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Synthesis of Substituted Azulenes via Pt(II)-Catalyzed Ring-Expanding Cycloisomerization

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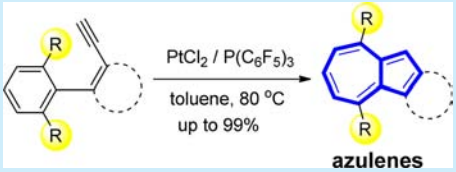
Supporting Information

ABSTRACT: Substituted azulenes, valuable structures for electronic devices and pharmaceuticals, have been synthesized by the platinum(II)-catalyzed intramolecular ring-expanding cycloisomerization of 1-en-3-yne with ortho-disubstituted benzene. This novel method provides an alternative route for the efficient synthesis of substituted azulenes. The reaction mechanism of selected catalytic transformations was explored using density functional calculations.



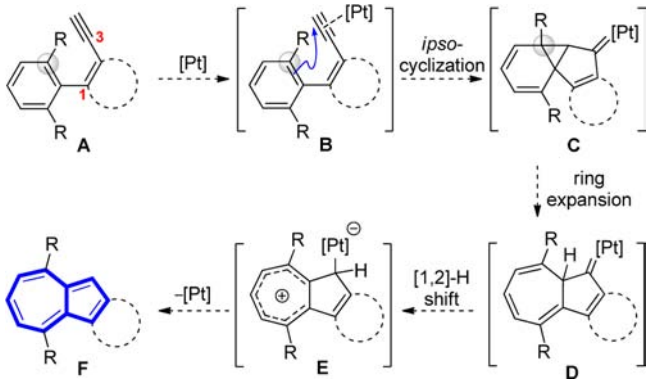
Azulene ($C_{10}H_8$) and its derivatives, which are brilliant blue nonbenzenoid aromatic hydrocarbons, have attracted much attention because of their remarkable electronic and optical properties. Significantly, azulene exhibits a large dipole moment (1.08 D) due to its ability to shift electron density from the seven-membered ring toward the five-membered ring.[1] Hence, azulene possesses a donor−acceptor character that may be exploited in advanced functional electronic, optoelectronic, and electrochromic devices.[2] Azulenes have also been utilized as building blocks for a broad range of pharmaceutically active compounds. Some synthetic azulene analogues possess antioxidative,[3] anticancer,[4] and anti-inflammatory activities.[5] Because of the wide variety of applications, the development of a simple and efficient synthesis of azulene derivatives would be very useful.

Traditional methods for the construction of an azulene scaffold include long, low-yielding synthetic procedures that in many cases do not afford the desired substitution patterns.[6] Although sophisticated synthetic methodologies for the introduction of functional groups on the seven-membered ring have been reported recently,[6a,7] it is imperative to develop facile synthetic methods for novel substitution motifs in order to extend the applications of azulenes.

π-Acidic, metal-catalyzed skeletal rearrangements of alkyne derivatives have attracted considerable attention as efficient methods to facilitate the atom-economical construction of complex molecules.[8] Matsuda and co-workers reported the synthesis of azulenophenanthrenes by the platinum-catalyzed skeletal rearrangement of 2,2′-di(arylethynyl)biphenyls.[9] We recently reported that azulene-fused helicenes are formed as a minor product through the synthetic study of 1-functionalized [5]helicenes by Pt(II)- catalyzed cycloisomerization, presumably via a cyclopropyl platinum carbene intermediate.[10]

Therefore, we sought to develop a new strategy toward the construction of azulene skeletons by Pt(II)-catalyzed cycloisomerization. We envisioned that substrate **A**, with an *ortho*-disubstituted benzene bearing a lateral 1-en-3-yne unit, could undergo Pt(II)-catalyzed cyclization of the *ipso*-carbon on the phenyl ring to produce **C**. Cyclopropyl platinum carbene **C** could yield **D** with a 7-memberd ring through a Büchner ring expansion.[7a,11] Finally, a subsequent [1,2]-H shift of **D** could afford substituted azulene **F** (Scheme 1). This is a rare example

Scheme 1. Synthetic Strategy for the Construction of Substituted Azulenes



of a Pt(II)-induced intramolecular *ipso*-cyclization of an 1-en-3-yne. In this paper, we describe the successful realization of this concept, the Pt(II)-catalyzed ring expanding cycloisomerization of **1** to give substituent azulene derivative **2**. To our knowledge, this is the first Pt(II)-catalyzed ring-expanding cycloisomerization method to prepare substituted azulenes.

As a model for this study, easily accessible substrate **1a** with an embedded 1-en-3-yne moiety was subjected to Pt(II)-catalyzed cycloisomerization (Table 1). In the presence of $PtCl_2$ (10 mol %) or $PtCl_4$ (10 mol %),[12] the reaction of **1a** proceeded at 80 °C in toluene to give the desired 5,9-dimethyl-1,2,3,4-tetrahydrobenzo[*a*]azulene **2a** in low yield (entries 1 and 2).[7d,13] Use of $PtCl_2(H_2O)$ slightly increased the yield (28%, entry 3).[14] Treatment of **1a** with $PtCl_2$ (10 mol %) under an atmosphere of CO (1 atm)[15] led to an improved yield of **2a** (56%, entry 4). Next, the influence of phosphane ligands (2 equiv compared to $PtCl_2$) such as PPh_3, P-*t*-Bu_3, $P(OPh)_3$,

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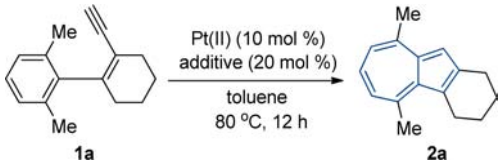
Table 1. Cycloisomerization of 1a: Investigation of Reaction Conditions[a]



			yield[b] (%)	
entry	catalyst	additive	2a	1a
1	$PtCl_2$	none	17	
2	$PtCl_4$	none	18	
3	$PtCl_2$	H_2O[c]	28	
4	$PtCl_2$	CO (1 atm)	56	
5	$PtCl_2$	PPh_3	5	45
6	$PtCl_2$	P^tBu_3	16	
7	$PtCl_2$	$P(OPh)_3$	trace	84
8	$PtCl_2$	$P(C_6F_5)_3$	93 (86)[d]	
9[e]	$PtCl_2$	COD	37	<1
10[f]	$[PtCl_2(C_2H_4)]_2$	none	23	46
11[f]	$[PtCl_2(C_2H_4)]_2$	$P(C_6F_5)_3$	47	19

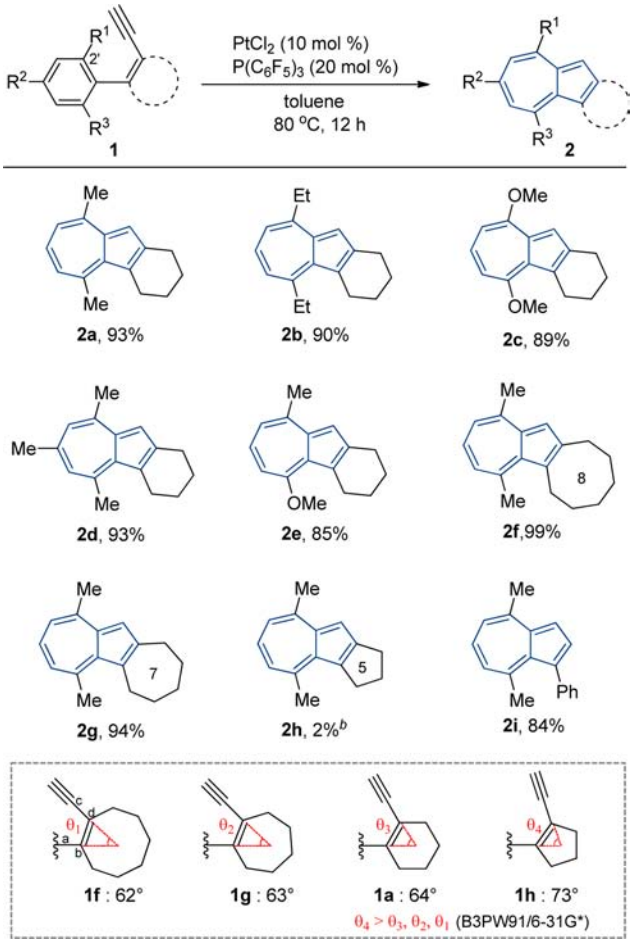
[a]Reaction conditions: reaction was performed with **1a** (0.38 mmol) and Pt catalyst (10 mol %) in toluene (1.5 mL) at 80 °C for 12 h. [b]Yield of isolated product. [c]Reaction was performed in wet toluene. [d]Yield in parentheses refers to the ratio of Pt:ligand = 1:1. [e]Reaction carried out for 12 h at room temperature. [f]The catalyst loading was 5 mol %. Reaction carried out for 1 h at room temperature. COD = 1,5-cyclooctadiene.

and $P(C_6F_5)_3$ was examined (entries 5–8). In contrast to the phosphane-free conditions (entries 1–3), the reaction was retarded and gave diminished yields (entries 5–7). Interestingly, the addition of strongly π-accepting ancillary phosphine ligand $P(C_6F_5)_3$ led to a drastic increase in the yield of **2a** to 93% (entry 8).[16] The use of COD as an additive gave **2a** at room temperature, but in a poor yield (37%, entry 9). Although the use of Zeise's dimer ($[PtCl_2(C_2H_4)]_2$) by itself was ineffective (entry 10), the combination of Zeise's dimer and catalytic amounts of $P(C_6F_5)_3$ (2 equiv, based on monomeric Pt) improved the yield of the reaction (47%, entry 11). Thus, the use of $PtCl_2$ (10 mol %) and $P(C_6F_5)_3$ in toluene at 80 °C was found to be the most efficient and was subsequently used as the standard condition.

With the optimized reaction conditions in hand, we screened the scope of alkynes for the cycloisomerization (Scheme 2).[17] A variety of derivatives bearing different substituents at the *ortho*-position of the phenyl ring ($R^1 = R^3 =$ Et, $R^2 =$ H (**1b**), $R^1 = R^3 =$ OMe, $R^2 =$ H (**1c**), $R^1 = R^2 = R^3 =$ Me (**1d**)) were well-tolerated, affording the products in high yields (84–93%). When using an unsymmetric alkyne **1e** ($R^1 =$ Me, $R^2 =$ H, $R^3 =$ OMe), a highly regioselective cycloisomerization occurred on the *ipso* carbon of the methyl group side. This observed regioselectivity would be attributed to the higher electron density at *ipso* carbon atom ($C^{2'}$) of alkyne **1e** (Figure S3, Supporting Information). The structure of **2e** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[18]

In addition, we found that the cycloalkenyl ring size had an influence on the reaction. Although **1f** and **1g** bearing a 8- or 7-membered ring showed almost the same yield (94–99%) as that of **1a** with a 6-membered ring, **1h** with a small 5-membered ring was converted in very low yield (2%) into the corresponding **2h**. The differences in reactivity should be

Scheme 2. Scope of the Platinum(II)-Catalyzed Ring-Expanding Cyclisomerization[a]



[a]Isolated yield. [b]58% of **1h** was recovered.

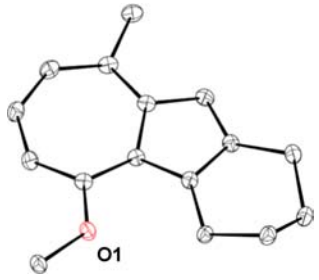


Figure 1. X-ray crystallographic structure of **2e**.

primarily attributed to increasing of the θ angle (see within a square dotted line, Scheme 2). Moreover, **2i** was also successfully formed, which might expand the scope of the products.

To gain insight into the reaction mechanism and to rationalize how the $P(C_6F_5)_3$ ligand influences the reaction, a computational DFT study was carried out using the B3PW91 hybrid functional with Gaussian 09 programs (LANL2DZ for Pt atom and 6-31G* for other atoms).[19] The computed energy profile of the favored pathway between **1a** and **2a** is illustrated in Figure 2 and shows the relative Gibbs free-energies in the gas phase. For both Pt(II) catalytic systems, the reactions begin with coordination of Pt to the alkyne framework forming a π-complex $\mathbf{IM1}_{a/b}$, which is much more exergonic for ligand-free,

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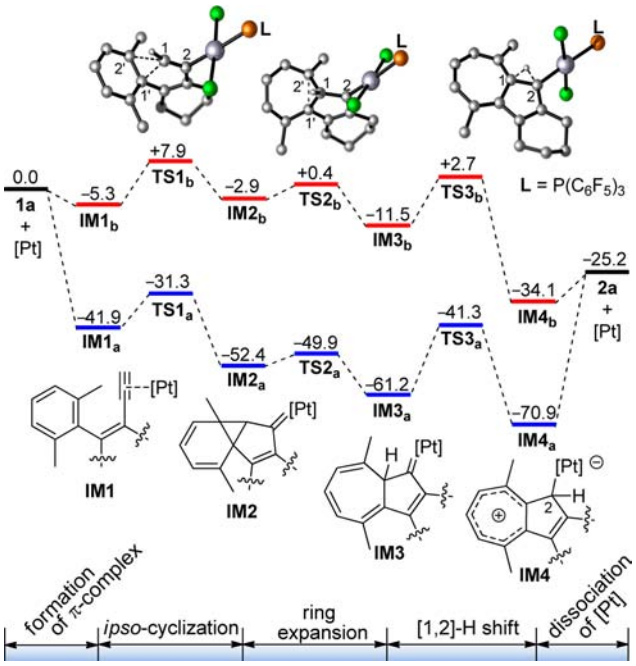

Figure 2. Computational investigation of the cycloisomerization pathway. The relative free energies (kcal mol^{-1}, at 298 K) for stationary points were calculated using B3PW91 with the 6-31G* basis set for P, F, C, and H and LANL2DZ for Pt. Most of the hydrogen atoms have been omitted for clarity. IM = intermediate, TS = transition state.

$IM1_a$ (−41.9 kcal mol^{-1} for $PtCl_2$ vs −5.3 kcal mol^{-1} for $(C_6F_5)_3P{\cdot}PtCl_2$).[20a] The next *ipso*-cyclization step would give the cyclopropyl platinum carbene **$IM2_{a/b}$** via **$TS1_{a/b}$**, involving energy barriers of 10.6 and 13.2 kcal mol^{-1}, respectively.[21] The formation of **$IM2_a$** from **$IM1_a$** is exothermic at −10.5 kcal mol^{-1}, whereas the conversion of **$IM1_b$** → **$IM2_b$** is slightly endothermic at 2.4 kcal mol^{-1}. The Büchner ring expansion to **$IM3_{a/b}$** with a 7-membered ring would be quite facile (barriers of less than 3 kcal mol^{-1}) and did not depend on the nature of the $(C_6F_5)_3P$ ligand. From **$IM3_{a/b}$**, a platinum σ-bond complex **$IM4_{a/b}$**[23] would be formed by a [1,2]-hydride transfer via **$TS3_{a/b}$** with energy barriers of 19.9 and 14.2 kcal mol^{-1}, respectively.

$PtCl_2$ dissociation from **$IM4_a$** was found to be highly endergonic (45.6 kcal mol^{-1}),[20b] as the geometry of **$IM4_a$** showed a strong interaction between the C^2 and Pt atoms, with a C^2−Pt separation of 2.04 Å. It may be responsible for the catalyst deactivation of $PtCl_2$. Moreover, positive-mode ESI-HRMS (in acetonitrile) of the prepared aliquot of the mixture of **2a** and $PtCl_2$ gave an ion peak, m/z 440.07, consistent with the platinum species $[\mathbf{2a}\text{-PtCl}]^+$ ($C_{16}H_{18}ClPt$, calcd m/z 440.07).[24] This result implies that **$IM4_a$** could be formed in this cycloisomerization reaction. In comparison with **$IM4_a$**, the $(C_6F_5)_3P{\cdot}PtCl_2$ dissociation energy from **$IM4_b$** was significantly lower (8.9 kcal mol^{-1}).[20b] The longer C^2−Pt bond (2.21 Å) of **$IM4_b$** suggested that the C^2−Pt bond was weaker than that of **$IM4_a$**. This result agreed well with the low value of the C^2−Pt bond order in **$IM4_b$**.[25] Thus, the dissociation of Pt would be thermodynamically favorable in the presence of the $P(C_6F_5)_3$ ligand. These calculations substantiate the beneficial effect of $P(C_6F_5)_3$ whose coordination facilitates the platinum catalyst dissociation, leading to the formation of **2a**.

In conclusion, we have developed a platinum(II)-catalyzed intramolecular ring-expanding cycloisomerization for the synthesis of substituted azulenes from 1-en-3-yne with *ortho*-disubstituted benzene, using phosphine ligands for the Pt catalyst. It is a simple and efficient method for constructing substituted azulenes. We believe that this method should provide a new approach toward functional azulene synthesis. Further studies regarding the expansion of the substrate scope are in progress in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details including synthesis, characterization data (^1H and ^{13}C NMR, IR, and mass spectrometry), and computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectroscopy.

(18) CCDC 1016769 (**2e**) 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.

(19) See the Supporting Information for details.

(20) (a) Basis set superposition errors (BSSE) corrected binding energy of alkyne **1a** is computed to be −46.6 and −14.2 kcal mol^{-1} for $PtCl_2$ and $(C_6F_5)_3P{\cdot}PtCl_2$, respectively. (b) $PtCl_2$ and $(C_6F_5)_3P{\cdot}PtCl_2$ dissociation energy from **IM4**$_{a/b}$ is computed to be ΔE_{BSSE} = 51.0 kcal mol^{-1} and ΔE_{BSSE} = 16.8 kcal mol^{-1}, respectively..

(21) This energy difference can be understood by comparing the key C−C distances in transition states **TS1**$_a$ and **TS1**$_b$, which shows that the calculated C1−C1′ and C1−C2′ distances are 2.18 and 2.63 Å, respectively, in **TS1**$_b$, but longer in **TS1**$_a$ (2.27 and 2.69 Å) reflecting an earlier transition state and hence energetically lower transtion state.[22]

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(24) On the basis of theoretical isotope pattern modelling, a monoisotopic peak (m/z = 440.07) represents a complex of the cationic portion ([**2a**-PtCl]$^+$) of **IM4**$_a$, consistent with the loss chloride (Figure S1, Supporting Information).

(25) Wiberg bond indices (WBI) for the C^2-Pt bond in model of **IM4**$_b$ bear a WBI of 0.396, which is relatively lower than that of **IM4**$_a$ (WBI = 0.711).