C–H Bond Activation

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Rhodium(III)-Catalyzed Allylic C(sp^3)–H Activation of Alkenyl Sulfonamides: Unexpected Formation of Azabicycles

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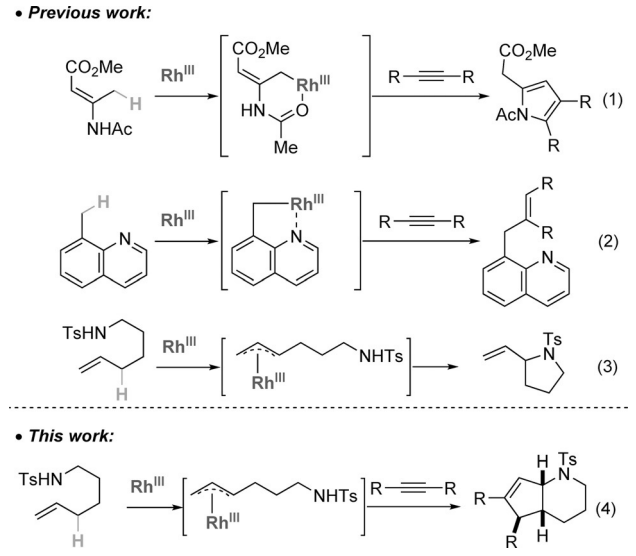
Abstract: *Unsaturated N-sulfonamides undergo a Rh^{III}-catalyzed allylic C(sp^3)–H activation followed by insertion with an exogenous internal alkyne. The reaction generates [3.3.0], [4.3.0], and [5.3.0] azabicyclic structures with excellent diastereoselectivity. Deuterium labeling experiments implicate a 1,3-Rh shift as a key step in the mechanism.*

Transition-metal-catalyzed C–H bond activation has emerged as a reliable method to access complex molecules in an atom- and step-economical fashion.[1] To this end, rhodium(III) has been extensively studied,[2] and numerous aromatic[3] and vinylic[4] C(sp^2)–H bond activations have been reported by our group and others. Activation of C(sp^3)–H bonds with transition-metal catalysts and their subsequent elaboration represents a highly desirable yet largely elusive goal, with few rhodium(III)-catalyzed examples having been reported. In 2010, Glorius and co-workers described the formation of pyrroles by allylic C(sp^3)–H activation of enamines [Scheme 1, Eq. (1)].[5] Wang and co-workers discovered that a reactive benzylic C–H bond of 8-methylquinolines is susceptible to activation followed by alkenylation [Scheme 1, Eq. (2)].[6] We were particularly intrigued by a recent report by Cossy and co-workers, who demonstrated that unsaturated sulfonamides afford vinylpyrrolidines by allylic C–H bond amination [Scheme 1, Eq. (3)].[7] This latter reaction presumably proceeds via a π-allyl Rh intermediate and we hypothesized that we could intercept this intermediate to access different structures. Herein, we report the coupling of unsaturated sulfonamides and alkynes via an allylic C(sp^3)–H activation/electrocyclization sequence. The reaction affords stereochemically complex azabicyclic products[8] with complete control of diastereoselectivity [Scheme 1, Eq. (4)].



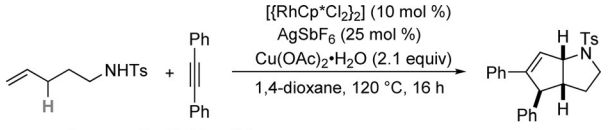
Scheme 1. Rh^{III}-catalyzed C(sp^3)–H activation.

We first investigated the reactivity of unsaturated *N*-tosylsulfonamide **1a** and diphenylacetylene **2a** with [{RhCp*Cl_2}$_2$] (5 mol%), $AgSbF_6$ (25 mol%) and Cu(OAc)$_2$·H_2O (2.1 equiv) in 1,4-dioxane (0.1M, 120°C, 16 h). We were pleased to observe formation of 1-azabicyclo[3.3.0]octane **3aa** with complete control of the relative stereochemistry of the three contiguous stereocenters formed during the reaction (Table 1, entry 1).

Single-crystal X-ray analysis of this compound confirmed our structural assignment and revealed that the phenyl group is located on the *exo* face of the molecule.[9]

Although **3aa** was obtained in low yield (26%), a higher catalyst loading drastically improves the yield to 70% (Table 1, entry 1). The most important conclusions resulting from our optimization studies are: (1) other potential catalysts for C–H activation, such as Ir^{III} [10] or Ru^{II} [11] complexes, did not give satisfactory conversions (Table 1, entries 3 and 4); (2) control experiments demonstrated that the presence of Rh^{III}, Ag^{I}, and Cu^{II} species are all necessary for the reaction to take place (Table 1, entries 5–7); and (3) lowering the tem-

Table 1: Optimization of the conditions for the formation of **3aa**.



Entry	Variation from the optimized conditions	Yield [%]
1	none	70
2	5 mol% [{RhCp*Cl_2}$_2$]	26
3	5 mol% [IrCp*Cl_2]$_2$	trace
4	5 mol% [Ru(*p*-cymene)Cl_2]$_2$	0
5	no [{RhCp*Cl_2}$_2$]	0
6	no $AgSbF_6$	0
7	no Cu(OAc)$_2$·H_2O	0
8	80°C instead of 120°C	0

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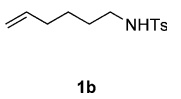
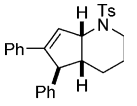
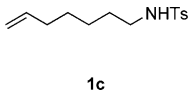
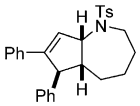
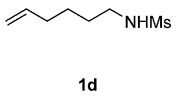
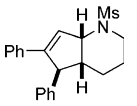
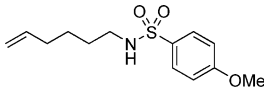
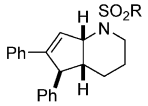
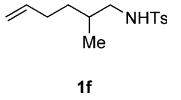
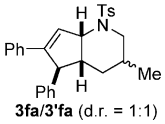
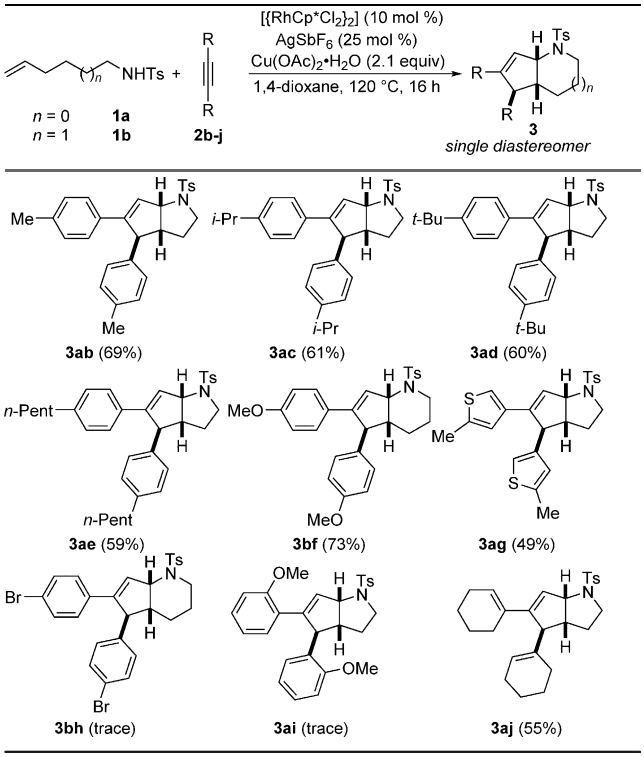
Table 2: Scope of the unsaturated sulfonamide.[a]

Entry	Alkenyl sulfonamide	Product	Yield [%][b]
1	 **1b**	 **3ba**	72
2	 **1c**	 **3ca**	66
3	 **1d**	 **3da**	70
4	 **1e**	 **3ea** (R = *p*-OMe-C_6H_4)	70
5	 **1f**	 **3fa/3′fa** (d.r. = 1:1)	42

[a] Reactions were conducted with 1.0 equiv of **1** and 1.25 equiv of **2a**, in the presence of 10 mol% [{RhCp*Cl_2}$_2$], 25 mol% $AgSbF_6$, 2.1 equiv $Cu(OAc)_2{\cdot}H_2O$ in dioxane at 120°C. [b] Yield of isolated products.

Table 3: Scope of the alkyne substrate.[a]



[a] See footnotes in Table 2.

perature to 80°C completely shuts down the reactivity (Table 1, entry 8).[12]

With these optimized conditions in hand, we examined the tolerance of the reaction of various sulfonamide substrates with diphenylacetylene **2a**. We were pleased to discover that *N*-tosylsulfonamide **1b** could be converted into **3ba** with good yield and complete diastereoselectivity (Table 2, entry 1). It is worth noting that the presence of the alkyne completely shuts down the potential C(sp^3)–H amination pathway, because no trace of pyrrolidine [Scheme 1, Eq. (3)] is observed during this transformation.[7]

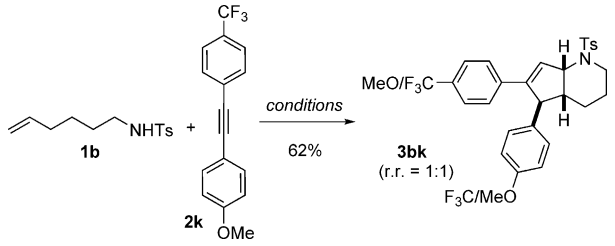
Interestingly, larger bicyclic compounds can also be accessed; for example, the azabicycle **3ca** bearing a seven-membered ring was obtained as a single diastereomer from sulfonamide **1c** (Table 2, entry 2). Different electron-rich sulfonamides have successfully been involved in this transformation where methanesulfonamide **1d** and *p*-methoxybenzenesulfonamide **1e** lead to azabicyclic products **3da** and **3ea**, respectively (Table 2, entries 3 and 4). The very high diastereoselectivity observed during these transformations prompted us to investigate the reactivity of branched unsaturated *N*-tosylamide **1f**. Upon treatment with the optimized conditions, the expected 1-azabicyclo[4.3.0]nonane was generated as a 1:1 mixture of diastereomers **3fa** and **3′fa** (Table 2, entry 5).

An array of diversely substituted alkynes were treated with *N*-tosylamides **1a** or **1b** under the optimized conditions (Table 3). Symmetrical tolanes **2b–f** bearing an electron-donating alkyl or methoxy substituent in the *para* position are well tolerated and afford the corresponding azabicycles **3ab**–**3ae** and **3bf** as single diastereomers. Gratifyingly, heteroaryl moieties are also tolerated and azabicyclo-[3.3.0]octane **3ag** is obtained from reaction of alkyne **2g**.

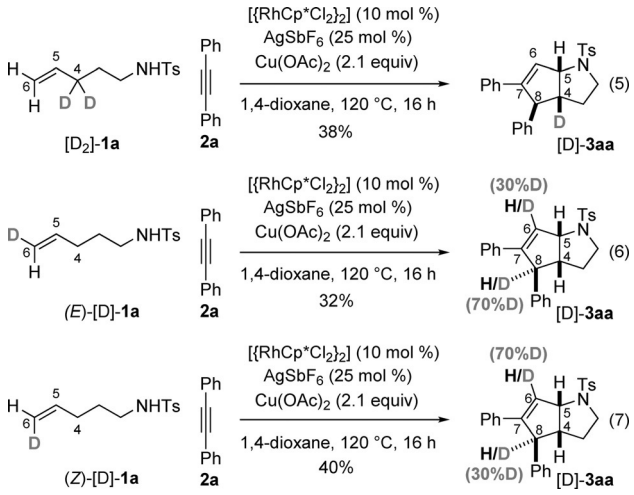
This transformation appears to be sensitive to the electronics of the alkyne, as electron-withdrawing substituted tolane **2h** only affords trace amounts of the corresponding bicycle **3bh**. Steric hindrance also seems to play a crucial role because no reaction occurs with electron-rich symmetrical alkyne **2i** bearing methoxy groups at the *ortho* positions. We were pleased to observe that the transformation proceeds smoothly with dienyne **2j** to form azabicycle **3aj** as a single diastereomer (Table 3).

We next investigated the regioselectivity of this transformation by examining the behavior of the unsymmetrical alkyne. Tolane **2k** was treated under the usual conditions with *N*-toluenesulfonamide **1b** and the C(sp^3)–H activation/cyclization sequence readily takes place. Although the expected bicyclic compound was synthesized in good yield, the electronic properties of the alkyne did not seem to influence the selectivity of the transformation as a mixture of **3bk** and **3′bk** was obtained in a 1:1 ratio (Scheme 2).

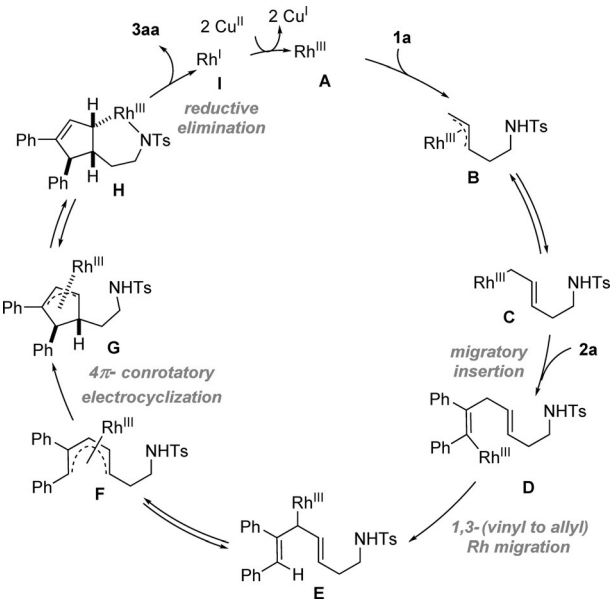
To shed light on the mechanism of the reaction that generates these unexpected products, we conducted a series of deuterium-labeling experiments. The use of dideuterated substrate [D_2]-**1a** with the labels at the reactive allylic position furnished exclusively the monodeuterated product [D_2]-**3aa** [Scheme 3, Eq. (5)]. Of more interest is the reaction between **2a** and tosylamides (*E*)-[D]-**1a** and (*Z*)-[D]-**1a** deuterated at the terminal position of the olefin (position 6). In both cases, analysis of the ^{1}H NMR spectra of the resulting products [D]-**3aa** shows deuteration at position 6 and at



Scheme 2. An unsymmetrical alkyne.



Scheme 3. Deuterium-labeling experiments.



Scheme 4. Proposed mechanism.

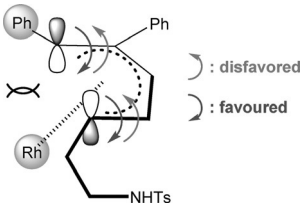


Figure 1. Model to rationalize diastereoselectivity.

position 8, providing evidence that a 1,3-shift could be involved during the transformation [Scheme 3, Eqs. (6) and (7)].

Based on these observations, we propose a mechanism for this transformation (Scheme 4). First, the active Rh^{III} catalyst **A** activates the allylic C(sp^3)–H bond of **1a** to provide a η^3 π-allyl complex **B** in equilibrium with its haptotropic η^1 isomer **C**. Complexation with alkyne **2a** followed by migratory insertion affords the vinylrhodium(III) complex **D**, which undergoes a direct vinyl-to-allyl 1,3-Rh migration to produce the bis(allyl)rhodium(III) species **E**.[13] A 4π-electrocyclization through intermediate **F** leads to π-allylrhodium(III) complex **G**. This diastereodetermining step proceeds via a conrotatory mechanism in which the torquoselectivity is governed by steric factors highlighted in an empirical model (Figure 1). A counter-clockwise cyclization (up arrows) creates a destabilizing steric repulsion on the bottom face of the pentadienyl moiety between the rhodium catalyst and the bulky phenyl group while a more favorable clockwise cyclization (down arrows) occurs with a steric repulsion between the rhodium and the less bulky alkyl chain. After *N*-metalation, the rhoda(III)azacyclohexane **H** is obtained and generates the azabicyclic compound **3aa** by reductive elimination. This late *N*-cyclization step is in agreement with the absence of diastereocontrol with branched sulfonamide **1f**. A final copper-mediated oxidation of the resulting Rh^I complex **I** closes the catalytic cycle.

To conclude, we have discovered a new rhodium(III)-catalyzed allylic C(sp^3)–H activation/4π-electrocyclization sequence of unsaturated sulfonamides and alkynes that generates 1-azabicycles with complete control of the three newly formed stereocenters.[14] Deuterium-labeling experiments reveal a rare direct vinyl-to-allyl 1,3-Rh migration. Studies to provide insight into this new reactivity and expand it to other useful synthetic applications are ongoing.

Experimental Section

N-Tosylamide **1a** (47.9 mg, 0.200 mmol), diphenylacetylene **2a** (44.6 mg, 0.250 mmol, 1.25 equiv), $Cu(OAc)_2{\cdot}H_2O$ (83.9 mg, 0.420 mmol, 2.1 equiv), $AgSbF_6$ (17.2 mg, 0.050 mmol, 25 mol%), and [{RhCp*Cl_2}$_2$] (12.3 mg, 0.020 mmol, 10 mol%) were added to a 1.5 dram vial. After addition of 1,4-dioxane (2 mL, 0.1M), the vial was sealed and heated at 120°C for 16 h. The resulting blue mixture was filtrated through a short plug of silica and Celite (hexanes/EtOAc 30:70) and concentrated under reduced pressure. Analysis of the crude material by ^{1}H NMR and ^{13}C NMR spectroscopy revealed the presence of a single diastereomer (d.r. > 96:4). Purification by flash chromatography (hexanes/EtOAc 95:5 to 80:20) gave 58.3 mg (70%) of **3aa** as a colorless oil.

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Keywords: 4π-electrocyclization · azabicycles · C–H insertion · 1,3-migration · rhodium

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[12] The use of a higher ratio of silver salt to Rh dimer (4:1) leads to lower yields of isolated products (18%). Furthermore, the use of cationic Rh (MeCN complex) as a precatalyst leads to very low conversions under these conditions. Whether this implicates a monocationic Rh intermediate as the active catalyst remains unclear.

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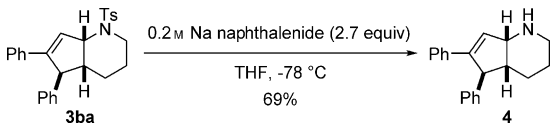
[14] The protecting tosyl group of compound **3ba** was removed by treatment with a solution of sodium naphthalenide in THF, and the bicyclic secondary amine **4** was obtained in good yield. See the Supporting Information for details.



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