C–H Activation

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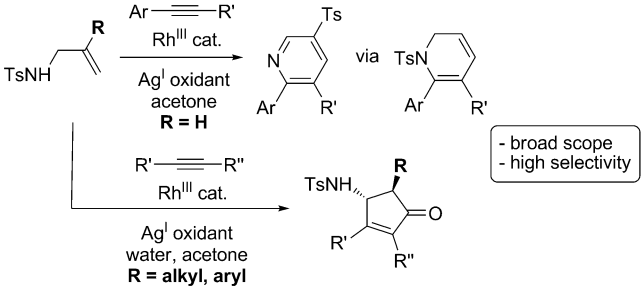
Diverse Reactivity in a Rhodium(III)-Catalyzed Oxidative Coupling of *N*-Allyl Arenesulfonamides with Alkynes**

*Dongqi Wang, Fen Wang, Guoyong Song, and Xingwei Li**

Metal-catalyzed C–H activation has been explored widely for the construction of C–C, C–N, and C–O bonds.[1,2] This process is advantageous in that C–H bonds are ubiquitous, and the direct functionalization of C–H bonds is a step-economical approach to bond formation. Although, arguably, palladium compounds are most well-known for the activation of C–H bonds for coupling reactions,[1b,d,j,l] stable rhodium(III) complexes have been used increasingly in the past five years and stand out as highly active catalysts for C–H activation with high selectivity, broad substrate scope, and high functional-group compatibility.[2] Furthermore, rhodium(III) can complement other metals in terms of selectivity and reactivity.[3]

Chelation assistance is a common strategy in rhodium(III)-catalyzed C–H activation.[2] Various nitrogen[4] and oxygen directing groups have been successfully employed[2] for the construction of a variety of heterocycles, such as isocoumarin,[5] indole or pyrrole,[6] pyridine,[7] isoquinoline,[8] lactam,[9] and 2-pyridone derivatives.[10] Although readily available, sulfonamides have found limited application as directing groups for C–H activation.[11] If sulfonamides could be used effectively as directing groups, it would significantly expand the synthetic utility of Rh^{III} catalysis for the construction of heterocyclic cores. In continuation of our interest in rhodium(III)-catalyzed C–H activation, we now report the efficient construction of pyridine and cyclopentenone rings in a rhodium(III)-catalyzed oxidative coupling of *N*-allyl sulfonamides with alkynes (Scheme 1). To the best of our knowledge, cyclopentenone scaffolds have not been constructed previously by C–H activation.

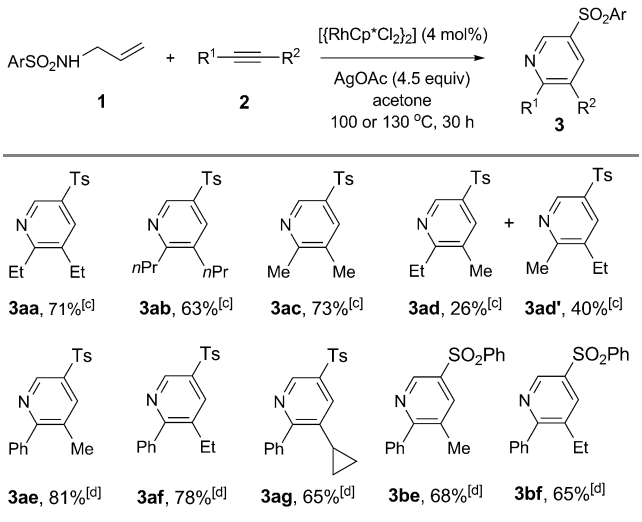
The activation of olefinic C–H bonds under Rh^{III} catalysis[7,10,12] has been studied less than the activation of aryl C–H bonds. We embarked on our studies with the coupling of *N*-allyl *p*-tolylsulfonamide (**1a**) with 3-hexyne (**2a**). When $[\{RhCp^*Cl_2\}_2]$ (4 mol%; Cp* = pentamethylcyclopentadienyl) was used as a catalyst, both Ag_2CO_3 and $Cu(OAc)_2$ failed to effect this coupling reaction with high conversion and high selectivity. In contrast, AgOAc (4.5 equiv) proved to be an efficient oxidant. When the reaction was carried out in the presence of AgOAc (4.5 equiv) and the catalyst in acetone at 100 °C, product **3aa** was isolated in 71% yield (Table 1). The yield of **3aa** was much lower (32%) when only 2.1 equivalents of AgOAc were used, which suggests that a twofold oxidation process occurs. Indeed, product **3aa** was characterized as a 3-sulfonylpyridine on the basis of NMR spectroscopic analysis (see the Supporting Information).



Scheme 1. Diverse reactivity in the oxidative coupling of *N*-allyl sulfonamides with alkynes. Ts = *p*-toluenesulfonyl.

Under the optimal coupling conditions, a series of dialkyl-substituted alkynes readily underwent coupling with *N*-allyl

Table 1: Synthesis of 3-sulfonylated pyridines.[a,b]



[a] Reaction conditions: sulfonamide (0.3 mmol), alkyne (0.36 mmol), $[\{RhCp^*Cl_2\}_2]$ (4 mol%), AgOAc (1.35 mmol), acetone (3 mL), 30 h. [b] The yield of the isolated product is given. [c] The reaction was carried out at 100 °C. [d] The reaction was carried out at 130 °C.

[*] D. Wang, F. Wang, Dr. G. Song, Prof. X. Li
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
Dalian 116023 (China)
E-mail: xwli@dicp.ac.cn
D. Wang
State Key Laboratory of Pharmaceutical Biotechnology
School of Life Sciences, Nanjing University
Nanjing 210093 (China)

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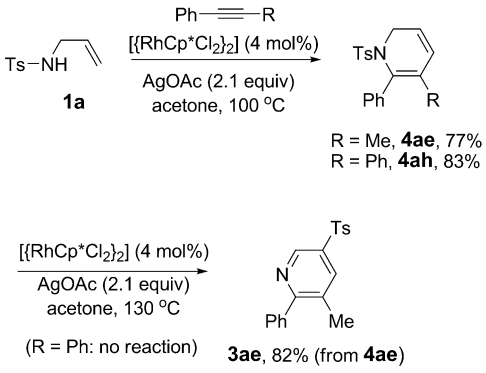
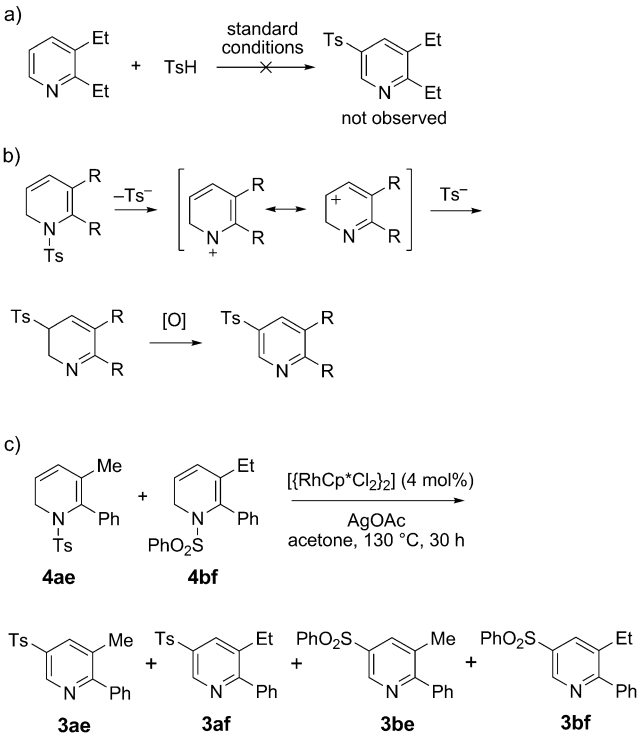
sulfonamides. The resulting substituted pyridines were isolated in 63–73% yield. When the unsymmetrical alkyne MeC≡CEt was used, two separable regioisomers, **3ad** and **3ad′**, were obtained. The regioisomers were characterized by NOESY spectroscopy, which showed a slight preference of the bulkier Et group to be distal to the nitrogen atom (as in **3ad′**). Unsymmetrical alkynes bearing an alkyl and an aryl group are also suitable substrates, but only at an elevated temperature (130 °C). Thus, products **3ae**–**3bf** were isolated in good yield as a single regioisomers. NOESY analysis of these products revealed that the phenyl group of the alkyne unit is oriented closed to the pyridine nitrogen atom.

To establish which intermediates are formed in this twofold oxidation process, we carried out the coupling of **1a** and PhC≡CMe (**2e**) at a lower temperature in the presence of 2.1 equivalents of AgOAc (Scheme 2). The 1,2-dihydropyridine **4ae**, a product at a low oxidation level, was isolated in 77% yield and fully characterized. The formation of **4ae** corresponds to oxidative coupling through C–H and N–H bond cleavage and C–C and C–N bond formation.[2,4] The use of diphenylacetylene as the alkyne led to **4ah** in 83% yield. When an isolated sample of **4ae** was stirred at 130 °C in the presence of AgOAc and the Rh catalyst, pyridine **3ae** was obtained in 82% yield (Scheme 2). This result indicates that dihydropyridine **4ae** is an intermediate in the overall reaction of **1a** with alkyne **2e** to form pyridine **3ae**. Furthermore, in the absence of the catalyst, **3ae** was formed from **4ae** in a slightly lower yield. In contrast, no reaction occurred when dihydropyridine **4ah** was subjected to the above conditions, which suggests that the second oxidation step is kinetically favored by an electron-donating alkyl group in the alkyne unit. Thus, the reactivity order MeC≡CMe > PhC≡CMe > PhC≡CPh was established for the one-pot synthesis of 3-sulfonylated pyridines.



Scheme 2. Intermediacy of a 1,2-dihydropyridine.

We carried out several experiments to probe the mechanism of oxidation of the 1,2-dihydropyridine. When 2,3-diethylpyridine was treated with *p*-tolylsulfinic acid (TsH) under the standard conditions, none of the desired pyridine but only decomposition was detected (Scheme 3a). This result ruled out a pathway of TsH elimination[13] of the dihydropyridine, followed by oxidative C–S bond formation. A likely mechanism is proposed in Scheme 3b: Dissociation

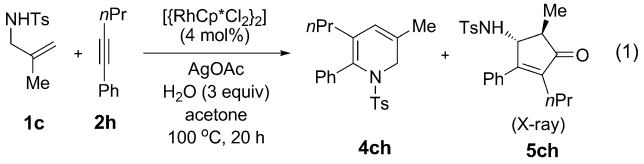


Scheme 3. Mechanism of the formation of 3-sulfonated pyridines.

of Ts^- generates a carbocation, and an S_N1-type substitution affords an isomeric 2,3-dihydropyridine intermediate. Subsequent oxidative aromatization furnishes the final product of a formal oxidative 1,3-shift of the sulfonyl group.[14] We carried out cross-over experiments to probe the intermolecularity of the sulfonyl 1,3-shift (Scheme 3c).[15,16] When an equimolar mixture of **4ae** and **4bf** was heated at 130 °C under the catalytic conditions, the four expected products **3ae**, **3af**, **3be**, and **3bf** were detected by GC in a 1.1:1.4:1:1.1 ratio, which is consistent with our proposed mechanism. An intermolecular 1,3-shift of Ts^- in a pyrrole synthesis was also reported recently.[16]

To better define the scope of the C–H activation with respect to the allyl moiety, we treated *N*-methallyl *p*-tolylsulfonamide (**1c**) with PhC≡C*n*Pr (**2h**) under the conditions for twofold oxidation [Eq. (1)]. As the 1,3-migration of the sulfonyl group would no longer be possible owing to the introduction of a methyl (blocking) group into the olefin unit, the formation of a 1,2-dihydropyridine product was expected. Surprisingly, ^{13}C NMR and IR spectroscopic analysis of the major product, **5ch**, isolated from this reaction pointed to a ketone functionality, although a small amount (< 5%) of 1,2-dihydropyridine **4ch** was also generated [Eq. (1)]. In particular, ^{13}C NMR spectroscopy revealed a carbonyl group ($\delta = 207.6$ ppm, $CDCl_3$). No regioisomers of **5ch** were observed. The identity of cyclopentenone **5ch** was unambiguously confirmed by X-ray crystallography.[17] The methyl and NHTs groups are in a *trans* arrangement. In this reaction, the ketone oxygen atom most likely originates from adventitious water. Indeed, when water (3 equiv) was added to the reaction mixture, **5ch** was isolated in reproducibly good

yield. In sharp contrast, **4ch** was the major product isolated (65% yield) when 2.1 equivalents of AgOAc were used [Eq. (1)]. Thus, the reaction selectivity is controlled by the amount of AgOAc used.

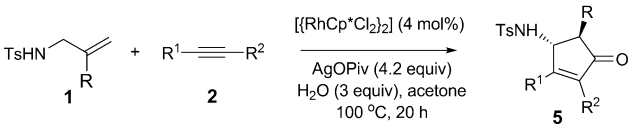


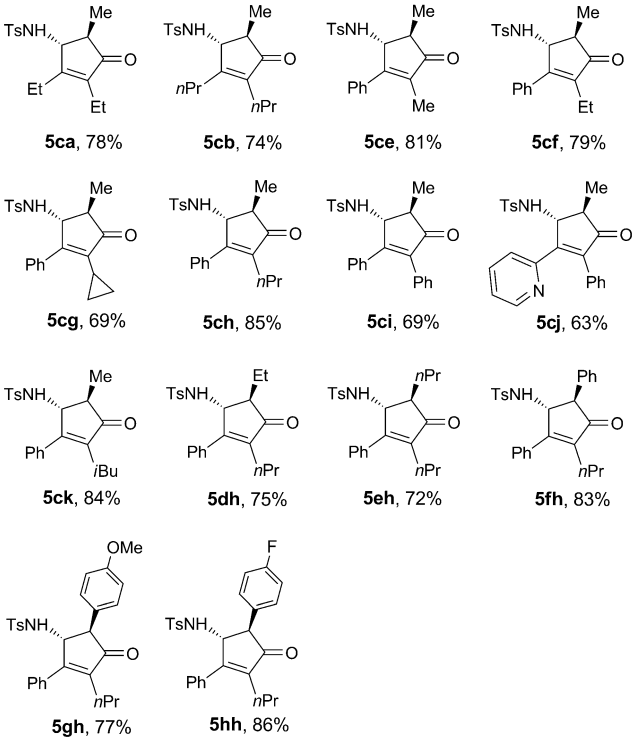
	4ch	5ch
2.1 equivalents of AgOAc	65%	<5%
4.5 equivalents of AgOAc	<5%	66%

Despite the successful synthesis of **5ch**, we failed to obtain the corresponding cyclopenteneone product for PhC≡CPh or PhC≡CMe. Instead, only the dihydropyridine product formed. Gratifyingly, when AgOAc was replaced with AgOPiv (4.2 equiv; Piv = pivalate), the desired cyclopentenone product was isolated in consistently high yield and with high selectivity. Under these optimal conditions, different diaryl-, dialkyl-, and mixed alkyl- and aryl-substituted alkynes reacted with **1c** with high efficiency (63–84% yield) and high regio- and diastereoselectivity (Table 2). The substituent in the olefin unit is not restricted to a methyl group. Thus, the introduction of Et, *n*Pr, and aryl groups in the 2-position of the olefin was well-tolerated in the coupling with PhC≡C*n*Pr, with the corresponding products formed in 72–86% yield. However, no reaction occurred in the attempted coupling of *N*-crotyl *p*-tolylsulfonamide with PhC≡C*n*Pr. Nevertheless, this methodology provides efficient and expedient access to a wide range of functionalized cyclopentenones from readily available starting materials under operationally simple conditions.

When an isolated sample of **4ch** was exposed to our standard reaction conditions, essentially no reaction occurred. We could thus rule out the intermediacy of this dihydropyridine in the formation of **5ch**. Therefore, these two products must be generated by two competitive pathways. We propose a mechanism in which the cyclometalation of **1c** first affords a five-membered rhodacycle **A**, which undergoes regioselective alkyne insertion to generate a seven-membered metallacycle **B** (Scheme 4). The fate of this metallacycle intermediate is determined by two possible pathways: intermediate **B** undergoes C–N reductive elimination to give a dihydropyridine **4** when a smaller amount of Ag^I is present; alternatively, in the presence of a larger amount of Ag^I, a β-hydride-elimination pathway to afford a cyclometalated imine **C** is preferred. Intermediate **C** should readily undergo migratory insertion of the alkenyl rhodium ligand into the *N*-Ts imine[18] to afford a rhodium(III) hydride species **D**. A second β-hydrogen-atom elimination[18c] generates an imine **E** and a rhodium(III) dihydride species, which can be oxidized to regenerate the Rh^{III} active catalyst (4 equivalents of Ag^I are needed). The final product **5** could be formed from imine **E** in a sequence involving the conjugate addition of water (to give **F**), followed by cyclopentadiene isomerization and ketone–enol tautomerization (via **G**). Although the exact role of the excess Ag^I oxidant in shifting the selectivity of the reaction is unclear at this stage, it might act as a base to facilitate HX elimination from **C** so as to shift the equilibrium between **B** and **C** toward **C**. It might also interact with the *N*-Ts imine to enhance the electrophilicity of the imine.

Table 2: Rhodium(III)-catalyzed synthesis of cyclopentenones.[a,b]

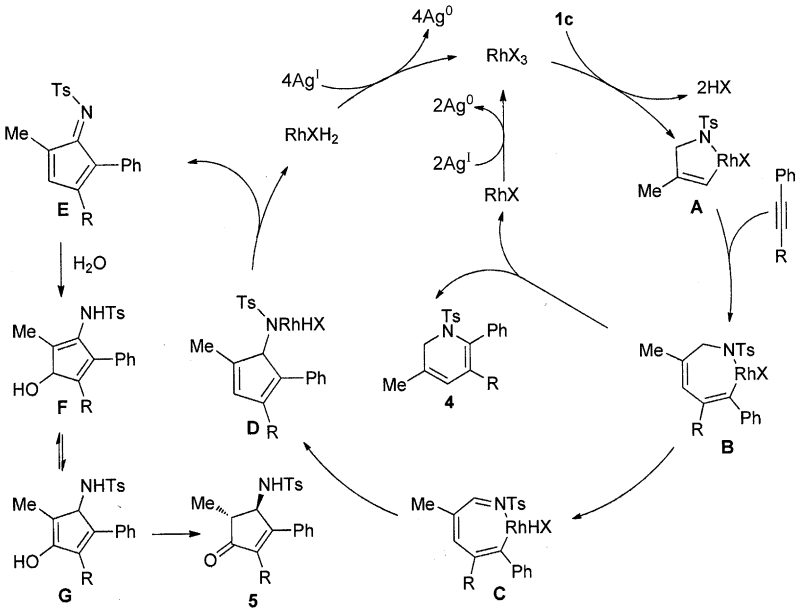




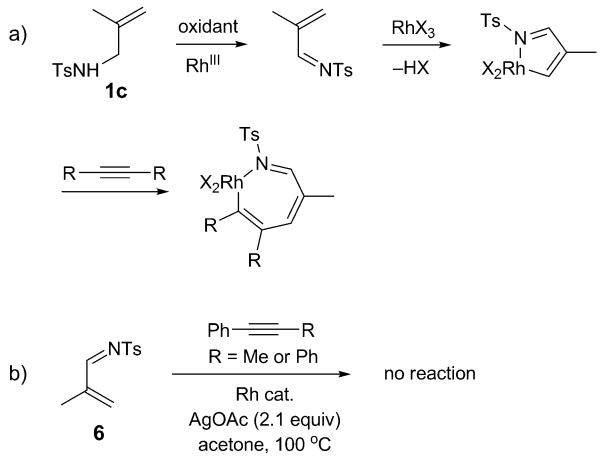
[a] Conditions: sulfonamide (0.3 mmol), alkyne (0.36 mmol), [{RhCp*Cl$_2$}$_2$] (4 mol%), AgOPiv (1.26 mmol), H_2O (0.9 mmol), acetone (3 mL), 100 °C, 20 h. [b] The yield of the isolated product is given.

Amine-assisted cyclometalation is not the only possible mechanistic pathway. Alternatively, amine **1c** might initially be oxidized to an *N*-Ts imine (either by Ag^I or by acetone; Scheme 5). Cyclometalation of this unsaturated imine[19] and insertion of an alkyne would afford a seven-membered rhodacyclic intermediate analogous to **C** (Schemes 4 and 5a). To probe this possibility, we prepared the *N*-Ts imine **6**; however, no coupling occurred when **6** was treated with various alkynes under the usual catalytic conditions (Scheme 5b). Thus, the amine-cyclometalation pathway is more likely.

In summary, we have demonstrated the oxidative synthesis of several important cyclic scaffolds, including pyridines and cyclopentenones, from readily available *N*-allyl sulfonamides and alkynes through rhodium(III)-catalyzed C–H activation. The reactions have broad scope in terms of both substrates. The selectivity of the reaction is determined by the allyl moiety of the sulfonamide, the identity of the alkyne, and



Scheme 4. Proposed reaction mechanism.



Scheme 5. Unlikelihood of an alternative pathway.

the catalytic conditions. Such versatility in C–H activation reactions directed by a sulfonamide is unprecedented. Studies on the detailed mechanisms of these transformations are underway in our laboratory.

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