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PtCl$_2$-Catalyzed Cycloisomerization of 1,6-Enynes for the Synthesis of Substituted Bicyclo[3.1.0]hexanes

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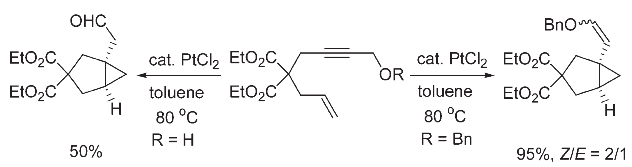
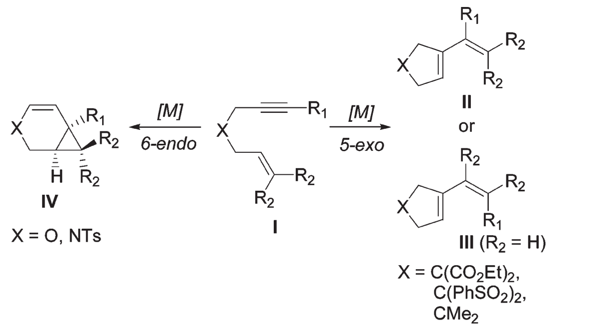


The mild and efficient PtCl$_2$-catalyzed cycloisomerization of 1,6-enynes containing a heteroatom substituent at the propargylic position is described. The reactions led to the formation of 1-alkenylbicyclo[3.1.0]hexanes in good to excellent yields or 2-(bicyclo[3.1.0]hex-1-yl)acetaldehydes in moderate yields.

Transition-metal-catalyzed cycloisomerization reactions of enynes provide a rapid access to functionalized cyclic structures.[1] Such reactions are perfectly suited to meet the high demands for atom economy[2] in newly developed methods. It was well documented that the gold and platinum complexes catalyzed the cycloisomerization reactions of 1,6-enynes to allow the generation of a variety of cyclic products under mild conditions.[3] For example, the 5-*exo-dig* cyclization of carbon-tethered 1,6-enynes afforded the 1-alkenylcyclopentene products **II** or **III** via the cyclopropyl metal carbene intermediates (Scheme 1).[4] Depending on the substituents on the alkene part, the cyclopropyl metal carbene may undergo a 1,2-alkyl migration or fragmentation steps leading to dienes **II** or **III**, the latter being generally observed in the case of monosubstituted alkenes.[1,4] On the other hand, the *O*- or *N*-tethered 1,6-enynes underwent 6-*endo-dig* cyclization to generate the metal carbenes, which led to the corresponding bicyclo[4.1.0]heptenes **IV** via 1,2-hydride migration (Scheme 1).[5] The difference in these two types of cyclic products revealed that the presence of a heteroatom in the tether might facilitate the 1,2-hydride migration of the cyclopropyl metal carbenes.[5]

SCHEME 1



We have been interested in studying the heteroatom effect when introduced into the cycloisomerization of carbon-tethered 1,6-enynes. With the above background and keeping in mind some recent reports,[6,7] we envisioned that the

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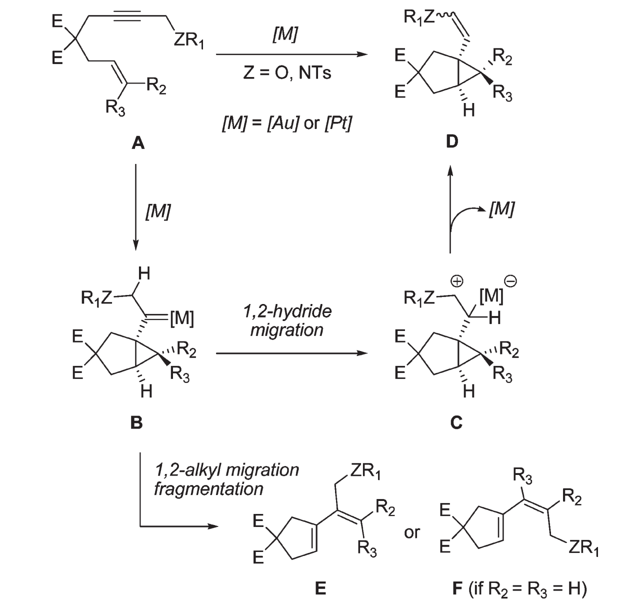
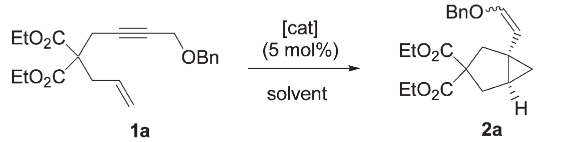
SCHEME 2



carbon-tethered 1,6-enyne **A** with a heteroatom substituent at the propargylic position might undergo 5-*exo-dig* cyclopropanation to produce the cyclopropyl metal carbene **B**, which might undergo facile 1,2-hydride migration to give zwitterion **C**.[7] Subsequent elimination of the metal fragment might produce 1-alkenylbicyclo[3.1.0]hexane **D** probably as a mixture of *Z*- and *E*-isomers (Scheme 2). A 1,2-alkyl migration step would be competitive and would give dienes **E** or **F** according to a similar process for the formations of **II** and **III**. Herein, we report that the utilization of $PtCl_2$ as the catalyst for the cyclization of 1,6-enynes provides a convenient and general approach to substituted bicyclo[3.1.0]hexanes under mild conditions.

To test the hypothesis in Scheme 2, we prepared diethyl 2-allyl-2-(4-(benzyloxy)but-2-yn-1-yl)malonate **1a**[8] as the model substrate for the optimization of reaction conditions (Table 1). We first examined the reaction of **1a** under the conventional $PPh_3AuCl/AgSbF_6$ catalysis[5e] (entry 1). When the mixture was stirred at room temperature (rt) for 10 min, the starting material was consumed, leading to a complex mixture of products including only a trace amount of the expected product **2a**. Substrate **1a** also underwent decomposition with only $AgSbF_6$ as the catalyst, while no reaction occurred under the catalysis of PPh_3AuCl alone (entries 2 and 3). We then turned to $PtCl_2$. The reaction of **1a** with 5 mol % of $PtCl_2$ in toluene did not occur at rt (entry 4). To our delight, when the reaction temperature was raised

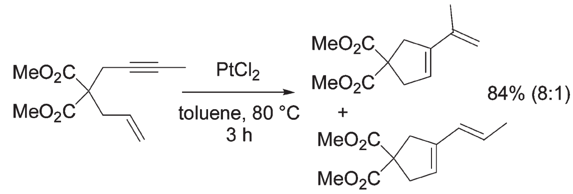
TABLE 1. Cycloisomerization of 1,6-Enyne 1a[a]



entry	catalyst [cat]	conditions	yield[b] (%)	ratio Z/E[c]
1	PPh_3AuSbF_6	CH_2Cl_2, rt, 10 min	trace[d]	n/a
2	PPh_3AuCl	CH_2Cl_2, rt, 12 h	NR	n/a
3	$AgSbF_6$	CH_2Cl_2, rt, 2 h	-[d]	n/a
4	$PtCl_2$	toluene, rt, 12 h	NR	n/a
5	$PtCl_2$	toluene, 80 °C, 1 h	99[e]	2/1
6	$PtCl_2$	toluene, 80 °C, 12 h	88	2/1
7[f]	$PtCl_2$	toluene, 80 °C, 1 h	96	3/1
8	$PtCl_2$	dioxane, 80 °C, 1 h	35[g]	2/1
9	$PtCl_2$	PhH, 80 °C, 12 h	trace[h]	n/a

[a]The reaction of **1a** (0.2 mmol) was carried out in the presence of 5 mol % of catalysts in solvents (2 mL). [b]Yield based on **1a** was determined by ^1H NMR using an internal standard; NR = no reaction. [c]Ratio was determined by ^1H NMR; n/a = not applicable. [d]Most of the material was decomposed. [e]95% isolated yield. [f]A stoichiometric amount of CH_3CN was introduced. [g]85% conversion. [h]< 5% conversion.

SCHEME 3. Murai's Cycloisomerization Reaction



to 80 °C, the reaction proceeded smoothly, the bicyclic product **2a** was achieved in 99% yield (95% isolated yield) within 1 h, and the ratio of *Z*-alkene and *E*-alkene was about 2:1 (entry 5). When this reaction was conducted for 12 h, the yield was slightly decreased to 88% due to the hydrolysis of the enol ether **2a**, where an aldehyde product was detected by ^1H NMR (entry 6). A stoichiometric amount of CH_3CN as an additive was also introduced,[9] and the expected product was obtained in 96% yield with a slight increase of the ratio of two isomers (entry 7). Switching the solvent from toluene to dioxane decreased the yield to 35% (85% conversion), and the use of benzene as the solvent led to a very low conversion (entries 8 and 9). The very low conversion observed in benzene may be due to a lower solubilization of $PtCl_2$.

The formation of bicyclo[3.1.0]hexane **2a** strongly indicates that the cyclopropyl metal carbene intermediate **B** generated from the above reaction may undergo facile 1,2-hydride migration to produce the intermediate **C** (Scheme 2). As a comparison, the reaction of the 1,6-enyne with a methyl substituent at the alkyne terminus under the same conditions reported by Murai[4b] afforded 1-alkenyl-1-cyclopentene products, while no bicyclo[3.1.0]hexanes were observed (Scheme 3). Therefore, the heteroatom effect is proved to be indispensable in the formation of bicyclo[3.1.0]hexanes such as **2a**.

With the optimized conditions in hand (entry 5, Table 1), we then set out to explore the generality of this method. The results are summarized in Table 2. A number of heteroatom substituents at the propargylic position of substrates **1** were

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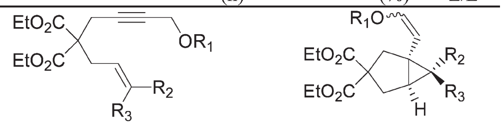
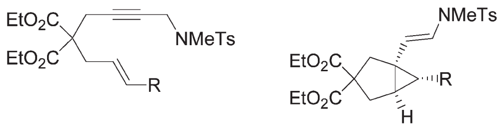
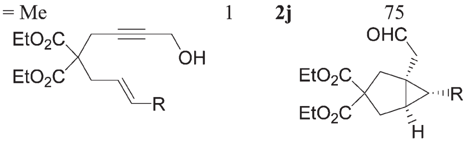
TABLE 2. $PtCl_2$-Catalyzed Cycloisomerization of 1,6-Enynes 1[a]

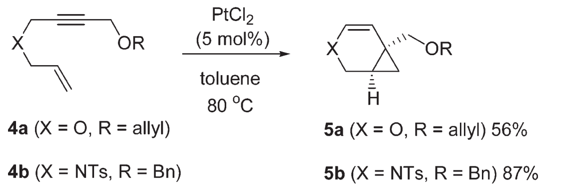
Entry	Substrate	Time (h)	Product	Yield (%)[b]	Ratio *Z*/*E*[c]
					
1	**1a** R_1 = Bn; R_2 = R_3 = H	1	**2a**	95	2/1
2	**1b** R_1 = Bn; R_2 = Me; R_3 = H	1	**2b**	89	7/1
3	**1c** R_1 = Bn; R_2 = Ph; R_3 = H	24	**2c**	NR	/
4	**1d** R_1 = Bn; R_2 = R_3 = Me	48	**2d**	0	/
5	**1e** R_1 = Me; R_2 = R_3 = H	1	**2e**	85	1/1
6	**1f** R_1 = R_2 = Me; R_3 = H	1	**2f**	81	4/1
7	**1g** R_1 = TBS; R_2 = R_3 = H	2	**2g**	80	6/1
8	**1h** R_1 = TBS; R_2 = Me; R_3 = H	3	**2h**	81	1/0
					
9	**1i** R = H	1	**2i**	73	
10	**1j** R = Me	1	**2j**	75	
					
11	**1k** R = H	3	**2k**	50	
12	**1l** R_1 = Me	9	**2l**	42	

[a]All reactions were carried out with **1** (0.2 mmol) in the presence of 5 mol % of $PtCl_2$ in toluene (2 mL) at 80 °C. [b]Isolated yield based on **1**. [c]Ratio was determined by ^{1}H NMR.

well tolerated, including benzyloxy (entries 1 and 2), methoxy (entries 5 and 6), siloxy (entries 7 and 8), sulfonamidyl (entries 9 and 10), and hydroxyl (entries 11 and 12) groups, leading to the corresponding substituted bicyclo[3.1.0]-hexanes products in 42−95% yields.

The range of heteroatoms used and their corresponding substituents (Bn, H, TBS) leads one to preclude the idea of a heteroatom chelation effect.[10] In all the cases tested, no corresponding 6-*endo-dig* cyclization products could be detected. The stereoselectivity was based on the proposed mechanism for the Pt-catalyzed reaction.[5,11] It is worth mentioning that alcohols **1k** and **1l** produced aldehydes **2k** and **2l**, respectively, via enol intermediates in moderate yields, while no products resulting from the intramolecular attack of the hydroxyl group on the cyclopropyl metal carbene intermediates were observed.[12] Such behavior had been already observed on an analogous 1,6-enyne derivative of **1k**.[7b] Also noteworthy is the cyclization of substrates

SCHEME 4. $PtCl_2$-Catalyzed Reactions of 1,6-Enynes 4a and 4b



containing a sulfonamidyl substituent in which the expected products were achieved as single *E*-isomers (entries 9 and 10). The reactivities of substrates with a terminal vinylic substituent were also investigated. The cyclization reactions of methyl substituted *E*-alkenes afforded the desired products in good to excellent yields with higher ratios of two isomers due to the possible steric effect (entries 2, 6, and 8). Surprisingly, the reaction of phenyl-substituted *E*-alkene **1c** did not occur (entry 3). Trisubstituted alkene **1d** did not afford the corresponding bicyclic product. Instead, alkenylmethylenecyclopentane **3** was isolated in 68% yield[13] (entry 4).

To further expand the scope of this method, we also carried out the cycloisomerization of *O*-tethered 1,6-enyne **4a** and *N*-tethered 1,6-enyne **4b**. As anticipated,[5] only 6-*endo dig* cyclization was observed leading to the formation of bicyclo[4.1.0]heptenes **5a** and **5b** in 56% and 87% yields, respectively (Scheme 4).

In summary, we have extended and developed an efficient $PtCl_2$-catalyzed method for the synthesis of substituted bicyclo[3.1.0]hexanes from carbon-tethered 1,6-enynes with heteroatom substituents at the propargylic position. Further studies will be focused on applications of this methodology.

Experimental Section

General Procedure for Pt-Catalyzed Cyclization Reaction. To the solution of diethyl 2-allyl-2-(4-(benzyloxy)but-2-ynyl)-malonate (**1a**) (72 mg, 0.2 mmol) in dry toluene (2 mL) was added $PtCl_2$ (2.7 mg, 0.01 mmol) under nitrogen atmosphere. The mixture was stirred at 80 °C for 1 h. After removal of the solvent, the residue was then purified by flash chromatography on silica gel using hexane−ethyl acetate (15:1) as the eluent to give bicyclo[3.1.0]hexane **2a** (68.5 mg, 95% yield) as a colorless oil.

Two isomers in 2:1 ratio: ^{1}H NMR (400 MHz, $CDCl_3$) *Z*-isomer δ 7.29−7.38 (5H, m), 5.92−5.94 (1H, d, J = 6.8 Hz), 4.77 (2H, s), 4.32−4.33 (1H, d, J = 6.8 Hz), 4.11−4.21 (4H, m), 2.80 (1H, d, J = 14.0 Hz), 2.45−2.63 (3H, m), 1.43−1.48 (1H, m), 1.22−1.28 (6H, m), 0.78 (1H, t, J = 7.6 Hz), 0.44 (1H, dd, J = 5.6, 4.4 Hz); *E*-isomer δ 7.29−7.38 (5H, m), 6.34−6.37 (1H, d, J = 12.4 Hz), 4.97−5.00 (1H, d, J = 12.4 Hz), 4.70 (2H, s), 4.11−4.21 (4H, m), 2.80 (1H, d, J = 14.0 Hz), 2.45−2.63 (3H, m), 1.18−1.28 (7H, m), 0.60 (1H, t, J = 7.6 Hz), 0.40 (1H, dd, J = 5.6, 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *Z*-isomer δ

(10) Even if the heteroatom substitution effect seems to be the governing element, an agostic hydrogen interaction in the cyclopropanation step cannot be ruled out.

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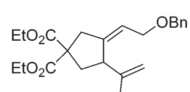
(13) The reaction of **1d** under the standard reaction conditions resulted in the complete consumption of the starting material. However, the only product isolated was **3** (68% yield). Similar results were reported by Echavarren et al. See: Mendez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511.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173.0, 172.0, 144.9, 137.7, 128.4, 127.8, 127.2, 109.3, 73.9, 61.6, 61.4, 59.8, 40.5, 35.9, 26.4, 26.0, 17.1, 14.0; *E*-isomer δ 172.7, 171.9, 146.1, 137.1, 128.5, 127. 9, 127.6, 108.7, 71.5, 61.7, 61.4, 59.7, 39.7, 36.0, 27.3, 25.2, 15.7, 14.0; ESI-MS m/z = 359.1 (M^+ + H), 381.1 (M^+ + Na); HRMS-EI calcd for $C_{21}H_{26}O_5$ (M^+) 358.1780, found 358.1772.

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Supporting Information Available: Typical experimental procedures and characterizations of compounds **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.