Mechanistic Insights into Rhenium-Catalyzed Regioselective *C*-Alkenylation of Phenols with Internal Alkynes

Masahito Murai,*[a,b] Masaki Yamamoto,[a] and Kazuhiko Takai*[a]

Abstract: A (μ-aryloxo)rhenium complex was isolated and confirmed as a key precatalyst for rhenium-catalyzed *ortho*-alkenylation (*C*-alkenylation) of unprotected phenols with alkynes. The reaction exclusively provided *ortho*-alkenylphenols, and formation of *para*- or multiply alkenylated phenols and hydrophenoxylation (*O*-alkenylation) products were not observed. Several mechanistic experiments excluded a classical Friedel-Crafts type mechanism, leading to the proposed phenolic hydroxyl group-assisted electrophilic alkenylation as the most plausible reaction mechanism. For this purpose, the use of rhenium, a metal between the early and late transition metals in the periodic table, was key for the activation of both the soft carbon–carbon triple bond of the alkyne and the hard oxygen atom of the phenol at the same time. *ortho*-Selective alkenylation with allenes also provided the corresponding adducts with a substitution pattern different from that obtained by the addition reaction with alkynes.

Introduction

Catalytic functionalization of unactivated C–H bonds is a straightforward and atom-economical approach to target molecules without requiring tedious prefunctionalization of the starting materials.[1] While late transition metal complexes containing elements such as ruthenium, rhodium, and palladium *etc*, are frequently used as catalysts, what we focused on as an attractive new candidate was a rhenium, a group 7 metal located in the middle of early and late transition metals in the periodic table.[2] In particular, rhenium carbonyl complexes turned out to be very reactive, and many catalytic transformations based on the cleavage of not only C–H bonds but also C–C and B–H bonds have been achieved.[2,3] Despite their unique catalytic performance, understanding the origin of unique reactivity based on the isolation of *catalytically active* rhenium carbonyl species has remained elusive, which is surprising because many reports on the photophysical properties and wire-performance of structurally well-characterized rhenium-based functional molecules having bipyridyl or cyclopentadienyl ligands have been published.[4] Although Wang and coworkers recently reported the isolation and characterization of a catalytically active five-membered ring rhenacycle intermediate for [4+1]annulation reaction of azobenzenes and aldehydes,[5] further study could provide valuable new insights into the design of more efficient rhenium-catalyzed transformations.[6]

Phenol units are important and fundamental structural motifs found in many natural products, biologically active compounds, and pharmaceuticals.[7] Thus, regioselective functionalization of unprotected phenol derivatives is a fundamental, but still nontrivial research subject due to the ready availability and synthetic versatility of phenol derivatives. Chelation-assisted functionalization by heteroatom-containing directing groups introduced on the phenolic hydroxy group is one promising strategy.[8] However, this approach requires preactivation of starting molecules and additives (bases, ligands). Thus, development of an operationally simple and direct regioselective *C*-alkenylation method for unprotected phenols remains challenging. Unfortunately, sporadic studies on the direct *C*-alkenylation of unprotected phenol derivatives (C–C bond forming alkenylation) *via* addition to alkynes have been reported.[9] However, three main obstacles exist for alkenylation of unprotected phenols. First, an unprotected phenolic hydroxy group has an acidic proton, and usually acts as an oxygen-based nucleophile to provide *O*-alkenylated adducts *via* hydrophenoxylation (C–O bond formation).[10] Although the reaction course could be changed by interaction 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.[11] Second, controlling the regiochemistry of the addition reaction is difficult as indicated by the inherent strong *ortho*/*para*-orientation of a phenolic hydroxy group. This lack of selectivity has been suppressed by the introduction of substituents on the phenol rings. Third, some phenol derivatives are sensitive toward oxidants and acids, and require mild conditions for their transformations. Since the pioneering work by Yamaguchi and coworkers on *ortho*-selective alkenylation with terminal alkynes using a stoichiometric amount of $SnCl_4$ or $GaCl_3$,[12] several regioselective *C*-alkenylation have been reported. However, existing intermolecular catalytic addition protocols are suitable only for electronically activated alkynoates and terminal acetylenes.[13]

Very recently, we found that the dirhenium decacarbonyl, $Re_2(CO)_{10}$, could serve as an efficient catalyst for intermolecular *ortho*-selective *C*-alkenylation of phenols with *internal* alkynes (eq 1).[14] The reaction did not require external ligands or additives to provide functionalized alkenylphenols with high atom-efficiency. Elucidation of the reaction mechanism is crucial for expanding the synthetic diversification of phenol chemistry. In an effort to clarify the origin of this unique catalytic performance of transition metal complexes,[15] the present study describes results from a mechanistic investigation of the regioselective alkenylation of phenols based on the isolation of a reactive rhenium precatalyst.[16]

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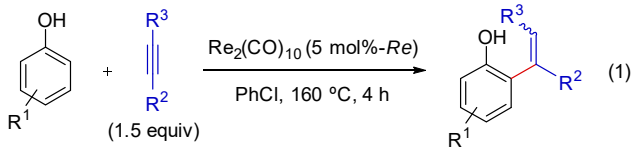

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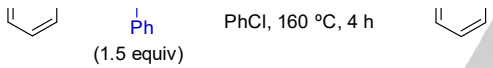
Results and Discussion

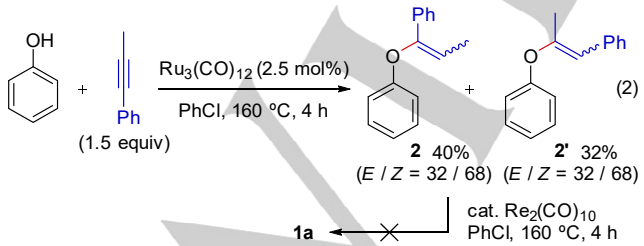
Regioselective Catalytic Alkenylation of Phenols with Internal Alkynes: Our recent work revealed that $Re_2(CO)_{10}$ and $[HRe(CO)_4]_n$ effectively promoted *ortho*-alkenylation leading to **1a**, whereas $[ReBr(CO)_3(thf)]_2$ and $ReBr(CO)_5$ did not possess any catalytic activity with the recovery of phenol intact (Table 1).[14] The major stereoisomer had the *Z* configuration, and formation of regioisomers was not observed. As expected from the previous work,[10] several catalysts, including $Ru_3(CO)_{12}$, promoted hydrophenoxylation leading to **2** and **2'** selectively without formation of **1a** (eq 2). Neither **2** nor **2'** was converted to **1a** upon treatment with $Re_2(CO)_{10}$, indicating that the current *ortho*-alkenylation leading to **1a** did not proceed *via* typical hydrophenoxylation. Other metal complexes, such as $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, $Mn_2(CO)_{10}$, $ReCl_5$, $Fe_2(CO)_9$, $Ir_4(CO)_{12}$, AgOTf, $AuCl_3$, and $GaCl_3$ did not show any catalytic activity and the phenol was recovered intact. Chlorobenzene gave the best result among the solvents tested, and alkenylation did not occur in polar solvents (DMF, THF, and MeCN).[17]

Table 1. Effects of catalyst



entry	catalyst	Yield / % (*E* / *Z*)[a]
1	$Re_2(CO)_{10}$	89 (16 / 84)
2	$[HRe(CO)_4]_n$	44 (17 / 83)
3	$ReBr(CO)_5$	3[b]
4	$[ReBr(CO)_3(thf)]_2$	trace[b]
5	$GaCl_3$	0

[a]Determined by ^1H NMR. [b]Stereoselectivity could not be determined.



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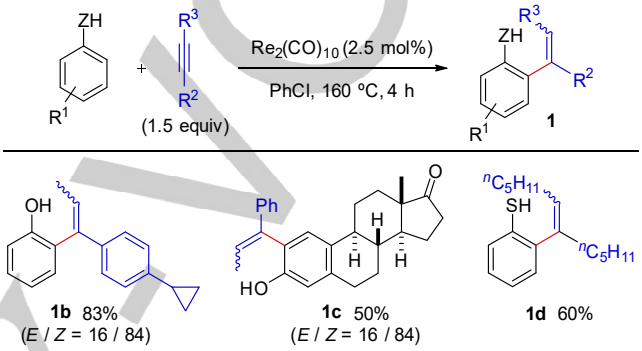
In addition to the scope demonstrated in the recent our report,[14] alkenylation with 1-aryl-1-propyne containing a cyclopropyl group on the benzene ring also provided the corresponding adduct **1b** in 83% yield, without the detection of any cyclopropane ring-opening adducts (Table 2).[18]

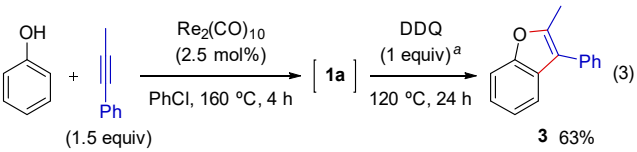
Alkenylation was also applied to biologically active estron. The reaction proceeded selectively at the least sterically hindered position to afford **1c** in 50% yield without affecting the stereogenic center or carbonyl group. This result demonstrates the potential of the current alkenylation for late-stage modification of biologically active molecules.[19] Thiophenol was also applicable as a substrate, and alkenylation proceeded even with electronically unactivated 6-dodecyne to give the expected alkenylation product **1d** in 60% yield.

Table 2. Rhenium-catalyzed *ortho*-selective alkenylation of phenols and thiophenol (see ref. 14 for the other scope)



[a]Maximum yield was 95% as noted in footnote 18.

Combination of this regioselective *C*-alkenylation with DDQ-promoted dehydrogenative cyclization[20] allowed rapid construction of a benzofuran skeleton (eq 3). Note that synthesis of 3-alkyl-2-arylbenzofurans was reported by Sahoo *et al. via* [3+2]cycloaddition reaction of phenol with alkylarylacetylenes,[10b] and their isomers, 2-alkyl-3-arylbenzofurans, could be obtained selectively in the current protocol. Overall, addition of phenols to alkynes can provide a divergent approach to variously functionalized heterocycles, with the potential to be useful in the pharmaceutical industry.



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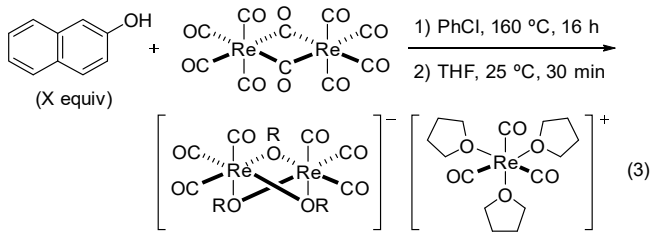
[a] 0.5 equiv of DDQ was added at the beginning and the remaining DDQ was added after 12 h.

Isolation, Structural Characterization, and Reactivity of (μ-Aryloxo)rhenium Intermediates: A mechanistic study commenced with obtaining insights into the unique reactivity of $Re_2(CO)_{10}$. Treatment of 2-naphthol with $Re_2(CO)_{10}$ in chlorobenzene at 160 °C for 16 h followed by the addition of THF produced the (μ-naphthoxo)rhenium complex, $[Re_2(\mu\text{-}ONaph)_3(CO)_6][Re(CO)_3(thf)_3]$ (**4**), as a colorless powder (eq 3).[21] The structure of **4** was unambiguously determined by single crystal X-ray diffraction (Figure 1). The ORTEP drawing confirmed a dinuclear rhenium structure bridged by three aryloxo ligands. Elemental analysis also supported this proposed structural formula.



4 (R = 2-Naph)
45% (X = 5), 66% (X = 10), 85% (X = 20)
Yields were determined by ^{1}H NMR.

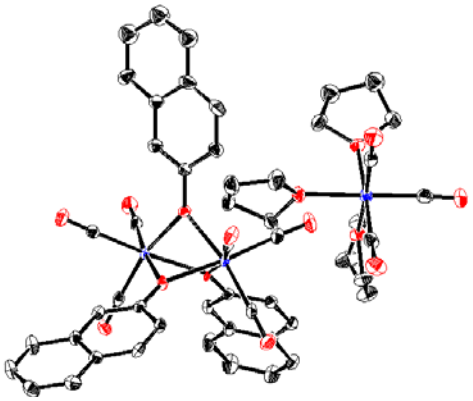
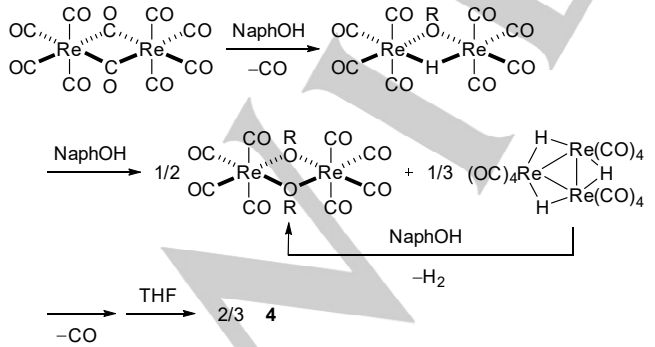


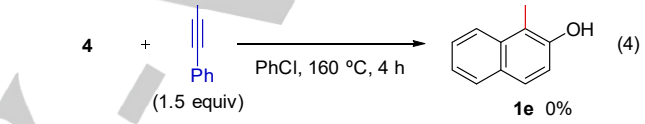
Figure 1. X-ray crystal structure of $[Re_2(\mu\text{-}ONaph)_3(CO)_6][Re(CO)_3(thf)_3]$ **4**. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are drawn at the 50% probability level. Blue: Re, red: O, black: C. See Table S1 in SI for details.

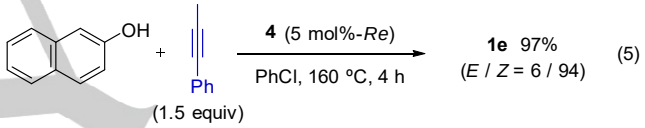
$Re_2(CO)_{10}$ was reported to convert into tetrameric $[Re(\mu\text{-}OH)(CO)_3]_4$ by reaction with H_2O under photoirradiation *via* the formation of trimeric $[HRe(CO)_4]_3$.[22] Thus, $[Re_2(\mu\text{-}ONaph)_3(CO)_6][Re(CO)_3(thf)_3]$ (**4**) is thought to form *via* a mechanism similar to that as shown in Scheme 1. Monitoring the reaction mixture by ^{1}H NMR spectra confirmed that the appearance of the characteristic signal corresponded to a bridging hydride ligand of $[HRe(CO)_4]_3$ at -17.3 ppm in toluene-d_8.[23] This peak gradually disappeared, and the isolable complex **4** was finally formed upon treatment of THF.

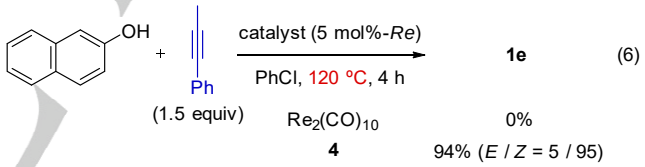


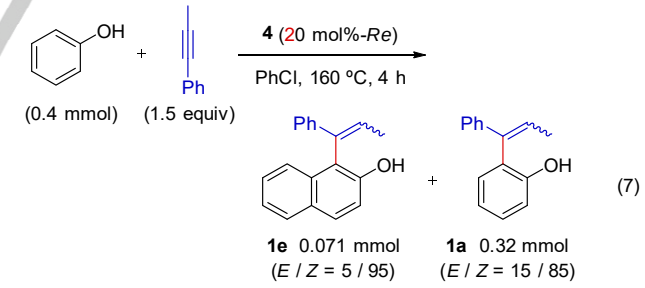
Scheme 1. Proposed mechanism for the formation of (μ-naphthoxo)rhenium complex **4** (R = 2-Naph)

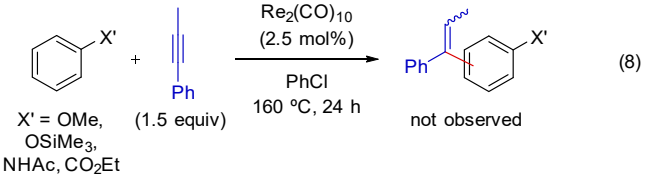
The reactivity of **4** was confirmed through the following control experiments. First, stoichiometric reaction of the isolated **4** with 1-phenyl-1-propyne did not provide 1-alkenyl-2-naphthol **1e**, suggesting that the naphthoxo ligand on a rhenium center of **4** was not reactive toward alkenylation (eq 4). In contrast, **4** showed the excellent catalytic performance in alkenylation with 2-naphthol (eq 5). These results indicate that alkenylation occurred on a rhenium center of a (μ-naphthoxo)rhenium species with a bridged naphthoxo ligand intact. The catalytic performance of **4** was high enough to promote alkenylation even at 120 °C, while formation of alkenylated product **1e** was not observed when $Re_2(CO)_{10}$ was employed as a catalyst at this temperature (eq 6). The reaction profile for the alkenylation of 2-naphthol was monitored at 160 °C by ^{1}H NMR, which revealed that the induction period and sigmoidal reaction profile observed with $Re_2(CO)_{10}$, were not present with **4** (Figure S1 in SI). This appears to be consistent with the *in situ* formation of **4** from $Re_2(CO)_{10}$ and 2-naphthol in THF.

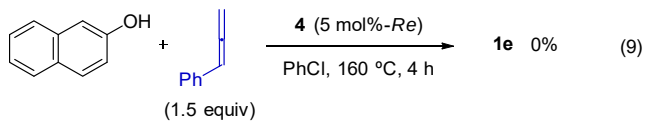












Second, crossover reaction of phenol with 1-phenyl-1-propyne in the presence of 20 mol%-*Re* of **4** provided **1e** in 89% yield (based on the number of rhenium units of **4**) along with **1a** in 80% yield (eq 7). Although the original naphthoxo ligand on a rhenium center of **4** was unreactive, it could be easily interchanged with free phenol. This interchange released free 2-naphthol, which then was converted to **1e** by alkenylation promoted by the corresponding (phenoxo)rhenium species. Third, the phenolic hydroxyl group was key to control the reactivity and selectivity of the addition reaction. The use of anisole, acetanilide, and ethyl benzoate, which are common substrates for regioselective functionalization based on C–H bond activation,[24] in place of phenol did not afford any alkenylated products with recovery of these aromatic compounds (eq 8). Fourth, the current alkenylation occurred by direct addition to the triple bond of alkynes, because reaction with phenylallene, which could be potentially generated by isomerization of 1-phenyl-1-propyne, did not produce any **1e** (eq 9).

A roughly linear relation between the yield of **1e** and time was observed during the initial stage of the reaction at 160 °C (Figure 2(a)), and the initial rate of alkenylation was one third-order-dependent on catalyst loading (Figure 2(b)). This order dependency indicates that alkenylation was promoted by the mononuclear rhenium species, such as [Re^{I}(OPh)(CO)$_3$(thf)], generated prior to the turnover limiting transition state.

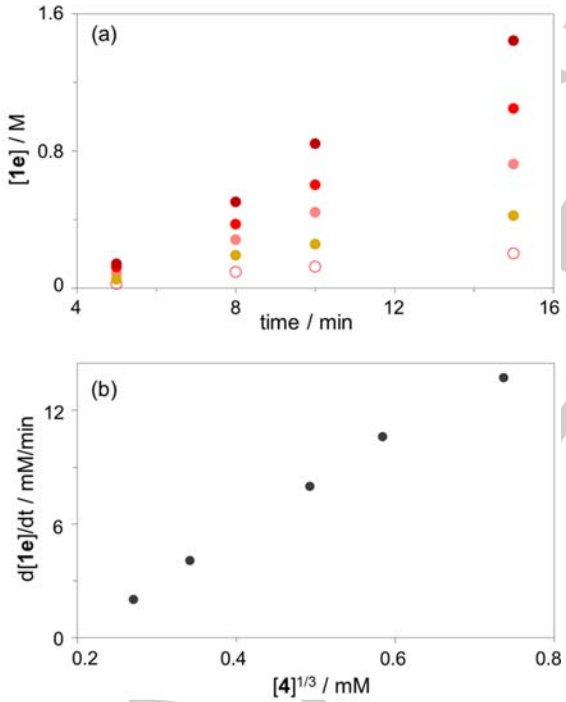
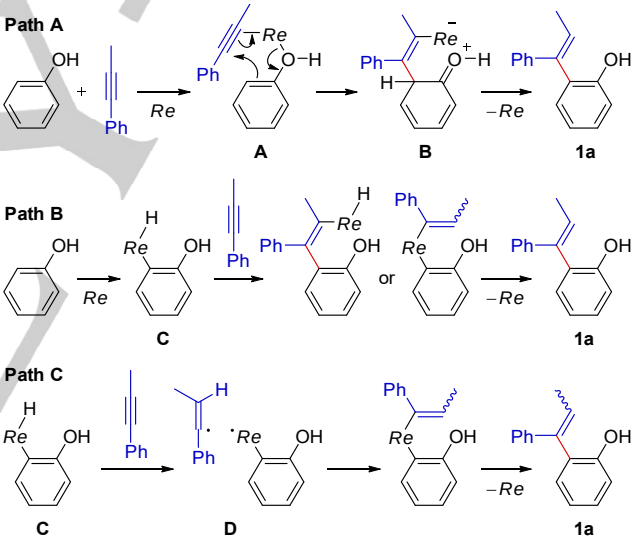


Figure 2. (a) Reaction profile for alkenylation of 2-naphthol in PhCl at 160 °C with 1 mol% (○), 2 mol% (●), 6 mol% (●), 10 mol% (●), and 20 mol% (●) of **4**. (b) Plot of initial rate for the formation of **1e** *vs* concentration of **4**.

Reaction Mechanism and Reactivity of (μ-Aryloxo)rhenium Intermediates: Three possible mechanisms for the current regioselective *C*-alkenylation are illustrated in Scheme 2, which shows the reaction of phenol with 1-phenyl-1-propyne. Considering the results obtained from eqs 4 and 5, "*Re*" in Scheme 2 represents "Re(OPh)(CO)$_3$". In Path A, nucleophilic attack of the phenol to alkyne occurs regioselectively at the *ortho*-position of the phenolic hydroxy group, which is assisted by coordination of both phenol and alkyne to a rhenium center in intermediate **A**. Because rhenium is located in the middle of early and late transition metals in the periodic table, we believe that they can possess both soft and hard Lewis acidity. Thus, low-valent rhenium carbonyl complexes could interact with both the soft carbon–carbon triple bonds of alkynes and the hard oxygen atom of phenols at the same time, promoting the addition reaction. Another possible mechanism involves carborhenation or hydrorhenation of arylrhenium species **C** followed by reductive elimination to regenerate the rhenium active species (Path B). Finally, Path C involves hydrogen atom transfer from the arylrhenium species **C** to the alkyne followed by radical recombination and reductive elimination. Path C was proposed based on a recent mechanistic study on rhenium-catalyzed alkylation of phenols with alkenes.[16c]

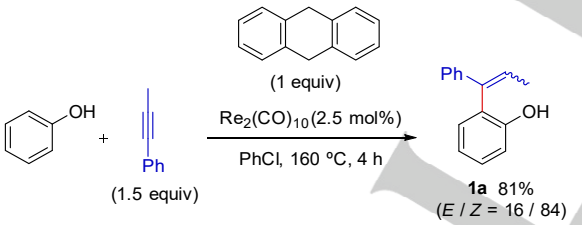


Scheme 2. Possible reaction mechanism for *C*-alkenylation of phenol (*Re* = Re(OPh)(CO)$_3$)

Reversible H/D exchange observed upon treatment of phenol-d_5 with $Re_2(CO)_{10}$ under standard conditions suggested the formation of arylrhenium species **C** (eq 10 and Figure S2 in SI). Considering the number of potentially cleavable C–H bonds (2 for *ortho* positions and 1 for the *para* position), the exchange rate of deuterium atoms at the *para* position was greater than that at the *ortho* position after 30 min. However, alkenylation products at the *para* position were not observed with most of alkynes in the current alkenylation (see eq 15 for an exception using sterically hindered (phenylethynyl)silane). These experimental results can be rationalized by the following three explanations. (1) Reductive elimination to yield *para*-alkenylated products did not occur after the reversible insertion of

arylrhenium species into the triple bond of the alkyne. (2) Arylrhenium species **C** did not participate in a catalytic cycle of the *ortho*-alkenylation reaction. (3) The aforementioned H/D exchange occurred not *via* formation of **C**, but through nucleophilic attack of the phenol to the phenoxy proton of other phenol activated by $Re_2(CO)_{10}$ through coordination to the phenoxy oxygen atom. Either way, Path B can be ruled out as the reaction mechanism, because the C–C bond was reportedly formed preferentially on the methyl group-substituted alkynyl carbon by insertion of the Ar–$Re(CO)_n$ bond into the triple bond of 1-phenyl-1-propyne, resulting in production of the regioisomer opposite of **1a**.[25]

It is difficult to rule out completely the possibility of a radical pathway (Path C). The common radical inhibitors, such as TEMPO and Galvinoxyl free radical, shut down the current alkenylation, not due to trapping of reactive radical species but because due to deactivation of reactive phenoxyrhenium species.[26] This is further supported by results of addition of a radical scavenger, 9,10-dihydroanthracene, that did not contain any heteroatoms, and did not result in the inhibition or disturbance of the alkenylation (eq 11). In addition to these results, electronic effects of substituents (see Figure 3) and the stereochemistry of the initial adducts (see Figure 4) indicate that Path A is more plausible than the radical pathway (Path C) for the current alkenylation reaction.



We believe that the chelation-assisted electrophilic alkenylation mechanism (Path A in Scheme 2), in which the phenolic hydroxyl group controlled regioselectivity of the addition reaction as a coordinating directing group,[27] is the most plausible based on the following four observations. (1) The time-dependent reaction profile for 4-methoxyphenol, *p*-cresol, phenol, and 4-chlorophenol, monitored by ^{1}H NMR, revealed that alkenylation proceeded most rapidly with electron-rich 4-methoxyphenol (Figure 3). This reactivity trend is consistent with an electrophilic aromatic substitution mechanism. The induction period observed in Figure 3 is consistent with *in-situ* dissociation of (μ-aryloxo)rhenium species, $[Re_2(\mu\text{-}OAr)_3(CO)_6][Re(CO)_3(thf)_3]$, to the monomeric rhenium carbonyl species, $Re(OAr)(CO)_3$. (2) Stereoselectivity of the alkenylation changed during the reaction, and the stereochemistry of the initial alkenylation product was *E*.

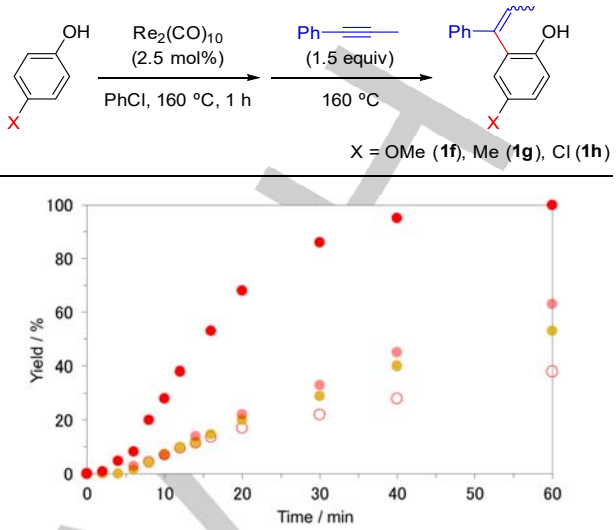


Figure 3. Reaction profile for alkenylation of *para*-substituted phenol (X = OMe ●, Me ●, H ●, Cl ○) with 1-phenyl-1-propyne at 160 °C with 2.5 mol% of $Re_2(CO)_{10}$.

This was confirmed by the stereoselectivity profile observed for alkenylation with 4-chlorophenol depicted in Figure 4. Although *E*-**1h** was obtained selectively at the early stage of the reaction, the ratio of *Z*-**1h** increased with time. The *E*-**1h** was thought to be produced directly by quenching of alkenylrhenium intermediate **B** in Scheme 2, while *Z*-**1h** was derived from the rapid and competitive isomerization of *E*-**1h**. The rapid isomerization occurred by heating a pure *E*-**1h** (*E* / *Z* = >98 / 2) with $Re_2(CO)_{10}$ to produce a mixture of stereoisomers of **1h** (*E* / *Z* = 18 / 82) (eq 12). Note that this isomerization occurred even without $Re_2(CO)_{10}$. Although rhenium-assisted interconversion between *E*- and *Z*-**1h** cannot be ruled out, isomerization proceeded mainly *via* rapid 1,5-H shift. Thus, these results support the participation of intermediate **B** in Path A in the current regioselective alkenylation. (3) Partial deuterium incorporation on the alkenyl carbon was observed in alkenylation with phenol-d_5, which can be rationalized by considering the derhenation process of intermediate **B** in Scheme 2 by proton on the oxygen atom or the deuterium on the phenol ring (eq 13). (4) A value of 1.16 for the parallel kinetic isotope value (k_H / k_D) was obtained from two side-by-side reactions of phenol *vs* phenol-d_5

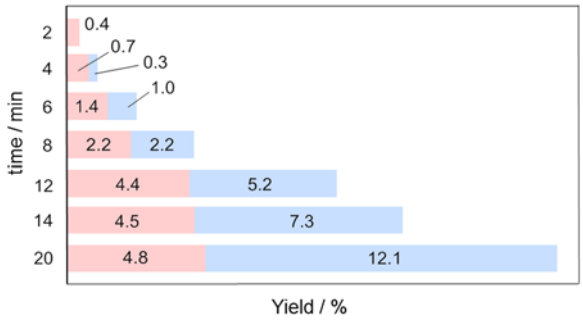
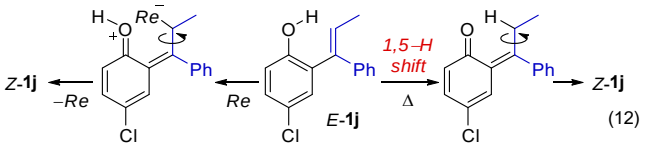
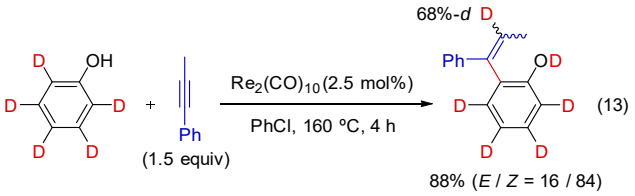
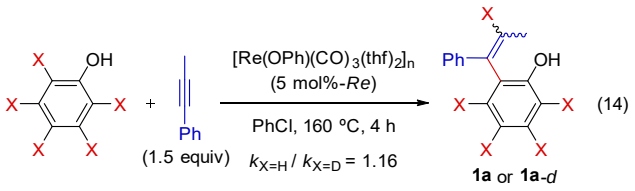


Figure 4. Ratio of *E*-**1h** ● and *Z*-**1h** ● for alkenylation of 4-cholorophenol with 1-phenyl-1-propyne at 160 °C with 2.5 mol% of $Re_2(CO)_{10}$.

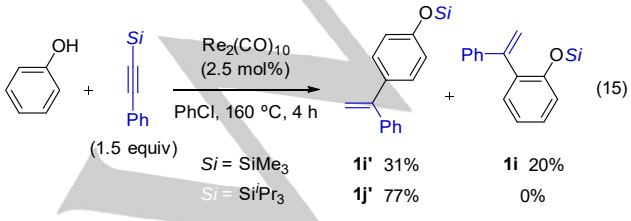
with 1-phenyl-1-propyne indicating that C–H bond cleavage was not involved in the rate-determining step (eq 14). This is consistent with Path A, where C–H bond cleavage should occur relatively fast because it regenerates the aromaticity of the phenol ring.



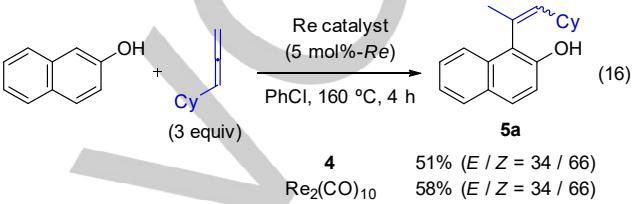




As demonstrated in eq 8, the phenolic hydroxyl group plays a key role in controlling reactivity as well as selectivity for the current alkenylation of phenols. Different regioselectivity was observed in the alkenylation with trimethyl(phenylethynyl)silane (eq 15, *Si* = $SiMe_3$). In this case, alkenylation occurred mainly at the *para* position of the phenolic hydroxyl group to produce **1i'**, probably due to prevention of *ortho*-alkenylation through steric repulsion between the bulky silyl groups and the rhenium center. Therefore, intermolecular nucleophilic attack of the phenoxyrhenium species to π-alkyne rhenium species might occur predominantly in this case. Because this intermolecular attack occurred preferentially at *para* position of the phenolic hydroxyl group to minimize the steric repulsion, the *para*-alkenylation product **1i'** was obtained as a major compound. Note that rapid migration of the silyl group from the alkenyl terminal carbon of the initial adduct to its phenolic hydroxyl group was observed to yield the overall adduct as a silylether in this reaction. As expected, *para*-alkenylated adduct **1j'** was obtained as the sole product by using (phenylethynyl)silane containing a bulkier triisopropylsilyl group. This result supports the participation of intermediate **A** (see Path A of Scheme 2) in *ortho*-selective alkenylation, which was assisted by coordination of both the phenol and alkyne to a rhenium center.[28]



Regioselective Alkenylation of Phenols with Allenes: As shown in eq 9, the use of arylallene in place of 1-aryl-1-propyne did not provide the alkenylated product. However, further study revealed that 2-naphthol added to the less sterically hindered double bond of cyclohexylallene to produce **5a** (eq 16). Both isolated **4** and $Re_2(CO)_{10}$ catalyzed this addition reaction. The central carbon atom of the accumulated double bond of the allene was selectively attacked by the aromatic ring, which accompanied by addition of a hydrogen atom to the terminal carbon atom.[29] Thus, the substitution pattern of the resultant alkenylated products **5** was opposite to that of **1** obtained from the addition reaction with alkynes (Figure 4).



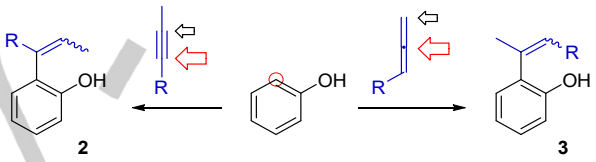
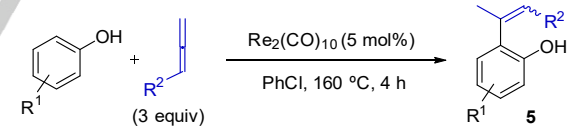
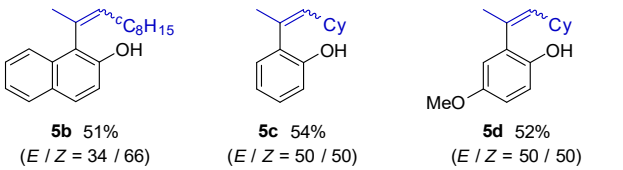


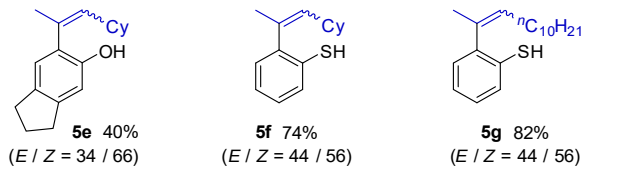
Figure 4. Comparison of regioselectivity

Alkenylation with cyclooctylallene provided the corresponding adduct **5b** in moderate yield (Table 3). Neither multiply alkenylated products nor alkenylation at the *para* position was

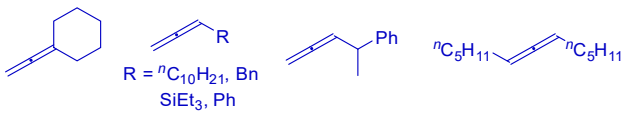
Table 3. Rhenium-catalyzed regioselective alkenylation of (thio)phenols with allenes[a]







The following allenes did not provide the alkenylated products in the reaction with phenol.



[a] The maximum yield was 90% as noted in footnote 18.

observed. A similar outcome was obtained for the reaction of phenol. 4-Methoxyphenol reacted smoothly with cyclohexylallene to provide **5d**, and a potentially coordinating methoxy group did not disturb the site-selectivity.[24] Regioselective alkenylation occurred for 5-indanol at the less sterically hindered *ortho* position of the phenol ring to provide **5e**. However, reactivity of allenes was significantly affected by the substitution pattern, and di- and monosubstituted allenes having less sterically demanding acyclic alkyl chains, including benzylallenes, silylallenes, and 1,2-tridecadiene, did not provide any adducts in reaction with phenol due to their competitive oligomerization. Thiophenol was also applicable as a substrate, and the expected 2-alkenylthiophenol **5f** was obtained in 74% yield without hydrothiophenoxylation products. In reaction with thiophenols, even 1,2-tridecadiene gave the corresponding adduct **5g** in high yield.

Conclusions

A mechanistic study of a recently reported rhenium-catalyzed *ortho*-selective monoalkenylation of phenols[14] was conducted. The use of a rhenium carbonyl complex as a catalyst was essential, and X-ray single crystallographic analysis revealed that formation of a (μ-aryloxo)rhenium complex was key for these unique transformations. This is a rare example of isolation of reactive rhenium carbonyl precatalysts.[5,6] Several control experiments revealed that phenolic hydroxyl group-assisted electrophilic alkenylation is the most plausible as a reaction mechanism, instead of classic Friedel-Crafts type electrophilic functionalization (proceeds with *ortho*- and *para*-orientation to yield a mixture of mono- and multiple adducts). Because rhenium, a group 7 metal located in the middle of early and late transition metals in the periodic table, low-valent rhenium carbonyl complexes could activate both soft carbon–carbon triple bonds of an alkyne and hard oxygen atoms of phenol at the same time, and might promote the current rare class of addition reactions.

Based on successful addition reactions with internal alkynes, alkenylation with allenes was also demonstrated. Thiophenols as well as phenols can be used as substrates, and formation of classic hydrophenoxylation (*O*-alkenylation) products were never observed in these reactions. Although high temperatures were required, these reactions proceeded with readily available starting materials under neutral conditions without additional ligands. The synthetic potential of the current alkenylation was also demonstrated by the concise synthesis of a benzofuran derivative, which is a basic core of many biologically active compounds and medicines. These results offer new insights into the reactivity of phenols, and open up their new potential as a readily available and inexpensive chemical feedstock.

Experimental Section

General Methods. All reactions were carried out in dry solvent under an argon atmosphere. Chlorobenzene was purchased from Tokyo Chemical Industry, and was dried by the usual methods, distilled, and degassed with an argon gas for 20 min before use. Phenol-d_5 and $Re_2(CO)_{10}$ were purchased from Sigma-Aldrich. Unless otherwise noted, other chemicals obtained from commercial suppliers were used without further purification. Column chromatography was performed with silica gel 60N (neutral, 40-50 μm) purchased from Kanto Chemical. ^{1}H (400 or 300 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL JNN-LA400 spectrometer. Proton chemical shifts are reported in ppm based on the solvent resonance resulting from incomplete deuteration ($CDCl_3$ at 7.26 ppm, acetone-d_6 at 2.05 ppm) as the internal standard. ^{13}C NMR was recorded with complete proton decoupling and the chemical shifts are reported relative to $CDCl_3$ at 77.00 ppm or acetone-d_6 at 29.84 ppm. The following abbreviations are used; brs: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded on a SHIMADZU IRAFFINITY-1 100V J. High-resolution mass spectra (HRMS) was measured with JEOL JMS-700 MStation FAB-MS. Melting points were measured on a Yanaco micromelting point apparatus and are uncorrected.

General Procedure for Rhenium-Catalyzed *ortho*-Selective Alkenylation of Phenol Derivatives with Alkynes. A flame-dried test tube was charged with $Re_2(CO)_{10}$ (3.3 mg, 5.0 μmol), phenol derivatives (0.20 mmol), alkynes (0.30 mmol), and chlorobenzene (0.10 mL), and then the resulting mixture was stirred at 160 °C for 4 h. The residue was directly subjected to flash column chromatography on silica gel to afford the corresponding alkenylated phenols **1**.

One-Pot Synthesis of 2-Methyl-3-phenylbenzofuran (3): A flame dried test tube was charged with $Re_2(CO)_{10}$ (3.3 mg, 5.0 μmol), phenol (18.8 mg, 0.20 mmol), 1-phenyl-1-propyne (34.8 mg, 0.30 mmol), and chlorobenzene (0.10 mL), and then the resulting mixture was stirred at 160 °C for 4 h. The reaction mixture was cooled down to 25 °C, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (24.9 mg, 0.50 mmol) and chlorobenzene (2.0 mL) were added. After stirring at 120 °C for additional 24 h, the reaction mixture was cooled down to 25 °C, and 2,3-dichloro-5,6-dicyano-1,4-benzo- quinone (24.9 mg, 0.50 mmol) was added again. After stirring at 120 °C for additional 24 h, the residue was directly subjected to flash column chromatography on silica gel with hexane / EtOAc = 5 / 1 as the eluent to afford 26.2 mg (0.13 mmol, 63% yield) of **3** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.20-7.29 (m, 2H), 7.35-7.39 (m, 1H), 7.45-7.53 (m, 5H), 7.57-7.59 (m, 1H). The analytical data match those reported in the literature.[30]

Synthesis of $[Re_2(ONaph)_3(CO)_6]^-[Re(CO)_3(thf)_3]^+$ Complex 4. A flame-dried Schlenk flask was charged with $Re_2(CO)_{10}$ (326 mg, 0.50 mmol), 2-naphthol (721 mg, 5.0 mmol), and chlorobenzene (1.0 mL), and then the resulting mixture was stirred at 160 °C for 16 h. The solvent was removed under reduced pressure, and the residue was dissolved in THF (3.0 mL) at 25 °C. Precipitation of solid was observed soon, which was collected, dried under reduced pressure, and recrystallized from THF / hexane at -20 °C twice to afford 240.0 mg (0.16 mmol, 22% yield) of (μ-naphthoxo)rhenium complex 4 as a colorless powder. Although the yield of **4** was determined to be 66% by ^{1}H NMR analysis of the crude product, the amount isolated after purification by recrystallization was low due to the difficulty of removing unreacted 2-naphthol completely. ^{1}H NMR (400 MHz, acetone-d_6): δ 1.77-1.80 (m, 12H), 3.61-3.64 (m, 12H), 7.25 (t, J = 8.4 Hz, 1H), 7.39 (t, J = 6.8 Hz, 1H), 7.62 (dd, J = 2.0 Hz, 9.2 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 26.2, 68.1, 109.7, 109.8, 119.1, 119.2, 123.7, 127.0, 128.5, 129.4, 130.3, 136.0, 197.1, 197.2. IR (KBr / cm^{-1}): 2960, 2021, 1915, 1888, 1593, 1460, 1246,

877. Anal. Calcd for $(C_{17}H_{15}O_5Re)_3$: C, 42.06; H, 3.11. Found: C, 42.45; H, 3.15.

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Keywords: Phenol • Rhenium • Alkenylation • Regioselective

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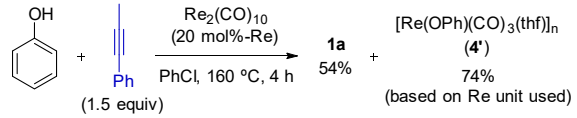
[18] For alkenylation under the conditions shown below, 74% yield of $[Re(OPh)(CO)_3(thf)]_2$ **4'** was obtained based on the $Re_2(CO)_{10}$ employed. This result suggested that two equivalents of phenol derivatives relative to the amount of $Re_2(CO)_{10}$ were consumed in the formation of the (μ-aryloxo)rhenium complex, and did not participate in catalytic alkenylation. Thus, the maximum yield listed in Table 2 was 95%.



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[21] Isolation and structural characterization of the dinuclear complex, $[Re(\mu\text{-}OAr)(CO)_3]_2$, was reported in the previous our report (see ref 14), while trinuclear complex, $[Re_2(\mu\text{-}OAr')_3(CO)_6][Re(CO)_3(thf)_3]$ was isolated in the current work. The difference should be derived from ligand (Ar = 2-iminophenoxy and Ar' = 2-naphthoxy), and coordination by imino group of 2-iminophenoxy ligand blocked the formation of a trinuclear complex in the previous study. Additionally, the structure of phenoxorhenium complex was deduced to be "$[Re(\mu\text{-}OPh)(CO)_3]_2$" based on the result of elemental analysis in the previous study. The reason is commented in footnote 16 of the previous study as follows: "Since all attempts to obtain the exact molecular weight of $[Re(OPh)(CO)_3(thf)]_n$ 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.". Although the structure of naphthoxorhenium complex was found to be trinuclear in the current study, the exact structure of phenoxorhenium complex is still unclear.

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[23] For X-ray study of $[HRe(CO)_4]_3$, see: a) N. Masciocchi, A. Sironi, G. D'Alfonso, *J. Am. Chem. Soc.* **1990**, *112*, 9395. For structural data of related rhenium hydride complexes, see: b) A. Davison, J. A. McCleverty, G. Wilkinson, *J. Chem. Soc.* **1963**, 1133. c) R. D. Wilson, R. Bau, *J. Am. Chem. Soc.* **1976**, *98*, 4687. d) N. Masciocchi, G. D'Alfonso, W. Kockelmann, W. Schäferc, A. Sironi, *Chem. Commun.* **1997**, 1903. e) M. Bergamo, T. Beringhelli, G. D'Alfonso, *J. Am. Chem. Soc.* **1998**, *120*, 2971. See also ref. 6.

[24] For methoxy group-directed C–H bond functionalization, see: a) J. Oyamada, M. Nishiura, Z. Hou, *Angew. Chem. Int. Ed.* **2011**, *50*, 10720. b) J. Oyamada, Z. Hou, *Angew. Chem. Int. Ed.* **2012**, *51*, 12828. c) X. Shi, M. Nishiura, Z. Hou, *J. Am. Chem. Soc.* **2016**, *138*, 6147. d) X. Shi, M. Nishiura, Z. Hou, *Angew. Chem. Int. Ed.* **2016**, *55*, 14812. e) C. Xue, Y. Luo, H. Teng, Y. Ma, M. Nishiura, Z. Hou, *ACS Catal.* **2018**, *8*, 5017. f) F. Romanov-Michailidis, B. D. P. Ravetz, D. W. Paley, T. Rovis, *J. Am. Chem. Soc.* **2018**, *140*, 5370.

[25] a) Y. Kuninobu, Y. Nishina, A. Kawata, M. Shouho, K. Takai, *Pure Appl. Chem.* **2008**, *80*, 1149. b) Y. Kuninobu, K. Takai, *Bull. Chem. Soc. Jpn.* **2012**, *85*, 656.

[26] Attempted rhenium-catalyzed alkenylation of phenol with 1-phenyl-1-propyne did not provide **1a** in the presence of 2,2,6,6-tetramethylpiperidine and anthraquinone, which implies that the common radical trapping experiments using TEMPO and Galvinoxyl free radical were not able to rule out the possibility of Path A.

[27] Because formation of *para*-alkenylated phenols was not observed in the current alkenylation unless a sterically hindered silylacetylene was used (see eq 15), intermolecular nucleophilic attack of phenols to alkynes without proceeding through intermediate **A** in Scheme 2 can be ruled out.

[28] The use of (3,3-dimethyl-1-butyn-1-yl)benzene as an alkyne gave the corresponding *ortho*-alkenylated product in less than 20% yield without forming other regioisomers. Thus, a silyl group at the β-position enhanced the electronically deficient character at the benzyl position of (phenylethynyl)silane, which accelerated alkenylation at this position. The more sterically bulky tri(isopropyl)silyl group might prevent the oligomerization of the alkyne, which increased the overall yield of the alkenylated product. In contrast, alkenylation did not occur even with (phenylethynyl)silanes, when anisole, acetanilide, or ethyl benzoate was used in place of phenol. Thus, a phenolic hydroxyl group is crucial to produce a catalytically active phenoxyrhenim species, even for alkenylation at the para position.

[29] Similar regioselectivity was reported in the hydroarylation of pyridine derivatives to allenes. See: G. Song, B. Wang, M. Nishiura, Z. Hou, *Chem. Eur. J.* **2015**, *21*, 8394.

[30] M. P. Kumar, R.-S. Liu, *J. Org. Chem.* **2006**, *71*, 4951-4955.

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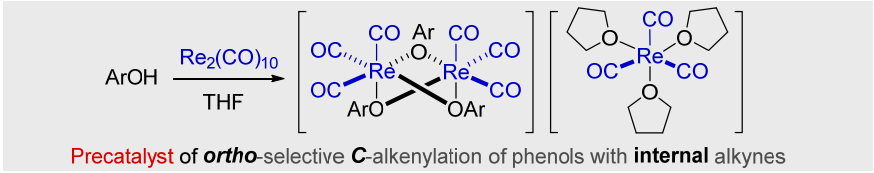

Precatalyst of ***ortho***-selective ***C***-alkenylation of phenols with **internal** alkynes

A (μ-aryloxo)rhenium complex was isolated and confirmed as a key precatalyst for rhenium-catalyzed *ortho*-alkenylation (*C*-alkenylation) of unprotected (thio)phenols with internal alkynes. Several control experiments revealed that phenolic hydroxyl group-assisted electrophilic alkenylation is the most plausible as a reaction mechanism, instead of classic Friedel-Crafts type electrophilic functionalization. *ortho*-Selective alkenylation of phenols with allenes was also demonstrated.

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Mechanistic Insights into Rhenium-Catalyzed Regioselective *C*-Alkenylation of Phenols with Internal Alkynes