of choice due to solubility factors. Further optimization was investigated with the same substrate and with varied oxidants like *m*-CPBA, sodium peroxide, and oxone that produced no reaction (Table 1, ii–iv). Replacing the additive with tetrapropyl ammonium hydroxide (TPAH) improved the yield to 60% (Table 1, v). This conveyed the requirement of an optimal dielectric constant for a successful reaction. A detailed standardization suggested TBAF and BTEACl with $KBrO_3$ were the candidates for the best combination (Table 1, vi). BTEACl was preferred because it was less expensive than TBAF. Electron-donating or -withdrawing substituents attached to the tethered chain did not pose any effect in the reaction [Table 2, **2(A)**, **2(J)**, **2(L)**, and **2(B)**].

Repeating the reaction with only tetrapropyl ammonium perruthenate [Ru(VII)] (10 mol %) in place of $RuCl_3{\cdot}3H_2O$ without any co-oxidant did not produce any reaction. Addition of one drop of a $KBrO_3$ solution immediately triggered the reaction (detailed reaction conditions are given in the Supporting Information).

After the optimal reaction conditions had been achieved, we attempted to generalize the reaction with different side chain alcohols. Exposure of a wide range of side chain alcohols delivered the corresponding spiroethers in excellent yields (Table 2).

Reactions with electron-donating substituents in the side chain [Table 2, **2(D)**, **2(F)**, and **2(K)**] as well as a long carbon chain [Table 2, **2(I)**] promoted better yields compared to those with electron-withdrawing substituents [Table 2, **2(L)** and **2(B)**]. Initial experiments with a focus on the enantioselectivity variant were performed with **2(M)** and chiral (2*R*,4*S*,5*R*)-1-benzyl-2-[(*S*)-hydroxy(quinolin-4-yl)-methyl]-5-vinylquinuclidin-1-ium bromide as the ammonium salt under the same reaction conditions that produced 60% ee and are still being explored.

Table 2. Substrate Scope of Spiro-Furano-Naphthalones[a]



	R	yield (%)
2(A)	-Me	92
2(B)	$-CH_2-C_6H_4-F$	75
2(C)	$-(CH_2)_2-CH_3$	95
2(D)	$-(CH_2)_4-CH_3$	89
2(E)	$-3\text{-Me-}C_6H_4$	94
2(F)	$-4\text{-Me-}C_6H_4$	90
2(G)	-H	92
2(H)	-Ph	92
2(I)	$-(CH_2)_7-CH_3$	96
2(J)	-Et	98
2(K)	$-CH_2-CH(CH_3)_2$	85
2(L)	$-4\text{-Br-}C_6H_4$	75
2(M)	$-CH_2-CH_2-C_6H_5$	95
2(N)	$-CH_2-C_6H_5$	82

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), BTAECl (10 mol %), and 1 equiv of $KBrO_3$. The yield was determined after chromatographic separation.

The substrate scope was further extrapolated with chiral substrates bearing asymmetric centers under the optimized reaction conditions (Table 3). The substitutent variety on the alcohol was tolerated well with moderate diastereoselectivity (4:1 dr) and excellent yield. Large substituents like aryls delivered better diastereoselctivity. All entries (*R*,*R*-spiro-furano-napthalones) were found to be the major diastereomer. The stereochemical assignment was made on the basis of nuclear Overhauser effect experiments. The detailed data are given in the Supporting Information.

With an already established correlation with our previous work on tribromide-cast dearomatizations,[15] we sought to explore the plausible effect of ammonium counterparts of the additives on the diastereoselectivity of spiro-etherification in naphthols. 1-(3-Hydroxy-5-phenylpentyl)naphthalen-2-ol [**3(P)**] was chosen as the model substrate, and *ipso*-cyclization was attempted in the presence of different ammonium salts. The diastereoselectivity changed moderately with the ammonium counterpart, which suggested a possible coordinated key reactive intermediate (shown in the Supporting Information).

The probable existence of moderate diastereoselectivity may arise due to the presence of intimate ion pair arrangement of the ammonium counterpart and the less sterically crowded alkaloate, which attacks the *exo* face of the reactive intermediate with minimal stereoelectronic repulsion (Figure 2).

A compatible combination of the coordinated ammonium counterpart with an aliphatic alcohol followed by both π-

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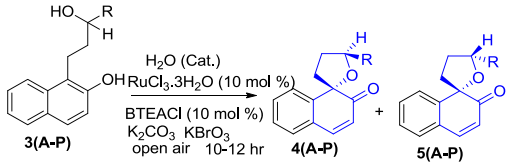
Table 3. Substrate Scope of Diastereoselective Spiro-Furano-Naphthalones[a]



	R	overall yield (%)	dr (4:5)
3(A)	-4-Me-C_6H_4	73	3:1 [4(A):5(A)]
3(B)	-Et	80	3:1 [4(B):5(B)]
3(C)	-Pr	72	7:3 [4(C):5(C)]
3(D)	-$(CH_2)_4$-CH_3	85	4:1 [4(D):5(D)]
3(E)	-CH-$(CH_2)_4$	82	3:1 [4(E):5(E)]
3(F)	-$(CH_2)_3$-CH_3	87	3:1 [4(F):5(F)]
3(G)	-$(CH_2)_7$-CH_3	75	5:1 [4(G):5(G)]
3(H)	-CH-$(CH_2)_5$	81	8:1 [4(H):5(H)]
3(I)	-CH_2-4-F-C_6H_4	65	4:1 [4(I):5(I)]
3(J)	-Ph	88	3:1 [4(J):5(J)]
3(K)	-CH-$(CH_3)_2$	68	3:1 [4(K):5(K)]
3(L)	-CH_2-C_6H_4	92	3:1 [4(L):5(L)]
3(M)	-CH_3	83	2:1 [4(M):5(M)]
3(N)	-$C_{10}H_7$	67	7:3 [4(N):5(N)]
3(O)	−4-F-C_6H_4	65	3:2 [4(O):5(O)]
3(P)	-CH_2-CH_2-C_6H_5	91	4:1 [4(P):5(P)]

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), BTAECl (10 mol %), and 1 equiv of $KBrO_3$. The yield was determined after chromatographic separation. Diastereoselectivity was measured for the mixture via NMR, which is given in the Supporting Information.

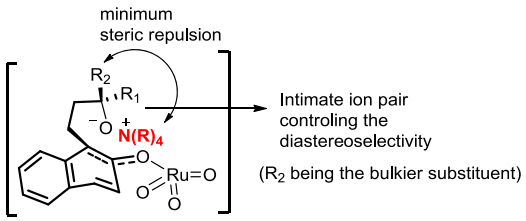


Figure 2. Reactive intermediate (R_1).

stackings (π-stacking 1 and π-stacking 2) and *syn* hydrogen–hydrogen interaction was taken into consideration for the best stereoselectivity (Figure 3). We further propose that from varied projections of spiro-furans in Figure 4 conformation **4** suffers with minimal stereoelectronic interaction and thus is more thermodynamically stable than **5** (Figure 4). Thus, the overall diastereoselectivity achieved is a combination of both

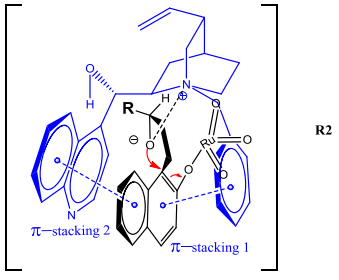


Figure 3. Proposed ion pairing of an alkoxide with a bulky ammonium counterpart (R_2).

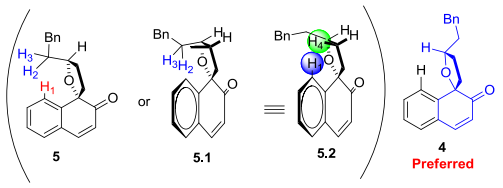
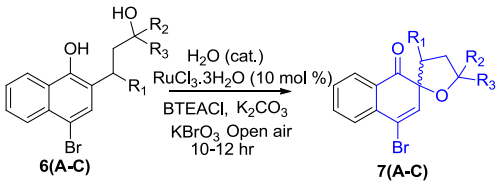


Figure 4. Spiroether conformation.

the thermodynamically stable reaction intermediate (R_2) and the conformational stability of the product that is achieved.

Spirocycles with a 1-naphthol backbone are rarely reported in the literature. 4-Substituted 1-naphthols also delivered the spiro-oxacycles under similar reaction conditions with moderate to good yields (Table 4).

Table 4. Substrate Scope of Spiro-Oxacycles in 1-Naphthols[a]



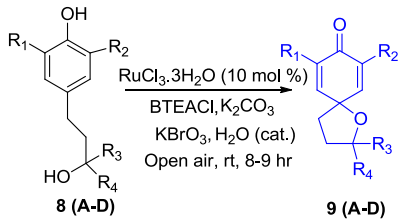
	R_1	R_2	R_3	yield (%)
7(A)	Ph	Et	H	65
7(B)	H	Bn	H	65
7(C)	H	Et	H	60

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), BTAECl (10 mol %), and 1 equiv of $KBrO_3$. The yield was determined after chromatographic separation.

Not only naphthols but also the developed protocol was applicable in the case of properly substituted 2,6-disubstituted phenols that delivered the cyclohexaoxaspirodienones in excellent yields, but the *ortho* positions were required to be substituted for a successful reaction (Table 5).

With the wider substrate scope of spiro-etherification of naphthols and phenols in hand, the next target was to expand

Table 5. Substrate Scope of Synthesized Oxa-Spirodienones[a]



	R_1	R_2	R_3	R_4	yield (%)
9(A)	Pr	Me	benzyl	benzyl	93
9(B)	Me	Me	Ph	Ph	95
9(C)	Me	Me	H	H	92
9(D)	Pr	Me	H	H	96

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), BTAECl (10 mol %), and 1 equiv of $KBrO_3$. The yield was determined after chromatographic separation.

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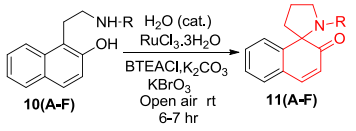
the synthetic utility of our methodology with different δ-amino naphthols to perform the same *ipso*-cyclization to deliver the spiro-azacyclodienones in good to excellent yields (Table 6).

Table 6. Substrate Scope of Synthesized Spiropyrrolidones[a]



	R	yield (%)
11(A)	allyl	86
11(B)	cyclohexyl	95
11(C)	benzyl	95
11(D)	butyl	92
11(E)	propyl	91
11(F)	4-Cl-C_6H_4	82

[a]Reaction performed on a 0.5 mmol scale, with 1 equiv of substrate, 1 equiv of K_2CO_3, $RuCl_3{\cdot}3H_2O$ (10 mol %), BTAECl (10 mol %), and 1 equiv of $KBrO_3$. The yield was determined after chromatographic separation.

To the best of our knowledge, the catalysis involves a red–ox cycle of Ru(III) to Ru(VIII).[16]

We may propose that the catalytic cycle continues with two-phase oxidations of Ru(III) to Ru(VI) and Ru(VI) to Ru(VIII) in the presence of $KBrO_3$.

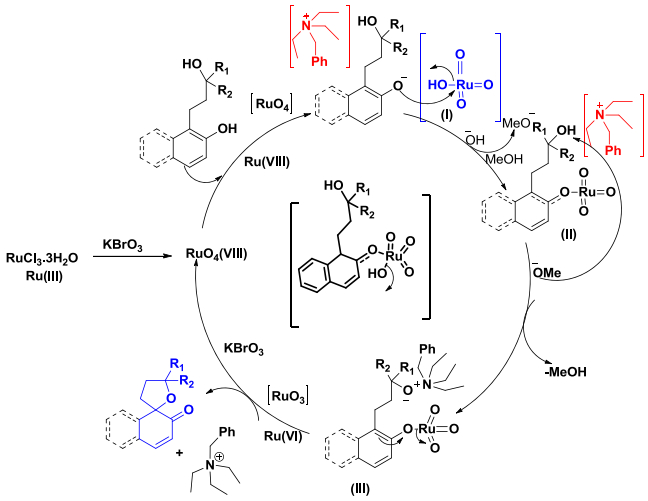
To further comply with the observation, regardless of whether Ru(VIII) was the active species, the reaction mixture was exposed to spectroscopic methods such as ultraviolet (UV), cyclic voltammetry (CV), and electron paramagnetic resonance (EPR) (details given in the Supporting Information).

The combined data derived from EPR, UV, and CV experiments complied and ruled out the possibilities of Ru(VII) and the presence of Ru(VIII) as an active species in the catalytic cycle.

From the experimental outcome mentioned above and the proposed mechanism of ruthenium-catalyzed oxidative dearomatization of indoles,[14] a mechanistic outlook is proposed. The catalytic cycle begins with the oxidation of $RuCl_3{\cdot}3H_2O$ to Ru(VIII) in the presence of $KBrO_3$. The active species $Ru(VIII)O_4$ forms a hydrogen ruthenate complex with the alcoholic naphthoxide and generates a spirofuran and ruthenium(VI) oxide. The ruthenium(VI) oxide is further oxidized to Ru(VIII) by $KBrO_3$. We further propose that the chiral ammonium counterpart of the additive maintains a coordinated sphere throughout the catalytic cycle that produces the moderate diastereoselectivity (Scheme 1).

In conclusion, open air *in situ* ruthenium(VIII)-catalyzed *ipso*-dearomative spiro-etherification and spiro-amination of phenols are reported. It is noteworthy that employing chiral ammonium tribromides as additives tuned the stereoselective outcome of *spiro*-oxacycles. Thus, it is clearly evident that fine-tuning of the ammonium counterpart maintains an asymmetric reaction sphere, and thus, better diastereoselectivity can be achieved in *spiro*-cycle synthesis. The reaction has been also successful with 1-naphthols as backbones. The asymmetric version is presently being studied in our laboratories.

Scheme 1. Catalytic Cycle for Oxidative Spiro-Etherification



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01322.

Copies of ^1H and ^{13}C NMR spectra of all new compounds and EPR, CV, and UV data of related reaction mixtures (PDF)

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Notes

The authors declare no competing financial interest.

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