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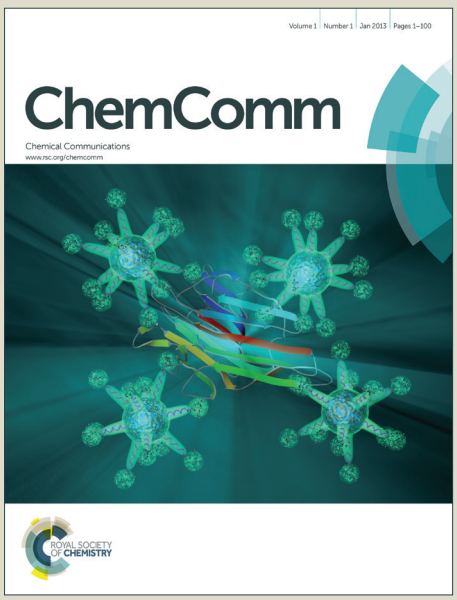

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Rhodium(III)-Catalyzed Olefinic C-H Alkynylation of Enamides at Room Temperature

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Rh(III)-catalyzed C-H olefinic alkynylation of enamides for the stereospecific construction of synthetically useful *Z*-type enynamides is reported. This protocol displays good functionality tolerance and operational simplicity thus providing an alternative synthetic opportunity for the ease of access to specific 1,3-enyne derivatives.

Over the past decades, transition-metal-catalyzed alkynylation reaction has emerged as one of the most general and reliable methods in synthetic chemistry for introducing alkynyl functionalities into naturally occurring compounds, advanced materials and pharmaceutics.[1] In this regards, much effort was put in and extraordinary strategies, including Sonogashira reaction, Cu-promoted Castro-Stephens reaction[2] and Pd-catalyzed Negishi reaction,[3] have been well established. Futhermore, with the surge of C-H functionalization,[4] the Pd-catalyzed C-H alkynylation was also developed and has been shown to be desirable in a number of cases.

In the realm of Csp^2-Csp bond formation, while much progress has been received in the area of aromatic alkynylations,[5] relatively less success has been achieved for the realization of alkynylation of alkenes. Commonly, the most general and reliable methods are transition-metal-catalyzed cross-coupling between prefunctionalized alkenes,[6,7] such as vinyl halides or metal alkenes, and terminal alkynes or alkynylmetals. In this context, the olefinic Sonogashira reaction[7] is the most popular protocol among the others. However, the employment of prehalogenated alkenes as well as the formation of stoichiometric amount of halogenated wastes contradicts with the principle of modern synthetic chemistry. As an alternative strategy, the Heck-type alkynylation of simple terminal alkenes obviates the use of pre-activated alkenes, but the relatively forcing reaction conditions and inaccessibility of *cis*-enyne skeleton, which is frequently found in natural products, limits its wide applicability to some extent.[8] As such, the development of highly stereoselective and efficient method for olefinic alkynylation, which not only shows a broad range of functionality tolerance but is also applicable for the synthesis of complex molecules, is still in great demand.

Because of its dense functionality and being able to act as an effective directing group, enamide represents a type of synthetically useful template in the transition-metal-catalyzed direct C-H functionalizations.[9] In this regard, we had reported a set of useful elaborations of enamides through C-H activation mode, such as arylation, trifluoromethylation as well as olefination.[10] Recently, we have reported a mild and general protocol for the alkynylation of arenes through rhodium-catalyzed C-H activation (Scheme 1). [11,12] With the aim of extending our recent achievement to the imaginable but nontrival olefin counterpart and as a continuation of our interest in alkene functionalization[13] and rhodium catalysis,[14] herein, we would like to report the Rh-catalyzed alkynylation of enamide through direct olefinic C-H activation. Within this protocol, alkynyliodonium reagent **1**, which is widely used in transition-metal-catalyzed aromatic alkynylation reactions as electrophilic hypervalent iodonium reagent was adopted as the alkyne donor (Scheme 1).[15]

The reaction condition was optimized between *N*-(1-phenylvinyl) acetamide (**2a**) and the alkynyliodonium reagent **1**, which led to the optimized reaction condition: 2 mol% $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as catalyst, 10 mol% PivOH as additive,[16] acetone as solvent at room temperature for 12h (see supporting information for details). It needs to be pointed out that in contrast to the Heck-type olefinic alkynylation of **2a**, which predominately

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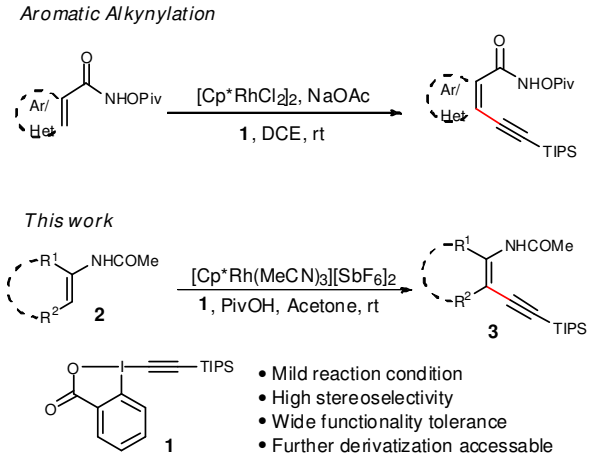
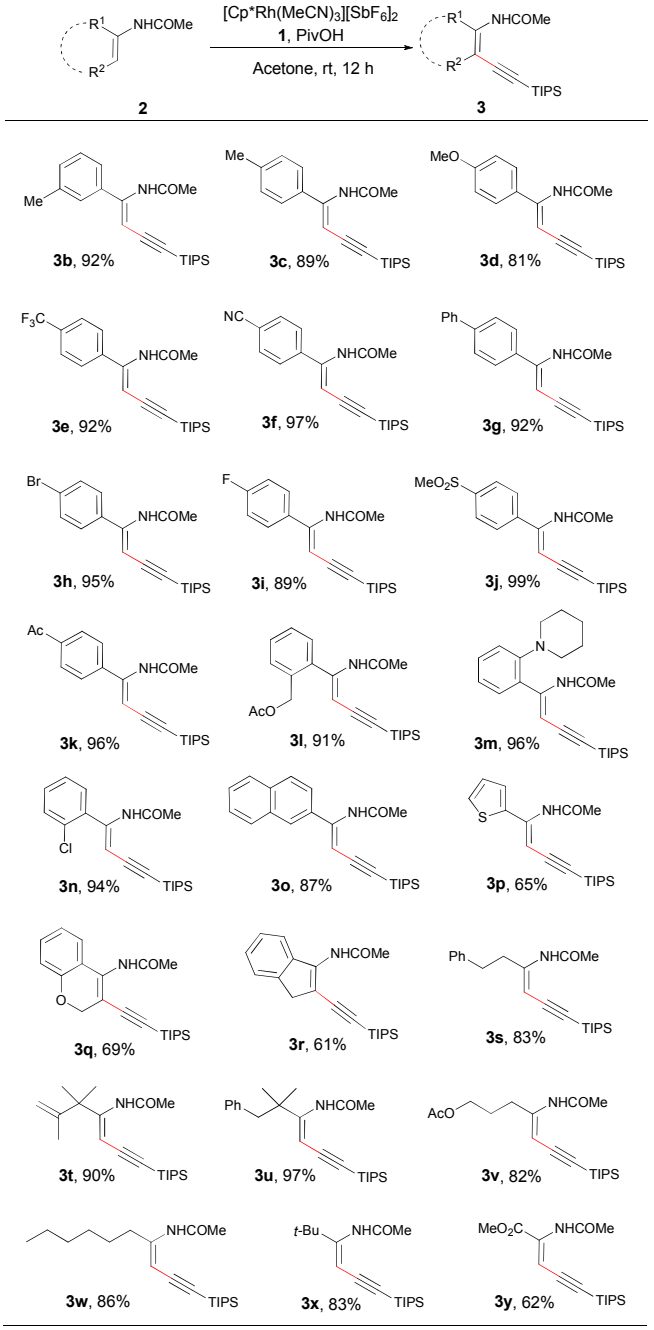
affords the thermodynamically stable *trans*-products, this alkynylation occurs selectively on the *cis*-position with the respect to the amido group.[17] The absolute structure of **3g** was unequivocally confirmed by single-crystal X-ray diffraction,[18] thus indicating the involvement of directing effect of amido group at the C*sp*^{2}-C*sp* bond formation step within the catalytic cycle. It also needs to be pointed out that when halogenated ethynyltriisopropylsilane was utilized as the electrophilic alkynyl donor, instead of alkynyliodonium reagents, trace product was obtained.[19]



Scheme 1 Rh(III)-catalyzed directed C-H alkynylation.

With respect to the aryl-substituted enamides, substrates containing both electron-donating and electron-withdrawing functional groups regardless of substitution position on the phenyl ring were all well tolerated (Table 2, **3b-3n**). Functional groups, such as methoxy (**3d**), trifluoromethyl (**3e**), cyano (**3f**), sulfonyl (**3j**) acetyl (**3k**), and halogen atoms (**3h**, **3i**, **3n**), which are of synthetic importance or amenable to further useful transformation, proved to be well compatible with this reaction condition. Moreover, *ortho*-substituents did not show any deleterious effect on this C-H alkynylation reaction as in the case of **2l**, **2m** and **2n**. Among these, the elegant performace of **2m** was much more intriguing, considering the ability for coordination as well as the sterics of *ortho*-piperidinyl substituent. In addition, the heterocycle based enamide such as **2p** also participated in this alkynylation reaction, albeit generating the product **3p** in relatively lower yield. Furthermore, the enamides derived from chromanone and indanone were also effective, affording the desired products in good yields (Table 2, **3q**, **3r**). It is worth mentioning that this reaction is not limited to aryl substituted enamides, aliphatic counterparts, even those functionalized ones, were nicely accommodated (Table 2, **3s-3x**). When **2t**, which contains an extra olefin pendent, was employed, the C-H alkynylation chemoselectively and stereoselectively occurred on the *cis*-position of enamide moiety to afford **3t** in 90% yield, with the olefin pendent being intact throughout the reaction. Furthermore, the sterical bulk of alkyl substituents did not exhibit any impediment on the reaction efficiency as displayed in the case of **2t**, **2u** and **2x**. Notably, pyruvate derived enamide **2y** was also proved to be applicable in this reaction to produce the product **3y** in moderate yield. The fact that *N*-vinylacetamide and *N*-benzyl-*N*-(1-phenylvinyl)acetamide did not provide any desired product indicate the critical role of α-substituent and the N-H moiety in this reaction.[20]

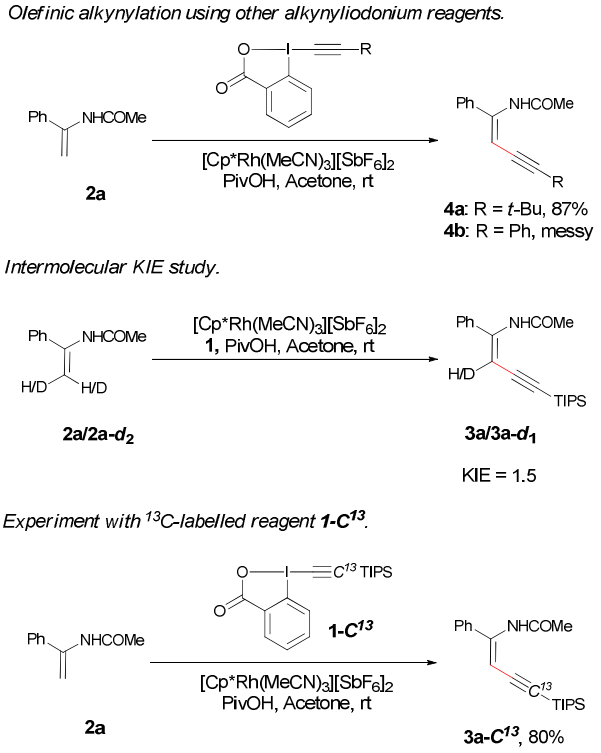
Table 2 Reaction scope of enamide derivatives.[a, b]



[a] Unless otherwise noted, the reactions were carried out using enamide **2** (0.1 mmol), hypervalent aklynyliodonium reagent **1** (0.11 mmol), PivOH (0.01 mmol), [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (0.002 mmol) in acetone (0.5 mL) and stirred at room temperature for 12 h. [b] Isolated yields.

With the aim of examining reaction generality with respect to akynyl reagents, other analogues were also tried. While *tert*-

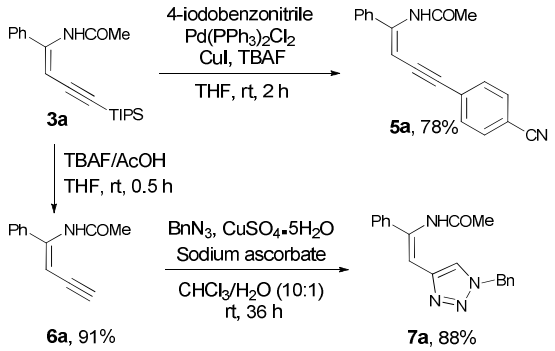
butyl based alkynyliodonium reagent reacted well with **2a** to afford the desired product **4a** in 87% yield, the reaction with phenyl derived alkynyliodonium reagent turned out to be rather messy. The intermolecular KIE experiment was also conducted between **2a** and **2a-d_2** with alkynyliodonium reagent **1**, which produced a KIE value of 1.5(refer to supporting information). Furthermore, when ^{13}C labelled alkynyliodonium reagent **1-C^{13}** was subjected to the standard reaction condition with **2a**, the desired product was obtained in 80% yield, indicating that no silyl-migration occurred during the catalytic cycle (Scheme 2).



Scheme 2 Alkynylation using other alkynyl reagents and isotope experiment.

In order to showcase the applicability of alkynylation products, further transformations by taking advantage of the alkynyl group were explored (Scheme 3). Desilylation of **3a** worked smoothly with TBAF/HOAc system, which generated the terminal alkyne **6a** in 91% yield. In addition, desilylation/ Sonogashira coupling between **3a** and 4-iodobenzonitrile also proceeded nicely to afford **5a** in 78% yield. In addition, triazole **7a** could be generated in 88% yield by the copper-catalyzed cycloaddition between terminal alkyne **6a** and benzyl azide.

In conclusion, we have developed a novel protocol for the synthesis of functionalized 1,3-enyne motifs using Rh(III)-catalyzed C-H olefinic alkynylation of enamides. By taking advantage of *ortho*-directing effect of amide group, this reaction underwent stereospecific activation of olefinic C-H bonds, thus providing a straightforward and efficient manner for the construction of *cis*-enynamide frameworks. Because of the very mild reaction condition, a large variety of synthetically useful functional groups were nicely tolerated. Furthermore, the enynamide products thus obtained through C-H alkynylation could be easily transformed into structurally relevant motifs by virtue of Sonogashira coupling or cycloaddition reactions.



Scheme 3 Synthetic transformations of enynamide **3a**.

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16 PivOH may help to abstract the H-atom during the C-H activation.

17 For Heck-type alkynylation of enamide (see supporting information).

18 CCDC 980753 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc. com. ac. uk/data_request/cif.

19 Both bromo- and iodo-ethynyltriisopropylsilane were proved to be ineffective as the alkynyl donor in this reaction.

20 Both *N*-vinylacetamide and *N*-benzyl-*N*-(1-phenylvinyl)acetamide did not provide any desired product in this reaction.