ORGANIC LETTERS

2012
Vol. 14, No. 21
5506–5509

Ruthenium- and Sulfonamide-Catalyzed Cyclization between *N*-Sulfonyl Imines and Alkynes

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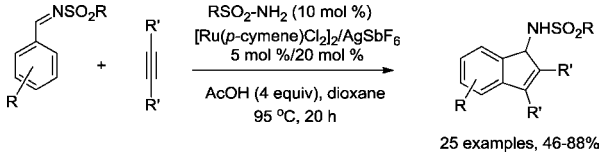
Received September 20, 2012

ABSTRACT



Ruthenium(II)-catalyzed redox-neutral annulative coupling of *N*-sulfonyl imines with alkynes has been achieved for the synthesis of indenamines, where a sulfonamide cocatalyst is necessary.

Transition-metal-catalyzed C−H bond activation has been increasingly explored and has been realized as a widely used strategy in the synthesis of complex structures.[1] The advantage of C−H activation lies in the harnessing of ubiquitous yet often unreactive C−H bonds. Transition-metal-catalyzed cyclization via C−H activation represents an efficient method for the construction of carbocycles and heterocycles.[2,3] This method is powerful because no pre-activation of the C−H bond to traditionally used carbon−halogen and carbon−main group metal bonds is necessary. Carbocyclization via C−H activation and insertion of a π-bond leads to very useful synthetic methods, where mechanistically distinct reactions are successfully combined in a tandem process.

Recently, catalytic insertion of C−H bonds into alkynes (hydroarylation) has been increasingly explored using

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10.1021/ol302594w
Published on Web 10/23/2012

rhodium,[2] ruthenium,[3] iridium,[4] cobalt,[5] palladium,[6] and nickel[7] catalysts. In particular, in 2005 Takai[8] reported pioneering work on the carbocyclization of imines with alkynes, leading to the synthesis of indenamines. By using rhodium and ruthenium catalysts, the groups of Bergman and Ellman,[2b] Shi,[2d,e] Li,[2i] Zhao,[2k] Cramer,[2f] Glorius,[2j] Cheng,[2h] and Jeganmohan[3f] have revealed that cyclometalation can be followed by alkyne insertion to generate a metal alkenyl intermediate that undergoes (intramolecular) nucleophilic addition to a carbonyl or imine group, leading to C−C bond formation or redox-neutral cyclization reactions (Figure 1). In addition, Grignard-type addition of a transition metal−carbon bond into an aldehyde has been achieved via a Rh(III)-catalyzed C−H activation pathway under chelation assistance.[2i,9] Thus in these carbocyclization reactions, the role of the directing group is twofold: it acts as a directing group as well as an electrophile. Despite the success, the substrate scope is still limited, and Rh(III) complexes are mostly used, while less expensive ruthenium complexes have been less explored.[3f] In this context, C−H activation and coupling reactions of readily available arene substrates should provide important protocols for accessing diversely functionalized arenes, which broadens the utility of C−H bond activation, particularly using cost-effective transition metals such as ruthenium.

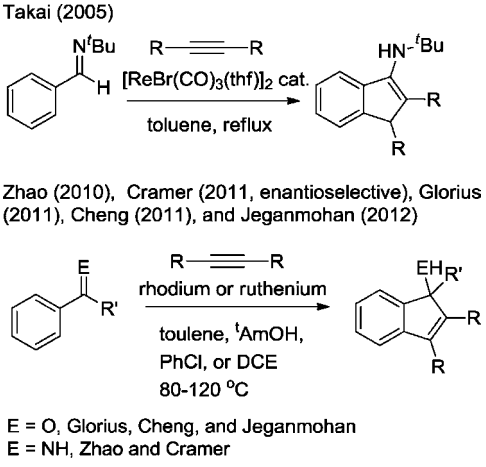
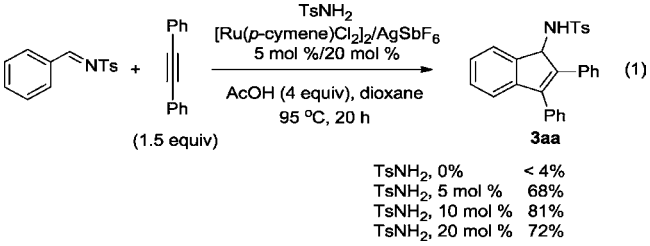


Figure 1. Carbocylization via C−H activation.

We reasoned that *N*-sulfonyl imines of benzaldehyde are bifunctional and can serve this purpose. If C−H activation is achievable, the imine group is sufficiently activated to allow for intramolecular nucleophilic attack by a metal−C(sp^2) bond. However, the cyclometalation of an *N*-sulfonyl imine can be problematic because the electron density on the nitrogen is depleted by a conjugated sulfonyl group. Indeed, no C−H activation of *N*-sulfonyl imines has been previously reported, although *N*-aryl or *N*-OR substituted imines have been well studied for C−H activation.[2m,10]



We initiated our studies with the screening of the reaction conditions for the coupling of PhCH=NTs (**1a**) with diphenylacetylene. No reaction occurred with or without an acetic acid additive when [RhCp*Cl$_2$]$_2$ or [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ was applied as a catalyst. In addition, no reactivity was observed when [Ru(*p*-cymene)Cl$_2$]/AgSbF$_6$ (5 mol %/20 mol %) was used as a catalyst in the presence of AcOH (4 equiv) (dioxane, 120 °C), a set of conditions that has been used in the ruthenium(II)-catalyzed hydroacylation of alkynes.[11] Thus the low reactivity of PhCH=NTs is likely ascribable to the low donor ability of this imine group. We reasoned that addition of a catalytic amount of an amine such as TsNH$_2$ should reversibly yield a gem-diamine intermediate, which may allow for cyclometalation and subsequent reactions. Gratifyingly, when TsNH$_2$ (5 mol %) was introduced into these ruthenium-catalyzed conditions, the expected indenamine **3aa** was isolated in 68% yield (eq 1), and an optimal isolated yield of 81% was achieved when the amount of TsNH$_2$ was increased to 10 mol %. In contrast, [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ and [RhCp*Cl$_2$]$_2$ all failed to catalyze this reaction when the TsNH$_2$ cocatalyst (10%) was provided.

With the optimal conditions in hand, we next examined the scope and generality of this coupling reaction (Scheme 1).

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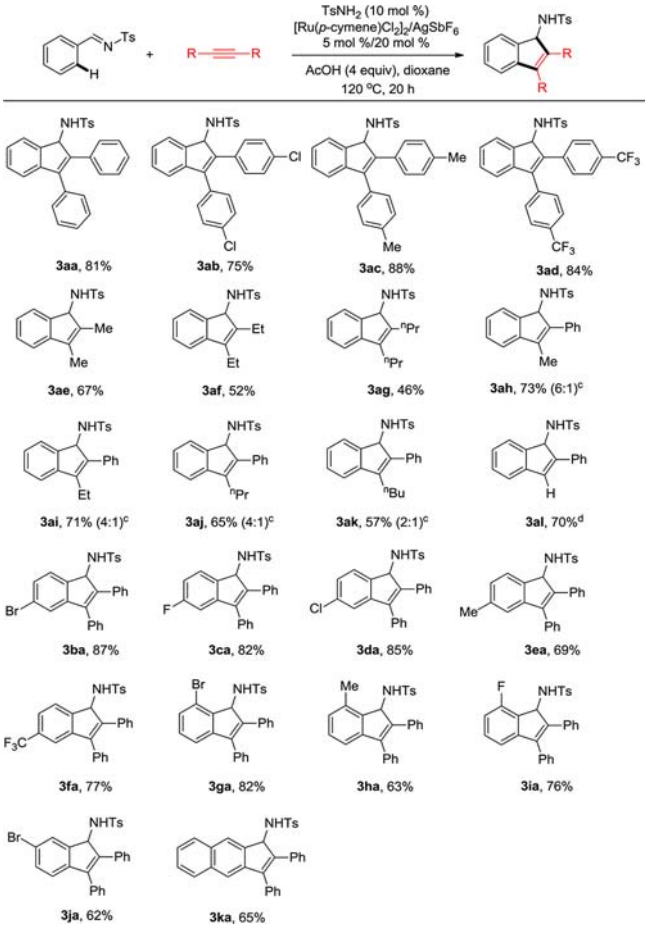
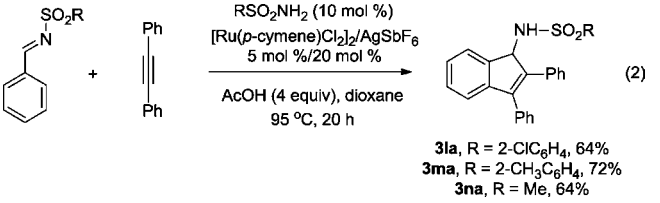
A series of symmetrically substituted diarylalkynes readily coupled with **1a** to give indenamides **3aa**−**3ad** in good isolated yield (75−88%). Aliphatic alkynes are also applicable but generally with lower reactivity (46−76%). When PhC≡CMe was used, a mixture of two inseparable regioisomers (**3ah** and **3ah′**) was obtained in a 6:1 ratio, where the phenyl group is oriented vicinal to the NHTs group in the major product (**3ah**). Moreover, the regioselectivity decreased as the steric bulk of the alkyl group (R) in PhC≡CR increases (**3ai**, **3aj**, and **3ak**), with a small regioselectivity of 2:1 being obtained for PhC≡C^{n}Bu (**3ak**). A silylated alkyne can be applied but with clean desilylation under the reaction conditions. Thus product **3al** was isolated in 70% yield when PhC≡CSiMe$_3$ was coupled with **1a**. Here the PhC≡CSiMe$_3$ acts as a surrogate for the terminal alkyne that is inapplicable in this reaction.

Scheme 1. Coupling of *N*-Sulfonyl Imines with Alkynes[a,b]

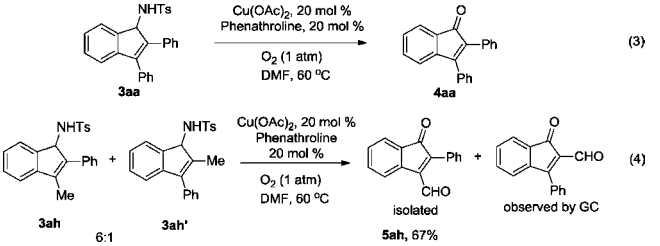


[a] Reaction conditions: imine (0.4 mmol), alkyne (0.6 mmol), [Ru(*p*-cymene)Cl$_2$]$_2$ (0.02 mmol), AgSbF$_6$ (0.08 mmol), AcOH (1.6 mmol), 1,4-dioxane (4 mL), 120 °C, 20 h. [b] Isolated yield after column chromatography. [c] Only the structure of the major isomeric product was shown. [d] PhC≡CSiMe$_3$ was used.

The scope of the imine substrate was defined next using diphenylacetylene as a coupling partner. *N*-Ts imines bearing halogen (**3ba**−**3da**), methyl (**3ea**), and CF$_3$(**3fa**) groups at the *para* position of the benzene ring all underwent smooth coupling without significant variation of the isolated yield (69−87%). In contrast, *N*-Ts imine with a *para* OMe group gave rather low conversion and no analytically pure product can be isolated, indicating that a *para* electron-donating group lowered the reactivity. Substituents at the *ortho* position are also tolerated, and the steric effect caused by *ortho* substitution has no detrimental effect as in the isolation of **3ga**−**3ia** in good yield (63−82%). When a *meta* substituent was introduced, the C−H functionalization occurred selectively at the less hindered site (**3ja** and **3ka**). In addition to the *N*-Ts substituent, other *N*-sulfonyl groups such as arenesulfonyl and methanesulfonyl are also effective (eq 2).



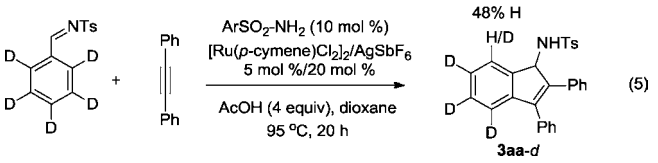
Derivatization of the indenamine product was carried out next. When catalyzed by a Cu(OAc)$_2$−phenathroline system (20 mol % and20 mol %), O$_2$ (1 atm) oxidation of **3aa** afforded indenone **4aa** in 82% yield (eq 3). In addition, a one-pot synthesis of **4aa** can be achieved. After the annulative coupling of **1a** with diphenylacetylene was completed, the solvent was removed and was replaced by DMF. Addition of Cu(OAc)$_2$•H$_2$O and stirring at 100 °C afforded **4aa** in comparably high yield (85%). Two-step oxidation of analogous indenamines to indenones has been recently reported.[12] Furthermore, a single step synthesis of this type of indenone product has been recently reported by Shi by employing a Rh(III)-catalyzed C−H activation strategy.[2d] Furthermore, when a mixture of **3ah** and **3ah′** was subjected to the copper-catalyzed aerobic oxidation conditions, aldehyde-functionalized indenone **5ah** was isolated as a major product in 67% yield (eq 4). Here the allylic methyl was oxidized to an aldehyde group.



To probe the mechanism of this reaction, the KIE was measured from the competition of **1a** and **1a**-d_5 with diphenylacetylene, and a value of k_H/k_D = 1.6 was obtained. While this value is indeterminate and no solid conclusion on C−H activation can be drawn, further information in this regard was obtained when a labeling

(12) Wang, S.-Y.; Zhu, Y.-X.; Wang, Y.-G.; Lu, P. *Org. Lett.* **2009**, *11*, 2615.

experiment was performed using **1a**-d_5 and diphenylacetylene (eq 5). In the isolated product, significant H/D exchange (48% H) at the *ortho*′ position of the phenyl group was observed on the basis of ^{1}H NMR analysis.[13] This result suggests that the *ortho* C−H activation is reversible, and importantly this reversible process should be faster than subsequent steps in the catalytic cycle. Therefore, the C−H cleavage is not involved in the rate-determining step.



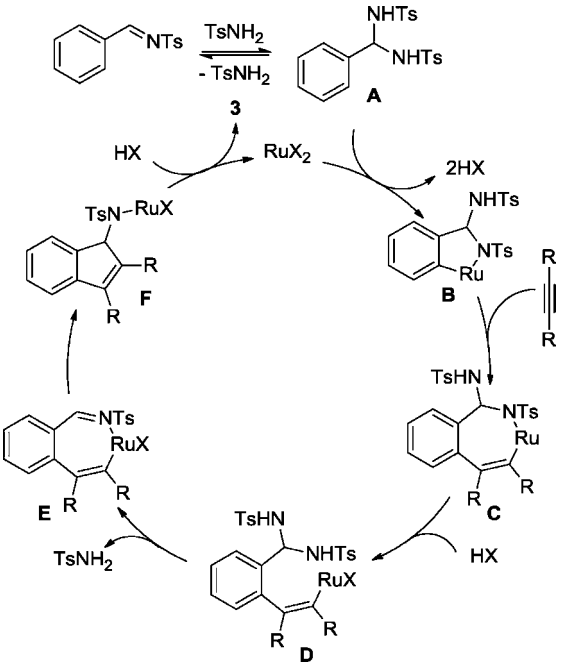
A proposed catalytic cycle is given in Scheme 2. Nucleophilic addition of $TsNH_2$ to the PhCH=NTs gives a diamine **A** which is coordinatively activated. Deprotonation and cyclometalation afford an active ruthenium(II) intermediate **B**. Alkyne insertion into the Ru−C bond generates a seven-membered metalacycle **C**, which is proposed to undergo reversible protonolysis of the Ru−N bond to give **D**. Elimination of a $TsNH_2$ gives an imine-bound metalacycle (**E**) that should undergo Grignard-like migratory insertion of the Ru-alkenyl bond to yield an amide intermediate **F**. The final product **3** was released upon protonolysis of the Ru−N bond. The protonolysis can be facilitated by the acetic acid additive in this reaction.[9,11] In addition, the acetate group can also act as a bridging base to facilitate the C−H activation via a concerted metalation−deprotonation (CMD) mechanism.[14] This working hypothesis is also consistent with the poor reactivity of (4-OMeC$_6$H$_4$)CH=NTs. With the introduction of a donating OMe group into the *para* position, both the nucleophilic addition of $TsNH_2$ and the subsequent migratory insertion of the Ru−C bond into the imine are kinetically disfavored. In line with this observation, the *N*-tosylimine derivative of 2-furaldehyde failed to undergo the same reaction, likely due to electronic effects.

In summary, we have developed a ruthenium(II)-catalyzed annulative coupling of *N*-sulfonyl imines of benzaldehydes with alkynes, leading to indenamines. In this coupling

(13) Control experiments revealed that the incorporation of hydrogen cannot be ascribable to postreaction H/D exchange of this product because no H/D exchange occurred when **3aa** and acetic acid-d_4 (10 equiv) were allowed to react under the same conditions.

(14) For a recent review, see: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

Scheme 2. Proposed Catalytic Cycle



system, the primary sulfonamide plays an important role in activating the imine substrate toward cyclometalation. A broad scope of the imine and the alkyne substrates has been demonstrated, and the indenamine product can be further oxidized to indenones under simple conditions. The operational simplicity of the coupling reaction, the prevalence of sulfonamide functionality in pharmaceuticals, and the derivatization of the direct products likely make this synthetic method useful in synthetic chemistry and in mechanistic studies.

Acknowledgment. We thank the Dalian Institute of Chemical Physics, Chinese Academy of Sciences for financial support.

Supporting Information Available. Synthetic procedure, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.