Platinum-Catalyzed Transformation of Alkyne Allyl Alcohols and Sulfonamides into Heterotricyclo[3.3.1.0^{2,8}]nonanes

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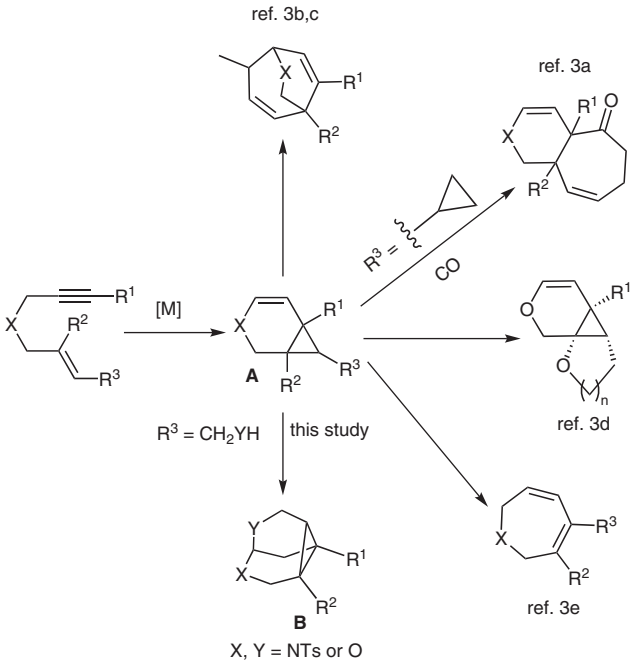
Abstract: Platinum chloride catalyzed cycloisomerization of alkyne allyl alcohols and alkyne allyl sulfonamides gave new cycloisomerization products, diaza-, azaoxa-, and dioxatricyclo-[3.3.1.0^{2,8}]nonanes, in reasonable to high yields.

Key words: alkyne allyl alcohols, alkyne allyl sulfonamides, platinum chloride, cycloisomerization, nucleophilic attack

Transition-metal-catalyzed cycloisomerization reactions can provide a variety of cyclic scaffolds from readily available starting materials that cannot be easily obtained by conventional synthetic methods.[1] In particular, bicyclo[4.1.0]hept-2-ene derivatives (**A** in Scheme 1) are a class of the products which can be easily obtained by transition-metal-catalyzed cycloisomerization of enynes.[2] Although the unique structure of bicyclo[4.1.0]hept-2-ene derivatives can give rise to an array of very interesting characteristic transformations, their use in the organic synthesis of more complex compounds is still quite rare.[3]



Scheme 1 Metal-catalyzed cycloisomerization and consecutive thermal reactions

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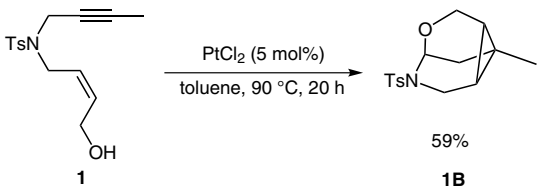
We envisioned that if an enyne bearing a pendent hydroxy group was used as a substrate, we would obtain a bicyclo-[4.1.0]heptene having a pendent hydroxy group, which might undergo a nucleophilic attack to give bicyclic compounds. Enynes bearing a hydroxyallyl group have been used as substrates in rhodium-,[4] iridium-,[5] nickel-,[6] and palladium-,[7] and gold-catalyzed cycloisomerization reactions.[8] In all cases, Alder–ene-type reaction products were isolated and used in a subsequent reaction. However, very recently, we reported[9] a gold-catalyzed cycloisomerization of alkynyl hydroxyallyl tosylamides to 4-oxa-6-aza-tricyclo[3.3.0.0^{2,8}]octane. Although platinum chloride has been widely used as a catalyst in the transformation of enynes to bicyclo[4.1.0]heptenes,[10] there has been no report on the use of platinum chloride in the cycloisomerization of enynes bearing a hydroxyallyl group. Encouraged by the above, we closely examined the platinum chloride catalyzed cycloisomerization reaction of alkyne allyl alcohols in the hope of finding new bicyclic skeletons. We herein communicate a facile method for the stereoselective construction of heterotricyclo[3.3.1.0^{2,8}]-nonanes from alkyne allyl alcohols through bicyclo[4.1.0]heptene intermediates based on the platinum chloride catalyzed cycloisomerization and nucleophilic addition reactions.

Using an alkyne allyl alcohol **1** as the model substrate, the platinum-catalyzed cycloisomerization was studied (Equation 1 and Table 1).



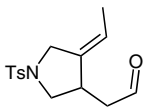
Equation 1 $PtCl_2$-catalyzed cycloisomerization of **1**

When **1** was reacted with 5 mol% $PtCl_2$ in toluene at 90 °C for 20 hours, **1B** was isolated in 59% yield (entry 1). No other products were found. Formation of **1B** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic investigations, and high resolution mass spectrometry.[11] Tricyclo[3.3.1.0^{2,8}]nonane, **1B**, was derived from a cyclopropanation followed by a nucleophilic addition of a pendent hydroxy group. The skeleton of **1B** was first exposed in this study. Encouraged by the above result, we initially screened the reaction parameters such as the reaction sol-

Table 1 Reaction of **1** under Various Conditions[a]

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	5 mol% $PtCl_2$	toluene	90	20	59[c]
2	10 mol% $PtCl_2$	dioxane	90	24	74
3	5 mol% $PtCl_2$–CO(1atm)	dioxane	90	24	18
4	10 mol% $PtCl_4$	dioxane	90	16	80
5	10 mol% $PtCl_4$	dioxane	25	5	69
6	10 mol% $PtCl_4$	THF	70	24	25
7	10 mol% $PtCl_4$	DCE	80	17	25
8	10 mol% $PtCl_4$	toluene	100	17	23
9	10 mol% $IrCl_3$	dioxane	90	24	0
10	5 mol% $[Ir(cod)Cl]_2$	toluene	90	22	23 [**1C**][d]
11	10 mol% $RuCl_3$	dioxane	90	24	15 [**1C**][d]

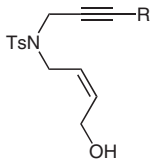
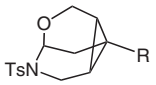
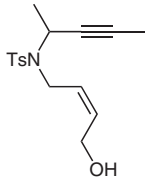
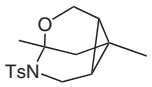
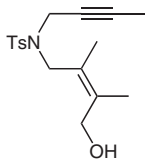
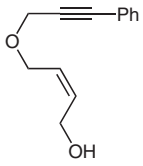
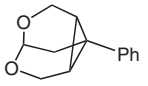
[a] Compound **1** (44 mg, 0.15 mmol) in solvent (2 mL) was used.
[b] Isolated yields.
[c] Compound **1** (90 mg, 0.3 mmol) in solvent (3 mL) was used.
[d] The structure of **1C** is shown below:



vent, the reaction temperature, and the reaction time. When 10 mol% $PtCl_2$ was used in dioxane at 90 °C for 24 hours, the yield of **1B** increased to 74% (entry 2). When the same reaction was carried out in the presence of carbon monoxide, **1B** was isolated in 18% (entry 3). Use of $PtCl_4$ instead of $PtCl_2$ afforded the 80% yield of **1B** and the reaction time was shortened to 16 hours (entry 4). Using $PtCl_4$ as a catalyst, the same reaction could be carried out to give **1B** in 69% yield even at room temperature (entry 5). Thus, reaction media, including THF (25%), DCE (25%), and toluene (23%), were screened using $PtCl_4$ as a catalyst (entries 6–8). The reaction was highly sensitive to the reaction solvent. Different metal complexes such as $IrCl_3$, $[Ir(cod)Cl]_2$, and $RuCl_3$ were screened as catalyst (entries 9–11). Interestingly, when $[Ir(cod)Cl]_2$ or $RuCl_3$ were used, a cyclopentane derivative, **1C**, bearing an exocyclic double bond and an aldehyde, was isolated in low yields (23% and 15%, respectively). Formation of cyclopentane derivatives, having an exocyclic double bond and an aldehyde, **C**, in the rhodium-catalyzed asymmetric cycloisomerization of terminal enynes bearing a hydroxy group, was recently reported by Nicolaou.[4b] In case of $IrCl_3$, no reaction was observed. Thus the formation of **1B** was a unique reaction of $PtCl_2$ or $PtCl_4$.

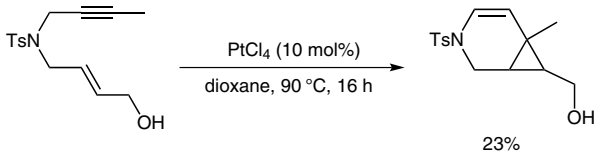
Using $PtCl_4$ as a catalyst, we investigated the Pt-catalyzed cycloisomerization of various alkyne allyl alcohols (Table 2).[12,13] The cycloisomerization reaction works well with *cis*-allyl alcohols. However, the corresponding *trans*-allylic alcohol gave the cyclopropanated compound in rather low yield (23%; Equation 2).

Table 2 $PtCl_4$-Catalyzed Cycloisomerization of Alkyne Allyl Alcohols[a]

Entry	Substrate	Time (h)	Product (%)[b]
			
	1–5		**1B–5B**
1	R = Me	16	80
2	H	14	42
3	Et	17	50
4	cyclopropyl	24	88
5	cyclohexenyl	17	49
6			
	6	24	**6B** 44
7			
	7		0
	8–12		**8B–12B**
8	R = Ph	19	45
9	4-ClC_6H_4	4	42
10	4-$MeOC_6H_4$	2	87
11	3,5-$Me_2C_6H_3$	17	53
12	4-MeC_6H_4	6	48
13			
	13	3	**13B** 60

[a] Reaction conditions: substrate (0.15 mmol) and $PtCl_4$ (10 mol%) were reacted in dioxane (2 mL) at 90 °C.
[b] Isolated yield.

When an enyne with a terminal alkyne was used as a substrate (entry 2), the yield was 42%. An introduction of an



Equation 2 $PtCl_4$-catalyzed cycloisomerization of *trans*-allylic alcohol

ethyl group instead of a methyl group to the terminal alkyne diminished the yield from 80% to 50% (entry 3). However, the introduction of a cyclopropyl group to the alkyne terminal (entry 4) enhanced the yield to 88%. The introduction of a cyclohexenyl group to the terminal alkyne (entry 5, 49%) or an introduction of a methyl group to the 3-position of 1,6-enyne (entry 6, 44%) led to rather low yields. However, the introduction of two methyl groups to the alkene moiety (compound **7,** entry 7) was detrimental to the reaction: all of the reactant decomposed and no separable compounds were formed. When an aryl group was introduced to the terminal alkyne (entries 8–12), the yield ranged from 42% to 87%. Thus the yield was highly sensitive to the substituent on the aromatic system. Among them, the methoxy substituent on the aromatic system exerts the most profound influence on the yield of the reaction (entry 10, 87%). Introducing a halo or methyl group had a small impact on the yield. It seems that the introduction of an electron-donating group increases the yield of the reaction. When an oxygen-tethered enyne with a phenyl substituent on the aromatic ring was used as a substrate (entry 13), the corresponding dioxatricyclic compound **13B** was isolated in 60% yield. Thus the process tolerates an oxygen-tethered substrate. The structure of **B** was confirmed by X-ray diffraction analysis of **8B** (Figure 1).[11]

Next we investigated the platinum-catalyzed cycloisomerization of enynes bearing a sulfonamide (Table 3).[14] We envisioned that the sulfonamide nitrogen atom may undergo a nucleophilic attack to give bicyclic compounds like a pendent hydroxy group. As we expected, enynes

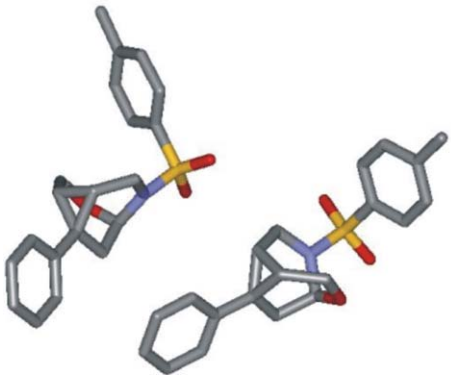
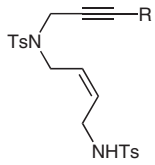
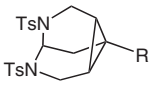
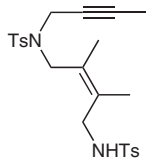
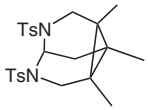
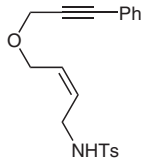
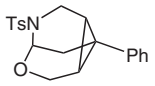


Figure 1 X-ray structure of **8B**. C, N, O, and S atoms are shown in gray, violet, red, and yellow, respectively. Hydrogen atoms are omitted for clarity.

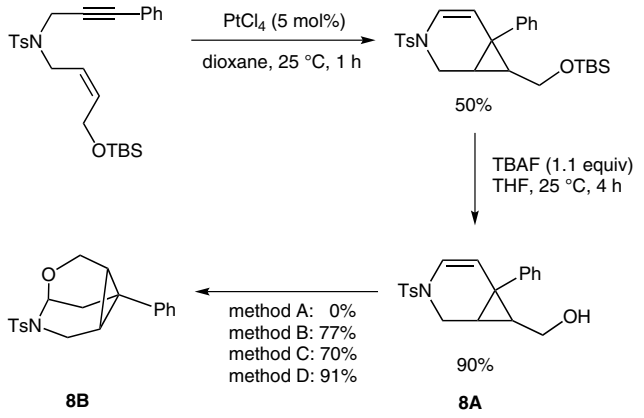
with an internal alkyne (entries 1–6) in the presence of $PtCl_4$ at 90 °C produced a diazatricyclo[3.3.1.0^{2,8}]nonane derivative in reasonable yields (51–70%). The reaction was rather fast compared to that of the enyne alcohols. Interestingly, in contrast to the case of entry 7 in Table 2, the introduction of two methyl groups to the alkene (entry 7 in Table 3) led to isolation of a stable product with a good yield (68% vs. 0%). When an oxygen-tethered enyne **21** was used as a substrate (entry 8), another kind of azaoxatricyclo[3.3.1.0^{2,8}]nonane derivative, **21B**, was isolated in 60% yield. Thus, the platinum-catalyzed cycloisomerization of enynes followed by a nucleophilic attack of a pendent functional group is quite general.

Table 3 $PtCl_4$-Catalyzed Cycloisomerization of Alkyne Allyl Sulfonamides[a]

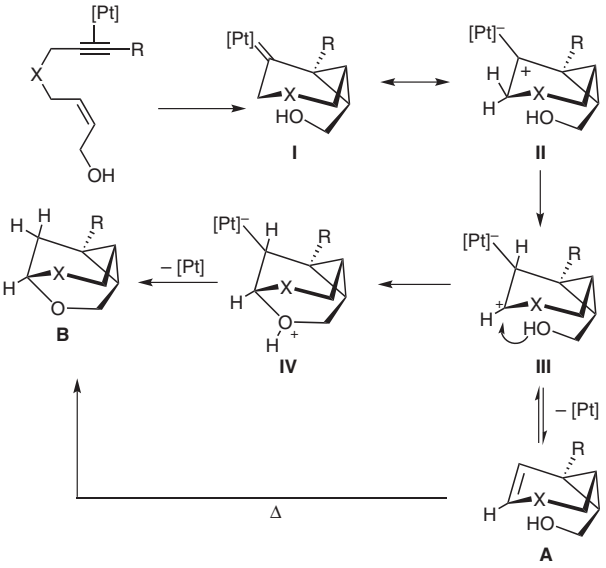
Entry	Substrate	Time (h)	Product (%)[b]
	 **14–19**		 **14B–19B**
1	R = Me	1	54
2	Et	1	57
3	Pr	4	55
4	Ph	1	70
5	4-ClC_6H_4	4	51
6	3,5-$Me_2C_6H_3$	1	64
7	 **20**	1	 **20B** 68
8	 **21**	3	 **21B** 60

[a] Reaction conditions: substrate (0.15 mmol) and $PtCl_4$ (10 mol%) were reacted in dioxane (2 mL) at 90 °C.
[b] Isolated yield.

To get some insight into the reaction mechanism, a bicyclo[4.1.0]hept-2-ene bearing a hydroxy group prepared from an enyne having a protecting group TBS was reacted (Scheme 2).



Scheme 2 Synthetic outline for the formation of **8B**. The yields were isolated. *Reagents and conditions*: method A: dioxane, 25 °C, 24 h; method B: dioxane, 90 °C, 24 h; method C: $PtCl_4$ (10 mol%), 25 °C, 2 h; method D: $PtCl_4$ (10 mol%), 90 °C, 30 min.



Scheme 3 A plausible mechanism

When an enyne having protecting group TBS was treated with $PtCl_4$, a cyclopropanated compound was isolated in 50% yield. Treatment of the cyclopropanated compound having TBS with TBAF afforded **8A** in 90% yield. When **8A** was heated at 90 °C in dioxane for 24 hours (method **B** in Scheme 2), **8B** was formed quantitatively when judged by ^{1}H NMR. This observation indicated that the final cyclization via an attack of the hydroxy group could be done without the aid of a catalyst. However, the longer reaction time (24 h) suggested that there might be some $PtCl_4$-assisted portion in the reaction. To know whether the cycloisomerization was assisted by $PtCl_4$ or not, **8A** was reacted in the presence of $PtCl_4$ at room temperature for two hours (method **C** in Scheme 2). Compound **8B** was isolated in 70% yield. However, no reaction was observed when the same reaction was carried out in the absence of $PtCl_4$ at room temperature for 24 hours. These observations suggested that the platinum catalyst may coordinate to the alkene moiety to enhance a nucleophilic attack of the pendent hydroxy group;[15] the thermal contribution being marginal under our reaction conditions.

Based on the above experimental results and previous studies,[2,16] a plausible reaction mechanism has been proposed (Scheme 3). The first step entails a metal-based alkyne activation, which is followed by intramolecular cyclopropanation to give an intermediate metal carbene **I**. Carbene **I** can resonate with an intermediate **II**. The intermediate **II** is expected to undergo a facile [1,2]-hydride shift to afford intermediate **III**. The presence of a heteroatom in the tether (X = O or NR) is expected to favor this process due to the stabilization of an intermediate cation **III** by the heteroatom lone pair. A hydroxy group may act as a nucleophile to attack at the site where the developing positive charge is best stabilized. Thus the nucleophilic interception of the intermediate **III** by the hydroxy group leads to form an intermediate **IV**. Proton transfer followed by protodemetalation afforded **B** and regenerated the Pt catalyst, which enters the next catalytic cycle. The thermal reaction of **A** to **B** is a feasible route at high temperatures even though its contribution to the overall reaction is not great.

In conclusion, we have demonstrated that judicious choice of metal catalyst enables different cycloisomerization pathways to be exploited and unique products to be obtained. Using platinum-catalyzed cycloisomerization and nucleophilic attack, an efficient strategy for the synthesis of heterotricyclo[3.3.1.0^{2,8}]nonanes from readily available starting materials has been developed. The skeleton of the tricyclo[3.3.1.0^{2,8}]nonane has been exposed for the first time in this study. Since bicyclo[4.1.0]hept-2-enes are easily accessible by different catalysts, this method should find useful applications for the stereoselective preparation of a variety of heterotricyclo-[3.3.1.0^{2,8}]nonanes.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) The synthetic procedures and spectroscopic data of the new compounds are summarized in the Supporting Information. CCDC-813816 (**8B**) 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.cam.ac.uk/data_request/cif.

(12) **General Procedure**: To a flame-dried 10-mL Schlenk flask capped with a rubber septum, dioxane (2 mL) and $PtCl_4$ (5 mg, 10 mol%) were added under N_2 flow. To the flask, **1** (44 mg, 0.15 mmol) was added under N_2. The reaction mixture was stirred at 90 °C and was monitored by TLC. After the reaction mixture was cooled to r.t., the reaction mixture was filtered and all the solvent was evaporated under reduced pressure. A flash column chromatography on a silica gel eluting with *n*-hexane and Et_2O (8:2) gave **1B** in 80% yield.

(13) **1B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 5.62 (s, 1 H), 4.00 (dd, *J* = 11.5, 5.5 Hz, 1 H), 3.83 (dd, *J* = 11.5, 3.5 Hz, 1 H), 3.41 (d, *J* = 11.4 Hz, 1 H), 3.12 (d, *J* = 11.5 Hz, 1 H), 2.43 (s, 3 H), 2.03 (dd, *J* = 12.7, 3.8 Hz, 1 H), 1.87 (d, *J* = 12.5 Hz, 1 H), 1.13 (s, 3 H), 0.96 (d, *J* = 6.1 Hz, 1 H), 0.83 (dd, *J* = 8.3, 5.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 135.3, 129.5, 128.2, 78.7, 58.2, 39.7, 32.1, 24.0, 21.8, 20.1, 18.9, 12.0. HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}O_3NS$: 293.1086; found: 293.1087.

(14) **14B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 4 H), 7.30 (d, *J* = 8.1 Hz, 4 H), 6.10 (t, *J* = 3.2 Hz, 1 H), 3.79 (m, 2 H), 3.13 (d, *J* = 12.2 Hz, 2 H), 2.43 (s, 6 H), 1.74 (d, *J* = 3.2 Hz, 2 H), 0.96 (s, 3 H), 0.92 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 135.7, 129.8, 127.9, 63.8, 38.5, 33.0, 23.9, 21.8, 18.4, 12.9. HRMS (EI): *m*/*z* calcd for $C_{22}H_{26}O_4N_2S_2$: 446.1334; found: 446.1332.

(15) For an activation of a double bond by platinum catalyst, see: Bell, F.; Holland, J.; Green, J. C.; Gagné, M. R. *Organometallics* **2009**, *28*, 2038.

(16) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.

