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Platinum-Catalyzed Cycloisomerization of 1,4-Enynes via 1,2-Alkenyl Rearrangement

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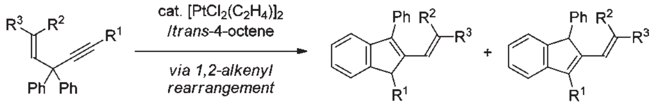
ABSTRACT



1 **2** **2′**

The cycloisomerization of 1,4-enyne 1 in the presence of platinum(II) catalyst afforded 1,2,3-trisubstituted 1*H*-indene 2 and 2′ in good to excellent yields. The reaction proceeded through an unprecedented 1,2-alkenyl rearrangement that afforded a novel reaction topology of 1,4-enynes.

The cycloisomerizations of enynes catalyzed by π-electrophilic transition metals such as platinum and gold complexes offer unique chemo- and stereoselectivities and production of unique structures, such as multisubstituted carbocycles and heterocycles, via mild reaction conditions, and thus have been indispensible for the construction of multifunctionalized carbon frameworks. Several researchers have recently expanded this cycloisomerization methodology to include short, tethered 1,4-enynes, which exhibited unique reactivities that differ from those of long-tethered enynes such as 1,5-, 1,6-, and 1,7-enynes.[1] The pioneering work of the gold-catalyzed cycloisomerization of 1,4-enynes was reported in 2005 by Toste and co-workers for their synthesis of enantioselective cyclopentenones.[2a] In the same year, Sarpong and co-workers reported an efficient pentannulation of 1,4-enynes.[2b] In both cases, the key intermediary step was the π-activation of alkynes followed by 1,2-acyloxy rearrangement, known as the Rautenstrauch rearrangement[3] (Scheme 1, a). In 2006, Nolan and co-workers reported a gold-catalyzed cycloisomerization of propargyl acetates containing an aryl moiety at the propargylic position (Scheme 1, b).[2c] A bicyclo[3.1.0]hexene synthesis that involves a 1,3-acetoxy migration was reported by Gagosz and co-workers.[2d] Although most reactions of 1,4-enynes involve the reactivity of the propargylic esters, Liu and co-workers have very recently reported the platinum-catalyzed cycloisomerization of 1,4-enynes that do not possess propargylic ester functionalities (Scheme 1, c).[2e] To the best of our knowledge, however, direct rearrangement of a carbon substituent on alkyne carbons of 1,4-enynes has yet to be reported.[4] To achieve this, we envisioned the rearrangement of carbon substituents involving 1,4-enynes as substrates; specifically, a “bulky” 1,4-enyne that favors a slipped η^1-alkyne complex (Scheme 2), which facilitates the behavior of an uncoordinated alkyne carbon as the electrophile. Herein we report the

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(1) Selected recent reviews on platinum- and gold-catalyzed enyne cycloisomerizations: (a) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (f) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936. (g) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

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(3) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950–952.

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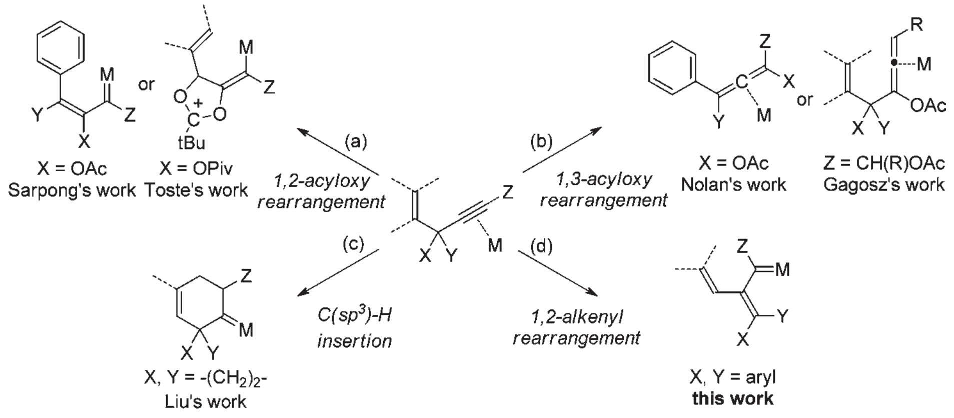
(5) Wagner−Meerwein type of 1,2-alkenyl rearrangement in a gold-catalyzed reaction: Zhao, X.; Zhang, E.; Tu, Y.-Q.; Zhang, Y.-Q.; Yuan, D.-Y.; Cao, K.; Fan, C.-A.; Zhang, F.-M. *Org. Lett.* **2009**, *11*, 4002–4004.

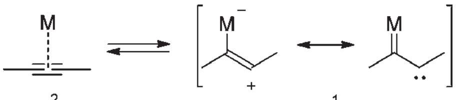
(6) 1,3-Alkenyl shift in a silver-catalyzed reaction: Oh, C. H.; Karmakar, S.; Park, H. S.; Ahn, Y. C.; Kim, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 1792–1792.

10.1021/ol202104c

Scheme 1. Intermediary Step of the 1,4-Enyne Reactions



Scheme 2. Structures of the π-Activated Alkynes



cycloisomerizations of 1,4-enynes via an unprecedented 1,2-alkenyl rearrangement,[5−7] which apparently is a novel catalytic reaction topology of 1,4-enynes (Scheme 1, d).

First, we investigated the platinum-catalyzed cycloisomerization of 1,1′,1″-(5-methylhex-4-en-1-yne-1,3,3-triyl)tribenzene (**1a**) (eq 1). In the presence of $PtCl_2$ (10 mol %), the reaction of **1a** proceeded at 100 °C in toluene to give 2-(2-methylprop-1-en-1-yl)-1,3-diphenyl-1*H*-indene (**2a**) in 39% yield. The preliminary experiment showed that platium−olefin complex $[PtCl_2(che)]_2$ exhibited good catalytic activity toward the present reaction. In contrast, the use of $AuBr_3$, instead of $PtCl_2$, gave only a trace amount of **2a**, whereas other metals such as $PdCl_2$ did not induce any reactions. Subsequently, the reaction conditions were optimized using **1b**, which afforded a mixture of 1,2,3-trisubstituted 1*H*-indene regioisomers **2b** and **2b′** (Table 1). In the presence of di-μ-chlorobis[chloro(cyclohexene)-platinum(II)] ($[PtCl_2(che)]_2$), the reaction of **1b** in cyclohexane gave regioisomers **2b** and **2b′** in a ratio of 21:79 with a combined yield of 64% (Table 1, entry 1). The use of other solvents such as toluene and α,α,α-benzotrifluoride resulted in lower yields and/or regioselectivities (Table 1, entries 2 and 3). Although the use of Zeise's dimer ($[PtCl_2(C_2H_4)]_2$) by itself was ineffective (Table 1, entry 4), the combination of Zeise's dimer and catalytic amounts of *trans*-4-octene (2.2 equiv, based on monomeric Pt) significantly improved the yield of the reaction (81%, Table 1, entry 8).[8] The use of other olefin ligands such as (−)-α-pinene and (−)-β-pinene gave the corresponding products in lower yields; the regioselectivities of the reactions, however, remained unaffected (Table 1, entries 5 and 6).

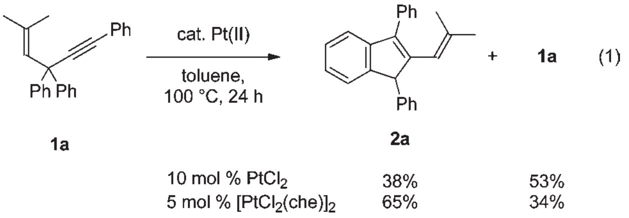
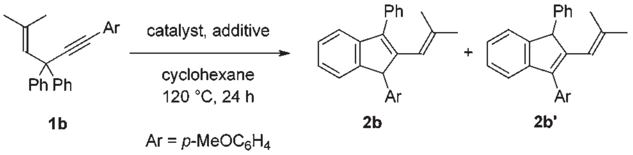


Table 1. Optimization of the Reaction of **1b**[a]



entry	catalyst	olefin	yield[b] (%)	2b/2b′	1b (%)
1	$[PtCl_2(che)]_2$	none	64	21:79	25
2[c]	$[PtCl_2(che)]_2$	none	64	27:73	21
3[d]	$[PtCl_2(che)]_2$	none	40	42:58	44
4	$[PtCl_2(C_2H_4)]_2$	none	19	23:77	64
5	$[PtCl_2(C_2H_4)]_2$	β-pinene[e]	33	24:76	54
6	$[PtCl_2(C_2H_4)]_2$	α-pinene[e]	48	22:78	44
7	$[PtCl_2(C_2H_4)]_2$	*trans*-4-octene[e]	64	23:77	19
8	$[PtCl_2(C_2H_4)]_2$	*trans*-4-octene[f]	81	24:76	2

[a] The reactions of **1b** (0.2 mmol) were carried out in the presence of the catalyst (2.5 mol %) in cyclohexane (0.4 mL) at 120 °C for 24 h, unless otherwise stated. [b] The combined yields of **2b** and **2b′** were determined using ^1H NMR with CH_2Br_2 as the internal standard. [c] In toluene instead of cyclohexane. [d] In α,α,α-benzotrifluoride instead of cyclohexane. [e] In the presence of 5.5 mol % of olefin. [f] In the presence of 11 mol % of olefin.

The results of the optimized reactions are summarized in Table 2. The reaction of **1a** in the presence of Zeise's dimer

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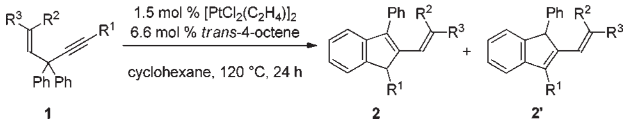
(7) A mechanistic insight for metal-catalyzed skeletal rearrangements of enynes including 1,2-alkenyl shift: Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916–5923.

(8) Enhancement of catalytic activity by the use of the olefin is presumably due to enhanced electrophilicity of the alkyne moiety in the intermediate **A** by the strongly back-donating of the olefin ligand, as well as improved solubility of the platinum catalyst by forming the olefin complex.

Table 2. Pt-Catalyzed Cycloisomerization of 1,4-Enyne **1**[a]

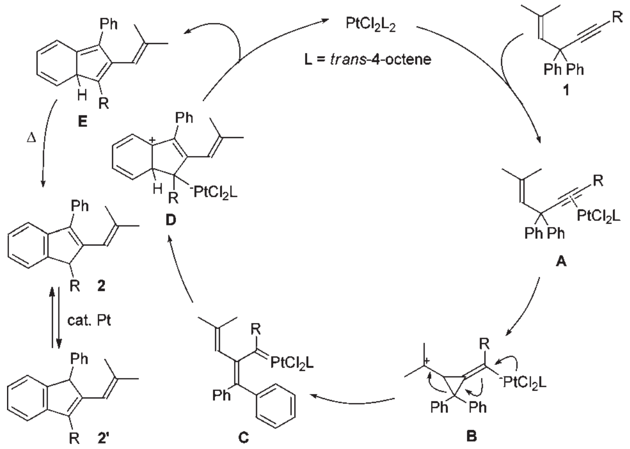


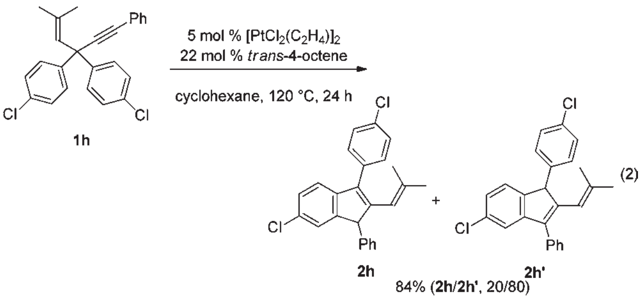
entry	**1**	R^1	R^2	R^3	yield[b] (%)	**2/2′**
1	**1a**	Ph	Me	Me	97, **2a**	
2[c]	**1b**	*p*-MeOC$_6$H$_4$	Me	Me	85, **2b** + **2b′**	23:77
3	**1c**	*p*-ClC$_6$H$_4$	Me	Me	89, **2c** + **2c′**	19:81
4	**1d**	3,5-Cl$_2$C$_6$H$_3$	Me	Me	92, **2d** + **2d′**	18:82
5	**1e**	*p*-F$_3$CC$_6$H$_4$	Me	Me	95, **2e** + **2e′**	13:87
6	**1f**	*n*-Pr	Me	Me	trace (**2f**/**2f′**)[d]	
7	**1g**	Ph	H	*p*-MeOC$_6$H$_4$	quant, **2g**	

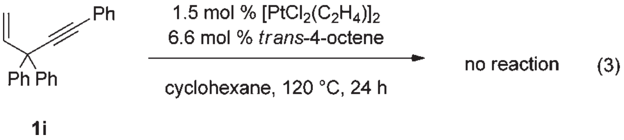
[a] The reactions of **1** (0.2 mmol) were carried out in the presence of Zeise's dimer (1.5 mol %) and *trans*-4-octene (6.6 mol %) in cyclohexane (0.4 mL) at 120 °C for 24 h, unless otherwise stated. [b] Combined yields of **2** and **2′**, except for entries 1 and 6. [c] The reaction was carried out in the presence of 3 mol % of Zeise's dimer and 13.2 mol % of *trans*-4-octene. [d] Inseparable mixture of **2f**, **2f′** and unidentified byproducts was obtained.

(1.5 mol %) and *trans*-4-octene (6.6 mol %) proceeded to give **2a** as the sole product in 97% yield (Table 2, entry 1). As a note, the reaction of **1b** required higher catalyst loadings (Zeise's dimer, 3 mol %; *trans*-4-octene, 13.2 mol %) to drive the reaction to completion to give **2b** with a yield of 85% and a regioisomeric ratio of 23:77 (Table 2, entry 2). For **1c**, **1d**, and **1e**, the reactions were carried out in the presence of Zeise's dimer (1.5 mol %) and *trans*-4-octene (6.6 mol %) to give the corresponding mixtures of products in yields of 89, 92, and 95% and ratios of 19:81, 18:82, and 13:87, respectively (Table 2, entries 3−5). The reaction of **1f** having an alkyl group at the alkyne terminus was sluggish, and an inseparable mixture including the products **2f** and **2f′** and unidentified byproducts derived from **2f** and **2f′** was obtained (Table 2, entry 6). In the case of **1g**, which possesses a *p*-methoxystyryl group instead of isobutenyl, the reaction proceeded smoothly to quantitatively afford (*E*)-isomer **2g** as the sole product (Table 2, entry 7). The reaction of **1g**, which possesses two *p*-chloro-substituted phenyl groups at the tethering quaternary carbon of the enyne, gave a mixture of **2h** and **2h′** with a yield of 84% and a ratio of 20:80 (eq 2). It is noteworthy that, in the case of **1i**, in which the alkenyl moiety is replaced with a simple vinyl group, the reaction did not proceed; moreover, **1i** remained unreacted without any decomposition (eq 3).

Scheme 3. Proposed Mechanism







A proposed mechanism of the present reaction is illustrated in Scheme 3. The in situ generation of the active catalyst species *trans*-PtCl$_2$(*trans*-4-octene)$_2$ causes the formation (via ligand exchange) of alkyne complex **A**, which possesses highly polarized η^1-character because of the bulkiness of the tethering quaternary carbon atom. The subsequent 3-*exo*-*dig* cyclization forms methylenecyclopropane carbocation **B**, in which the distal bond readily cleaves to give platinum−carbene **C**. Nucleophilic attack of the benzene ring onto the carbene moiety and subsequent protodemetalation of the resulting intermediate **D** forms tetraene **E**. Finally, **E** undergoes a [1,5]-sigmatropic rearrangement to afford **2** as one of the final products. The fact that a mixture of **2** and **2′** was obtained can be attributed to the interconversion between the regioisomers in the presence of the platinum catalyst. Although the mechanistic details remain unclear, experimental results support the reaction mechanism as described above. The structures of **2h** and **2h′**, which were confirmed by NMR spectroscopy, clearly support the intermediary 1,2-alkenyl rearrangement step despite the possibilities of alternative 1,2-aryl rearrangements; specifically, the substitution pattern of the chloro groups of **2h** and **2h′** do not indicate 1, 2-aryl rearrangement. Furthermore, the reaction of **1i** strongly implies the presence of carbocation **B** as an intermediate due to its temporary conversion into a carbocation. In addition, the much lower reactivity of **1f** having an alkyl group at the alkyne terminus than that of **1a**−**e** having an aryl group is presumably due to destabilization of the transition state of 3-*exo*-*dig* cyclization from **A** to **B** by the electron-donating alkyl group, as well as stabilization of the platinum carbene intermediate **C** by the aromatic ring.

In conclusion, we have successfully achieved a platinum-catalyzed cycloisomerization of 1,4-enynes via 1,2-alkenyl rearrangement. Further investigations into the mechanism of the 1,2-alkenyl rearrangement are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.