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Cyclobutene Formation in $PtCl_2$-Catalyzed Cycloisomerizations of Heteroatom-Tethered 1,6-Enynes

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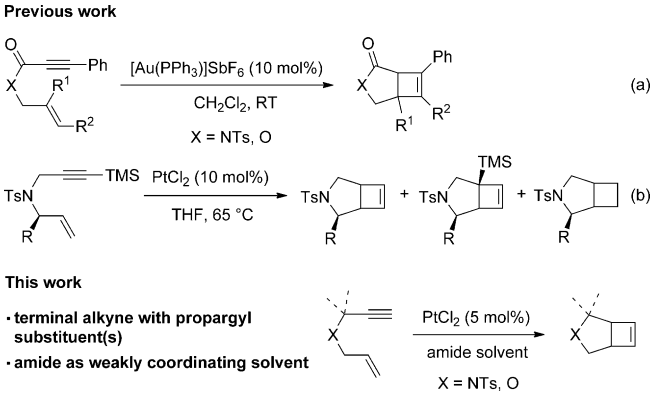
Abstract: Aza(oxa)bicyclo[3.2.0]heptenes are accessed through the $PtCl_2$-catalyzed cycloisomerizations of heteroatom-tethered 1,6-enynes featuring a terminal alkyne and amide as the solvent. It is shown that the weak coordinating properties of the solvent and alkyl substituent(s) at the propargylic carbon atom favor the formation of cyclobutenes instead of other possible cycloisomerization products such as 1,3-diene derivatives or cyclopropane-fused heterocycles.

Transition-metal-catalyzed cyclization reactions of enynes based on π-alkynophilic metal complexes have become one of the fastest growing areas in modern organic chemistry,[1] with many interesting applications to the syntheses of natural products.[2] Mechanistic investigations using theoretical calculations have been conducted to gain a more detailed understanding of the intimate processes involved in the reactions.[3] According to the nature of the catalyst and the structural patterns of enynes, the cycloisomerizations of heteroatom-tethered 1,6-enynes give rise to various (bi)cyclic compounds. Simple allyl-propargyl ethers or amines can be converted into cyclopropanated heterocycles with platinum or gold catalysts.[4] However, cyclobutene formation with these enynes remains unusual. Kang and Chung reported that cationic gold catalysts are able to convert electronically biased enynes such as allyl alkynoates (or alkynamides) into cyclobutene-fused lactones (or lactams) (Scheme 1, a), whereas platinum(II) catalysts are totally ineffective.[5] One important feature of these reactions involves the use of enynes bearing an aryl substituent at the terminus sp carbon atom to stabilize ionic intermediates. Examples of cyclobutene adducts from nitrogen-tethered enynes substituted with a TMS group at the alkyne moiety were reported, but the reactions suffer from a lack of selectivity, giving TMS-containing adducts along with protodesilylated and over-reduced compounds (Scheme 1, b).[6] It is worth noting that, to the best of our knowledge, no cyclobutene formation has been reported with heteroatom-tethered 1,6-enynes having terminal alkynes. Our group and others showed that cycloisomerizations of heteroatom-tethered enynes with *gem*-dialkyl substitution



Scheme 1. Gold- and platinum-catalyzed cycloisomerizations of heteroatom-tethered 1,6-enynes.

at the propargylic position took place with 1,2-alkyl migration to form cyclopropanated heterocycles.[7] With the knowledge that structural patterns of enynes can influence the outcome of the reactions, we examined the behavior of substrates with structural modifications on the alkyne. Herein, we report platinum-catalyzed cyclobutene formation from nitrogen and oxygen-tethered enynes with terminal alkynes and propargyl substituents through the use of amides as weakly coordinating solvents.

We initiated our studies with enyne **1a** bearing *gem*-substitution at the propargylic carbon atom and conducted a solvent screening investigation (Table 1). Alongside the typical cycloisomer products **2a** and **3**,[8] compound **1a** could also undergo a competitive [1,2]-alkyl shift, leading to ring-extended cycloisomer **5**.[7] A typical nonpolar solvent such as toluene was competent only when the reaction was carried out under a CO atmosphere[10] to give diene **3** through single bond carbon–carbon cleavage (entries 1 and 2). The reaction in MeOH afforded only the C–N bond-cleavage product **4** (entry 3). The cycloisomer **5** was not observed with the solvents screened in Table 1. Finally, we were pleased to find that amide and even imide solvents were uniquely able to produce cyclobutene **2a**[9] in satisfactory yields (entries 4–7), with DMA proving to be the best solvent (entry 7). The beneficial effect of DMA was still observed when it was used in catalytic amounts (20 mol% with respect to **1a**) in toluene, however, the yield of **2a** dramatically decreased (entry 10). Consequently, the reactions of various *N*,*N*-allylpropargylamines were conducted in DMA to give the expected cyclobutenes in fair to excellent yields (Table 2). Minor amounts of other compounds were detected (1–5%) in the ^{1}H NMR spectra of the crude reaction mixtures.

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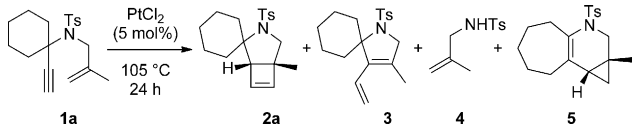
Table 1. Solvent screening for the reaction of enyne **1** with $PtCl_2$.[a]

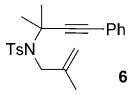


1a **2a** **3** **4** **5**

Entry	Solvent[b]	Product	Yield [%][c]
1	toluene	–	–[d]
2	toluene	**3**	65[d,e]
3	MeOH	**4**	74[f]
4	DMF	**2a**	63
5	DMPU	**2a**	88
6	NMP	**2a**	87
7	DMA	**2a**	98
8	DMA/toluene (1:1)	**2a**	78[g]
9	DMA/toluene (1:9)	**2a**	75[g]
10	DMA(20 mol%)/toluene	**2a**	63[d]

[a] Reaction conditions: $c = 0.2$ M, $PtCl_2$ (5 mol%), 105 °C, 24 h. [b] Ts = toluene-4-sulfonyl, DMF = *N*,*N*-dimethylformamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, NMP = *N*-methyl-2-pyrrolidone, DMA = dimethylacetamide. [c] Isolated yield. [d] Complex mixture of products. [e] Reaction carried out under CO atmosphere. [f] Reaction carried out at 70 °C. [g] Diene **3** (< 5%) was detected by ^{1}H NMR of the crude reaction mixture.

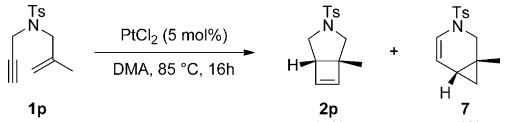
Azabicycloheptenes **2a**–**c**, featuring the spirocyclohexane ring and bearing a substituent at C-6, were observed in higher yields with respect to **2f**–**h**, exhibiting *gem*-dimethyl substitution. An enyne derivative with an allylsilane group was compatible with the reaction conditions, giving cyclobutene **2d**, with the TMS group retained.[11] Enynes monosubstituted at the propargylic position, which are prone to undergo [1,2]-H shift to give the cyclopropane-fused azacycles, were examined to evaluate the feasibility of the [2+2] cycloaddition pathway. In these cases, cyclobutenes **2j**–**m** were obtained as single diastereoisomers. The structure of **2m** and its relative stereochemistry was secured by a single-crystal X-ray diffraction analysis.[12] The diastereochemical outcome of the reaction enabled access to chiral azabicyclic alkenes. Subjecting chiral enyne (*R*)-**1l** (96% *ee*) to the cycloisomerization conditions afforded (1*S*,2*R*,5*R*)-**2l** in 62% yield and 98% *ee* after purification by chromatography. Variation of substituents at the nitrogen atom was briefly examined. Whereas the reactivity of *N*-methylsulfonyl enyne was similar to that of *p*-tolylsulfonamide **1a**, thus forming **2n** (96%), the *N*-benzoyl enyne reacted in a less satisfactory way to give **2o** in only 32% yield. Unexpectedly, enyne **6**, substituted with a phenyl group at the terminal carbon of alkyne (Scheme 2), was reluctant to undergo cycloisomerization.



6

Scheme 2. Unreactive enyne **6**.

Since the structural patterns of the enyne play an important role on the outcome of cycloisomerizations, the reactivity of unsubstituted enyne **1p** was evaluated. Under the developed conditions, cyclobutene **2p** was still formed in 17% yield alongside known cyclopropane **7**[11b] as the major cycloisomer (76%) (Scheme 3). It is noteworthy that cyclobutene **2p** was not observed when the reaction was performed in toluene.[11b] Thus, the [1,2]-H migration remains the preponderant path when no substituent is present at the propargylic carbon atom.



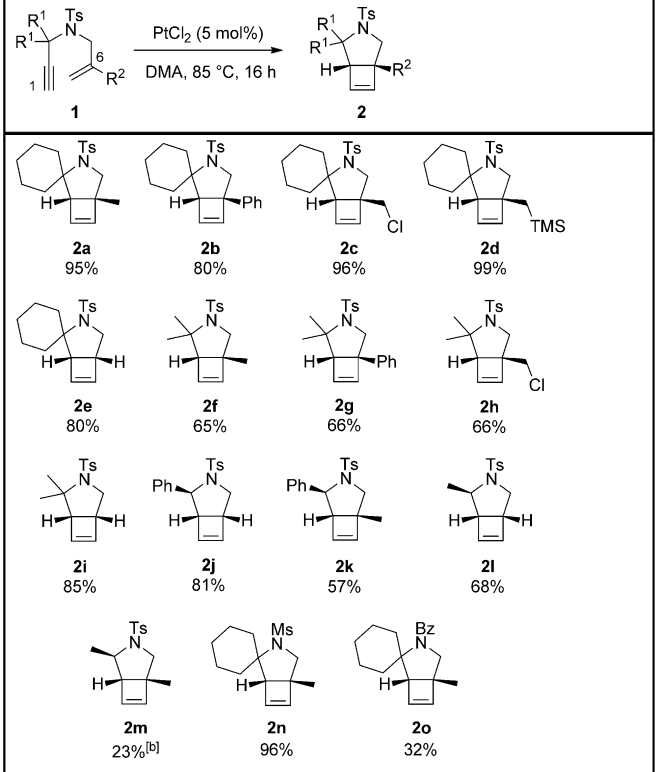
1p **2p** 17% **7** 76%

Scheme 3. Cycloisomerization of enyne **1p**.

These results suggested that, upon coordination of the alkyne to platinum, the propargylic substituent(s) induce a significant relative stabilization of the developing positive charge at the internal sp carbon through hyperconjugation. However, although this condition is necessary, it is not sufficient: DMA as the coordinating solvent plays a decisive role in the evolution of the ionic species to the cyclobutene. Nevertheless, the exact role of amide ligands in favoring the formation of cyclobutenes remains to be established.[13]

Oxygen-tethered enynes participate equally in the cycloisomerization to give the expected bicyclic ethers, although these products were more sensitive than the parent nitrogen compounds and were prone to decomposition (Table 3).[4b] To this end, the reactions of allylpropargyl ethers were performed with additional trimethylallylsilane to trap the adventitious acidic species responsible for decomposition. Cyclobutenes **9a**

Table 2. Cycloisomerization of nitrogen-tethered enynes.[a]



1 **2**

2a 95% **2b** 80% **2c** 96% **2d** 99%

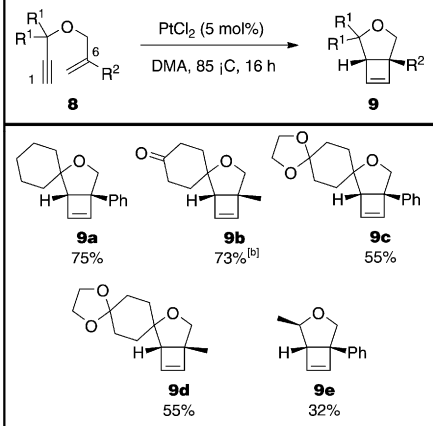
2e 80% **2f** 65% **2g** 66% **2h** 66%

2i 85% **2j** 81% **2k** 57% **2l** 68%

2m 23%[b] **2n** 96% **2o** 32%

[a] Reactions conditions: $PtCl_2$ (5 mol%), DMA (0.2 M), 85 °C, 16 h, isolated yields. [b] The remaining mass balance (65% yield) was composed of an inseparable mixture of products.

Table 3. Cycloisomerization of oxygen-tethered enynes.[a]

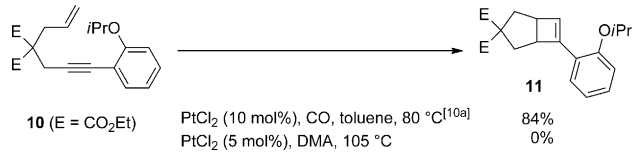


[a] Reactions conditions: $PtCl_2$ (5 mol%), allyltrimethylsilane (3 equiv), DMA (0.2 M), 80 °C, 8 h, isolated yields. [b] Reaction performed at 105 °C without allyltrimethylsilane.

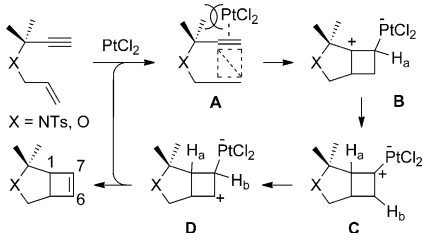
and **9b** were formed in higher yield than **9c** and **9d**, which contain an acid-sensitive protecting group. For instance, reaction of an enyne bearing a 1,3-dioxolane protecting group carried out without trimethylallylsilane afforded a mixture of **9b** and **9d**. Cyclobutene **9e**, which exhibits similar substitution patterns to those of **2m**, was formed in only 32% yield.

In this system, DMA can be regarded as a ligand (Table 1, entry 10), therefore the well-defined complex $[PtCl_2(DMA)_2]$[14] was prepared and used as catalyst (5 mol%) in toluene at 105 °C. Under these conditions, enyne **1a** was converted into cyclobutene **2a** in 56% yield along with diene **3** (11%) and *N*-prenyl-*p*-tolylsulfonamide **4** (9%). Considering the weak coordinating properties of DMA,[14] we presumed that $[PtCl_2(DMA)_2]$ is in equilibrium with $[PtCl_2(DMA)]$, and is thus able to activate alkyne coordination and to trigger the [2+2] cycloaddition. $[PtCl_2(DMA)]$, in turn, dissociates from DMA to form $PtCl_2$, which is believed to be responsible for side-product formation. To maintain a high concentration of the putative $[PtCl_2(DMA)]$, the reaction was performed with additional DMA (107 equiv with respect to Pt). These conditions suppressed the C–N bond cleavage path and afforded **2a** in increased yield (76%), along with **3** in only 5% yield. The coordinative properties of the amide (M–O bond) and the CO (M–C bond) are totally different and change the catalytic behaviour of the platinum center as highlighted by the controlled experiments described in Scheme 4. Fürstner showed that treatment of **10** with $PtCl_2$ in toluene under a CO atmosphere gave cyclobutene **11** in 84% yield.[10a] When the reaction was performed under our conditions (DMA, 105 °C), compound **10** was recovered unchanged.

Considering the peculiar structural patterns that favor the formal [2+2] cycloaddition, a mechanism based on cationic intermediates is proposed (Scheme 5). Activation of the alkyne by platinum(II) initiates cyclization of the enyne through **A** to generate a cyclobutyl cation **B**. Nonbonding interactions with substituent(s) at the propargylic carbon atom mean that the platinum cannot be located at the ring junction.[10a,15] Two consecutive [1,2]-H shifts through intermediates **C** and **D** followed by demetalation complete the formation of cyclobutene. This mechanism could explain the inertness of aryl-substituted enynes **6** and **10** and is reminiscent of the mechanism proposed for the isomerization of methylenecyclopropanes to cyclobutenes.[10c]

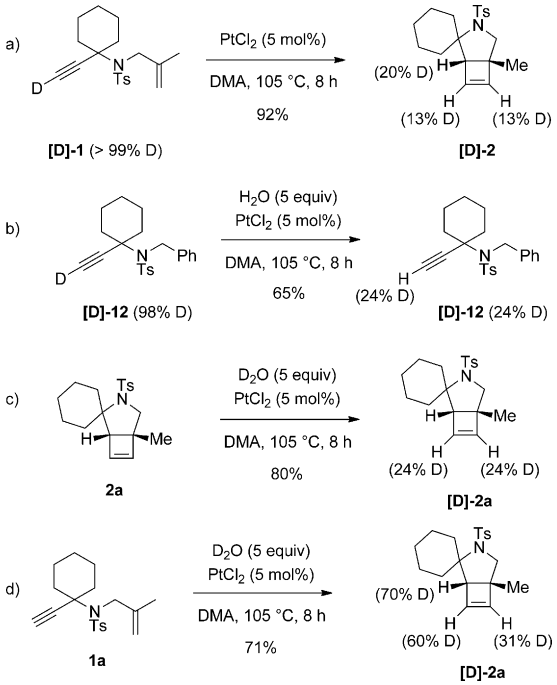


Scheme 4. Reactions of enyne **11**.



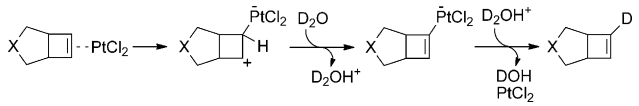
Scheme 5. Proposed reaction mechanism.

This proposal was probed with deuterium labeling experiments (Scheme 6). Cyclization of [D]-**1a** (> 99% D) gave cyclobutene [D]-**2a** with deuterium incorporation at C-1, C-6, and C-7 (Scheme 6, a). The depletion of deuterium to a significant extent was attributed to the presence of residual water. To this end, deuterium to proton exchange on terminal alkyne [D]-**12** (98% D) in the presence of H_2O was established (Scheme 6, b). This should presumably occur prior to the cyclization. The incorporation of deuterium at the sp^2 carbon atoms of [D]-**2a** is not so clear.[16] Heating cyclobutene **2a** with D_2O in the pres-



Scheme 6. Deuterium labeling experiments.

ence of $PtCl_2$ resulted in proton to deuterium exchange only at the C-6 and C-7 atoms (Scheme 6, c). Finally, consistent with the above experiments, cyclization of **1a** in the presence of D_2O formed [D]-**2a**, which exhibits the highest level of deuterium (70%) at C-1 (Scheme 6, d). These experiments are consistent with the occurrence of the "nonclassical" cation intermediate **A**, and showed that deuterium incorporation at the sp^2 carbon atoms is, to some extent, independent of the cyclization reaction. A rationale for hydrogen to deuterium exchange on sp^2 carbon atoms based on intermediate **D** (Scheme 6) is depicted in Scheme 7.



Scheme 7. Proposed mechanism for hydrogen to deuterium exchange at the sp^2 carbon atoms.

In summary, we have developed a straightforward route to 3-azabicyclo[3.2.0]hept-6-enes and their oxygen counterparts through the cycloisomerization of heteroatom-tethered 1,6-enynes catalyzed with platinum(II) dichloride. This study shows that hyperconjugation through alkyl substituent(s) at the propargyl position in conjunction with the use of DMA as a weakly coordinating solvent are the key elements favoring the formation of cyclobutenes.

Acknowledgements

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Keywords: cyclobutenes · cycloisomerization · enynes · platinum · small ring systems · solvent effects

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