C–H Activation

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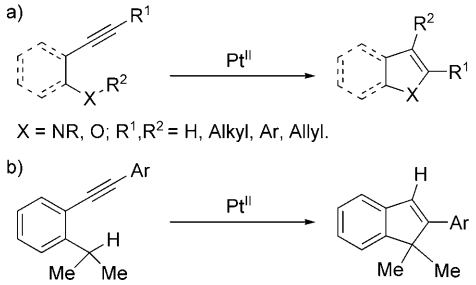
Platinum(II)-Catalyzed Intramolecular Cyclization of *o*-Substituted Aryl Alkynes through sp^3 C–H Activation**

*Shangdong Yang, Zigang Li, Xing Jian, and Chuan He**

Selective C–H bond functionalization is a potentially valuable approach for synthesis in areas ranging from fuels and commodity chemicals to pharmaceuticals.[1] Since Shilov and co-workers reported the platinum(II)-catalyzed oxidation of methane to methanol in 1972,[2a] extensive exploration of sp^3 C–H bond activation with platinum complexes has occurred.[2,3] Platinum salts have also been utilized to induce cyclization of alkynes for syntheses of five-membered carbo- and heterocycles (Scheme 1 a).[4] However, direct carbocyclization through sp^3 C–H bond activation is still rare (Scheme 1 b).[5] Such a method provides convenient access to highly functionalized indenes, which are abundant in natural products and pharmaceuticals.[6]

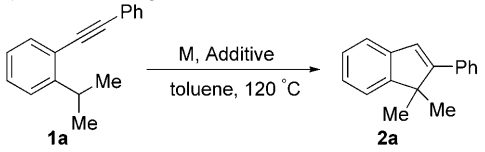


Scheme 1. Pt^{II}-catalyzed intramolecular cyclization.

To date, there has only been one report demonstrating a Pt-vinylidene carbene insertion into the C–H bond of benzylic carbon.[7] Herein, we describe the development of a platinum-catalyzed intramolecular cyclization of *o*-isopropyl or *o*-benzyl arylalkynes into functionalized indenes through sp^3 C–H bond activation. The preliminary mechanistic study suggested an uncommon 1,4-hydrogen migration pathway.

We previously found that gold(III) salts can catalyze sp^3 C–H bond activation for construction of a C–N bond.[8] We tested both Ph_3PAuCl and $AuCl_3$ for the reaction shown in Table 1. This reaction could occur but yields were low (13 and 17%, respectively). Thus, we turned our attention to other transition metals. Since platinum is well known for its ability to activate inert C–H bonds, we examined platinum complexes. When an *o*-isopropyl arylalkyne (**1a**) was heated with 5 mol% $PtCl_2$ in toluene at 120°C for 36 h, 1,1-dimethyl-2-phenylindene (**2a**) was isolated in 36% yield. Encouraged by this result, we further optimized the reaction conditions. Increasing the catalyst loading (10 mol%) proved worthwhile, and **2a** was isolated in 52% yield in 36 h, but the substrate was still not converted completely. Other metal salts, such as $AgBF_4$, $Pd(OAc)_2$, and $Cu(OTf)_2$, could not promote the same reaction. A screen of additives revealed that the use of CuBr (2.0 equiv) improved the reaction yield of **2a** to 82%. The addition of CuBr effectively reduces dimerization of the alkyne substrate, but the exact reason is still unclear.

Table 1: Cyclization through C–H activation under different conditions.[a]



Entry	MX (mol%)	Additive (equiv)	Yield [%][b]
1	$[Au(PPh_3)_2Cl]$ (5.0)		13
2	$AuCl_3$ (5.0)		17
3	$PtCl_2$ (5.0)		36[c]
4	$PtCl_2$ (10.0)		52[c]
5	$[Pt(cod)Cl_2]$ (10.0)		<5
6	$[Pt(PPh_3)_2Cl_2]$ (10.0)		<5
7	$[(diimine)Pt^{II}(Me)(tfe)]^+[BF_4]^-$ (10.0)		23
8	$PtCl_2$ (10.0)	$CuCl_2$ (2.0)	76[c]
9	$PtCl_2$ (10.0)	$CuCO_3$ (2.0)	<10
10	$PtCl_2$ (10.0)	$Cu(OAc)_2$ (2.0)	<10
11	$PtCl_2$ (10.0)	$Cu(OTf)_2$ (2.0)	<10
12	$PtCl_2$ (10.0)	CuCl (2.0)	71[c]
13	$PtCl_2$ (10.0)	CuBr (2.0)	82[c]
14	$PtCl_2$ (10.0)	CuBr(1.0)	66[c]
15	$PtCl_2$ (10.0)	CuI (2.0)	<10
16	$PtCl_2$ (10.0)	AgF (2.0)	<10
17	$PtCl_2$ (10.0)	$ZnCl_2$ (2.0)	<10
18	$Pd(OAc)_2$ (10.0)	CuBr (2.0)	5
19	$CuCl_2$ (10.0)		0
20	CuBr (10.0)		0

[a] All the reactions were carried out in the presence of 0.5 mmol **1a** in 5 mL toluene at 120°C for 36 h. [b] GC yields with *n*-decane as an internal standard. [c] Yields of isolated products. cod = cyclooctadiene; diimine = 1,4-bis(2,6-diisopropylphenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene; tfe = CF_3CH_2OH; Tf = trifluoromethanesulfonyl.

Different alkynes were prepared and subsequently examined under the optimal reaction conditions. Both methyl- and ethyl-substituted substrates failed to yield products (Table 2,

[*] S. Yang, Z. Li, X. Jian, Prof. C. He
Department of Chemistry, University of Chicago
929 East 57th Street, Chicago, IL 60637 (USA)
Fax: (+1) 773-702-0805
E-mail: chuanhe@uchicago.edu
Homepage: http://he-group.uchicago.edu/

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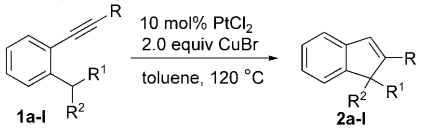
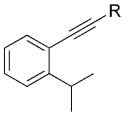
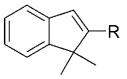
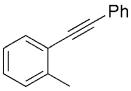
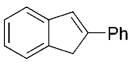
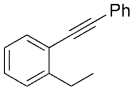
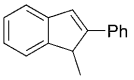
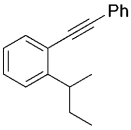
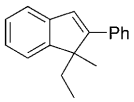
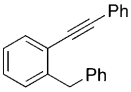
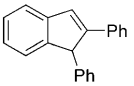
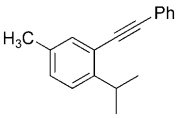
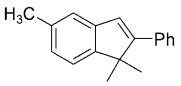
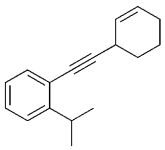
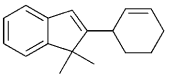
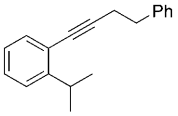
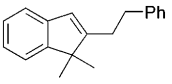
Table 2: $PtCl_2$-catalyzed cyclization with different substrates.[a]

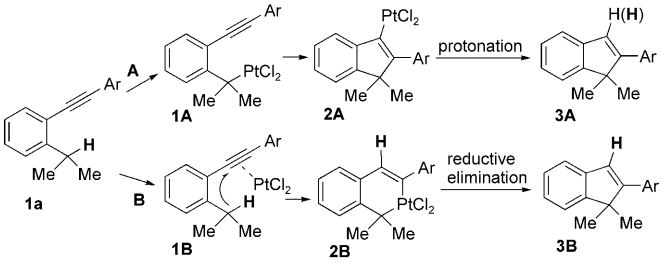


Entry	Substrate	Product	Yield [%][b]
1	 **1a** R = Ph, **1b** R = H, **1c** R = *p*-CH_3-Ph, **1d** R = *p*-OCH_3-Ph, **1e** R = *m*-Cl-Ph		**2a** 82, **2b** 79, **2c** 83, **2d** 72, **2e** 66
2	 **1f**		**2f** 0
3	 **1g**		**2g** 0
4	 **1h**		**2h** 76
5	 **1i**		**2i** 78
6	 **1j**		**2j** 81
7	 **1k**		**2k** 53
8	 **1l**		**2l** 71

[a] All of the reactions were carried out on the 0.5 mmol scale. [b] Yields of isolated products.

entries 2 and 3); reactions with substrates having weak C–H bonds proceeded smoothly, to afford the corresponding indene derivatives with good yields and high selectivity (Table 2, entries 1, 4–8). This reaction tolerates functional groups, such as methyl, methoxy, and chloride, at different positions of the aromatic ring. Electron-rich substituents at the aromatic ring were beneficial for this transformation, whereas an electron-withdrawing group on the ring decreased the reaction efficiency. This cyclization is regioselective and chemoselective. Compared with the previous methods, it is simple and works under relatively mild conditions.

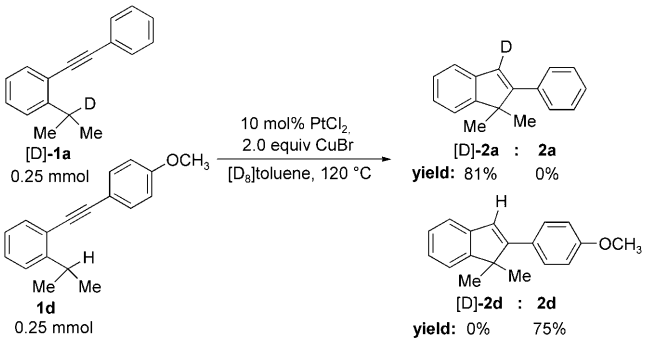
Platinum-catalyzed cyclization of alkynes commonly occurs with accompanying hydrogen or other group migration.[9] Several potential mechanistic scenarios could be considered based on our result and existing knowledge (Scheme 2). A reasonable first step is an electrophilic attack of the C–H group with platinum aided by binding to the



Scheme 2. Potential reaction mechanisms.

neighboring alkyne. Then, subsequent addition of the alkyl-Pt to the alkyne and protonation affords the product **3A** (Scheme 2, pathway A). A second plausible mechanism is proposed in pathway B (Scheme 2). Similar to Pd, Au, Ru, and Rh,[10] platinum may insert into an alkyne to form a vinyl-platinum species, which attacks the isopropyl C–H bond and 1,4-hydrogen migration to give rise to the six-membered-ring intermediate **2B** (this could be a concerted step). Reductive elimination yields the final product **3B**. Alternatively, the alkyne-bound platinum(II) could abstract a hydride from benzylic C–H to form a benzylic carbocation, which further reacts with the alkenyl-platinum(II) to afford the five-membered ring.[10f]

To gain further understanding of the mechanism, a deuterium labeling experiment with a mixture of deuterium-substituted *o*-isopropyl phenylalkyne (**[D]-1a**) and *o*-isopropyl *p*-methoxyphenylalkyne (**1d**) was carried out in the same flask under standard reaction conditions (Scheme 3). After the reaction only two products, **[D]-2a** (labeled with 100% deuterium at the C-2 position) and **2d**, were obtained. There was no deuterium labeling at other positions of the products. Potential thermally induced indene isomerizations did not seem to occur either.[11] The lack of proton scrambling rules out pathway A in Scheme 2. All our data, in particular the isotope labeling experiment, favor pathway B in Scheme 2. More detailed experiments are required to fully elucidate the mechanism of this reaction in the future.



Scheme 3. Deuterium labeling experiment with a mixture of [D]-**1a** and **1d**.

In summary, we have succeeded in the catalytic synthesis of indene derivatives through an intermolecular sp^3 C–H bond activation of *o*-isopropyl arylalkynes and *o*-benzyl arylalkynes. To our knowledge, only a few examples of 1,4-palladium migration have been observed in the past.[12] The unusual 1,4-alkyl hydrogen migration derived from C–H bond activation has not been reported. Further mechanistic studies may provide insight into this interesting activity. The method also provides efficient access to substituted indenes.

Experimental Section

1-Isopropyl-2-(phenylethynyl)benzene (**1a**; 110.0 mg, 0.5 mmol), CuBr (134.0 mg, 1.0 mmol, 2.0 equiv), and $PtCl_2$ (13 mg, 0.05 mmol, 0.1 equiv) were added to a Schlenck tube. After the addition of toluene (5.0 mL) by syringe, the reaction mixture was heated at 120 °C in an oil bath for 36 h. After the reaction was complete, the dark solid was removed by filtration through Celite, and the Celite bed was washed with diethyl ether (3 × 5 mL). In most cases, the combined filtrate was immediately concentrated, and the residue was purified by silica gel chromatography with hexanes. The desired product **2a** was dried under oil-pump vacuum.

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