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# Rhodium(III)-Catalyzed Olefinic C−H Alkynylation of Acrylamides Using Tosyl-Imide as Directing Group

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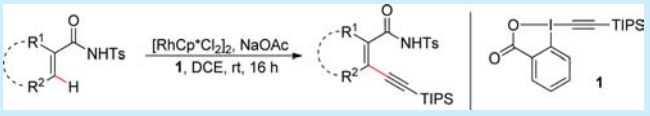
Supporting Information

**ABSTRACT:** The Rh(III)-catalyzed C−H alkynylation of acrylamide derivative is realized using a hypervalent alkynyl iodine reagent. The use of a weakly coordinating directing group proved to be of critical importance. This reaction displays broad functional group tolerance and high efficiency, which opens a new synthetic pathway to access functionalized 1,3-enyne skeletons.

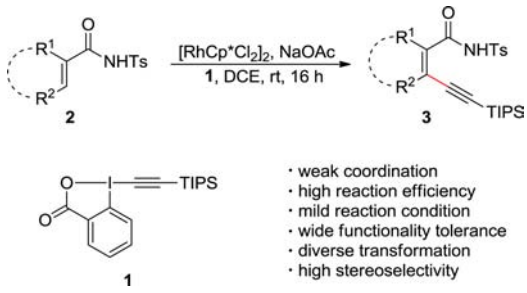



Directing-group assisted transition-metal-catalyzed C−H activation reactions, which allow site-selective manipulation of otherwise inert C−H bonds beyond their intrinsic electronic properties, offer an alternative to the traditional method for the construction of C−C and C−X bonds.[1] From the viewpoint of atom-economy and sustainability, transition-metal-catalyzed C−H activation reactions have been attracting increasing attention from the synthetic community. In this context, the past decade has witnessed an explosive advancement in this arena with a wide variety of chelating auxiliaries devised as effective directing groups. Specifically, hypervalent Rh(III) salt has recently been recognized as catalyst of choice for a large variety of C−H bond functionalizations.[2] Elegant works from the groups of Miura, Fagnou, Glorius, Rovis, Ellman, Ma, Shi, Li, and Chang among others not only substantially expanded this area but also demonstrated the high potential of Rh(III) catalyst in the process of C−H bond activation, thus drawing much attention from organic chemists.[3]

1,3-Enynes constitute a class of prevalent subunits widely found in naturally occurring compounds and pharmaceuticals and represent a key structural motif in synthetic chemistry because of their dense functionality, amenable to a diverse range of synthetic transformations.[4] Although considerable efforts have been made, the reported methods suffer from either a necessity of substrate preactivation or reliance on harsh reaction conditions; therefore the development of a mild and step-economical pathway for the synthesis of a 1,3-enyne framework is still required.[5]

Quite recently, Loh, Glorius and Li have developed rhodium-catalyzed alkynylation of arenes as well as alkenes through C−H activation, independently.[6] While much progress has been achieved, the realization of alkynylation of alkenes, which operate under milder reaction condition and accommodate a broad range of functionalities, are still highly desirable. With our ongoing interest in alkene functionalization,[7] we would like to report our recent achievement in the rhodium-catalyzed C−H alkynylation of electron-deficient alkenes, wherein the employment of weakly coordinating directing group proved to be critical for the accomplishment of this transformation (Scheme 1).

**Scheme 1. Rh-Catalyzed C−H Alkynylation of Electron-Deficient Alkenes**




At the very beginning, we commenced our study by exploring effective directing groups in the olefinic alkynylation of 2-phenyl acrylamide derivatives with the hypervalent alkynyl iodine reagent **1**.[8] Using $[Cp^*RhCl_2]_2$, NaOAc, and DCE as catalyst, additive, and reaction solvent, a series of different *N*-substituents was examined, and the results are shown in Table 1. It was found that the nature of amide directing group is critical for the initiation of alkynylation reaction. When *N*-alkyl substituted or aniline derived substrates were employed, no reaction occurred (Table 1, entries 1−4). It needs to be pointed out that 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline based amide auxiliary, which is frequently employed by Yu as an effective weakly coordinating directing group in palladium catalysis, proved to be ineffective in this reaction (Table 1, entry 3).[9] Pleasingly, by changing alkyl- or aryl-substituted amide to *O*-pivaloyl hydroxylamide as directing group, the C−H alkynylation product could be obtained in 35% yield (Table 1, entry 5). Further

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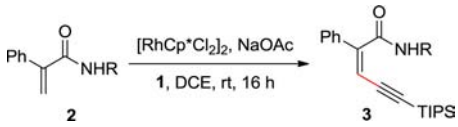
**Table 1. Optimization of Directing Group**[a]



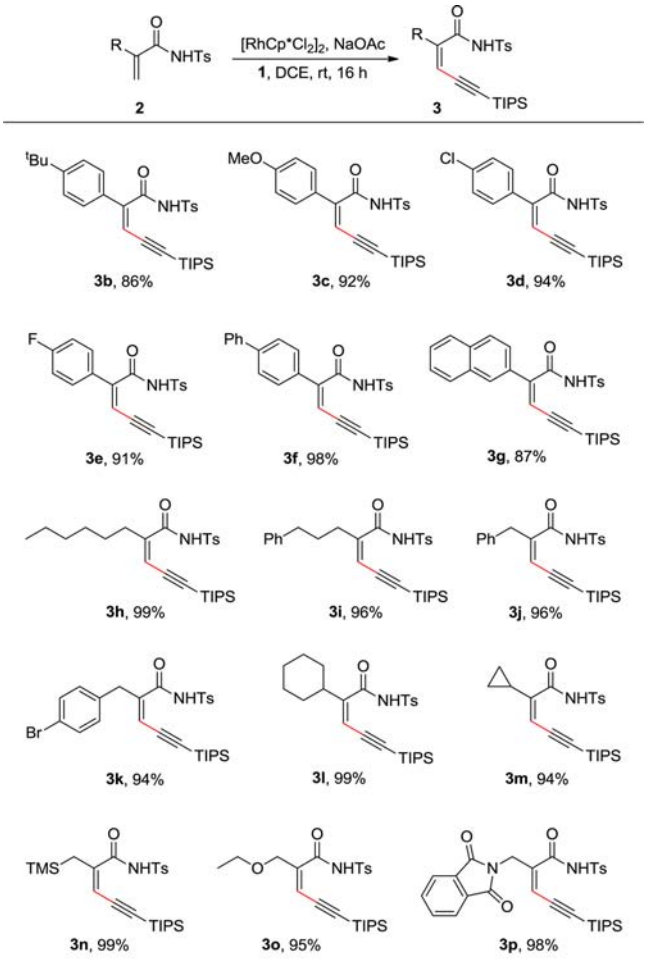

| entry | R | yield[b] (%) |
|---|---|---|
| 1 | Bn | NR |
| 2 | Ph | NR |
| 3 | $C_6F_4CF_3$ | NR |
| 4 | Me | NR |
| 5 | OPiv | 35 |
| 6 | OMe | 68 |
| 7 | Ts | 96 |
| 8[c] | Ts | 67 |
| 9[d] | Ts | NR |

[a]Unless otherwise noted, the reactions were carried out at room temperature using **2a** (0.1 mmol), hypervalent alkynyl iodine reagent **1** (0.11 mmol), NaOAc (0.1 mmol), and $[Cp^*RhCl_2]_2$ (0.002 mmol) in DCE (0.5 mL) for 16 h. [b]Isolated yields. [c]No NaOAc was added. [d]No rhodium catalyst was added.

improvement was attained with *O*-methyl hydroxylamide as directing group, which afforded the desired enyne product in 68% yield (Table 1, entry 6).[10] Much to our surprise, the reaction efficiency was extremely enhanced with the desired product being formed in 96% yield when Ts-imide was adopted as the directing group (**2a**, Table 1, entry 7). It is evident that the directing group with certain p$K_a$ value had a critical impact on this reaction process. The remarkable effect of Ts-imide as directing group was assumed to be due to its weakly coordinating ability, which rendered the formation of highly active ligated catalyst because of its weak $\sigma$-donation and the generation of thermodynamically labile metalacycle, making it more susceptible to the ensuing reaction steps. It is worth mentioning that the reaction still proceeded to a decent extent even in the absence of NaOAc, which is in sharp contrast with our previous finding in the alkynylation of arenes, thus further illustrating the competence of Ts-imide as directing group in this reaction (Table 1, entry 8).[6,10] As expected, the rhodium catalyst was found to be indispensable and the starting material **2a** remained intact with its absence (Table 1, entry 9). It needs to be emphasized that when **2a** was reacted with reagent **1-C**[13], no silyl-migration product was observed.[11]

With Ts-imide as the optimal directing group, the reaction generality with respect to electron-deficient alkene was thus investigated and presented in Scheme 2. The $\alpha$-aryl amides were first examined, showing that the electronic property of the aryl substituent exerted negligible effect on the reaction, with both electron rich and deficient ones being converted into the desired products in high to excellent yield. What needs to be pointed out is that halogen substituents, such as Cl and F were well tolerated, furnishing the opportunity for further synthetic manipulation. Furthermore, biphenyl and naphthalyl derived substrates were also amenable to this reaction condition, thus generating the products **3f** and **3g** in 98% and 87% yields, respectively. It is noteworthy that the present reaction was not limited to $\alpha$-aryl amide derivatives, $\alpha$-alkyl amides with a diverse range of functional groups were all nicely accommodated, highlighting the synthetic potential of this protocol. Specifically, linear alkyl based substrates such as **2h** and **2i** reacted smoothly with alkynyl reagent **1** to afford products **3h** and **3i** in 99% and 96% yields. In the case of acrylamides **2j** and **2k**, the reactions occurred

**Scheme 2. Substrate Scope of Acrylamides**[a,b]




[a]Unless otherwise noted, the reactions were carried out at room temperature using **2** (0.1 mmol), hypervalent alkynyl iodine reagent **1** (0.11 mmol), NaOAc (0.1 mmol), and $[Cp^*RhCl_2]_2$ (0.002 mmol) in DCE (0.5 mL) for 16 h. [b]Isolated yields.

selectively to produce 1,3-enyne products in excellent yield without the formation of alkene shift products, despite the presence of $\pi$-conjugation of aryl units.

In addition, carbocycle containing starting materials also engaged well in this transformation without any compromise in yield, among which the result when using $\alpha$-cyclopropylacrylamide **2m** is more meaningful as it precludes the possibility of the involvement of radical pathway in the reaction process. When $\alpha$-trimethylsilyl-methyl acrylamide **2n** was subjected to the standard reaction condition, the product **3n** was obtained in quantitative yield, with the silyl group remaining intact throughout the reaction, which indicated the C−H activation for the formation of metallacycle intermediate did not follow an electrophilic-metalation/deprotonation pathway. The tolerance of alcohol and amine derived functionalities, such as those of in **2o** and **2p**, further expanded the reaction scope and indicated the synthetic potential of this reaction in the course of complicated molecule synthesis. Last but not least, the present reaction was found to be highly stereoselective, with the alkynyl group incorporated into the cis-position with respect to the Ts-imide substituent. The structure of **3c** was unambiguously confirmed through a single-crystal X-ray diffraction analysis.[12]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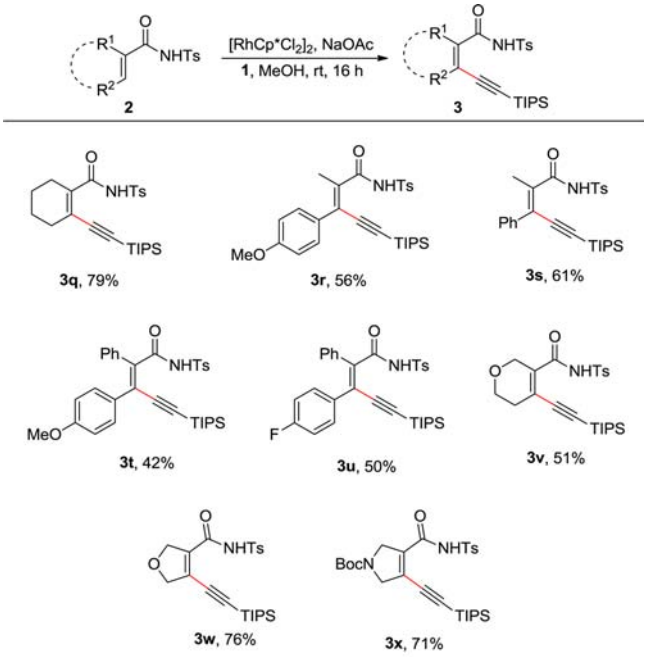
In order to further extend the reaction scope, α,β-disubstituted acrylamide derivatives were subsequently examined (Scheme 3).

**Scheme 3. Substrate Scope of Acrylamide Derivatives**[a,b]

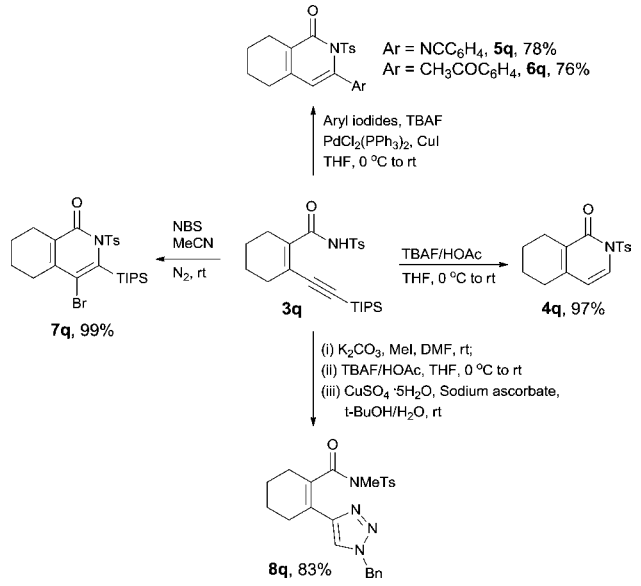



[a]Unless otherwise noted, the reactions were carried out at room temperature using **2** (0.1 mmol), hypervalent alkynyl iodine reagent **1** (0.11 mmol), NaOAc (0.1 mmol), and $[Cp^*RhCl_2]_2$ (0.002 mmol) in MeOH (0.5 mL) for 16 h. [b]Isolated yields.

After several attempts, it was revealed that using methanol as reaction solvent in place of DCE was proved to be beneficial. With such slight alteration, the introduction of alkynyl group to a diverse range of α,β-disubstituted acrylamides, either cyclic or acylic ones, could be successfully accomplished, thus generating the alkynylation products in moderate to good yields. To be more specific, 1-cyclohexenyl derived substrate **2q** reacted smoothly to furnish product **3q** in 79% yield. Furthermore, the reaction of acyclic substrates (**2r**−**2u**) either containing alkyl/aryl or aryl/aryl substituents worked without any difficult to afford related products in the yields ranging from 42% to 61%. It is noteworthy that heterocycle derived acrylamides such as **2v**, **2w**, and **2x**, which possess Lewis basic heteroatoms, also nicely engaged in this reaction to furnish desired products in good yield, thus further demonstrating the synthetic potential of this reaction.

To showcase the synthetic utility of the structural motif obtained with this method, a set of synthetic derivatizations were conducted with **3q** as a representation (Scheme 4); the TIPS group could be readily removed with TBAF to afford the terminal alkyne, which, however, was unstable and simultaneously underwent intramolecular cyclization to generate the pyridinone **4q** in 97% yield. In addition, the palladium-catalyzed desilylative Sonogashira reaction/intramolecular cyclization could be successfully applied without any compromise, thus delivering products **5q** and **6q** in 78% and 76% yields, respectively, when 4-cyanophenyl iodide and 4-acetylphenyl iodide were employed. When **3q** was reacted with NBS in acetonitrile, bromonium-induced electrophilic cyclization occurred nicely, giving rise to the product **7q** in 99% yield. Furthermore, with a sequence of

**Scheme 4. Synthetic Transformation of 3q**




methylation, desilylation, and copper-catalyzed azide alkyne cycloaddition, triazole **8q** could be isolated in 83% yield.

In conclusion, the rhodium(III)-catalyzed olefinic C−H alkynylation of electron-deficient alkenes was developed. The weakly coordinating directing group Ts-imide proved to be critical and responsible for the occurrence of C−H alkynylation in a highly efficient and stereospecific manner. By taking advantage of C−H activation and high functional group tolerance, mild reaction conditions, and operational simplicity, this protocol represents a straightforward and expedient method to access the functionalized 1,3-enyne structural motif. Further transformations into a series of pyridinone and triazole were also attempted to showcase the synthetic potential of alkynylation products obtained from this reaction.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, and $^1H$ and $^{13}C$ NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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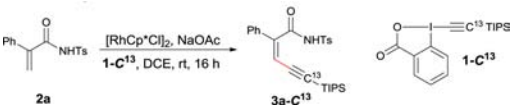
(10) Without the addition of NaOAc, no reaction occurred with acryl-NHOMe as substrate, while 65% of **3a** was obtained in the case of **2a**.

(11) The alkynylation reaction between **2a** and **1-C$^{13}$** generated **3a-C$^{13}$** without the migration of silyl substituent (see Supporting Information for details).




(12) CCDC 990346 (**3c**) 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.