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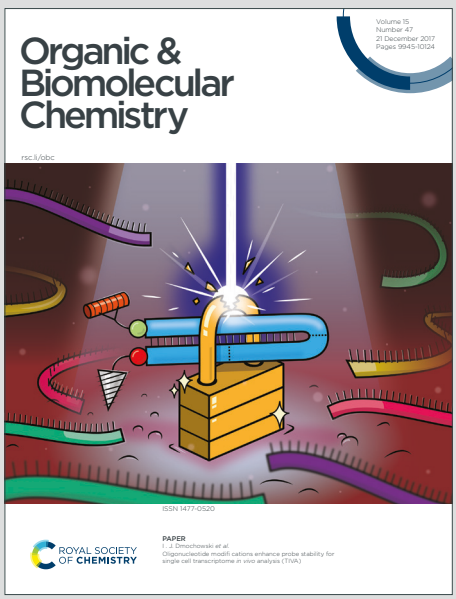

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DOI: 10.1039/C9OB01531K

COMMUNICATION

Rhodium(III)-Catalyzed Unreactive C(sp³)–H Alkenylation of *N*-alkyl-1*H*-pyrazoles with Alkynes

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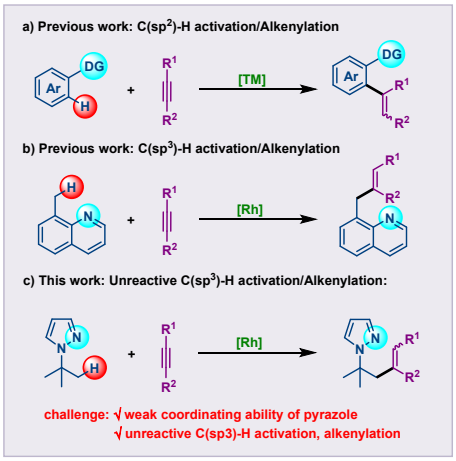
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The first example of pyrazole-directed rhodium(III)-catalyzed unreactive C(sp³)–H alkenylation with alkynes has been described, which showed relatively broad substrate scope with good functional group compatibility. Moreover, we demonstrated that the transitive coordinating center pyrazole could be easily removed under mild conditions.

Transition-metal-catalyzed C–H activation has emerged as a powerful strategy to accomplish various direct C–H functionalization reactions,[1] which has found many applications in the construction of C–X bonds.[2] Especially, rhodium(III) catalysts have shown good performance with respect to high activity, high selectivity, and good functional group tolerance.[3] In recent years, a variety of rhodium(III)-catalyzed C–H functionalization has been developed, which enables the formation of carbon–carbon and carbon–heteroatom bond.[4] A variety of coupling partners were conducted in rhodium(III)-catalyzed C–H transformations, such as methyleneoxetanones,[5] 7-azabenzonorbornadienes,[6] 2,2-difluorovinyl tosylates,[7] sulfoxonium ylides,[8] diazo compounds,[9] ketenes,[10] 2-carboxyl allylic alcohols,[11] alkenes,[12] alkynes[13] and strained rings.[14]

Alkynes are important coupling partners which have been widely used in transition-metal-catalyzed C–H activation systems.[13, 15] Since Hong's pioneering work,[16] especially in recent years, transition-metal-catalyzed directed C(sp²)–H alkenylation reactions with alkynes have attracted many researchers' interest. A variety of transition metals, including rhodium,[17] cobalt,[18] palladium,[19] nickel,[20] rhenium,[21] iridium,[22] ruthenium,[23] and manganese,[24] have been used to catalyze this type of reaction (Scheme 1a). In 2015, Wang[25] and co-workers reported a rhodium(III)-catalyzed benzylic C(sp³)–H alkenylation reactions of 8-methylquinolines with alkynes (Scheme 1b). However, the more challenging alkenylation of unreactive C(sp³)–H bond remains rare so far, probably due to the higher bond strength of inert C(sp³)–H bond. As our continued interest in rhodium(III)-catalyzed C–H functionalization using alkynes as coupling partners.[26] We set out to develop a rhodium(III)-catalyzed pyrazole-directed unreactive C(sp³)–H alkenylation with alkynes (Scheme 1c). The challenges associated with realizing this transformation are twofold. First, pyrazole directed C–H activation reactions are more challenging and the related reports are relatively rare,[27] probably due to the weak coordinating ability of pyrazole which hinders C–H transformations.[28] Second, unreactive C(sp³)–H functionalization is one of the most challenging C–H functionalization processes.[29] Herein we report the first example of rhodium(III)-catalyzed unreactive C(sp³)–H alkenylation of *N*-alkyl-1*H*-pyrazoles with alkynes.



Scheme 1. Transition-metal-catalyzed C-H activation/alkenylation

We initiated our studies with the screening of reaction conditions by reacting *N*-(*tert*-butyl)-1*H*-pyrazole **1a** with diphenylacetylene **2a** under various reaction parameters. The combination of **1a** (1.0 equiv), **2a** (2.0 equiv), Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (5 mol%), Cu(OAc)$_2$·H$_2$O (1.0 equiv) and Ag$_2$CO$_3$ (0.2 equiv) in DCE at 100 °C for 24 h was found to be optimal, affording **3aa** in 81% isolated yield (Table 1, entry 1). The reaction efficiency significantly decreased in the absence of

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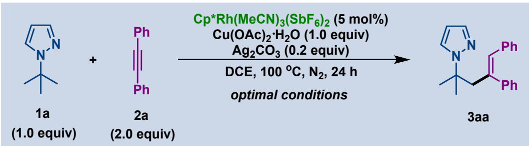
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Ag_2CO_3 or $Cu(OAc)_2{\cdot}H_2O$, and **3aa** was obtained in 55% and 16% yield, respectively (entries 2 and 3). Furthermore, the use of $[Cp^*RhCl_2]_2$ with $AgSbF_6$ or $Cp^*Rh(OAc)_2$ instead of $Cp^*Rh(MeCN)_3(SbF_6)_2$ led to greatly attenuated reactivity, and **3aa** was not observed in both cases (entries 4 and 5). Decreasing the reaction temperature to 80 °C led to **3aa** in 15% yield and incomplete conversion of **1a** (entry 6). The use of MeCN or HFIP as solvent led to inferior results comparable to those obtained using DCE (entries 7 and 8). Moreover, changing the loading of **2a** to 1.2 equiv. renders the reaction less efficient, and **3aa** was only obtained in 73% yield (entry 9). When the reaction was performed in air instead of under a nitrogen atmosphere, the result was poorer, which demonstrated that an inert atmosphere was important for this transformation (entry 10).

Table 1. Effects of Reaction Parameters[a]

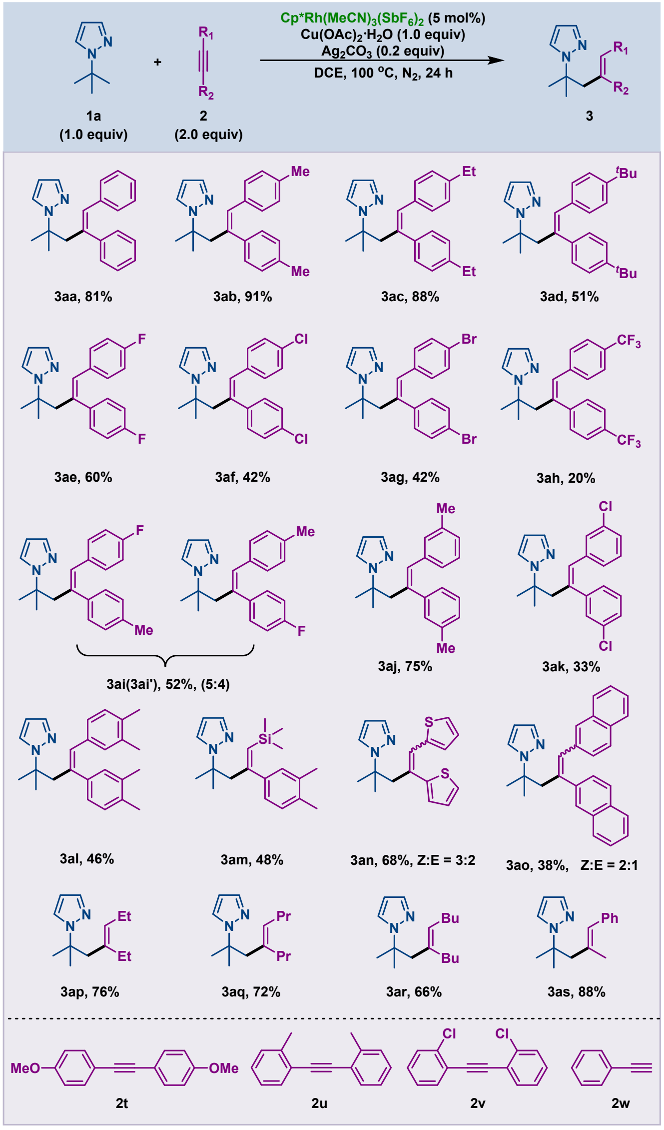


entry	change to optimal conditions	3aa[b]
1	none	81%
2	without Ag_2CO_3	55%
3	without $Cu(OAc)_2{\bullet}H_2O$	16%
4	$[Cp^*RhCl_2]_2$ with $AgSbF_6$ Instead of $Cp^*Rh(MeCN)_3(SbF_6)_2$	ND[c]
5	$Cp^*Rh(OAc)_2$ Instead of $Cp^*Rh(MeCN)_3(SbF_6)_2$	ND[c]
6	the reaction was run at 80 °C	15%
7	MeCN as solvent	ND[c]
8	HFIP as solvent	ND[c]
9	**2a** (1.2 equiv)	73%
10	in air instead of N_2 atmosphere	68%

[a] All reactions were carried out in sealed tube and run on 0.2 mmol scale. [b] Isolated yield. [c] ND = Not detected.

With an optimized set of conditions in hand, we then surveyed the substrate scope of alkynes in order to survey the generality of this reaction. As shown in Table 2, diarylalkynes **2b**-**2d** bearing electron-donating substituents on *para*-position of aromatic ring reacted effectively, to provide the corresponding products (**3ab-3ad**) in moderate to excellent yields (51%-91%). Moreover, electron-withdrawing substituents at *para*-positions of the phenyl groups, including fluoro, chloro, bromo and trifluoromethyl, were also tolerated, and the desired products, **3ae-3ah**, were obtained in 20%-60% yields. Notably, halide substituents (Cl, Br) were found to be compatible with this reaction, providing an opportunity to further functionalization. Diarylalkynes with electronically distinct substituents (methyl and fluoro), **2i**, was also tested, a mixture of products (**3ai** and **3ai'**) were obtained in 52% combined yields with moderate regioselectivity (5:4). Substrates bearing methyl or chloro group at the *meta*-position on the phenyl ring proceeded smoothly, afforded **3aj** and **3ak** in 75% and 33% yield, respectively. To our disappointment, substituents at *ortho*-position of aromatic ring were found to be incompatible, likely due to steric congestion (**2u** and **2v**). Dimethyl substituted diarylacetylene **2l** reacted smoothly to give the corresponding product **3al** in 46% yield. Gratifyingly, diarylacetylenes containing trimethylsilyl, thienyl, or naphthalenyl moieties were also compatible in this reaction (**3am-3ao**), while **3an** and **3ao** were obtained in moderate stereoselectivity. It is noteworthy that complete stereoselectivity was obtained was achieved when **2m** was employed, exclusively giving **3am** in 48% yield. Furthermore, C–H activation of **1a** with aliphatic alkynes was also achieved, affording **3ap-3ar** in 66%-76% yields. To our delight, when unsymmetrical phenyl alkyl alkynes, such as 1-phenylpropyne, was employed, exclusively giving **3as** in 88% yield with the methyl installed adjacent to the *N*-(*tert*-butyl)-1*H*-pyrazole core. Unfortunately, dimethoxyphenyl acetylene **2t** and phenylacetylene **2w** failed to undergo this transformation. Given that *N*-(*tert*-butyl)-1*H*-pyrazole contain three potential $C(sp^3)$–H bond, we were pleased to find that only monoalkenylation products were obtained without any multialkenylation products for every case.

Table 2. Variation of alkynes 2[a,b]

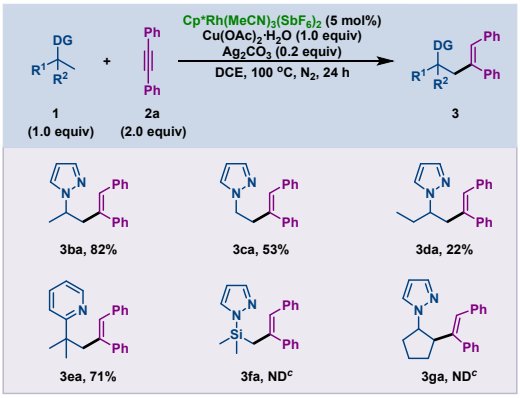


[a] All reactions were carried out in sealed tube and run on 0.2 mmol scale. [b] isolated yield.

DOI: 10.1039/C9OB01531K

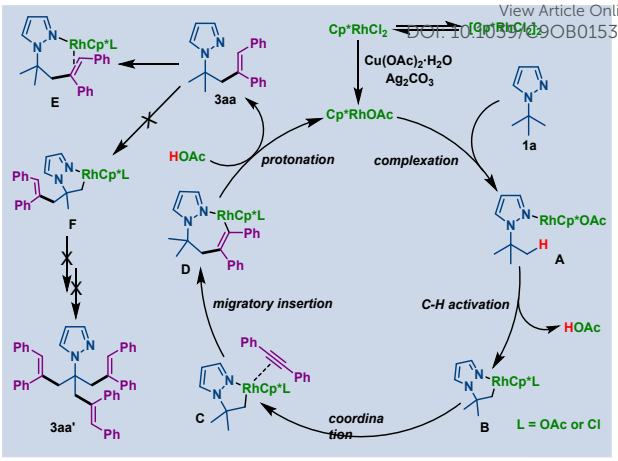
The scope of *N*-alkyl-1*H*-pyrazoles was also investigated. As shown in Table 3, *N*-isopropyl-1*H*-pyrazoles **1b**, *N*-ethyl-1*H*-pyrazoles **1c**, and *N*-(*sec*-butyl)-1*H*-pyrazoles **1d** all selectively alkenylated at the β-methyl position, providing monoalkenylation product **3ba**-**3da** in moderate to good yields. Furthermore, the directing group scope of this reaction was also investigated, 2-pyridyl directing group also provided C(sp^3)–H alkenylation product **3ea** in 71% yield. *N*-(trimethylsilyl)-1*H*-pyrazole **1f** was not suitable substrate for this C(sp^3)–H bond alkenylation process. Probably due to C(sp^3)–Si bond can be easily cleaved. Moreover, *N*-cyclopentyl-1*H*-pyrazole **1g** did not give the desired product **3ga**, and only the starting material was recovered. It is probable that methylene units are generally less reactive in C–H activation.

Table 3. Variation of **1**[a,b]



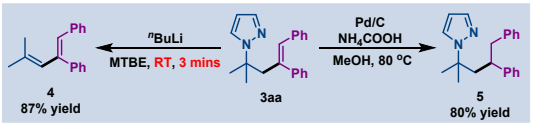
[a] All reactions were carried out in sealed tube and run on 0.2 mmol scale. [b] Isolated yield. [c] ND = Not detected.

The possible mechanism of this reaction was proposed in Scheme 2. First, the ligand exchange of Cp*$RhCl_2$ with $Cu(OAc)_2{\cdot}H_2O$ to form the active species Cp*RhOAc. Then, complexation of *N*-(*tert*-butyl)-1*H*-pyrazole **1a** with Cp*RhOAc using the pyrazole group forms a Rh(III) complex **A**, followed by C(sp^3)–H activation to form five-membered rhodium complex **B**. Subsequently, alkyne **2a** coordinates with rhodium and follows 1, 2-insertion into the C(sp^3)–Rh bond to give the seven-membered rhodacycle **D**. Finally, intermediate **D** was protonated by HOAc to give the mono C–H alkenylation product **3aa** and regenerate the rhodium species to finish a catalytic cycle. Probably due to the alkene moiety and pyrazole ring coordinate with rhodium simultaneously, intermediate **E** could be formed prior to intermediate **F**, which suppress the generation of multiple alkenylation product **3aa'**. Moreover, steric hindrance effect might be another reason for entire monoselectivity.



Scheme 2. Proposed mechanism

In order to highlight the synthetic utility of our strategy, further chemical transformations of product **3aa** were conducted (Scheme 3). Under basic conditions, transitive coordinating center pyrazole could be easily removed from product **3aa** in 3 minutes at room temperature, afforded the important conjugated diene product **4** in 87% yield,[27a] which is widely used as monomers in the polymer industry. Moreover, further functionalization of the olefin moiety was demonstrated, **3aa** was readily hydrogenated to give **5** in 80% yield.[29o]



Scheme 3. Further transformations of **3aa**.

Conclusions

In conclusion, this communication describes a rhodium(III)-catalyzed unreactive C(sp^3)–H alkenylation of *N*-alkyl-1*H*-pyrazoles with alkynes, which exhibits entire monoselectivity and relatively broad substrate scope. Pyrazole is used as a directing group to promote C(sp^3)–H alkenylation, which could be easily removed under basic conditions at room temperature in short reaction time. Further studies on pyrazole-directed rhodium(III)-catalyzed unreactive C(sp^3)–H functionalization is currently underway in our laboratory.

We gratefully acknowledge National Natural Science Foundation of China (21572160), the Science&Technology Development Fund of Tianjin Education Commission for Higher Education (2018KJ159) and the Program for Innovative Research Team in University of Tianjin (TD13-5074) for generous financial support.

Conflicts of interest

There are no conflicts to declare.

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DOI: 10.1039/C9OB01531K

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