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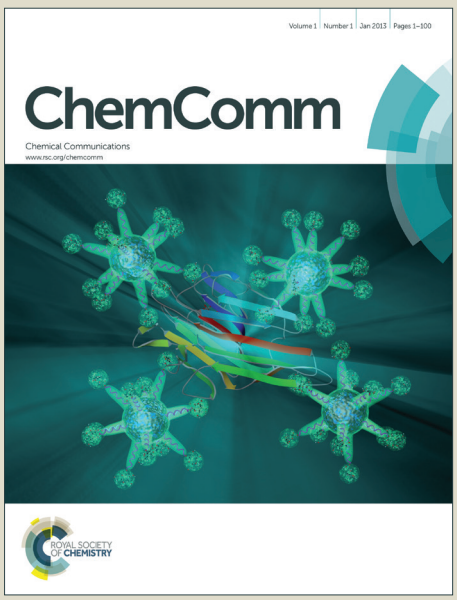

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Rhodium(III)-Catalyzed C-H Allylation of Electron-Deficient Alkenes with Allyl Acetates

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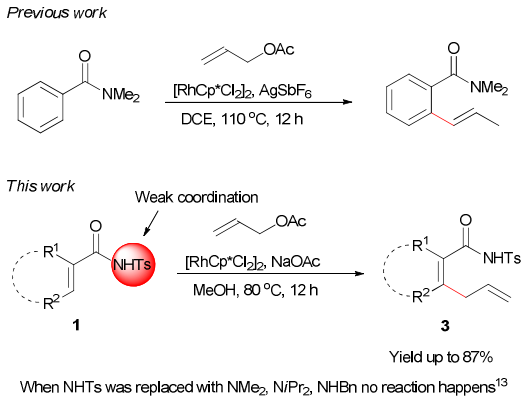
Rhodium-catalyzed C-H allylation of acrylamides with allyl acetates is reported. The use of weakly coordinating directing group enabled high reaction efficiency, broad functionality tolerance and excellent γ-selectivity, which opens a new synthetic pathway for the access of 1,4-diene skeletons.

Allylic alkylation ranks among the most important C-C bond formation methods in synthetic chemistry which has been widely applied for the synthesis of naturally occurring molecules and pharmaceuticals.[1] In this context, transition-metal-catalyzed allylic substitutions have been extensively studied. Among these, Pd-catalyzed stereo- and regioselectively allylation reactions of arenes, organic halides and organic boronic acids, which proceed *via* *β*-OAc elimination rather than *β*-H elimination,[2,3] are well established. On the other hand, copper catalysts are also proved to be competent for the asymmetric allylation using nonstabilized nucleophiles such as Grignard, organozinc, organoaluminum and organoborane reagents, within which high S_N2' regioselectivity guarantees the creation of stereogenic centers.[4]

In the realm of transition-metal-catalyzed C-C bond formation through C-H activation, rhodium catalysts have been gaining more and more attention for their broad functional group tolerance and high catalytic efficiency. Thus, many elegant works on Rh(III)-catalyzed C-H bond functionalization have been reported over the past decades.[5] Quite recently, the Rh(III)-catalyzed C-H allylation of arenes and alkenes using allenes as the allyl source were disclosed by Ma and Cramer, independently.[6] In 2011, Ellman and co-workers discovered an interesting allylation of arenes with allyl acetate as the coupling partner.[7] Although substoichiometric amount of $Cu(OAc)_2$ is still required to maintain the reaction efficiency, this discovery did set the stage for Rh(III)-catalyzed allylation reaction with allyl esters as the electrophilic coupling partner. Soon after that, the Rh(III)-catalyzed allylation of arenes with allyl carbonates was reported by Glorius.[8] Almost at the same time, our group developed an external oxidant-free olefination reaction of arenes with allyl acetate, within which allyl substitution product was formed as an intermediate with excellent *γ*-selectivity through *β*-OAc elimination process (Scheme 1).[9] With our ongoing interest in alkene functionalization and rhodium catalysis,[10,11] we assumed that the application of Rh(III)-catalyzed direct C-H allylation to alkene counterpart would be a fascinating and efficient strategy for the synthesis of functionalized 1,4-diene skeletons. Herein, we would like to report the first example of Rh(III)-catalyzed C-H olefinic allylation of electron-deficient alkenes with allyl acetates, wherein the weakly coordinating directing group Ts-imide prove to be the key point for the success of this protocol (Scheme 1).[12]



Scheme 1 Rh(III)-catalyzed C-H functionalization using allyl acetate.

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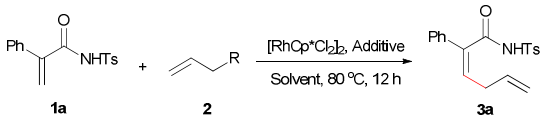
At the very beginning, we initiated our study by exploring the influence of different allyl eletrophiles. Using 2-Phenyl-*N*-tosylacrylamide **1a** as the model substrate, $[Cp^*RhCl_2]_2$ as catalyst, NaOAc as additive, the reaction was conducted in dichloroethane at 80 °C (Table 1, Entry 1 & 2). To our delight, both allyl carbonate and acetate provided the desired product **3a** without the observation of any double bond migration product. The *cis*-structure was latter confirmed through the NOESY NMR analysis of **3k**, which indicated the directing effect of amido group at the C-C bond formation step within the catalytic cycle.[14] With allyl acetate **2b** as the coupling partner, the reaction parameters were further examined, which lead to the identification of methanol as the best solvent and sodium acetate as the optimal additive (Table 1, Entry 3).[15] When $[Cp^*Rh(MeCN)_3]$ $[SbF_6]_2$ was employed as the catalyst, the reaction proceed to afforded the desired product in 51% yield (Table 1, Entry 4). Furthermore, the reaction was found to be sluggish and provided **3a** in 13% yield without sodium acetate (Table 1, Entry 5). As expected, no reaction occurred when rhodium catalyst was omitted (Table 1, Entry 6). It needs to be noted that this reaction was easily scalable and **3a** was obtained in 73% yield in a gram-scale reaction (Table 1, Entry 7).

Table 1 Optimization of reaction condition.[a]

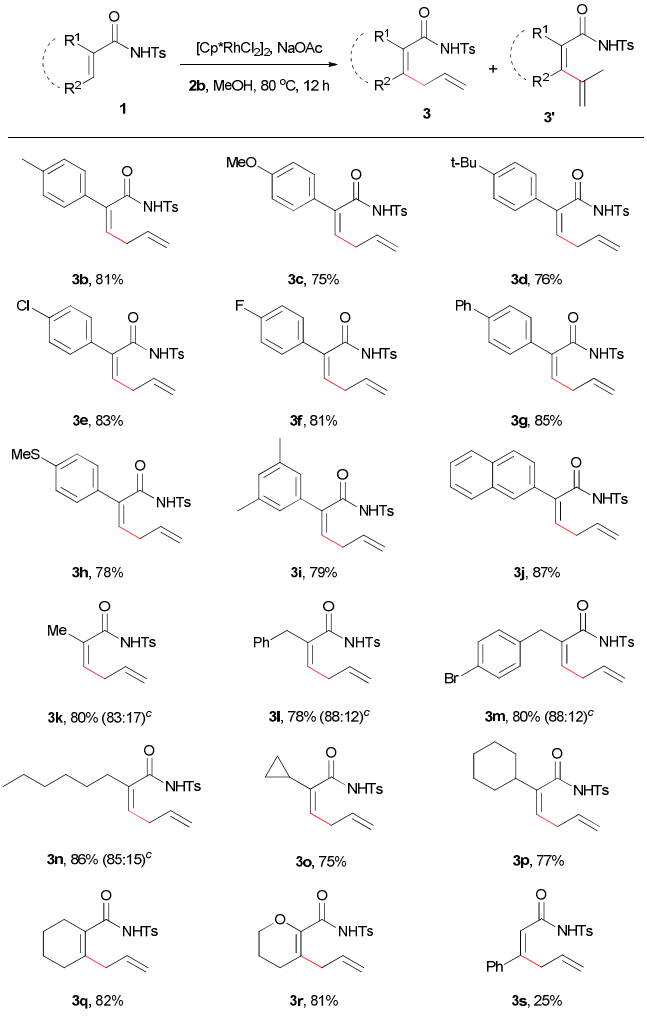


Entry	R	Additive	Solvent	Yield[b](%)
1	OCOOMe(**2a**)	NaOAc	DCE	58
2	OAc(**2b**)	NaOAc	DCE	63
3	**2b**	NaOAc	MeOH	84
4[c]	**2b**	NaOAc	MeOH	51
5[d]	**2b**	-	MeOH	13
6[e]	**2b**	NaOAc	MeOH	N.R.
7[f]	**2b**	NaOAc	MeOH	73

[a] Unless otherwise noted, the reactions were carried out at 80 °C using **1a** (0.1 mmol), **2** (0.4 mmol), Additive (0.1 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol) in solvent (0.5 mL) for 12 h. [b] Isolated yields. [c] $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as catalyst. [d] No NaOAc was added. [e] No rhodium catalyst added. [f] 1g scale.

With the optimal reaction conditions in hand, the reaction generality and limitations with respect to acrylamides were then investigated (Table 2). The α-aryl substituted acrylamide was first examined under standard reaction condition with allyl acetate **2b** as the reaction partner. Substrates containing functional groups, such as methyl, methoxy, chloro, fluoro and methylthio, at the para-position of the α-substituted phenyl ring were all well tolerated, thus providing corresponding *cis*-allylation product in high yields (Table 2, **3b-3h**). Notably, the sulfur-containing compound **1h** was nicely accommodated with this reaction and did not show any deleterious effect originating from catalyst deactivation. Furthermore, the meta-disubstituted phenyl acrylamide was also well adapted in this reaction, affording the desired product in 79% isolated yield (Table 2, **3i**). When **1j**, derived from 2-naphthyl acrylate, was employed as the substrate, the desired 1,4-diene product was generated smoothly in 87% isolated yield (Table 2, **3j**). In addition, this olefinic allylation strategy is not limited to the α-aryl substituted substrates, those with α-aliphatic substituents also proved to be effective substrates and participate in the olefinic allylation to afford 1,4-diene products in high yields (Table 1, **3k-3p**). It is intriguing that when α-methyl substituted acrylamide **1k** was used as the substrate, not only the desired allylation product **3k** but also an unexpected and inseparable isomer **3k'** containing conjugated diene moiety was generated with the ratio of **3k**:**3k'** as 83:17. When benzyl and hexyl substituted acrylamide was submitted to the standard reaction condition, the formation of a small amount of diene isomers was noticed as well (Table 2, **3l-3n**). However, when the substrates derived from 2-cycloalkylacrylate was employed, no obvious formation of conjugated diene was observed, thus providing the olefinic allylation products in high yields (Table 2, **3o** & **3p**). To further extend the scope of the reaction, α,β-disubstituted acrylamide derivatives were subsequently examined as well. 1-Cyclohexenyl derived substrate **1q**

Table 2 Reaction scope of acrylamide derivatives.[a, b]



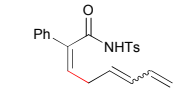
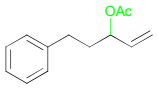
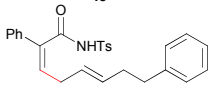
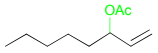
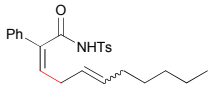
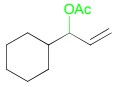
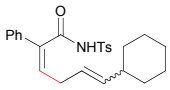
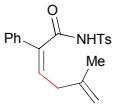
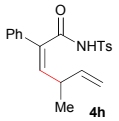
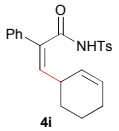
[a] Unless otherwise noted, the reactions were carried out at 80 °C using **1** (0.1 mmol), **2b** (0.4 mmol), NaOAc (0.1 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol) in

MeOH (0.5 mL) for 12 h. [b] Isolated yields. [c] Ratio for **3**:**3'** given in brackets were determined by ^{1}H NMR.

was well adapted in this reaction, furnishing product **3q** in 82% yield. It is noteworthy that heterocycle derived acrylamide **1r**, which prossess Lewis basic heteroatoms, also nicely engaged in this reaction to furnish desired products in good yield. Furthermore, cinnamamide **1s** was also found to be viable substrate, albeit generating the product **3s** in relatively low yield.[16]

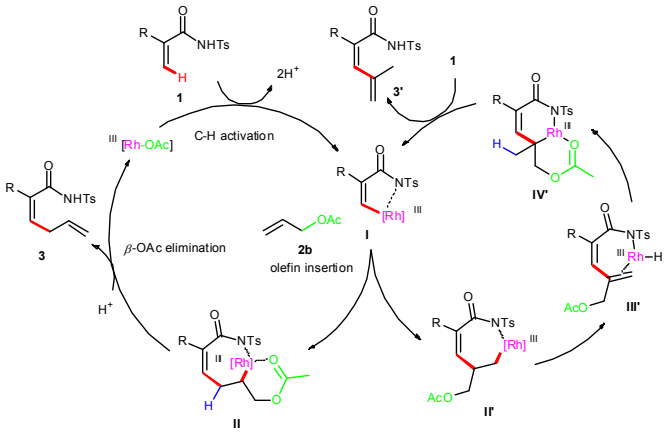
Table 3 Reaction scope of allyl acetates derivatives.[a, b]

1a 2

Entry	Allyl acetate derivatives	Desired product	Yield (%) (E/Z)
1	 2c	 4c	35% (77/23)
2	 2d	 4d	61% (99/1)
3	 2e	 4e	67% (87/13)
4	 2f	 4f	59% (83/17)
5	 2g	 4g	37% (-)
6	 2h	 4h	57% (-)
7	 2i	 4i	47% (-)

[a] Unless otherwise noted, the reactions were carried out at 80 °C using **1a** (0.2 mmol), **2** (0.4 mmol), NaOAc (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.004 mmol) in MeOH (1 mL) for 12 h. [b] Isolated yields.

To further illustrate the generality of this olefinic allylation reaction, allyl acetate derivatives were examined subsequently under the optimal reaction condition. With respect to α-substituted allyl acetates examined, synthetically useful chemical yields and moderate to high stereoselectivity along with excellent γ-selectivity were obtained (Table 3, entries 1-4). Although not so effective, the submission of α-vinyl allyl acetate allowed a straightforward introduction of 1,3-diene moiety to the alkene skeleton (Table 3, entry 1). In addition, the substitution on the β- or γ-carbon of allyl acetates were also allowable, albeit resulting somewhat attenuated reaction efficiency, which may be attributed to the steric interaction in the process of carborhodation. For example when 2-methylallyl acetate **2g** and but-2-en-1-yl acetate **2h** were subjected to the optimized reaction condition with **1a** the allylic alkylation proceed smoothly to afford the desired product **3g** and **3h** in 37% and 57% yields, respectively (Table 3, entries 5, 6). Moreover, cyclohex-2-en-1-yl acetate **2i** also well engaged in this reaction, affording the desired product in 47% yield.



Scheme 2 Plausible catalytic mechanism.

On the basis of the experimental results, a possible mechanism for the allylic alkylation was proposed in Scheme 2. The catalytic cycle is initiated by the imide directed C-H activation of acrylamide **1** by the in *situ* formed rhodium catalyst [Rh^{III}-OAc] to deliver intermediate **I** *via* a concerted-metalation-deprotonation (CMD) process. The ensuing migratory insertion of the allyl C-C double allows the formation of the seven-membered rhodacycle **II**, within which the coordination carbonyl of acetoxyl to the metal center is believed to be helpful for the induction of β-acetate elimination to afford the desired allylation product **3** and regenerates the active rhodium catalyst to reenter the catalytic cycle. As for the formation of dienes **3'**, intermediate **I** is assumed to undergo insertion of allyl acetate with reversed regioselectivity followed by hydride elimination/ reinsertion through intermediates **II'**, **III'** and **IV'**, which finally undergoes β-OAc elimination to get the target.

In conclusion, we have developed a novel rhodium-catalyzed intermolecular direct C-H olefinic allylation of electron-deficient alkenes with easily available allyl acetates as electrophiles. A broad range of functionalities and substitution patterns with respect to acrylamide and allyl acetate were tolerated. With the assistance of the weak-coordinating directing group, this protocol provides a straightforward and efficient method for the preparation of synthetically useful 1,4-diene skeletons through the allylic alkylation of alkene substrates.

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13 See in the supporting information.

14 The NOESY NMR analysis of **3k** see in the supporting information.

15 See the details in the supporting information.

16 Trace product was obtained with *N*-tosylacrylamide as the substrate, which indicates the importance of α-substituents.

