Homogeneous Catalysis

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Rhodium(III)-Catalyzed Alkenylation Reactions of 8-Methylquinolines with Alkynes by C(sp^3)–H Activation**

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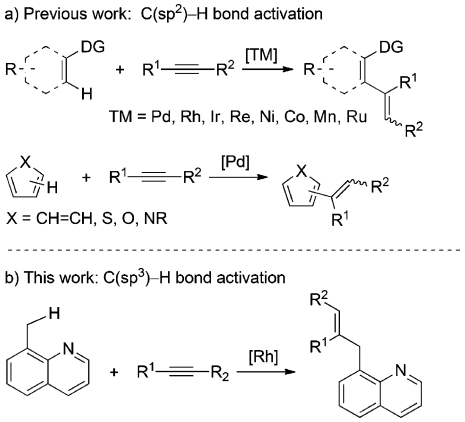
Dedicated to Professor Xiuzhong Zhou on the occasion of his 90th birthday

Abstract: *The alkenylation reactions of 8-methylquinolines with alkynes, catalyzed by [{Cp*RhCl$_2$}$_2$], proceeds efficiently to give 8-allylquinolines in good yields by C(sp^3)–H bond activation. These reactions are highly regio- and stereoselective. A catalytically competent five-membered rhodacycle has been structurally characterized, thus revealing a key intermediate in the catalytic cycle.*

Although catalytic activation of C–H bonds and their subsequent functionalization is one of the most challenging topics in organic chemistry, transition-metal-catalyzed C–C, C–O, and C–N bond formation by C–H bond activation has become one of the most useful methods in organic synthesis and total synthesis.[1] In 1979, Hong et al. first reported the rhodium-carbonyl-catalyzed alkenylation of benzene through phenyl C–H bond activation.[2] In 1995, the carbonyl-group-directed alkenylation reaction through activation of aromatic C–H bonds, catalyzed by a ruthenium complex, was reported by the group of Murai.[3] This kind of reaction is highly atom economical[4] and is a reaction in which every atom of the starting material becomes part of the final product.[5] With regard to this concept, a variety of transition metals, such as palladium, rhodium, iridium, rhenium, nickel, cobalt, manganese, and ruthenium, have been used to catalyze this type of reaction.[6–14] To our knowledge, all reported alkenylation reactions with alkynes proceed through C(sp^2)–H bond activation (Scheme 1 a). In principle, it should be possible to activate inert C(sp^3)–H bonds in a way that is similar to the activation of C(sp^2)–H bonds. However, the former does not have an empty low-energy orbital or filled high-energy orbital which could readily interact with the orbital of the metal atom, thus making the metal-mediated cleavage of C(sp^3)–H bonds slow, even much slower in the presence of alkynes, such that it competes with substrates for coordination to the metal center.[1m] Therefore, catalytic C(sp^3)–H bond activation represents a significant challenge, and an alkenylation reaction, by C(sp^3)–H bond activation catalyzed by transition-metals, with alkynes has not been reported up to now. Meanwhile, rhodium(III)-catalyzed C(sp^3)–H bond activation reactions are still rare.[15] Herein we report the first rhodium(III)-catalyzed C(sp^3)–H alkenylation reaction of 8-methylquinolines with alkynes (Scheme 1 b).



Scheme 1. Transition-metal-catalyzed alkenylation by C–H bond activation. DG = directing group.

Transition-metal-catalyzed C(sp^3)–H bond activation of 8-methylquinoline has been reported by the groups of Sanford, Vedernikov, Álvarez, and Muñiz,[16] thus proving that 8-methylquinoline is a good substrate because of its cyclometalation ability.[17] However, most of these reactions are catalyzed by palladium, and little work on the use of other metal catalysts are reported. There are no reports on the use of rhodium(III). Our group is interested in rhodium(III)-catalyzed C–H bond activation, and we recently reported an example of sequential cleavage of C(sp^2)–H/C(sp^3)–H and C(sp^2)–H/O–H bonds.[15f] To investigate C(sp^3)–H bond activation, we choose 8-methylquinolines as the substrates for reaction with alkynes in a [{Cp*RhCl$_2$}$_2$]-catalyzed system, thus achieving the alkenylation products.

To optimize the reaction conditions, 8-methylquinoline (**1a**) was chosen as the model substrate. As shown in Table 1, treatment of **1a** (0.5 mmol) with diphenylacetylene (**2a**; 1.0 mmol) in the presence of catalytic amounts of [{Cp*RhCl$_2$}$_2$] (0.025 mmol) and excess amounts of Cu-

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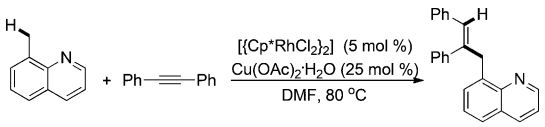
Table 1: Optimization of reaction conditions.[a,b]

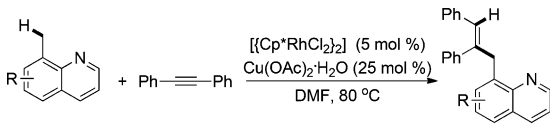


1a 2a 3aa

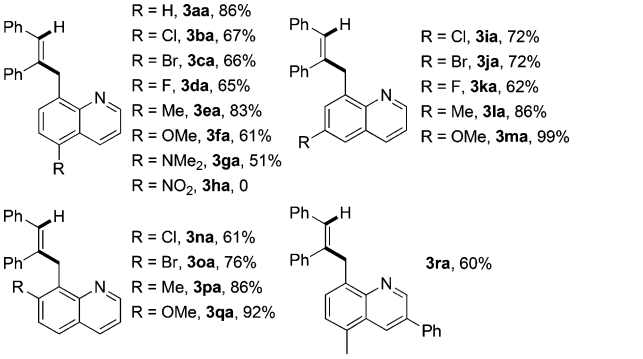
Entry	*T*	Equiv of [Cu]	Solvent	Additive	Yield [%]
1	100	1.5	*o*-xylene (2 mL)	–	trace
2	100	1.5	*t*AmOH (2 mL)	–	trace
3	100	1.5	DCE (2 mL)	–	trace
4	100	1.5	DMF (2 mL)	–	43
5	100	1.5	DMF (2 mL)	Cs_2CO_3	trace
6	100	1.5	DMF (2 mL)	Et_3N	trace
7	100	1.5	DMF (2 mL)	PivOH	29
8	100	1.5	DMF (2 mL)	NaH_2PO_4	32
9	100	1	DMF (2 mL)	–	63
10	100	1	DMF	–	71
11	80	1	DMF	–	69
12	80	1	DMF	$AgSbF_6$	70
13	80	0.5	DMF	–	84
14[c]	80	1	DMF	–	n.r.
15[d]	80	1	DMF	–	n.r.
16[e]	80	0.25	DMF	–	75
17[f]	80	0.25	DMF	–	81
18	80	0.25	DMF	–	91
19[g]	80	0.25	DMF	–	86

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [{Cp*RhCl$_2$}$_2$] (5 mol%), Cu(OAc)$_2$·H$_2$O, solvent (1.0 mL), 48 h, under Ar. [b] Yields of isolated products. [c] Without Cu(OAc)$_2$·H$_2$O. [d] Without [{Cp*RhCl$_2$}$_2$]. [e] [{Cp*RhCl$_2$}$_2$] (2.5 mol%). [f] Reaction time 12 h. [g] Reaction time 24 h. n.r. = no reaction. Cp* = C_5Me_5, DMF = *N*,*N*-dimethylformamide.

Table 2: Substrate scope of 8-methylquinolines.[a]



1a–p 2a 3aa–pa



[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), [{Cp*RhCl$_2$}$_2$] (5 mol%), Cu(OAc)$_2$·H$_2$O (25 mol%), DMF, (1.0 mL), 80°C, 24 h, under Ar. Yields are those of isolated products.

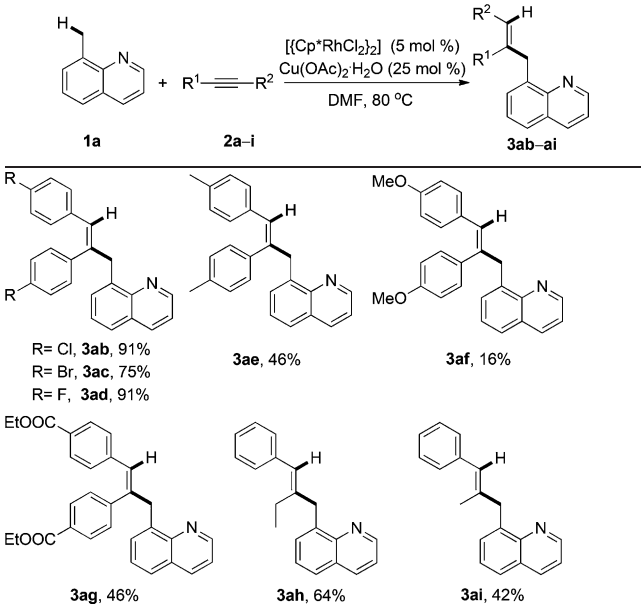
(OAc)$_2$·H$_2$O (1.0 mmol) in DMF (2 mL) at 100°C for 48 hours led to the stereoselective alkenylaton product 8-(2,3-diphenyl-allyl)quinoline (**3aa**) in 43% yield (entry 4). The structure of **3aa** was confirmed by its ^{1}H and ^{13}C NMR spectra, mass spectrometry data, and single-crystal X-ray diffraction analysis. No product was isolated when DMF was replaced by other solvents such as *o*-xylene, *t*AmOH, or DCE (entries 1–3). When bases like Cs_2CO_3 and NEt_3 were added, the yield decreased significantly (entries 5 and 6). Weak acids such as PivOH and NaH_2PO_4 also did not give positive results (entries 7 and 8). Addition of $AgSbF_6$ was also ineffective in increasing the yield of **3aa** (entries 11 and 12). When the amount of Cu(OAc)$_2$·H$_2$O was reduced, or the system was concentrated, the yield was increased (entries 4, 9, 10, and 13). Notably, the reaction could not proceed without Cu(OAc)$_2$·H$_2$O (entry 14).[8h,j,14a,f] When the reaction was carried out in the absence of the rhodium catalyst, no product was observed (entry 15). As the amount of Cu(OAc)$_2$·H$_2$O is important to this reaction, we performed additional screening. Finally, we chose 5 mol% of [{Cp*RhCl$_2$}$_2$] and 25 mol% of Cu(OAc)$_2$·H$_2$O in DMF (1 mL) at 80°C under argon for 24 hours (entry 19) as the standard reaction conditions.

With the optimal reaction conditions in hand, various substituted 8-methylquinolines (**1a–r**) were treated with diphenylacetylene (**2a**) and the corresponding 8-(2,3-diphenylallyl)quinoline derivatives **3aa–ra** were obtained (Table 2). When the substituent groups were located at the 5-position, both electron-rich or electron-deficient (except NO_2) substrates (**1b–g**) gave moderate to high yields (51–83%). When 6-substituted or 7-substituted substrates reacted with **2a**, higher yields (86–99%) were obtained with electron-donating groups (**3la, 3ma, 3pa, 3qa**) than those obtained with electron-withdrawing groups (**3ia, 3ka, 3na**). The multi-substituted substrate 5,8-dimethyl-3-phenylquinoline could also give a moderate yield (60%). The effect of steric hindrance was also investigated. When **1a** was replaced by 8-ethylquinoline, no product was detected. This outcome can also explain why the bis(alkenylation) product was not found.

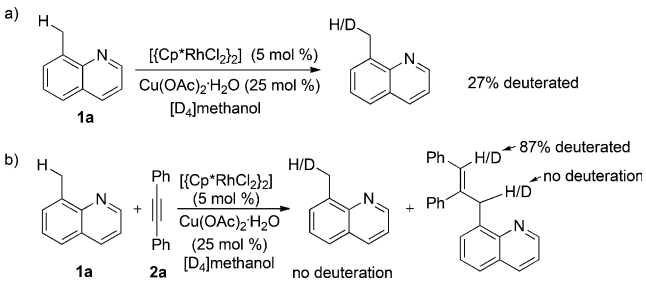
In addition to **2a**, other symmetrical alkynes (**2b–g**) were also tested for the present reaction (Table 3). When halogen-substituted diphenylacetylenes (**2b–d**) reacted with **1a**, the corresponding alkenylation products **3ab–ad** were obtained in high yields (75–91%). The electron-rich substrates **2f** and **2g** gave the corresponding **3af** in moderate yield (46%) and **3ag** in low yield (16%). The electron-deficient substrate **2e** also gave a moderate yield (46%). To provide evidence for the regioselectivity of the reaction, a few unsymmetrical alkynes were employed. In this case, two regioisomeric products could be possible. Fortunately, 1-phenyl-1-butyne (**2h**) and 1-phenyl-1-propyne (**2i**) gave the single regioisomeric products **3ah** and **3ai** in moderate to good yields (64 and 42%, respectively). The structure of **3ai** was confirmed by NOESY data (see the Supporting Information). However, terminal alkynes like phenylacetylene, or internal aliphatic alkynes such as dimethyl acetylenedicarboxylate and diethylacetylene, did not work under these reaction conditions.

To gain more insight into the mechanism of this reaction, KIE (kinetic isotope effect) experiments were performed in two independent reactions. The KIE was found to be $k_H/k_D = 4.0$, thus indicating that the cleavage of the methyl C–H bond was involved in the rate-determining step. H–D exchange reactions were also carried out. When the reaction was performed in the absence of **2a** (Scheme 2a), the methyl C–H bonds were deuterated only in the presence of Cu-

Table 3: Substrate scope of alkynes.[a]



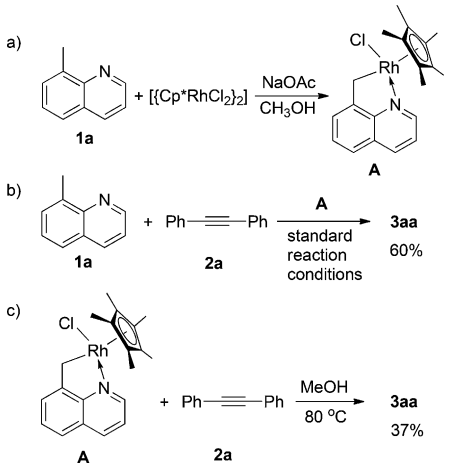
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), [{Cp*RhCl$_2$}$_2$] (5 mol %), Cu(OAc)$_2$·H$_2$O (25 mol %), DMF (1.0 mL), 80 °C, 24 h, under Ar. Yields of isolated products are shown.



Scheme 2. Deuterium exchange reactions.

$(OAc)_2{\cdot}H_2O$, thus indicating that $Cu(OAc)_2{\cdot}H_2O$ plays a key role in the first step of the catalytic cycle and that the C–H bond activation is reversible. In the presence of **2a** no deuteration of the methyl C–H bonds was detected and the proton of the olefinic unit of the product was deuterated (87%; Scheme 2b). This result indicates that the last step of the catalytic cycle may involve protonolysis and the reversibility of the C–H bond activation was altered by addition of diphenylacetylene.

Fortunately, the rhodacycle intermediate **A** was isolated by the reaction of **1a** with [{Cp*RhCl$_2$}$_2$] and NaOAc (Scheme 3a). Its structure was confirmed by ^{1}H and ^{13}C NMR spectra, mass spectrometry data, and single-crystal X-ray diffraction analysis. A similar five-membered rhodacycle complex was obtained from the reaction of **1a** with [$RhCl_3{\cdot}3H_2O$] as reported by Nonoyama, but no structural data was given.[18] The intermediate **A** was used as the catalyst instead of [{Cp*RhCl$_2$}$_2$] under the standard reaction conditions, and gave a 60% yield (Scheme 3b). A stoichiometric reaction was also performed and gave the final product in

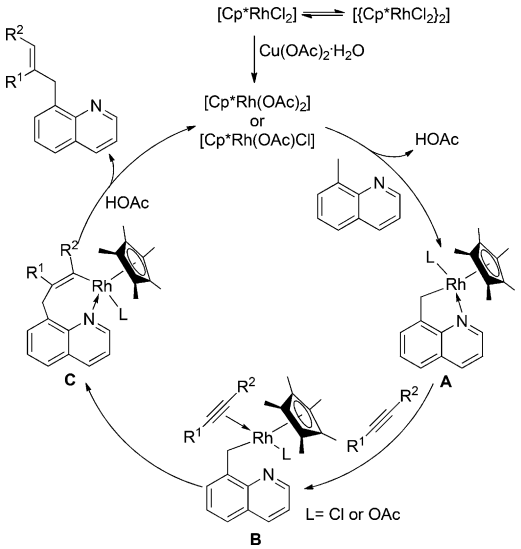


Scheme 3. Synthesis of the intermediate **A** and its use as either the catalyst or reactant in the alkenylation reaction.

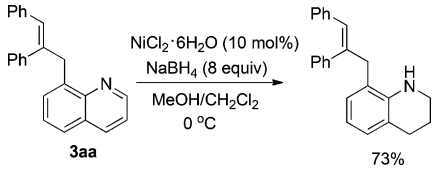
37% yield (Scheme 3c). These results confirm that the intermediate **A** is an active species in the reaction.

Based on the above experimental results and known transition-metal-catalyzed C(sp^2)–H bond alkenylation reactions,[8,14] a possible mechanism is proposed for the present catalytic reaction (Scheme 4). The first step is likely to be a C(sp^3)–H activation process thus affording the intermediate **A**. Then an alkyne coordinates to the rhodium atom (**B**) and follows a regioselective insertion into the Rh–C(sp^3) bond to give the seven-membered rhodacycle **C**. Finally, **C** reacts with HOAc to give the stereoselective alkenylation product and regenerate the rhodium species. When [$RhCp^*(OAc)_2$] was used instead of [{Cp*RhCl$_2$}$_2$] and $Cu(OAc)_2{\cdot}H_2O$, no product was observed, thus indicating that $Cu(OAc)_2{\cdot}H_2O$ is necessary for the catalytic reaction.

8-Allylquinoline derivatives were reported to possess high hepatoprotective effect.[19] So our work provides a new simple route to synthesize this kind of compound. To further



Scheme 4. Proposed mechanistic pathway of the alkenylation reaction.



Scheme 5. Reduction of **3aa**.

demonstrate the synthetic utility of 8-allylquinoline products, a derivatization reaction was done. The alkenylation product **3aa** could be reduced selectively by $NaBH_4/NiCl_2{\cdot}6H_2O$ to give 8-(2,3-diphenylallyl)-1,2,3,4-tetrahydroquinoline in 73% yield (Scheme 5).[20]

In conclusion, we have developed a rhodium(III)-catalyzed alkenylation reaction of 8-methylquionlines with alkynes to yield 8-allylquinolines in good yields. This work represents the first transition-metal-catalyzed alkenylation of $C(sp^3)$–H bonds for reaction with alkynes. Notably, the catalytic reaction is highly regio- and stereoselective. A catalytically competent five-membered rhodacycle has been structurally characterized, thus revealing a key intermediate in the catalytic cycle. Further applications of this method in the synthesis of other targets and a detailed mechanistic investigation are in progress.

Experimental Section

General procedure for the alkenylation reaction: A mixture of the substituted 8-methylquinoline **1** (0.5 mmol, 1 equiv), alkyne **2** (1 mmol, 2.0 equiv), $[\{Cp^*RhCl_2\}_2]$ (15.5 mg, 0.025 mmol, 5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (25.0 mg, 0.125 mmol, 25.0 mol%) were weighed in a Schlenk tube equipped with a stir bar. Anhydrous DMF (1.0 mL) was added and the mixture was stirred at 80°C for 24 h under Ar atmosphere. Afterwards, it was evaporated under reduced pressure and the residue was absorbed onto small amounts of silica. The purification was performed by flash column chromatography on silica gel (eluent: EtOAc/petroleum ether (1:50) and CH_2Cl_2/petroleum ether (1:2)).

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