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Ruthenium-Catalyzed Selective Aerobic Oxidative *ortho*-Alkenylation of Substituted Phenols with Alkenes through C–H Bond Activation

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Keywords: Synthetic methods / Cross-coupling / C–H activation / Ruthenium / Regioselectivity / Alkenylation

The oxidative coupling of phenyl carbamates and acetates with alkenes in the presence of a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and $Cu(OAc)_2{\cdot}H_2O$ under air provided substituted alkene derivatives in a highly regio- and stereoselective manner. The catalytic reaction was compatible with various alkenes such as acrylates, vinyl sulfones, acrylonitrile, and substituted styrenes. The present catalytic reaction was also compatible with phenyl carbamates and acetates with various electron-rich, electron-deficient, and halogen substituents on the aromatic ring. Further examination of the catalytic reaction was done with the substituted phenyl acetates. By using $LiOH{\cdot}H_2O$ or K_2CO_3 as a base, the substituted alkene derivatives were converted into the corresponding phenol derivatives. To account for the catalytic reaction, a possible mechanism is proposed that involves a six-membered ruthenacycle as the key intermediate.

Introduction

Transition-metal-catalyzed coupling of aromatic electrophiles or organometallic reagents with alkenes is a key reaction for constructing alkene derivatives in a highly stereoselective manner.[1] This type of alkenylation reaction has been widely used to synthesize various organic materials, natural products, and drug molecules.[2] Although this type of coupling reaction is highly useful in organic synthesis, a preactivated coupling partner such as a C–X or C–M moiety in the starting material is usually required for coupling with alkenes. Instead of using a preactivated species, a similar type of coupling reaction that is done by C–H bond activation would be even more useful in organic synthesis.[3] This type of reaction is highly atom economical and environmentally friendly. The Fujiwara group was first to describe that the alkenylation reaction of electron-rich aromatics with alkenes occurred through an electrophilic metalation pathway in the presence of a palladium catalyst.[4] The Lewis group demonstrated that the *ortho*-C–H bond of phenol can be ethylated by ethylene in the presence of a ruthenium catalyst.[5a] The Murai group showed that a selective alkylation at the *ortho*-C–H bond of carbonyl-substituted aromatics can take place with alkenes in the presence of a ruthenium(0) catalyst through a chelation-assisted metalation pathway.[5b,5c] Following these studies, Yu's, Cheng's, and other research groups have reported that the alkenylation at the *ortho*-C–H bond of heteroatom-substituted aromatics by alkenes occurred in the presence of a palladium catalyst by a chelation-assisted metalation pathway.[6,7] Subsequently, Miura and other research groups have shown that a similar type of alkenylation at the *ortho*-C–H bond of heteroatom-substituted aromatics can take place with alkenes in the presence of a rhodium catalyst through a chelation-assisted metalation pathway.[8] Recently, a *meta*-selective alkenylation by alkenes at the C–H bond of substituted aromatics in the presence of palladium complex has been described by Yu and Sanford.[9]

Very recently, because of its remarkable reactivity, compatibility, and selectivity, a less expensive ruthenium complex has gained tremendous attention in this type of heteroatom-directed *ortho*-alkenylation reaction. Interestingly, this type of ruthenium-catalyzed alkenylation reaction can be conducted under air or even in the presence of water as the solvent.[10–12] Several directing groups such as amine, imine, oxime, amide, pyridyl, COOH, phenol, OH, aldehyde, ketone, ester, acetate, and carbamate functional groups have been used in the metal-catalyzed C–H bond activation reaction. However, C–H bond activation by using weak directing groups such as aldehyde, ester, cyano, ketone, nitro, acetate, and carbamate functional groups is very challenging. Herein, we wish to report the oxidative coupling of phenyl carbamates and acetates with alkenes in the presence of a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and $Cu(OAc)_2{\cdot}H_2O$. Under air, this reaction provides substituted alkene derivatives in good to excellent yields in a highly regio- and stereoselective manner. The catalytic reaction is compatible with various substituted alkenes such as acrylates, sulfones, acrylonitrile, and styr-

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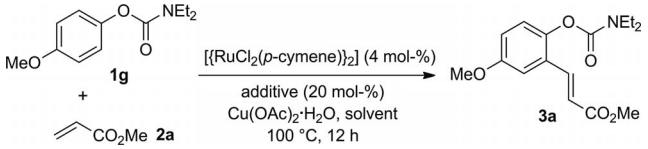
enes. By using $LiOH·H_2O$ or K_2CO_3, the corresponding alkenylated phenyl carbamates and acetates are converted into the corresponding phenols.

Results and Discussion

Initially, the coupling reaction was carried out with 4-methoxyphenol (**1a**) and methyl acrylate (**2a**) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (4 mol-%), $AgSbF_6$ (20 mol-%), and $Cu(OAc)_2·H_2O$ (2.20 mmol) in 1,2-dichloroethane (DCE) at 100 °C for 12 h [Equation (1)]. In this reaction, alkenylation was expected at the *ortho* position of phenol **1a**. However, no such coupling product was observed, and starting material **1a** was recovered. Next, the catalytic reaction was tested using phenol derivatives such as a substituted phosphorodiamidate **1b**, 4-methoxyphenyl diethylphosphate (**1c**), 4-methoxyphenyl mesylate (**1d**), 4-methoxyphenyl triflate (**1e**), and 4-methoxyphenyl dimethylsulfamate (**1f**), in which under similar reaction conditions, an additional heteroatom such as P=O or S=O was incorporated as a directing group to assist in the *ortho*-C–H bond activation. However, no coupling products were observed in these reactions as well.

Interestingly, under similar reaction conditions, the reaction between 4-methoxyphenyl diethylcarbamate (**1g**) and methyl acrylate (**2a**) produced coupling product **3a** in 65% yield (see Table 1). To increase the yield of **3a**, the catalytic reaction was carried out in various solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), toluene, dimethyl sulfoxide (DMSO), *t*BuOH, *tert*-amyl alcohol, 1,2-dimethoxyethane (DME), and CH_3CN. Among the solvents, DME was the best and provided coupling product **3a** in 93% yield (see Table 1, Entry 4). The remaining solvents were either less effective or totally ineffective in the coupling reaction. Next, we examined the influence of the additive (20 mol-%). A variety of additives such as $AgSbF_6$, $AgBF_4$, AgOTf, and KPF_6 were investigated (see Table 1, Entries 4–7). Among them, $AgSbF_6$ was very effective and gave **3a** in 93% yield (see Table 1, Entry 4). $AgBF_4$, AgOTf, and KPF_6 were less effective and afforded **3a** in 35, 46, and 20% yield, respectively (see Table 1, Entries 5–7). The catalytic reaction was also tested without any additive (see Table 1, Entry 8). In this case, coupling product **3a** was observed in only 15% yield. Similarly, the catalytic reaction was also studied without $Cu(OAc)_2·H_2O$ (see Table 1, Entry 9), but in this case, coupling product **3a** was not produced. Then, the amount of the oxidant $Cu(OAc)_2·H_2O$ was reduced from 2.20 mmol to a catalytic amount (30 mol-%), and the reaction was conducted under air. This catalytic reaction proceeded nicely and gave coupling product **3a** in 92% yield by NMR (see Table 1, Entry 10). On the basis of these optimization studies, we chose $[RuCl_2(p\text{-cymene})]_2$ (4 mol-%), $AgSbF_6$ (20 mol-%), and $Cu(OAc)_2·H_2O$ (30 mol-%) in DME at 100 °C for 12 h under air as the standard conditions for our coupling reaction. Under these optimized reaction conditions, product **3a** was observed in 86% isolated yield. Interestingly, only a catalytic amount of the oxidant $Cu(OAc)_2·H_2O$ (30 mol-%) was used in the present reaction. However, in most of the rhodium-catalyzed chelation-assisted C–H bond activation reactions, only a stoichiometric amount of the oxidant was required with the reaction conducted under nitrogen.[8]

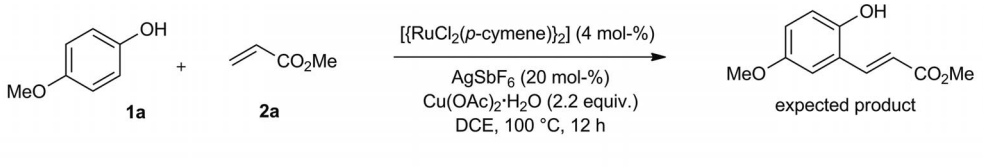
Table 1. Optimization studies.[a]

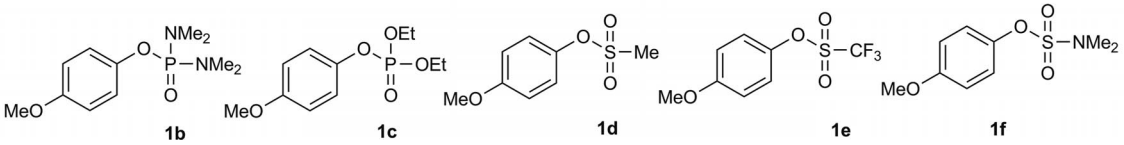


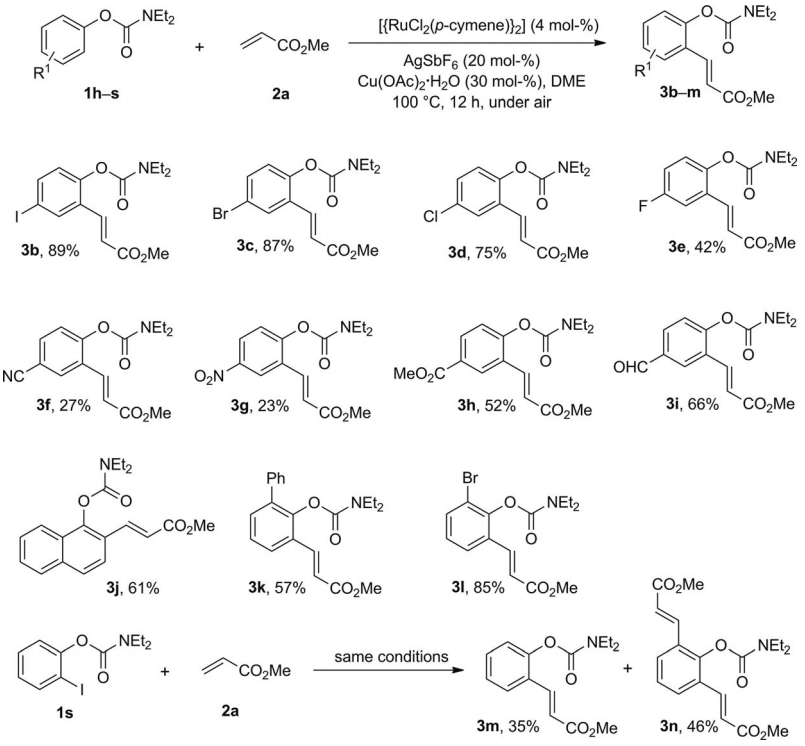
Entry	Solvent	$Cu(OAc)_2·H_2O$	Additive	% Yield of **3a**[b]
1	DCE	2.20 equiv.	$AgSbF_6$	65
2	THF	2.20 equiv.	$AgSbF_6$	52
3	*t*BuOH	2.20 equiv.	$AgSbF_6$	15
4	DME	2.20 equiv.	$AgSbF_6$	93
5	DME	2.20 equiv.	$AgBF_4$	35
6	DME	2.20 equiv.	AgOTf	46
7	DME	2.20 equiv.	KPF_6	20
8	DME	2.20 equiv.	–	15
9	DME	–	$AgSbF_6$	–
10	DME	30 mol-%	$AgSbF_6$	92[c]

[a] All reactions were carried out under the following conditions: **1g** (1.0 equiv.), **2a** (3.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (4 mol-%), additive (20 mol-%), and $Cu(OAc)_2·H_2O$ in DME at 100 °C for 12 h under N_2. [b] Yields were determined by ^1H NMR integration methods with mesitylene as an internal standard. [c] Under air, 86% isolated yield was observed.

To explore the scope of the coupling reaction, various substituted aromatic carbamates **1h**–**1s** were examined under the optimized reaction conditions (see Scheme 1). Thus,





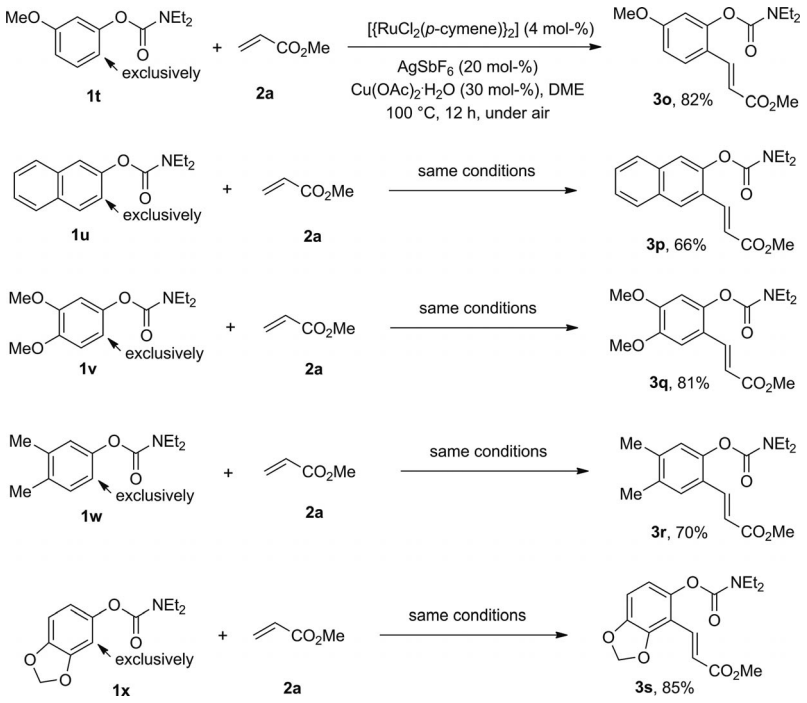


Scheme 1. Scope of substituted phenyl carbamates.

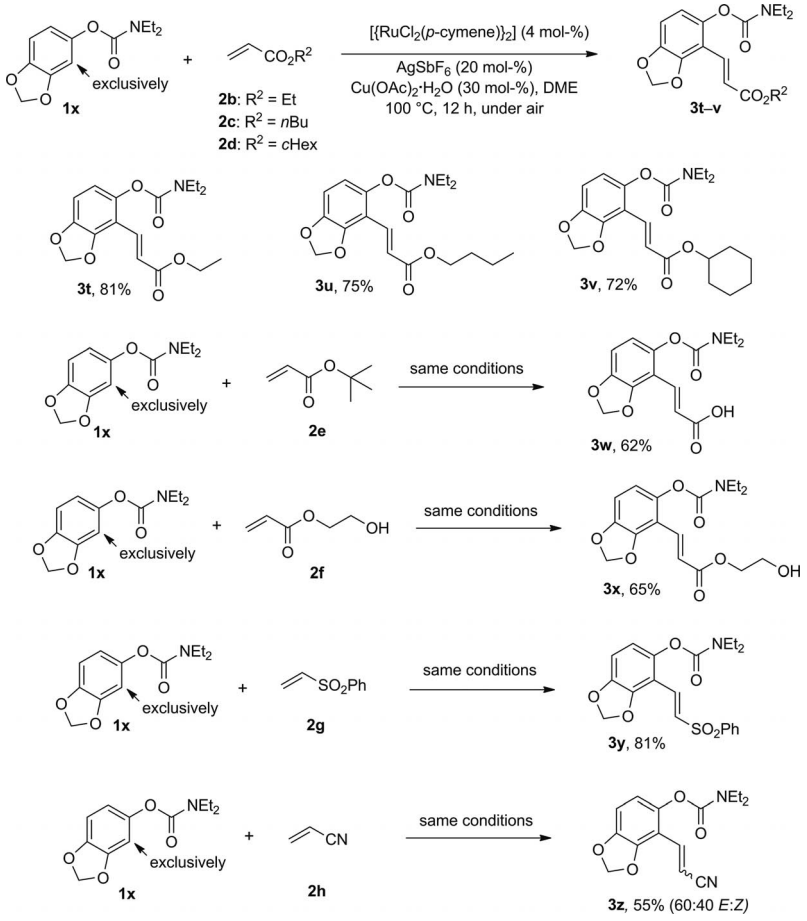
treating halogen-substituted aromatic carbamates such as 4-iodophenyl diethylcarbamate (**1h**), 4-bromophenyl diethylcarbamate (**1i**), 4-chlorophenyl diethylcarbamate (**1j**), and 4-fluorophenyl diethylcarbamate (**1k**) with methyl acrylate (**2a**) provided alkene derivatives **3b**–**3e** in excellent to moderate yields of 89, 87, 75, and 42%, respectively. Aromatic carbamates with electron-withdrawing group substituents such as 4-cyanophenyl diethylcarbamate (**1l**), 4-nitrophenyl diethylcarbamate (**1m**), methylester carbamate **1n**, and 4-formylphenyl diethylcarbamate (**1o**) also efficiently participated in the coupling reaction with methyl acrylate (**2a**) to give coupling products **3f**–**3i** in 27, 23, 52, and 66% yield, respectively. In these reactions, any remaining amount of starting material was recovered. It is important to note that the catalytic reaction was highly regioselective. Alkenylation occurred only at the C–H *ortho* to the carbamate substituent, and no alkenylation was found at the position *ortho* to the CN, NO_2, CO_2Me, or CHO groups on the aromatic ring. It is well-known that CO_2Me and CHO are also a good directing groups for a C–H bond activation reaction.[11] The present results show that Ru chelates with the carbamate group better than with CO_2Me and CHO. The reaction between 1-naphthyl diethylcarbamate (**1p**) and **2a** afforded coupling product **3j** in 61% yield. In addition, the catalytic reaction proceeded very well with *ortho*-substituted aromatic carbamates such as phenyl-substituted carbamate **1q** and 2-bromophenyl diethylcarbamate (**1r**), which yielded coupling products **3k** and **3l** in 57 and 85% yield, respectively. However, the reaction between 2-iodophenyl diethylcarbamate (**1s**) and methyl acrylate (**2a**) afforded coupling products **3m** and **3n** in 35 and 46% yield, respectively. Here, the *ortho*-I group of **1s** is involved in both the oxidative addition as well as the *ortho*-C–H bond activation.[1] The exact reason for double alkenylation occurring in the reaction between aryl iodide carbamate **1s** and alkene **2a** is unclear. A possible explanation might be that the C–I bond reacts first and then favors a second alkenylation with respect to other substrates.

Next, under the optimized reaction conditions, the regioselectivity of substituted carbamates **1t**–**1x** was examined (see Scheme 2). The *meta*-substituted phenyl carbamate 3-methoxyphenyl diethylcarbamate (**1t**) regioselectively coupled with **2a** at the less hindered C–H bond of **1t** exclusively to give coupling product **3o** in 82% yield. The reaction between 2-naphthyl diethylcarbamate (**1u**) and **2a** regioselectively occurred at the less hindered C–H bond of **1u** exclusively to yield coupling product **3p** in 66% yield. Similarly, 3,4-dimethoxyphenyl diethylcarbamate (**1v**) and 3,4-dimethylphenyl diethylcarbamate (**1w**) also underwent the coupling reaction regioselectively with **2a** to provide alkene derivatives **3q** and **3r** in 81 and 70% yield, respectively. Both of these reactions exclusively occurred at the sterically less hindered C–H bond of **1v** and **1w**. In contrast, the reaction between sesamol carbamate **1x** and **2a** took place regioselectively and exclusively at the highly sterically hindered C–H bond of **1x** to give coupling product **3s** in 85% yield.

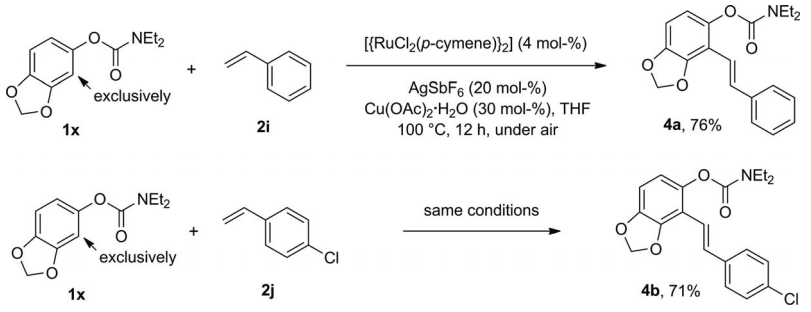
Under the optimized reaction conditions, the present alkenylation reaction was successfully extended to the various substituted alkenes **2b**–**2j** (see Schemes 3 and 4). Ethyl



Scheme 2. Regioselective studies of unsymmetrical phenyl carbamates.



Scheme 3. Scope of substituted alkenes.



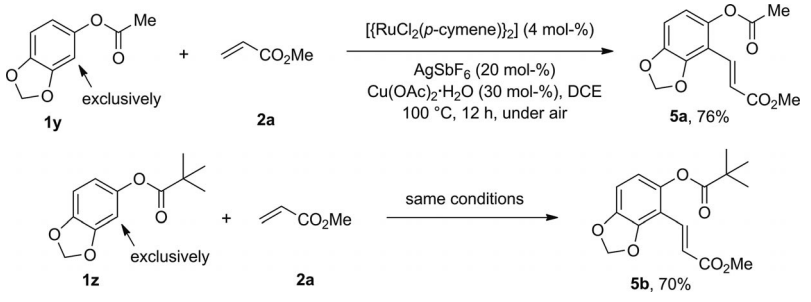
Scheme 4. Scope of substituted styrenes.

acrylate (**2b**), *n*-butyl acrylate (**2c**), cyclohexyl acrylate (**2d**), *tert*-butyl acrylate (**2e**), and 2-hydroxyethyl acrylate (**2f**) efficiently underwent reaction with sesamol carbamate **1x** to give the corresponding coupling products **3t**–**3x** in 81, 75, 72, 62, and 65% yield, respectively (see Scheme 3). However, in the reaction of *tert*-butyl acrylate (**2e**) with **1x**, the *tert*-butyl group was cleaved in the expected alkenylated product, and acrylic acid derivative **3w** was produced. In the meantime, the catalytic reaction between acrylic acid and **1x** was tested, but coupling product **3w** was not observed. It is noteworthy that the sensitive OH group in 2-hydroxyethyl acrylate (**2f**) did not affect the coupling reaction. Other activated alkenes such as phenyl vinyl sulfone (**2g**) and acrylonitrile (**2h**) were also compatible in the reaction. Thus, phenyl vinyl sulfone (**2g**) underwent coupling with **1x** to provide alkenylated product **3y** in an excellent 81% yield. However, acrylonitrile (**2h**) provided a stereoisomeric mixture of coupling products **3z** in a 55% combined yield and approximately a 60:40 *E*/*Z* ratio. In addition, other activated alkenes such as acrolein, ethyl vinyl ketone, and *N*,*N*-dimethylacrylamide were explored for use in the catalytic reaction. In these cases, no coupling products were observed.

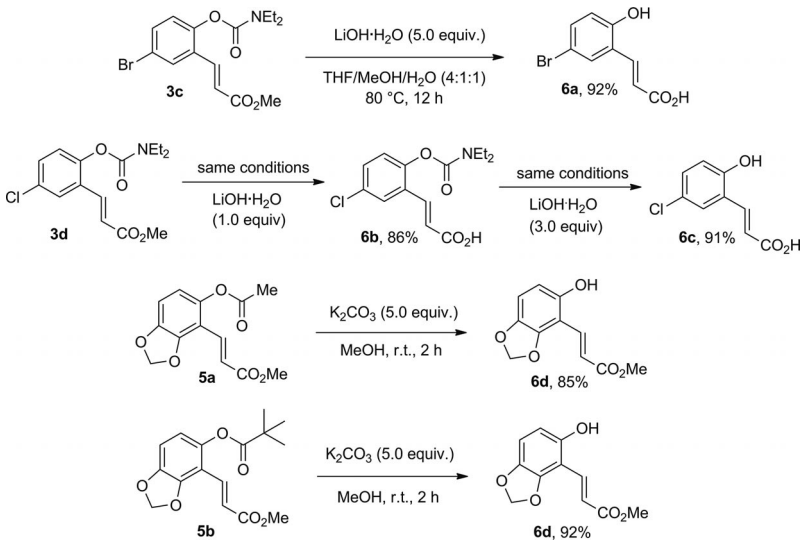
The catalytic reaction was also successful with substituted styrenes **2i** and **2j** (see Scheme 4). Thus, styrene (**2i**) and 4-chlorostyrene (**2j**) underwent an efficient reaction with **1x** to give alkene derivatives **4a** and **4b** in 76 and 71% yield, respectively. THF was used as a solvent in these reactions, as the DME solvent was not suitable. The reactions were also highly regioselective, and similar to the situation for product **3s**, the C–H bond activation took place exclusively at highly sterically hindered C–H bond of **1x**. It is noteworthy that the present catalytic reaction is compatible with electron-donating groups, halogens, and electron-withdrawing groups as substituents on the phenyl carbamates.

To further explore the scope of the coupling reaction, the *ortho*-alkenylation of substituted phenyl acetates was attempted (see Scheme 5). Treatment of sesamol acetate **1y** with methyl acrylate (**2a**) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (4 mol-%), $AgSbF_6$ (20 mol-%), and $Cu(OAc)_2 \cdot H_2O$ (30 mol-%) in 1,2-dichloroethane at 100 °C for 12 h under air gave coupling product **5a** in 76% yield. Similarly, sesamol pivalate **1z** underwent coupling with **2a** to provide alkenylated compound **5b** in 70% yield.

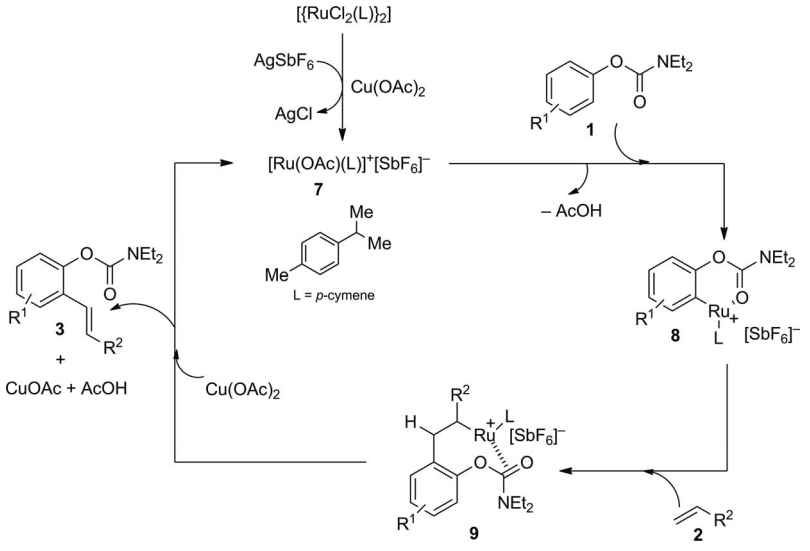
Carbamate is a versatile functional group that can be utilized for various organic transformations.[13] It is well-known that the carbamate group is a nice directing group for metal/base-mediated C–H bond activation reactions.[13a–13d] Furthermore, the carbamate group can also be used as an electrophile for cross-coupling reactions with arylboronic acids or nucleophiles in the presence of a nickel catalyst.[13e–13g] By using 5.0 equiv. of $LiOH \cdot H_2O$ in THF/MeOH/H_2O (4:1:1) at 80 °C for 12 h, both the ester and carbamate groups of **3c** were successfully cleaved to give substituted phenol derivative **6a** in 92% yield (see Scheme 6). Interestingly, in the presence of 1.0 equiv. of $LiOH \cdot H_2O$, the ester of **3d** was selectively cleaved to provide acrylic acid derivative **6b** in 86% yield, and the carbamate group of **6b** remained intact. However, in the presence of LiOH (3.0 equiv.), the carbamate group of **6b** was successfully cleaved to afford substituted phenol derivative **6c** in 91% yield. Surprisingly, in the presence of K_2CO_3 in MeOH for 2 h at room temperature, the acetyl (COMe) and pivaloyl (CO-*t*Bu) groups of **5a** and **5b** were selectively cleaved



Scheme 5. *ortho*-Alkenylation of phenyl acetate and phenyl pivalate with alkenes.



Scheme 6. Synthesis of phenols.



Scheme 7. Proposed mechanism.

to afford the corresponding phenol derivative **6d** in 85 and 92% yield, respectively. In these reactions, the ester group substituent on the alkene moiety of **5a** and **5b** remained intact.

A possible reaction mechanism to account for the present catalytic reaction involves a six-membered ruthenacycle as the key intermediate (see Scheme 7). The first step involves removal of the chloride ligand from the $[RuCl_2(p\text{-cymene})]_2$ complex by the $AgSbF_6$ salt to give cationic ruthenium species **7**. The coordination of the carbonyl group of carbamate **1** to the ruthenium cationic species **7** is followed by *ortho*-metalation to afford six-membered ruthenacycle **8**.[3c] A coordinative insertion of alkene **2** into the Ru–carbon bond of ruthenacycle **8** provides intermediate **9**, which undergoes a β-hydride elimination in the presence of $Cu(OAc)_2$ to give coupling product **3** and regenerate active ruthenium species **7** for the next catalytic cycle. In the reaction, only 30 mol-% of $Cu(OAc)_2$ is used as the internal oxidant. The remaining amount of $Cu(OAc)_2$ is regenerated under oxygen or air from the reduced copper source CuOAc.

Conclusions

We have described a ruthenium-catalyzed aerobic oxidative *ortho*-alkenylation of phenyl carbamates and acetates with alkenes. In this reaction, substituted alkene derivatives were produced in good to excellent yields in a highly regio- and stereoselective manner. Later, the substituted alkene derivatives were further converted quantitatively into the corresponding phenol derivatives by using $LiOH·H_2O$ or K_2CO_3 as a base. Further extensions of the coupling reaction through C–H bond activation by other chelating group-substituted aromatics, subsequent functionalizations with π-components, and detailed mechanistic investigations are in progress.

Experimental Section

General Procedure for the Coupling Reaction of Aromatic Carbamates 1 with Alkenes 2: $[RuCl_2(p\text{-cymene})]_2$ (0.04 mmol, 4 mol-%), $AgSbF_6$ (0.20 mmol, 20 mol-%), and $Cu(OAc)_2{\cdot}H_2O$ (0.30 mmol, 30 mol-%) were added to a 15 mL pressure tube, which was equipped with a magnetic stirrer and septum. (***Note:*** $AgSbF_6$ is moisture-sensitive. Thus, $AgSbF_6$ was handled inside a nitrogen glove box.) To the tube were added by syringe carbamate **1** (1.0 equiv.), alkene **2** (3.0 equiv.), and 1,2-dimethoxyethane (3.0 mL) as the solvent, and the reaction mixture was allowed to stir at room temperature for 5 min. During this time, the tube was covered with a septum. Then, the septum was removed, and the reaction mixture was stirred under open air for an additional 5 min. [***Note:*** During this time, the nitrogen gas that was initially in the pressure tube dispersed, and air entered the tube. In the reaction, only 30 mol-% of $Cu(OAc)_2{\cdot}H_2O$ was used for the internal oxidant. In fact, 2.20 equiv. of $Cu(OAc)_2{\cdot}H_2O$ was needed for the reaction. It is strongly believed that the remaining amount of $Cu(OAc)_2{\cdot}H_2O$ necessary for the reaction was regenerated under oxygen or air from the reduced copper source CuOAc. Therefore, we conducted the reaction under open air.] Next, the pressure tube was sealed with a screw cap, and the reaction mixture was stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and then filtered through Celite and silica gel. The filtrate was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **3**. For styrenes **2i** and **2j**, THF (3.0 mL) was used as the solvent. A similar procedure was followed for the coupling of phenyl esters **1y** and **1z** with **2a**, but these reactions were conducted at 100 °C for 12 h with 1,2-dichloroethane (3.0 mL) as the solvent.

Supporting Information (see footnote on the first page of this article): General procedure for the preparation of compounds **6a**–**6c**, procedure for the preparation of compound **6d**, spectroscopic data of **3a**–**3z**, **4a**, **4b**, **5a**, **5b**, and **6a**–**6d**, and copies of the ^1H and ^{13}C NMR spectra of all compounds.

Acknowledgments

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