Synthetic Methods

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Rhodium(III)-Catalyzed *ortho* Alkenylation of *N*-Phenoxyacetamides with *N*-Tosylhydrazones or Diazoesters through C–H Activation**

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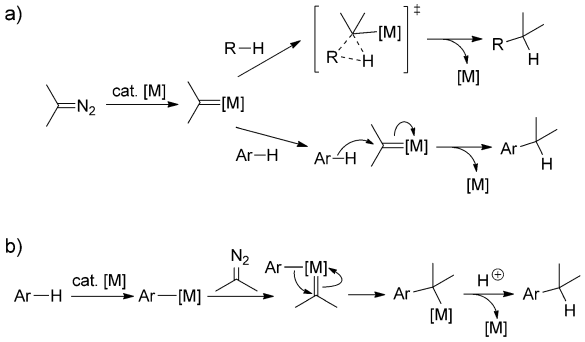
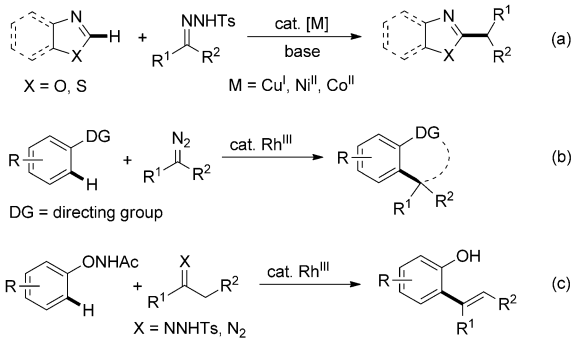
Abstract: *A coupling reaction of N-phenoxyacetamides with N-tosylhydrazones or diazoesters through Rh^{III}-catalyzed C–H activation is reported. In this reaction, ortho-alkenyl phenols were obtained in good yields and with excellent regio- and stereoselectivity. Rh–carbene migratory insertion is proposed as the key step in the reaction mechanism.*

Metal–carbene insertion into C–H bonds is a powerful approach to functionalize inert C–H bonds.[1] The classic metal–carbene insertion into C(sp^3)–H bonds follows a concerted reaction mechanism, while the corresponding insertion into aromatic C–H bonds involves an electrophilic aromatic substitution pathway (Scheme 1a).[2] In both cases, an electron-rich C–H bond shows higher reactivity toward electron-deficient carbene centers of metal–carbene species. In contrast to the traditional metal–carbene C–H insertions, a different reaction pattern of metal–carbenes has emerged recently as a new approach toward C(sp^2)–H functionalization. The reaction is considered to follow a pathway involving C–H metalation, metal–carbene formation, and migratory insertion (Scheme 1b).[3] For this type of reaction, electron-deficient C–H bonds show higher reactivity, because the C–H bond cleavage is in the step of C–H metalation.



Scheme 1. C–H bond functionalization with metal–carbenes.

We have demonstrated the first example of this type of C–H bond functionalization in the Cu-catalyzed C–H bond functionalization of 1,3-azoles with *N*-tosylhydrazones (Scheme 2a).[4] *N*-Tosylhydrazones have been known as the precursors for the in situ generation of diazo substrates (Bamford–Stevens reaction).[5] Recently, *N*-tosylhydrazones have been developed into a new type of coupling partner in transition-metal-catalyzed cross-coupling reactions.[6] The Cu-catalyzed C–H bond activation of 1,3-azoles with *N*-tosylhydrazones provides an efficient access toward C–H bond functionalization by secondary benzyl group. Miura and co-workers subsequently disclosed similar reactions with Ni^{II} or Co^{II} catalysts.[7] More recently, Cu^{I}-catalyzed C–H functionalization of *N*-iminopyridiniumylides with *N*-tosylhydrazones has been reported.[8]



Scheme 2. C–H bond functionalization with diazo compounds and *N*-tosylhydrazones.

On the other hand, Rh^{III} complexes have been recognized as competent catalysts for the C–H bond activation, and a wide range of unsaturated components, including alkenes, alkynes, allenes, imines, isonitriles, and isocyanates, have been explored as coupling partners in Rh^{III}-catalyzed direct aryl C–H functionalizations.[9,10] More recently, diazo compounds were used as coupling partners in Rh^{III}-catalyzed reactions. The groups of Yu,[11] Rovis,[12] Li,[13] Glorius,[14] and Cui[15] have demonstrated the successful exploration of diazo compounds in Rh^{III}-catalyzed *ortho* C–H bond functionalization with directing-group strategy (Scheme 2b). Mechanistically, these directing-group-assisted C–H bond functionalizations may follow a reaction pathway similar to that shown in

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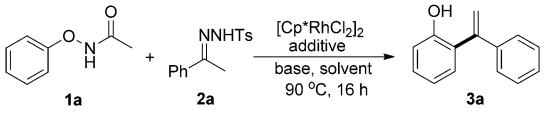
Scheme 1b. As a continuation of our interest in the C–H bond functionalization with metal–carbenes, we herein report a Rh^{III}-catalyzed C–H bond activation of *N*-phenoxyacetamides with *N*-tosylhydrazones or diazo compounds (Scheme 2c). This reaction explores the oxidizing directing group, which contains an N–O bond and has recently been developed by Liu, Lu, and co-workers.[16] The reaction provides an efficient and mild method for the synthesis of *ortho*-alkenyl phenols[17] with good yields and broad substrate scope.

At the outset of this study, *N*-phenoxyacetamide (**1a**) and *N*-tosylhydrazone (**2a**) were used as the substrates to optimize the reaction conditions. Thus, **1a** (1 equiv) and **2a** (1 equiv) were treated with $[Cp^*RhCl_2]_2$ (1.0 mol%), Cs_2CO_3 (1 equiv), and CsOAc (1 equiv) in toluene at 90°C for 16 h. To our delight, the expected product **3a** was obtained in 23% yield under the initial conditions (Table 1, entry 1). Screening

Table 1: Optimization of the reaction conditions.[a]



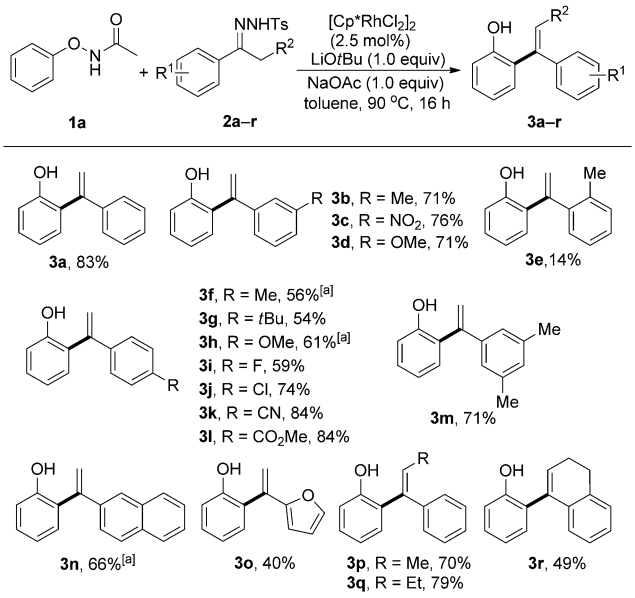
1a **2a** **3a**

Entry	Base	Additive	Solvent	Yield [%][b]
1	Cs_2CO_3	CsOAc	toluene	23
2	Cs_2CO_3	CsOAc	MeCN	trace
3	Cs_2CO_3	CsOAc	$(CH_2Cl)_2$	trace
4	LiO*t*Bu	CsOAc	toluene	63
5	LiO*t*Bu	NaOAc	toluene	56
6[c]	LiO*t*Bu	CsOAc	toluene	68
7[c]	LiO*t*Bu	none	toluene	72
8[c]	LiO*t*Bu	NaOAc	toluene	83
9[c]	LiO*t*Bu	KOAc	toluene	80
10[c]	LiO*t*Bu	AgOAc	toluene	0

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol%), base (1 equiv), and additive (1 equiv) in solvent (2 mL) at 90°C for 16 h. [b] Yields of isolated products. [c] $[Cp^*RhCl_2]_2$ (2.5 mol%) was used.

of solvents indicated that toluene was optimal, while the other two solvents, MeCN and $(CH_2Cl)_2$, only afforded trace amount of the desired product (Table 1, entries 2 and 3). When Cs_2CO_3 was replaced with Li*t*OBu, the yield increased to 63% (Table 1, entry 4).[18] Replacing CsOAc with NaOAc gave a comparable yield (Table 1, entry 5). Product **3a** was obtained with an improved yield when the catalyst loading was increased to 2.5 mol% (Table 1, entry 4 vs. entry 6). Finally, other acetate additives were examined, showing that NaOAc was suitable for this reaction (Table 1, entry 8). No product formation was observed when AgOAc was employed as the additive (Table 1, entry 10).

With the optimized conditions established, the scope of the *N*-tosylhydrazones was first examined. A variety of aryl ketone *N*-tosylhydrazones with *meta* or *para* substituents on the aromatic ring were reacted smoothly with *N*-phenoxyacetamide, affording the desired *ortho*-alkenyl phenols in good to excellent yields (**3b–d**, **f–l**). *N*-Tosylhydrazones with electron-deficient substituents on the aryl moiety were suitable for this transformation, affording the corresponding

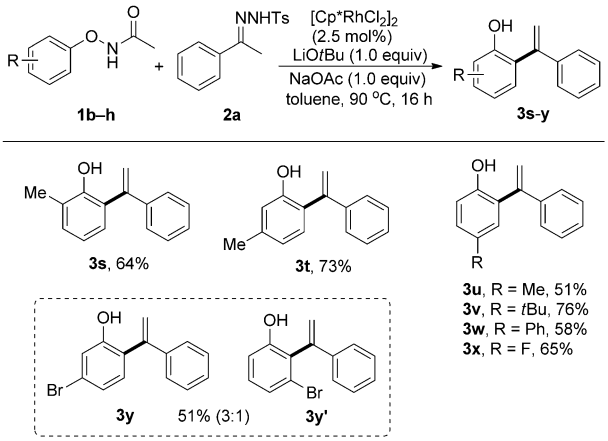


Scheme 3. Scope of *N*-tosylhydrazones. Reaction conditions: **1a** (0.30 mmol), **2a–r** (0.30 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), Li*t*OBu (1.0 equiv), and NaOAc (1.0 equiv) in toluene (3 mL) at 90°C for 16 h. [a] Reaction was conducted at 100°C.

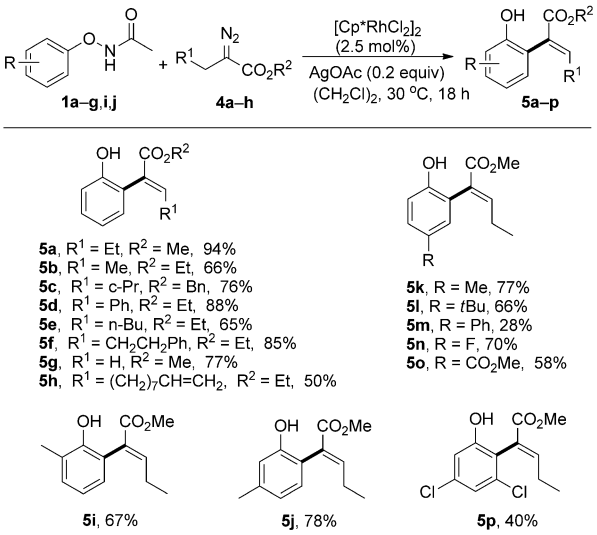
products in good to excellent yields, while the reaction with electron-rich substrates was sluggish under the standard conditions and an elevated reaction temperature was required (Scheme 3, **3f**, **3h**, and **3n**). The *N*-tosylhydrazone **2e**, which bears an *ortho* substitutent, was a poor substrate for this reaction, and the corresponding product **3e** was obtained in only 14% yield. The decreased yield of product **3e** presumably resulted from steric hindrance. It is notable that multiply substituted and polycyclic aromatic substrates **2m** and **2n**, respectively, were also tolerated to give the corresponding products **3m** and **3n** in 71% and 66% yields, respectively. A heteroaryl-bearing *N*-tosylhydrazone also worked well in the reaction, but gave the corresponding product in a diminished yield (Scheme 3, **3o**). It should be noted that this method is not restricted to the synthesis of terminal olefins; trisubstituted olefins, such as **3p**, **3q**, and **3r**, were also prepared in good yields under the same reaction conditions.[19]

Next, the scope of *N*-phenoxyacetamides was examined in this reaction (Scheme 4). The methyl-substituted substrates **1b–d** afforded the corresponding products **3s–u** in good yields, regardless of the position of the substituents on the aromatic ring. Notably, in the case of a *meta*-substituted substrate, **3t** was isolated as the sole product, in which the C–H bond activation occurred in *para* position to the methyl group, thus suggesting that the direct *ortho* alkenylation occurs at the less-hindered site.[16] However, when *N*-(3-*b*romophenoxy)acetamide (**1h**) was subjected to the reaction, two regioisomers were isolated (Scheme 4, **3y**:**3y′** = 3:1). The reaction does not seem to be sensitive to the electronic effects of the substituents (Scheme 4, **3v–x**).

Encouraged by the successful coupling of *N*-tosylhydrazones with *N*-phenoxyacetamide, we then proceeded to extend this transformation to diazoesters. However, when



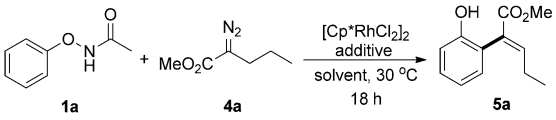
Scheme 4. Scope of *N*-phenoxyacetamides. Reaction conditions: **1b–h** (0.30 mmol), **2a** (0.30 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), LiO*t*Bu (1.0 equiv), and NaOAc (1.0 equiv) in toluene (3 mL) at 90°C for 16 h.



Scheme 5. Scope of diazoesters and *N*-phenoxyacetamides. Reaction conditions: **1** (0.30 mmol), **4** (0.33 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), and AgOAc (0.2 equiv) in $(CH_2Cl)_2$ (3 mL) at 30°C for 18 h.

1a and **4a** were subjected to the slightly modified reaction conditions (in the absence of base, 60°C), only trace amounts of the desired product **5a** could be obtained. Considering the importance of acetate additives in C–H activations,[11,16] we replaced CsOAc with AgOAc and observed the desired product **5a** in 32% yield (Table 2, entry 1). Then, a screening of solvents showed that $(CH_2Cl)_2$ and MeCN afforded good results in this reaction system (Table 2, entries 3 and 4), while reactions with other solvents resulted in lower yields (Table 2, entries 1, 2, and 5). As expected, increasing the catalyst loading from 1.0 to 2.5 mol% improved the yield to 78% (Table 2, entry 7). Moreover, a slightly increased amount of diazoester **4a** afforded product **5a** in 89% yield (Table 2, entry 8). Interestingly, further increase of the yield was observed when the amount of AgOAc was reduced to the catalytic loading (Table 2, entry 9). When the temperature was elevated to 60°C, only 25% yield was obtained (Table 2, entry 10).

Table 2: Optimization of reaction conditions.[a]



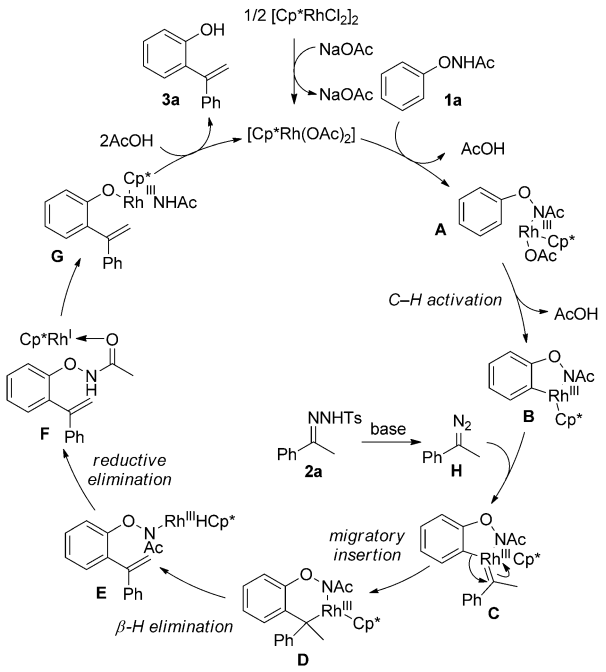
Entry	Additive (equiv)	Solvent	Yield [%][b]
1	AgOAc (1.0)	toluene	32
2	AgOAc (1.0)	dioxane	25
3	AgOAc (1.0)	$(CH_2Cl)_2$	60
4	AgOAc (1.0)	MeCN	60
5	AgOAc (1.0)	MeOH	20
6	CsOAc (1.0)	$(CH_2Cl)_2$	28
7[c]	AgOAc (1.0)	$(CH_2Cl)_2$	78
8[c,d]	AgOAc (1.0)	$(CH_2Cl)_2$	89
9[c,d]	AgOAc (0.2)	$(CH_2Cl)_2$	94
10[c,e]	AgOAc (1.0)	$(CH_2Cl)_2$	25

[a] Reaction conditions: **1a** (0.20 mmol), **4a** (0.20 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol%), and additive (0.2 mmol) in solvent (2 mL) at 30°C for 18 h. [b] Yields of isolated products. [c] $[Cp^*RhCl_2]_2$ (2.5 mol%) was used. [d] **4a** (0.22 mmol) was used. [e] The reaction was conducted at 60°C.

With the optimized catalytic system, the scope of diazo compounds was explored next (Scheme 5). A series of diazoesters (**4a–h**) bearing substituents such as methyl, ethyl, cyclopropyl, and benzyl all worked well in the reaction, affording the expected products in good to excellent yields (**5a–h**). Notably, the products were formed with high regioselectivity, and *E* isomers were isolated as the exclusive products in all cases. When the *meta*-methyl-substituted *N*-phenoxyacetamide (**1c**) was used, alkenylation occured in *para* position to the methyl group, which is a less-hindered site, providing product **5j** in 78% yield. Both electron-rich and electron-deficient *N*-phenoxyacetamides were effective (**5k–o**). Notably, *N*-(3,5-dichlorophenoxy)acetamide (**1j**) was also a competent coupling partner in this reaction, giving the product **5p** in 40% yield. The structures of **5d** and **5k** were confirmed by X-ray crystallographic analyses.[20]

A plausible mechanism, which is similar to those reported in the literature,[9,14] is shown in Scheme 6. First, an active catalyst $[Cp^*Rh(OAc)_2]$ is generated through anion exchange, which is followed by the coordination to substrate **1a** to form intermediate **A**. From intermediate **A**, a rhodacyclic intermediate **B** is formed by electrophilic C–H bond cleavage. Next, the Rh^{III}–carbene **C** is generated by dediazoniation of the in situ generated diazo substrate **H**. Subsequently, Rh^{III}–carbene migratory insertion from intermediate **C** affords rhodacyclic intermediate **D**. β-Hydride elimination and reductive elimination occur successively with the formation of intermediates **E** and **F**. Finally, oxidative addition of the N–O bond to Rh^{I} gives intermediate **G**. Upon protonation by acetic acid, product **3a** is formed along with the regeneration of Rh^{III} catalyst.

In summary, we have developed an efficient Rh^{III}-catalyzed synthesis of *ortho*-alkenyl phenols from *N*-phenoxyacetamides and *N*-tosylhydrazones/diazoesters through C–H bond activation. A wide range of substrates were tolerated in this transformation, and the products were obtained in



Scheme 6. Proposed reaction mechanism.

good to excellent yields. The reactions proceeded under mild conditions and did not need external oxidants. Further investigation of the C–H activation of *N*-phenoxyacetamides with carbene precursors are in progress in our laboratory.

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[19] The configuration of the double bond of products **3p** and **3q** was consistent with those reported in the literature, see Ref. [17b].

[20] CCDC 969847 (**5d**) and 969848 (**5k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

