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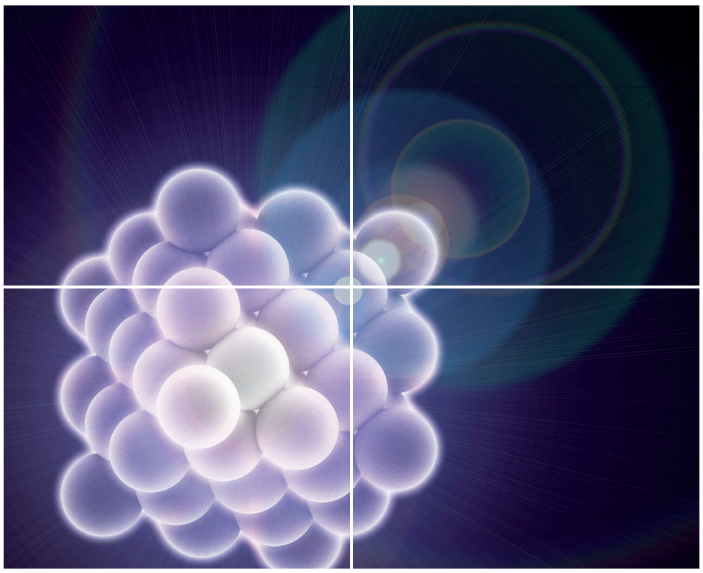

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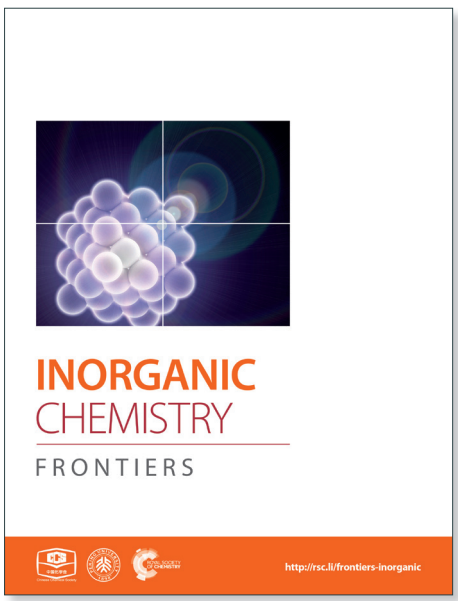

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Intramolecular oxidative cyclization of alkenes by rhodium/cobalt porphyrins in water

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

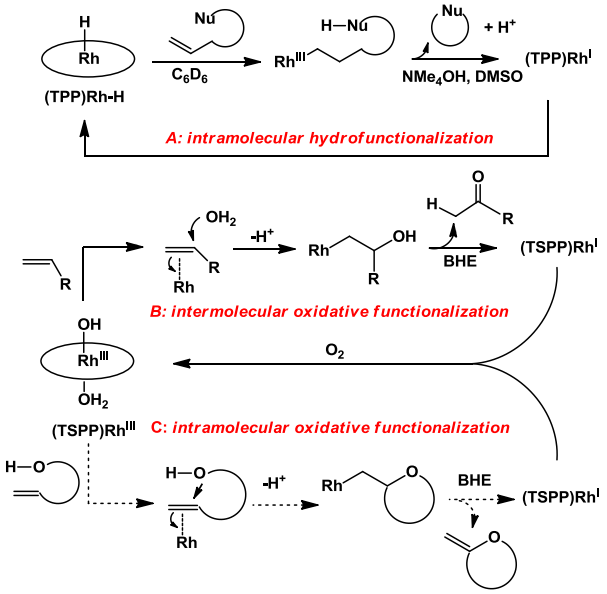
DOI: 10.1039/x0xx00000x

www.rsc.org/

Intramolecular oxidative cyclization of alkenes provides a unique pathway to obtain unsaturated heterocyclic compounds. The rhodium(III)/cobalt(III) tetra (p-sulfonatophenyl) porphyrin ((TSPP)M^{III}) in water was observed to mediate the intramolecular oxidative functionalization of alkenes to a series of unsaturated oxygen heterocyclic compounds.

The activation of alkenes by coordination to metal centers and subsequent functionalizations is one of the most widely exploited synthetic methodologies in the functionalization of organic molecules.[1-3] Intramolecular oxidative cyclization of alkenes provides a unique pathway to obtain unsaturated heterocyclic compounds. Transition metal complexes mediated intramolecular Wacker-type oxidative alkoxylation provides a straightforward access to oxygen heterocycles.[4] The retained C=C double bonds permit further functionalization of the resulting heterocycles. However, this process is far less developed compared with intramolecular hydrofunctionalization of alkenes[5-7] and most oxidative cyclization/functionalization studies focused on palladium catalysis.[1,8] Additionally, the importance of alkenes transformations and objectives of green chemistry justify the continuing search for new classes of catalyst materials and new pathway leading to novel oxidative functionalization in water.

Rhodium porphyrin complexes demonstrate a wide range of important substrate reactions.[9,10] Groves demonstrated intramolecular anti-Markovnikov hydrofunctionalization of olefins mediated by tetraphenyl porporphyrin rhodium hydride complex (Scheme 1A).[10] Previous work from our group has accomplished stoichiometric aerobic oxidation of olefins in water mediated by a water soluble rhodium porphyrin complex (TSPP)Rh^{III}.[11] Rhodium porphyrin β-hydroxyalkyl complexes were observed and isolated as the intermediates, which underwent β-hydrogen elimination (BHE) to give methyl ketones as the oxidation products (Scheme 1B). Based on these studies, we extended our interest towards the intramolecular oxidative cyclization of alkenes to form unsaturated heterocycles (Scheme 1C) through a four-step cycle involving: 1) alkenes coordination to (TSPP)Rh^{III}; 2) intramolecular nucleophilic attack by -OH group towards activated alkenes; 3) hydrogen elimination to give unsaturated cyclization products and 4) the reduced metal complex (TSPP)Rh^{I} was aerobically oxidized to (TSPP)Rh^{III}.



Scheme 1 The rhodium porphyrin complexes mediated transformation of alkenes.

Intramolecular nucleophilic activation of alkenes: Allylphenol was selected as the model substrate which showed good reactivity previously reported.[8,12] Addition of 2-allylphenol into a borate buffered (pH = 8.0) D_2O solution of (TSPP)Rh^{III} at room temperature resulted in an immediate color change from sanguine to orange-red. ^{1}H NMR experiment revealed complete

conversion of (TSPP)Rh^{III} to alkyl rhodium complex **1** which was conveniently identified by the appearance of a set of high field resonances attributed to the (2,3-dihydrobenzofuran-2-yl)methyl group bonded to the rhodium center. The ^{1}H NMR resonances centered at -5.67 and -5.81 ppm were associated with the diastereotopic α-CH_2 in complex **1**, indicating that the rhodium carbon bond was formed regioselectively at the terminal primary CH_2 unit (Figure 1). No intermolecular addition product was formed as the β-hydroxyl proton observed for reaction of allylbenzene was not found in the spectrum of complex **1** (Scheme 2B).[13] Independently synthesized rhodium alkyl complex by reaction of (TSPP)Rh^{I} with 2-(iodomethyl)-2,3-dihydrobenzofuran resulted the same ^{1}H NMR spectrum with that of complex **1**. ESI-MS result (C53H33N4O13RhS4, m/z = 291.99903, *calcd.* 291.99900; Fig. 1) also confirmed the structure of **1**. The intramolecular –OH attack reaction of (TSPP)Rh^{III} with 2-allylphenol to form **1** occurred through coordination of alkene towards rhodium center, followed by intramolecular nucleophilic attack of the phenoxyl group.[11]

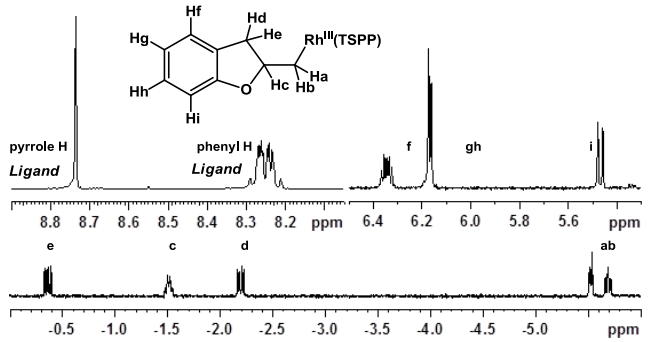
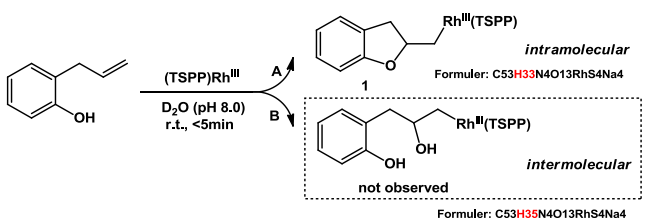


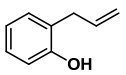
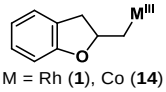
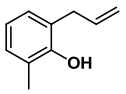
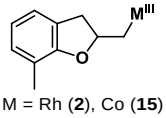
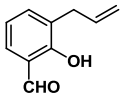
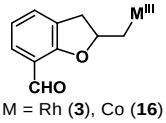
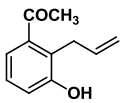
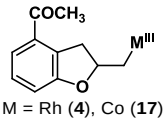
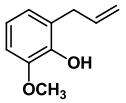
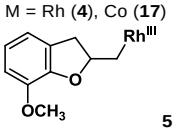
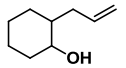
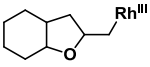
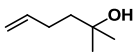
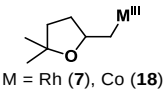
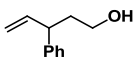
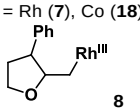
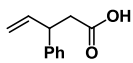
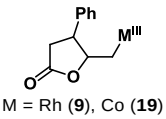
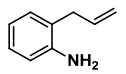
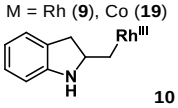
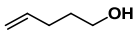
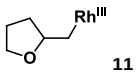
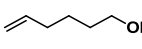
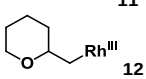
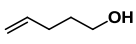
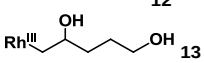
Fig. 1 ^{1}H NMR spectrum of complex **1** in CD_3OD.



Scheme 2 Reaction of (TSPP)Rh^{III} with 2-allylphenol to form complex **1**.

Following the same reactivity pattern, a series of phenyl substituted 2-allylphenol substrates (Table 1, entries 1-5) and a variety of alkenes with different nucleophiles (Table 1, entries 6-12) were observed to react rapidly and quantitatively with (TSPP)Rh^{III} in water and methanol. Changing from benzene ring to cyclohexane ring, 2-allylcyclohexanol reacted with (TSPP)Rh^{III} rapidly to form the cyclization product **6**, indicating that the less nucleophilic alcoholic hydroxyl group could also perform intramolecular oxidative alkoxylation reaction (Table 1, entry 6). 2-Methylhex-5-en-2-ol also experienced a 5-*exo-trig* ring closure reaction with (TSPP)Rh^{III} in water with formation of complex **7** (Table 1, entry 7). Primary alcoholic hydroxyl group could also act as the nucleophile to form the intramolecular cyclization product **8** (Table 1, entry 8). A γ-lactone containing rhodium alkyl complexe **9** was obtained from reaction of 3-phenyl-4-pentenoic acid substrate equipped with a carboxylic hydroxyl nucleophile (Table 1, entry 9). It is worth noting that 2-allylaniline also reacted with (TSPP)Rh^{III} in an intramolecular way with anilino group as nucleophile (Table 1, entry 10).

Table 1 Substrate scope towards intramolecular nucleophilic activation of alkenes by (TSPP)Rh(III)[a] and (TSPP)Co(III)[b]

Entry	Substrate	Product	Yield[c]
1		 M = Rh (**1**), Co (**14**)	**1**: > 95% **14**: > 95%
2[d]		 M = Rh (**2**), Co (**15**)	**2**: > 95% **15**: 73 %
3[d]		 M = Rh (**3**), Co (**16**)	**3**: > 95% **16**: 82 %
4[d]		 M = Rh (**4**), Co (**17**)	**4**: > 95% **17**: 88 %
5[d]		 **5**	> 95%
6		 **6**	> 95%
7		 M = Rh (**7**), Co (**18**)	**7**: > 95% **18**: > 95%
8		 **8**	> 95%
9[d]		 M = Rh (**9**), Co (**19**)	**9**: 86% **19**: 57%
10		 **10**	79%
11[e]		 **11**	> 95%
12[e]		 **12**	> 95%
13		 **13**	> 95%

[a] Reaction conditions: (TSPP)Rh^{III} (1.0 mmol L^{-1}), Alkene (10 equiv), D_2O (300 mL, pH 8.0 borate buffer), room temperature, < 5min.

[b] Reaction conditions: (TSPP)Co^{III} (1.0 mmol L^{-1}), Alkene (10 equiv), D_2O (300 mL, pH 9.0 borate buffer), room temperature, < 5min.

[c] Determined by ^{1}H NMR.

[d] 0.1 mL CD_3OD was added to increase solubility of the substrate.

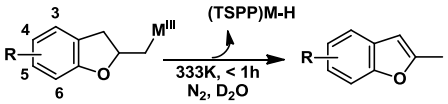
[e] Reactions were performed in CD_3OD.

Previously, we reported reactivity of pent-4-en-1-ol in water with rhodium porphyrins, and the reaction generated exclusively intermolecular nucleophilic attack product **13**.[11] Comparison of entries 7 and 8 where the substrates share similar skeleton with pent-4-en-1-ol revealed the "pre-organizing" function of both phenyl and di-methyl groups which resulted in immediate intramolecular nucleophilic cyclization reaction. Although no cyclization was observed for pent-4-en-1-ol in water, reaction with (TSPP)Rh^{III} in methanol solvent rapidly produced intramolecular alkoxylation rhodium alkyl complex **11** without observation of 6-*endo-trig* product (Table 1, entry 11). Similar reactivity was also observed for hex-5-en-1-ol which underwent 6-*exo-trig* cyclization to form **12** with high regioselectivity (Table 1, entry 12). The difference between the intermolecular reactivity in water lay on the nucleophilicity increase of the alcoholic hydroxyl groups in methanol where solvation effect is lower, and that the hydrophobic porphyrin ligand kept away the hydroxyl group on the alkyl chain.

The produced metal alkyl complexes of Table 1 were generally proposed as the key intermediates in Wacker-type oxidation and hydrofunctionalization of alkenes although only a few literatures reported direct observation of the intermediate.[14] Formation of new C-O bond in these reactions was thought to occur exclusively by nucleophilic attack of an oxygen nucleophile onto a metal-coordinated olefin.[1-3] Recently, migratory insertion of C=C bond into an M-O bond was proposed as an alternative pathway.[15] However, the four membered transition state of migration insertion would require unsaturation of metal center with an vacant *cis* coordination site, which was not conveniently accessible for alkyl rhodium porphyrin complexes.[11,16] Combined with previous studies on intermolecular (TSPP)Rh^{III} mediated aerobic oxidation of alkenes, formation of alkyl rhodium species in Table 1 was proposed to occur via the intramolecular nucleophilic attack towards coordinated alkenes.

Production of unsaturated heterocyclic compounds: In the absence of air, complex **1** was spontaneously transformed to (TSPP)Rh^{I} and 2-methylbenzofuran over 30 min at 333K in water (Scheme 3). The resulting product was extracted by $CDCl_3$ and identified by GC-MS and ^1H NMR. The product was proposed to be formed by β-hydrogen elimination of complex **1**. The stoichiometric reactivity of a series of phenyl substituted 2-allylphenol substrates was examined (Scheme 3). Reactions with (TSPP)Rh^{III} in pH 8.0 buffer solution were rapid and quantitative. The formed β-phenoxyalkyl rhodium porphyrins **2**-**5** underwent β-hydrogen elimination at 333K under nitrogen atmosphere to produce 2-methylbenzofurans quantitatively within 1 hour. The reaction exhibited a good tolerance of a decent range of substituents including alkyl, alkoxyl, acyl, and formyl groups.

(TSPP)Co^{III} mediated oxidative alkoxylation of alkenes: (TSPP)Rh^{III} showed an unusual pathway for oxidative alkoxylation/cyclization of alkenes in water. The cheap metal complex (TSPP)Co^{III} was much more attractive catalyst if this complex could react in the same reactivity pattern as those of (TSPP)Rh^{III}. However, (TSPP)Co^{III} did not react with alkenes through intermolecular pathway to form β-hydroxyl alkyl cobalt porphyrins. Fortunately, the intramolecular reaction occurred rapidly. Addition of 2-allylphenol into a pH 8.0 buffer solution of (TSPP)Co^{III} immediately led to formation of the cyclization product β-phenoxyalkyl cobalt complex **14** (Table 1, entry 1). Methyl, formyl, acyl substituted allylphenols also showed similar reactivates (Table 1, entries 2-4). Rapid formation of alkyl cobalt species **18** and **19** was also observed by reaction of 2-methylhex-5-en-2-ol and 3-phenyl-4-pentenoic with (TSPP)Co^{III} (Table 1, entries 7 and 9). These reactions provide rare examples of Co(III) mediated oxidation of alkenes,[17] since both the interaction of Co(III) with alkenes and the Co(III)-C bonding are weak, which explained the unfavorable intermolecular formation of Co^{III}-CR_2-CR_2OH. The efficient formation of complexes **14**-**19** through intramolecular nucleophilic addition pathway was ascribed to the entropy-driven effect. Upon heating to 333K, complex **14**-**17** gave oxidative cyclization product 2-methylbenzofuran as observed for **1** (Scheme 3).



M = Rh, R = H, 6-CH_3, 6-OCH_3, 6-CHO, 3-$COCH_3$
M = Co, R = H, 6-CH_3, 6-CHO, 3-$COCH_3$

Scheme 3 Formation of heterocyclic unsaturated compounds. See Table S1 in ESI for detailed experiment conditions and results.

The (TSPP)Rh-H species formed in elimination reactions in scheme 3 occurs in a rapid dissociation equilibrium with (TSPP)Rh^{I} and H^+. Rapid air oxidation of (TSPP)Rh^{I} to (TSPP)Rh^{III} completes the Wacker-type oxidation cycle which provides the potential for aerobic catalytic intramolecular cyclization of olefins with exclusive regioselectivity (eqn(1)).[18]

$$(TSPP)Rh^{I} + 1/2O_2 + H_2O \rightleftharpoons (TSPP)Rh^{III} + 2OH^- \quad (1)$$

Conclusions

In summary, we have described an unusual pathway for intramolecular oxidative cyclization of substituted 2-allyllphenols by (TSPP)Rh^{III} and (TSPP)Co^{III} to form 2-methylbenzofuran derivatives in water. Key intermediates β-phenoxyalkyl rhodium/cobalt porphyrin complexes were observed and characterized. A series of substrates including unsaturated alcohols, carboxylic acid, and aniline also reacted with (TSPP)Rh^{III} to form thermally stable β-hetero-functionalized alkyl rhodium porphyrins with exclusive regioselectivity. These complexes provide valuable insights into mechanistic studies of transition metal catalyzed Wacker-type oxidation of alkenes and novel construction protocol for heterocycle synthesis. Developing new methods for further cleavage of Rh-C bond, Co-C bond and catalytic intramolecular oxidative cyclization of alkenes is ongoing.

Acknowledgements

This work was supported by National Science Foundation of China (21171012).

Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

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13 Reaction of (TSPP)Rh^{III} and allylbenzene was performed in H_2O. The formed product ((TSPP)Rh-$CH_2CH(O\boldsymbol{H})CH_2C_6H_5$) was purified and dissolved in anhydrous DMSO-d_6 to observe the β-hydroxyl resonance (0.04ppm, d, $^3J_{H\text{-}H}$ = 5.6Hz). Similar work up was used for 2-allylphenol and no hydroxyl signal was observed on the ^1H NMR spectrum of **1** in DMSO-d_6.

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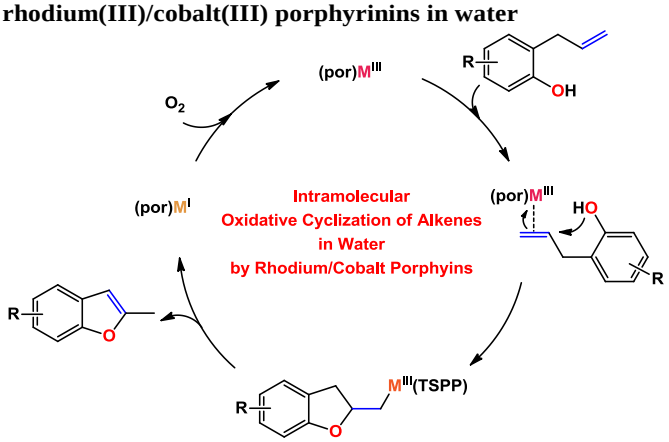

M = Rh, R = H, 6-CH_3, 6-OCH_3, 6-CHO, 3-$COCH_3$
M = Co, R = H, 6-CH_3, 6-CHO, 3-$COCH_3$
por = TSPP (tetra(*p*-sulfonatophenyl) porphyrin)