HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2016 November 02.

Published in final edited form as:

Angew Chem Int Ed Engl. 2015 November 2; 54(45): 13337–13340. doi:10.1002/anie.201504150.

Rh(III)-Catalyzed Allylic C(sp³)–H Activation of Alkenyl Sulfonamides: Unexpected Formation of Azabicycles**

Dr. Alexis Archambeau and **Prof. Tomislav Rovis**

Department of Chemistry, Colorado State University, Fort Collins, CO 80523 (USA), Homepage: http://sites.chem.colostate.edu/rovislab

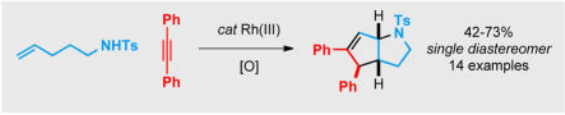
Tomislav Rovis: rovis@colostate.edu

Abstract

Herein we report that 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.

Graphical Abstract

Allylic C-H bond activation by Rh(III) catalyst precedes alkyne insertion leading to an unexpected azabicycle structure in good yield and excellent diastereoselectivity. The mechanism of the reaction was interrogated with deuterium labelling experiments and is proposed to involve a 1,3-Rh shift followed by an electrocyclization event.



Keywords

Rhodium(III); azabicycles; C(sp^3)-H insertion; Rh 1; 3-migration; 4π-electrocyclization

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 Rh(III)-catalyzed examples having been reported. In 2010, Glorius described the formation of pyrroles by allylic C(sp^3) –H activation of enamines (Scheme 1, eq 1).[5] Wang discovered that a reactive benzylic C–H bond of 8-

We thank NIGMS for support (GM80442), and Johnson Matthey for a generous loan of rhodium salts. We thank Natthawat Semakul (CSU) for solving the structure of **3aa.

Correspondence to: Tomislav Rovis, rovis@colostate.edu.

Supporting information for this article is given via a link at the end of the document.

methylquinolines is susceptible to activation followed by alkenylation (Scheme 1, eq 2).[6a] We were particularly intrigued by a recent report by Cossy and coworkers 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 valuable azabicyclic products[8] with complete control of diastereoselectivity (Scheme 1, eq 4).

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 $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv) in 1,4-dioxane (c 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: (a) 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), (b) 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 (c) lowering the temperature 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 since 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 since 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 unsymmetrical alkynes. 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).

In an effort 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 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 diastereo-determining step proceeds via a conrotatory mechanism where the torquoselectivity is governed by steric factors highlighted in an empirical model (Figure 1). A counter-clockwise cyclization (red pathway) 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 (blue pathway) 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 Cu mediated oxidation of the resulting Rh(I) complex **I** closes the catalytic cycle.

To conclude, we have discovered a new Rh(III)-catalyzed allylic C(sp^3)-H activation/4π-electrocyclization sequence of unsaturated sulfonamides and alkynes which 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 in this new reactivity and expand it to other useful synthetic applications are ongoing.

Experimental Section

In a 1.5 dram vial were added *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 %). 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 ^1H NMR and ^{13}C NMR 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

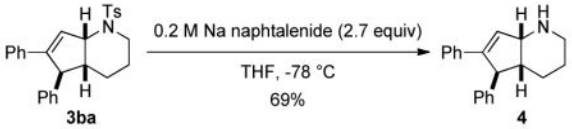
1. a) Crabtree RH. J Chem Soc Dalton Trans. 2001:2437–2450.b) Godula K, Sames D. Science. 2006; 312:67–72. [PubMed: 16601184] c) Lyons TW, Sanford MS. Chem Rev. 2010; 110:1147–1169. [PubMed: 20078038] d) Ackermann L. Chem Rev. 2011; 111:1315–1345. [PubMed: 21391562] e) Yeung CS, Dong VM. Chem Rev. 2011; 111:1215–1292. [PubMed: 21391561] f) Delord-Wencel J, Dröge T, Liu F, Glorius F. Chem Soc Rev. 2011; 40:4740–4761. [PubMed: 21666903] g) Arockiam PB, Bruneau C, Dixneuf PH. Chem Rev. 2012; 112:5879–5918. [PubMed: 22934619] h) Kuhl N, Hopkinson MN, Wencel-Delord J, Glorius F. Angew Chem. 2012; 124:10382–10401.Angew Chem Int Ed. 2012; 51:10236–10254.i) Beller, M.; Bolm, C., editors. Transitions Metals for Organic Chemistry. 2. Wiley-VCH; Weinheim: 2004. j) Yu, J-Q.; Shi, Z-J. C-H Activation. Springer; Berlin, Germany: 2010. k) Chen X, Engle KM, Wang DH, Yu JQ. Angew Chem. 2009; 121:5196–5215.Angew Chem Int Ed. 2009; 48:5094–5115.l) Engle KM, Mei TS, Wasa M, Yu JQ. Acc Chem Res. 2012; 45:788–802. [PubMed: 22166158] m) Rouquet G, Chatani N. Angew Chem. 2013; 125:11942–11959.Angew Chem Int Ed. 2013; 52:11726–11743.

2. For selected reviews, see: Colby DA, Bergman RG, Ellman JA. Chem Rev. 2010; 110:624–655. [PubMed: 19438203] Satoh T, Miura M. Chem Eur J. 2010; 16:11212–11222. [PubMed: 20740508] Patureau FW, Wencel-Delord J, Glorius F. Aldrichim Acta. 2012; 45:31–41.Song G, Wang F, Li X. Chem Soc Rev. 2012; 41:3651–3678. [PubMed: 22377832] Colby DA, Tsai AS, Bergman RG, Ellman JA. Acc Chem Res. 2012; 45:814–825. [PubMed: 22148885] Kuhl N, Shröder N, Glorius F. Adv Synth Catal. 2014; 356:1443–1460.

3. For selected examples of Rh(III)-catalyzed aromatic C(sp^2)-H activation, see: Ueura K, Satoh T, Miura M. Org Lett. 2007; 9:1407–1409. [PubMed: 17346060] Stuart DR, Bertrand-Laperle M, Burgess KMN, Fagnou K. J Am Chem Soc. 2008; 130:16474–16475. [PubMed: 19554684] Hyster TK, Rovis T. J Am Chem Soc. 2010; 132:10565–10569. [PubMed: 20662529] Guimond N, Gouliaras C, Fagnou K. J Am Chem Soc. 2010; 132:6908–6909. [PubMed: 20433170] Ryu J, Shin K, Park SH, Kim JY, Chang S. Angew Chem. 2012; 124:10042–10046.Angew Chem Int Ed. 2012; 51:9904–9908.Zhao D, Shi Z, Glorius F. Angew Chem. 2013; 125:12652–12656.Angew Chem Int Ed. 2013; 52:12426–12430.Liu G, Shen Y, Zhou Z, Lu X. Angew Chem. 2013; 125:6149–

6153.Angew Chem Int Ed. 2013; 52:6033–6037.Hyster TK, Ruhl KE, Rovis T. J Am Chem Soc. 2013; 135:5364–5367. [PubMed: 23548055] Hyster TK, Rovis T. Synlett. 2013:1842–1844. [PubMed: 25346576] Hu F, Xia Y, Ye F, Liu Z, Ma C, Zhang Y, Wang J. Angew Chem. 2014; 126:1388–1391.Angew Chem, Int Ed. 2014; 53:1364–1367.

4. For selected examples of Rh(III)-catalyzed vinylic C(sp^2)-H activation, see: Mochida S, Hirano K, Satoh T, Miura M. J Org Chem. 2009; 74:6295–6298. [PubMed: 19572577] Hyster TK, Rovis T. Chem Commun. 2011; 47:11846–11848.Kuhl N, Shröder N, Glorius F. Org Lett. 2013; 15:3860–3863. [PubMed: 23906080] Wang H, Beiring B, Yu DG, Collins KD, Glorius F. Angew Chem. 2013; 125:12657–12661.Angew Chem Int Ed. 2013; 52:12430–12434.Neely JM, Rovis T. J Am Chem Soc. 2014; 136:2735–2738. [PubMed: 24512241] Piou T, Rovis T. J Am Chem Soc. 2014; 136:11292–11295. [PubMed: 25093811]
5. Rakshit S, Patureau FW, Glorius F. J Am Chem Soc. 2010; 132:9585–9587. [PubMed: 20578748]
6. Liu B, Zhou T, Li B, Xu S, Song H, Wang B. Angew Chem. 2014; 126:4275–4279.Angew Chem Int Ed. 2014; 53:4191–4195.For a Rh(III)-catalyzed amidation of 8-methylquinolines, see: Wang N, Li R, Li L, Xu S, Song H, Wang B. J Org Chem. 2014; 79:5379–5385. [PubMed: 24807560]
7. Cochet T, Bellosta V, Roche D, Ortholand J-Y, Greiner A, Cossy J. Chem Commun. 2012; 48:10745–10747.
8. For examples of biologically active molecules bearing 1-azabicycle moieties, see: Linz W, Schindler U. US Patent No. 5,061,722. 1991Hermans H, Hubert KF, Knaeps GA, Willems JJM. US Patent No. 3,679,686. 1972Takano I, Yasuda I, Nishijima M, Hitotsuyanagi Y, Takeya K, Itokawa H. Bioorg Med Chem Lett. 1996; 6:1689–1690.
9. See SI.
10. For selected examples of C-H activation catalyzed by $[IrCp^*Cl_2]_2$, see: Kim H, Shin K, Chang S. J Am Chem Soc. 2014; 136:5904–5907. [PubMed: 24702587] Kim J, Chang S. Angew Chem. 2014; 126:2235–2239.Angew Chem Int Ed. 2014; 53:2203–2207.Xie F, Qi Z, Yu S, Li X. J Am Chem Soc. 2014; 136:4780–4787. [PubMed: 24593822] Kang T, Kim Y, Lee D, Wang Z, Chang S. J Am Chem Soc. 2014; 136:4141–4144. [PubMed: 24580093]
11. For selected examples of C-H activation catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$, see: Kim J, Kim J, Chang S. Chem Eur J. 2013; 19:7328–7333. [PubMed: 23616285] Bhanuchandra M, Yadav MR, Rit RK, Kuram MR, Sahoo AK. Chem Commun. 2013; 49:5225–5227.
12. The use of a higher ratio of silver salt to Rh dimer (4:1) leads to lower isolated yields (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.
13. Ikeda Y, Takano K, Kodama S, Ishii Y. Organometallics. 2014; 33:3998–4004.
14. The protecting tosyl group of compound 3ba was removed by treatment with a solution of sodium naphtalenide in THF and the bicyclic secondary amine **4** was obtained in good yield. See SI for details.



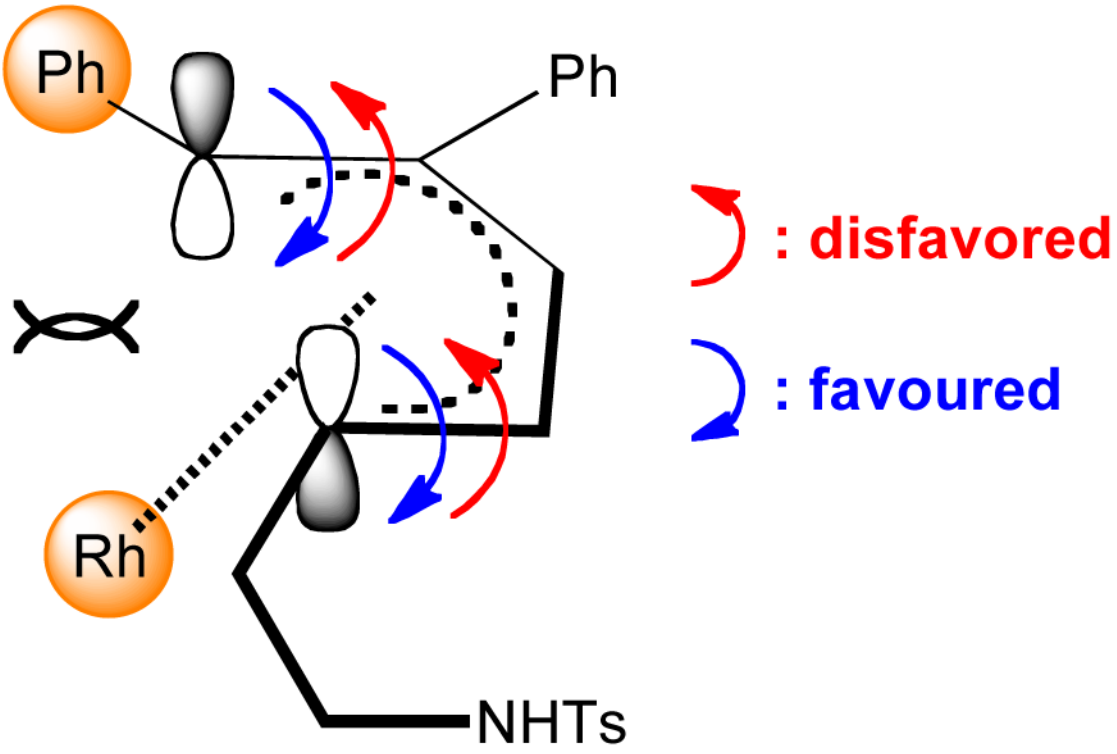
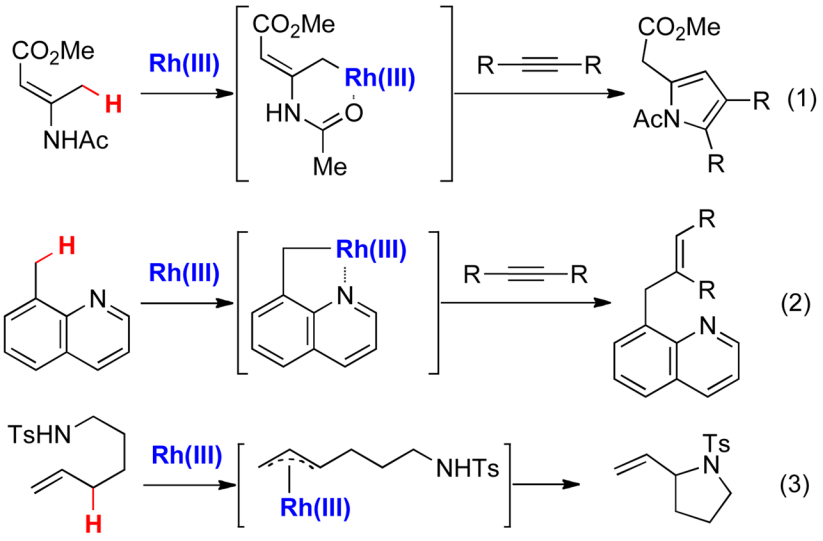
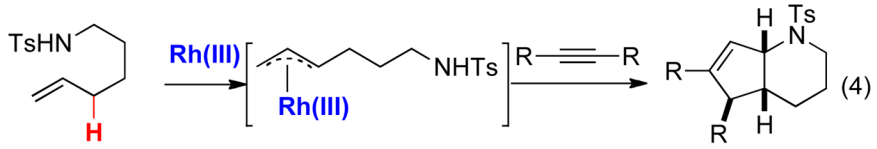


Figure 1.
Model to rationalize diastereoselectivity

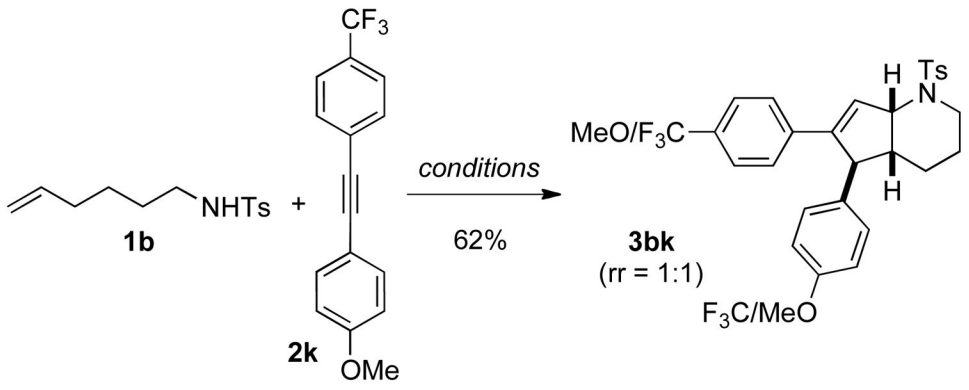
- ***Previous work:***



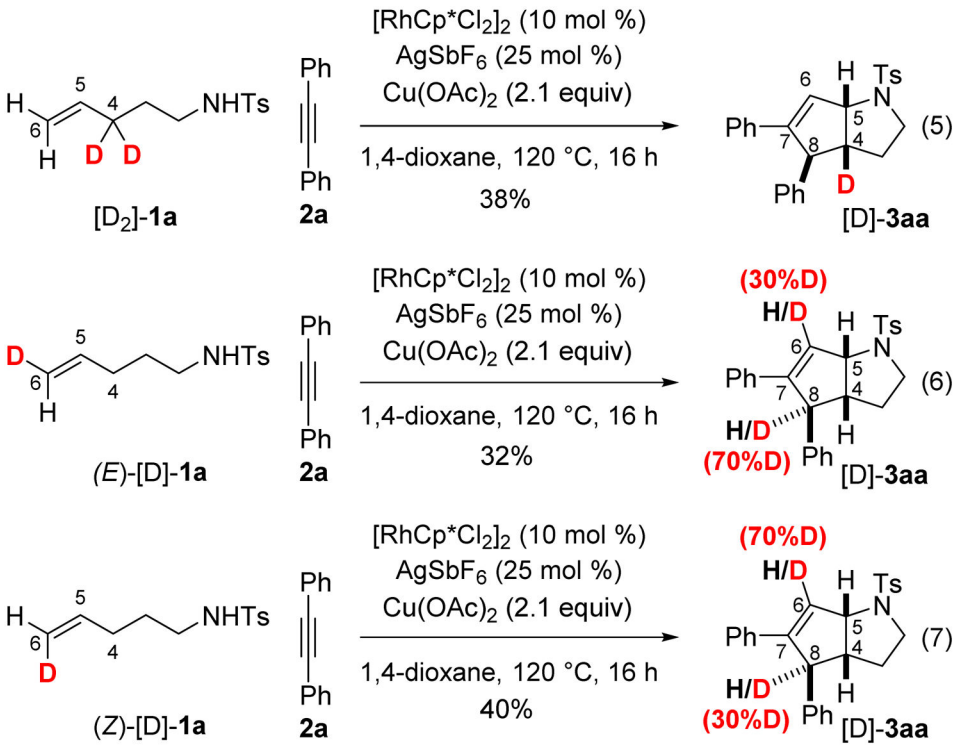
- ***This work:***



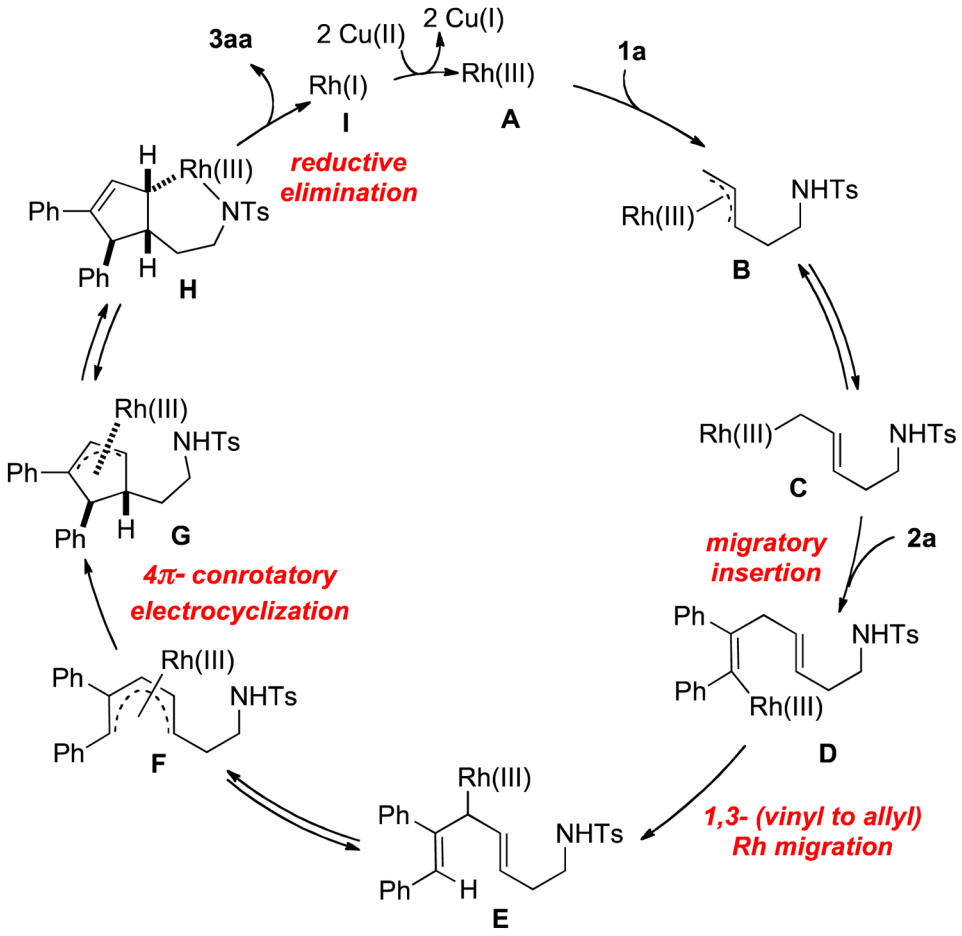
Scheme 1.
Rh(III)-Catalyzed C(sp^3)-H Activation



Scheme 2.
An Unsymmetrical Alkyne



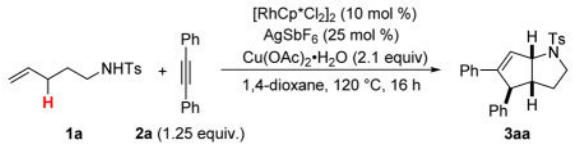
Scheme 3.
Deuterium Labeling Experiments



Scheme 4.
Proposed Mechanism

Table 1

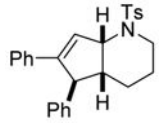
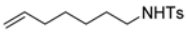
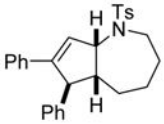
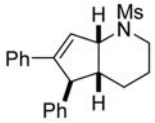
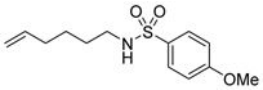
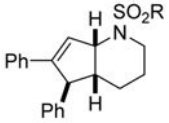
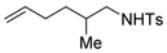
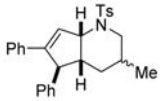
Optimization of the conditions for the formation of **3aa**



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 % $[Ru(p\text{-cymene})Cl_2]_2$	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

Table 2

Scope of the Unsaturated Sulfonamide[a]

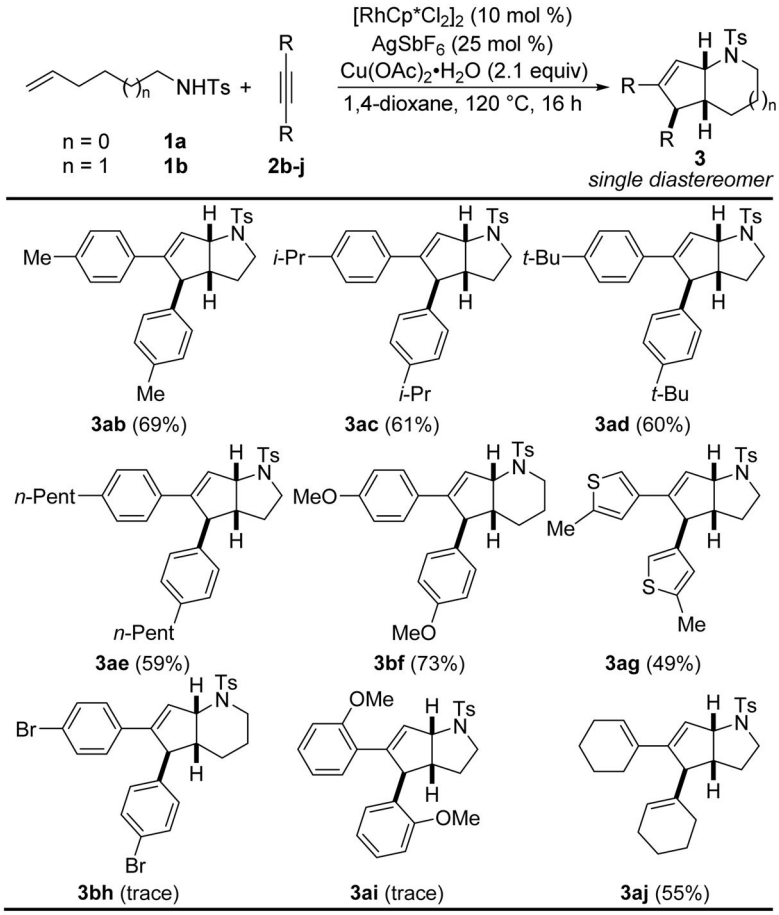
Entry	Alkenyl sulfonamide	Product	Yield (%)[b]
1	 **1b**	 **3ba**	72
2	 **1c**	 **3ca**	66
3	 **1d**	 **3da**	70
4	 **1e**	 **3ea** (R = *p*-OMe-C_6H_4)	70
5	 **1f**	 **3fa/3′fa**(dr = 1:1)	42

[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] Isolated yield.

Table 3

Scope of the Alkyne Substrate[a]



[a]See footnotes Table 2.