Rhenium-Catalyzed Regioselective *ortho*-Alkenylation and [3+2+1]Cycloaddition of Phenols with Internal Alkynes

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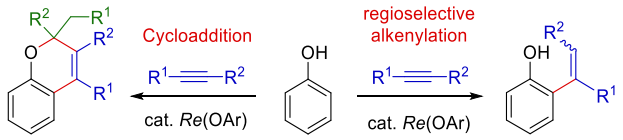
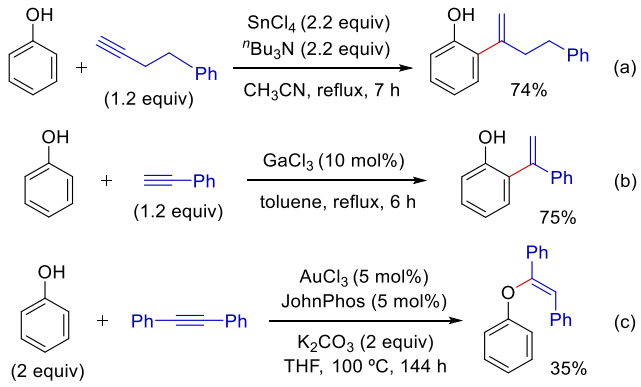


- **Catalytic** and ***ortho*-selective *C*-alkenylation of phenols with **internal** alkynes.
- [3+2+1]Cycloaddition using alkynes as both **two-** and **one-carbon units**.

ABSTRACT: An operationally simple and direct rhenium-catalyzed *ortho*-alkenylation (*C*-alkenylation) of unprotected phenols with alkynes was developed. The protocol provided *ortho*-alkenylphenols exclusively, and formation of *para*- or multiply alkenylated phenols and hydrophenoxylation (*O*-alkenylation) products were not observed. The [3+2+1]cycloaddition of phenols and two alkynes *via ortho*-alkenylation was also demonstrated, in which the alkynes functioned as both two- and one-carbon units. These reactions proceeded with readily available starting materials under neutral conditions without additional ligands.

Functionalization of inexpensive and abundant phenol derivatives for sustainable production of organic chemicals is an important challenge.[1] Phenols are ubiquitous structural motifs in biologically active compounds, pharmaceuticals, agrochemicals, lignin, and functional materials, and are versatile building blocks in organic synthesis.[1c] Thus, development of methods to promote facile and efficient functionalization at specific ring positions is desirable. Among these reactions, additions to alkynes is attractive, because it enables the introduction of synthetically useful phenoxy and double-bond functionalities in the target molecules in an atom-efficient manner. The pioneering work was reported by Yamaguchi using a stoichiometric amount of $SnCl_4$ or $GaCl_3$ (Scheme 1(a)).[2] However, catalytic *C*-alkenylation of phenols remains limited to protocols involving electronically activated alkynoates,[3b,d] terminal acetylenes,[3a,e,g] or intramolecular cyclizations[3c,f,h] (Scheme 1(b)). This is because the unprotected phenolic hydroxy group has an acidic proton, and usually acts as an oxygen-based nucleophile. Thus, hydrophenoxylation (C–O bond formation) occurs preferentially over C–C bond forming alkenylation of relatively inert C–H bonds (Scheme 1(c)).[4] Furthermore, functionalization of phenols often results in the formation of regioisomers and overreaction products due to the strong *ortho*/*para*-orientation of the phenolic hydroxy group.[3]

Although the reaction course and resulting addition strongly depend on interactions of phenol and alkyne in the transition state, the directing ability of the phenolic hydroxy group in well-established late transition metal-catalyzed C–H bond functionalization appears to be relatively weak.[5] We envisioned that rhenium, a group 7 metal located between the early and late transition metals in the periodic table, and therefore possesses both soft and hard Lewis acidity, can alter the addition manner of the reaction.[6,7] The present work demonstrated the rhenium-catalyzed *ortho*-selective *C*-alkenylation of unprotected phenols with alkynes. The resulting *ortho*-alkenyl phenols, classically synthesized by Claisen rearrangement of allylphenylethers, are useful compounds. The related and rare [3+2+1]cycloaddition of phenols with two alkynes leading to 2*H*-chromene derivatives is also described.

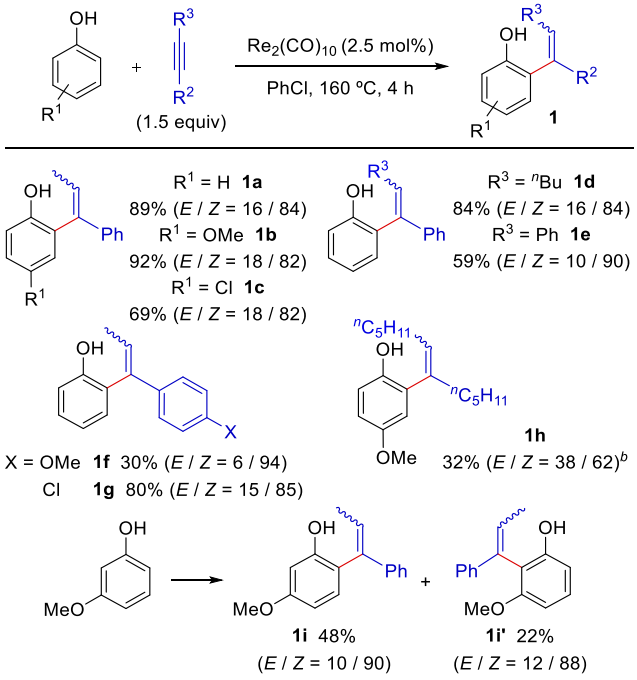


Scheme 1. Previously reported methods for alkenylation of phenols

We found $Re_2(CO)_{10}$ was effective for the alkenylation of phenol with 1-phenyl-1-propyne in chlorobenzene (2 M) at 160 °C. 2-Alkenylphenol **1a** was obtained in 89% yield as a mixture of two stereoisomers, and the major stereoisomer had the *Z* configuration as determined by nOe studies. The formation of regioisomers was not observed at all. The reaction can be conducted even on 5 mmol scale (see eq S1 in SI). Note that the use of $GaCl_3$, which was reported to promote alkenylation with terminal alkynes as shown in Scheme 1(c),[3d,e] failed

to provide **1a**. Using $Re_2(CO)_{10}$ as a catalyst, the scope of the *ortho*-selective alkenylation was examined (Table 1).[8] Electron-rich 4-methoxyphenol reacted smoothly with 1-phenyl-1-propyne to furnish **1b** in 92% yield. Despite the electronic nature of the substituents, alkenylation occurred selectively at the position *ortho* to the phenolic hydroxy group, and the potentially coordinating methoxy group did not disturb the site-selectivity.[9] Although the chloro group of 4-chlorophenol was well-tolerated and provided **1c**, substitution of these electron-withdrawing groups decreased reaction efficiency. Olefination of electron-poor 4-trifluoromethylphenol did not proceed, indicating that the current olefination reaction can be classified as electrophilic functionalization. Note that the reactivity trend was completely different from that of the classic Friedel-Crafts type electrophilic functionalization, in which multiple functionalizations and/or functionalization at the *para* position usually occurs as competitive side reactions. The electronic effect of substituents on the alkyne also affected reaction efficiency. Although **1d** was obtained in 84% yield by reaction with 1-phenyl-1-hexyne, olefination with more sterically hindered diphenylacetylene was sluggish, and furnished **1e** in moderate yield. The electron-rich methoxy group substituted arylalkyne provided the corresponding adduct **1f** in low yield due to competitive oligomerization of the alkyne under the reaction conditions. In contrast, alkenylation with relatively electron-poor 1-(4-chlorophenyl)-1-propyne gave the expected **1g** in 80% yield. Olefination with aliphatic alkynes, such as 6-dodecyne, was sluggish, and the corresponding adduct **1h** was obtained in low yield, even when heated at high temperature for a long period. When 3-methoxyphenol was used, formation of a regioisomeric mixture of the desired *ortho*-alkenylphenol was observed in 69 / 31 ratio in favor of the sterically less hindered **1i**. Unfortunate, terminal alkynes oligomerized under the current reaction conditions, and did not provide the corresponding alkenylated products.[10]

Table 1. Rhenium-catalyzed regioselective alkenylation of phenol derivatives[a]



[a]Maximum yields are 95% as noted in footnote 8. Stereoselectivity was determined by ^{1}H NMR. [b]200 °C, 24 h.

During these studies, selective formation of 2*H*-chromene derivatives **2** *via* alkenylation of phenols proceeded by simply increasing the reaction time and amount of alkene.[11] In contrast to the usual reactivity of alkynes as two-carbon annulation partners in [n+n'+2]cycloaddition,[12] this represents a rare example of [3+2+1]cycloaddition using alkynes as both two- and one-carbon units (Figure 1, left).[13] Reaction of phenols with alkynes was previously reported for the synthesis of benzofurans by formal [3+2]cycloaddition *via* hydrophenoxylation to alkynes (Figure 1, right).[14] Arylalkynes were used in these studies, resulting in selective attack by the oxygen atom of phenol on the aryl group-substituted carbon atom of the alkyne. In the current study, regioselectivity of the addition was the opposite, with the carbon atom of the phenoxy ring attacking the aryl group-substituted carbon atom of the alkyne.

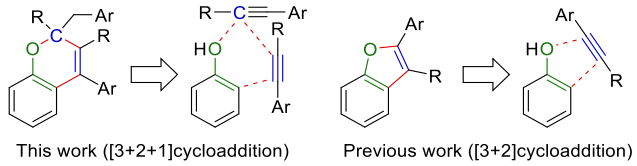
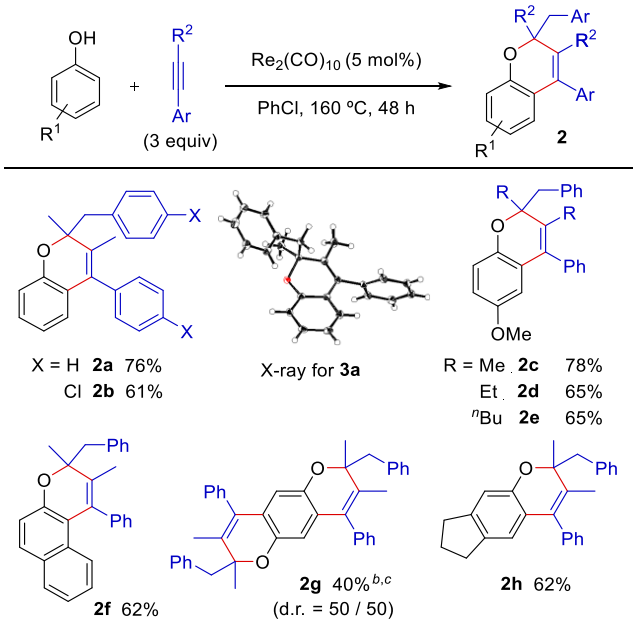


Figure 1. Novel reactivity of phenols toward internal alkynes

Since the 2*H*-chromene skeleton is a common structural motif in biologically active compounds and optoelectronic materials, the generality of the current novel approach by [3+2+1]cycloaddition was examined briefly (Table 2).[8,11] Cycloaddition of phenol with 1-phenyl- or (4-chlorophenyl)-1-propyne gave **2a** and **2b**, respectively, in moderate to good yield. The structure of **2a** was determined unambiguously by single-crystal X-ray crystallography (see Figure S2 in SI for details). Substitution of the methoxy group did not affect the reactivity and yielded the corresponding 2*H*-chromene derivatives **2c**, **2d**, or **2e**. 2-Naphthol was also a suitable substrate to afford benzo[*f*]chromene **2f** *via* regioselective *C*-alkenylation at the most electron-rich 1-position without the formation of other regioisomers. Two-fold [3+2+1]cycloaddition with

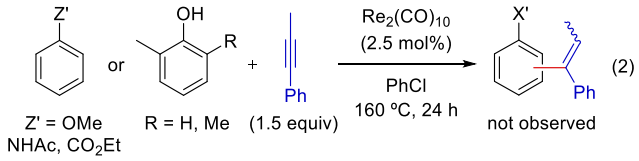
Table 2. [3+2+1] Cycloaddition reaction of phenol with internal alkynes[a]



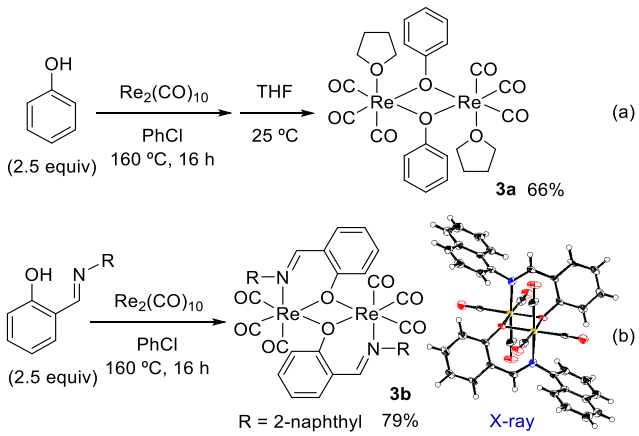
[a] The maximum yields are 90% as noted in footnote 10.
[b] $Re_2(CO)_{10}$ (10 mol%) or [c] alkyne (6 equiv) were used.

hydroquinone, which is susceptible to oxidation, provided **2g** as a mixture of two diastereomers. Cyclopentane-fused tricycle **2h**, a potentially useful building block for constructing biologically active compounds and functional materials,[15] was obtained through regioselective alkenylation at the least sterically hindered position of the phenol ring.

The current alkenylation proceeded selectively at the *ortho* position to provide only mono-alkenylated products. The use of anisole, acetanilide, and ethyl benzoate, which are common substrates for regioselective functionalization based on C–H bond activation, in place of phenol did not afford any alkenylation products, but resulted in the recovery of the aromatic starting materials (eq 2). Furthermore, sterically hindered phenol derivatives with a methyl group at the *ortho* position also prevented the alkenylation reaction at any position, indicating that interaction of the phenoxy oxygen atom with the rhenium center is key for the current transformation.

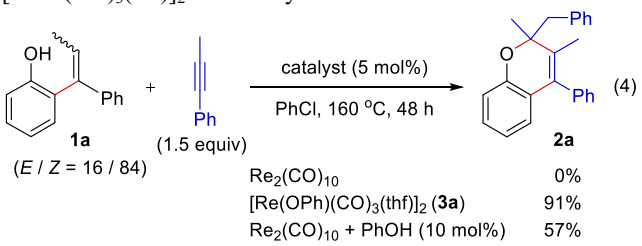


As expected, the phenoxy-bridged rhenium carbonyl dimer, $[Re(OPh)(CO)_3(thf)]_2$ **4a**, was obtained exclusively by reaction of $Re_2(CO)_{10}$ with phenol, followed by treatment with THF to stabilize the resulting complex (Scheme 2a). The structure was tentatively assigned by the results of NMR and elemental analysis (see SI for details).[16] A structurally characterizable single crystal of the (μ-phenoxo)rhenium complex **3b** was obtained using 2-iminophenol as a substrate (Scheme 2b). The ORTEP drawing clearly showed an aryloxy ligand-bridged dinuclear rhenium structure stabilized by coordination of nitrogen atoms of the imino groups at the apical position (see also Figure S3 in SI). The isolated **3a** was confirmed to perform well as a catalyst for the current alkenylation.



Scheme 2. Synthesis and X-ray crystal structure (yellow: Re, blue: N, red: O) of $[Re(OAr)(CO)_3(thf)_n]_2$ complexes **3**. Solvent atoms were omitted from the ORTEP drawing for clarity.

Complex **3a** also catalyzed the conversion of 2-alkenylphenol **1a** to 2*H*-chromenes **2a**, which demonstrated that **1** was an intermediate for formation of **2** (eq 4). Unexpectedly, this [5+1]cycloaddition did not proceed when only $Re_2(CO)_{10}$ was used as the catalyst, and addition of a catalytic amount of phenol was required. The (μ-phenoxo)rhenium complex **3a** prepared *in situ* by reaction of $Re_2(CO)_{10}$ and PhOH demonstrated catalytic performance. These results clearly show that the real catalyst was an aryloxyrhenium species, and phenol derivatives having substituents at the 2-position did not work as precursors as shown in eq 2 due to steric hindrance. While the exact role of the phenoxy ligand was not clear, it was indispensable for the current alkenylation and cycloaddition, and no reaction occurred with $[ReBr(CO)_3(thf)]_2$ as a catalyst.



Based on these results, the reaction mechanism for formation of 2-alkenylphenol **1a** and 2*H*-chromene **2a** is thought shown in Figure 2, which exemplifies reaction of phenol with 1-phenyl-1-propyne. First, nucleophilic attack of phenol occurred site-selectively at the position *ortho* to the phenolic hydroxy group, which was assisted by coordination of both the phenol and alkyne to the rhenium centers in intermediate **A**.[17,18] Only rhenium catalysts possessed activity toward the current *ortho*-alkenylation, to be due to the unique soft and hard Lewis acid nature of rhenium, a metal between the early and late transition metals in the periodic table.[6i,j] Thus, low-valent rhenium carbonyl complexes could activate both the soft carbon–carbon triple bonds of alkynes and the hard oxygen atoms of phenol at the same time, to promote the addition reaction. Subsequent protonation and isomerization initially furnished *E*-**1a**, which was rapidly isomerized *via* 1,5-H shift to a mixture of two stereoisomers *E*- and *Z*-**1a**. Then, phenolic hydroxy group-directed C(sp^2)–H bond activation in the *E*-configuration,[5,19] followed by insertion of an alkyne resulted in the 8-membered ring oxarhenacycle intermediate **C**. The terminal alkenyl carbon of **1a** selectively attacked the methyl group-substituted carbon atom of an alkyne, which proceeded *via* a C–H activation / insertion mechanism, not a Friedel-Crafts-type electrophilic alkenylation mechanism. Reductive elimination then afforded 2-dienylphenol intermediates, which finally converted into 2*H*-chromene **2a** *via* 1,7-H shift followed by oxa-6π-electro- cyclization of *ortho*-quinone methide intermediate **D**.[20,21]

Three-component coupling of phenol and two different alkynes *via* [3+2+1]cycloaddition was examined to demonstrate

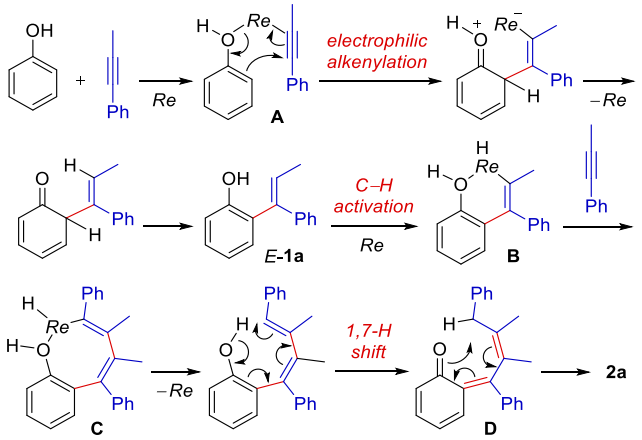
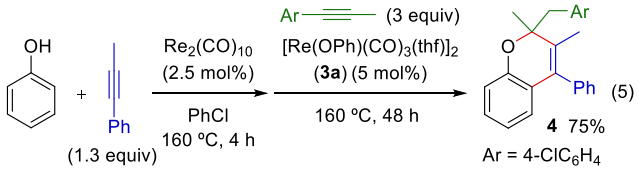


Figure 2. Proposed reaction mechanism (*Re* = $Re(OPh)(CO)_3$)

the utility of the present 2*H*-chromene synthesis. The expected multiple-substituted chromene derivative **4** was obtained in 75% yield by sequential treatment of two different alkynes (eq 5). Addition of a catalytic amount of (μ-phenoxo)rhenium complex **3a** along with treatment of the second alkyne greatly promoted the formation of 2*H*-chromene.



In conclusion, a facile and practical method for *ortho*-alkenylation of phenols with complete site- and regioselectivity was achieved using a rhenium catalyst. In contrast to classic Friedel-Crafts electrophilic functionalization (proceeding with *ortho*- and *para*-orientation to yield a mixture of mono- and multiple-substituted adducts), reaction occurred selectively at the position *ortho* to the phenolic hydroxy group, providing selectively mono-alkenylated phenols. Although a high temperature was required, these reactions proceeded with readily available starting materials under neutral conditions without additional ligands. These reaction schemes offer new insights into the reactivity of phenols, and open up their new potential as a readily available inexpensive chemical feedstock for synthesis of biologically active molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by a Grant-in-Aid for Scientific Research (No. 26248030) from MEXT, Japan.

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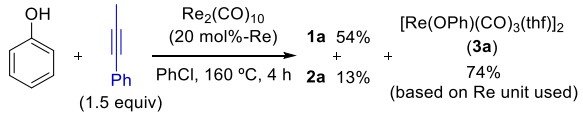
(8) For alkenylation under the conditions shown below, 74% yield of $[Re(OPh)(CO)_3(thf)]_2$ **3a** was obtained based on the $Re_2(CO)_{10}$ employed. This result suggested that two equivalents of phenol derivatives relative to $Re_2(CO)_{10}$ were consumed for the formation of (μ-phenoxo)rhenium complex **3a**, and did not participate in the catalytic alkenylation.



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(10) Phenol derivatives having amino and cyano groups failed to provide alkenylated products in the reaction with 1-phenyl-1-propyne. Addition of amines, such as triethylamine, DABCO, and pyridine, decreased the yield of **1a**. See ref 6f for the effect of amines in the rhenium-catalyzed transformation.

(11) Functionalized 2*H*-chromenes are important targets in organic synthesis. See: (a) Ferreira, S. B.; da Silva, F. de C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocyclic Chem.* **2009**, *46*, 1080. (b) Pratap, R.; Ram, V. J. *Chem. Rev.* **2014**, *114*, 10476. (c) Majumdar, N.; Paul, N. D.; Mandal, S.; de Bruin, B.; Wulff, W. D. *ACS Catal.* **2015**, *5*, 2329. (d) Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2012**, *14*, 1616, and references cited therein.

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(16) Since all attempts to obtain the exact molecular weight of $[Re(OPh)(CO)_3(thf)]_n$ (**3a**) by mass spectrometry failed, the number of rhenium nuclei was unclear. A tentative structure for the dimer is shown in Scheme 2. Catalyst loading in this study was calculated based on the number of rhenium units.

(17) Because formation of *para*-alkenylated phenols was not observed in the current transformation, intermolecular nucleophilic attack of phenols to alkynes without proceeding through intermediate **A** in Figure 2 can be ruled out. However,

(18) For a possible alternative mechanism for alkenylation *via* C–H bond activation of phenol followed by addition of rhenium hydride species *via* a stepwise radical rebound mechanism cannot be ruled out completely. See: Lehnherr, D.; Wang, X.; Peng, F.; Reibarkh, M.; Weisel, M.; Maloney, K. M. *Organometalllics* **2019**, *38*, 103.

(19) Although a concerted metalation / deprotonation mechanism is proposed for formation of intermediate **B** by C–H activation in Figure 2, an alternative route *via* dearomatization / rearomatization (see eq S2 in SI), cannot be ruled out.

(20) Oxacycles formation *via* 1,7-H shift followed by oxa-6π-electrocyclization is rare. See: (a) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2001**, *3*, 3875. (b) Ramachary, D. B.; Narayana, V. V.; Ramakumar, K. *Eur. J. Org. Chem.* **2008**, 3907. For reviews on the synthesis of chromene derivatives *via* electrocyclization of *ortho*-quinone methide intermediates, see: (c) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757. (d) Ferreira, S. B.; da Silva, F. C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocyclic Chem.* **2009**, *46*, 1080.

(21) Alternative mechanism for oxacycle formation *via* the following rhenium-catalyzed 6-*exo-dig* cyclization cannot be ruled out (see eq S3 in SI).