

# Pt<sup>IV</sup>-Catalyzed Cyclization of Arene–Alkyne Substrates via Intramolecular Electrophilic Hydroarylation

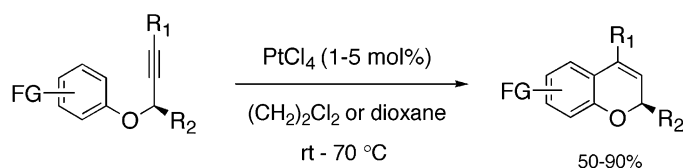
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## ABSTRACT



We herein report that PtCl<sub>4</sub> has proven to be a hydroarylation catalyst with an efficiency and substrate scope superior to previously known methods. This catalyst demonstrated consistent performance with arene–yne substrates of diverse structural features, including propargyl ethers, propargylamines, and alkynoate esters, providing good to excellent yields of the 6-endo products (chromenes, dihydroquinolines, and coumarins). In contrast, Pt(II), Pd(II), and Ga(III) salts were shown to be sensitive to the substitution on the alkyne moiety.

Intramolecular hydroarylation, a formal addition of arene C–H bonds across multiple bonds in an intramolecular manner, provides a direct route to valuable organic compounds such as annulated arene heterocycles and carbocycles. In contrast to the Heck reaction, a hydroarylation approach not only eliminates the requirement for a halogen (or triflate) substituent but also allows for multiple mechanistic possibilities, which in turn may lead to different regioisomeric products (Figure 1). These alternative mechanistic routes

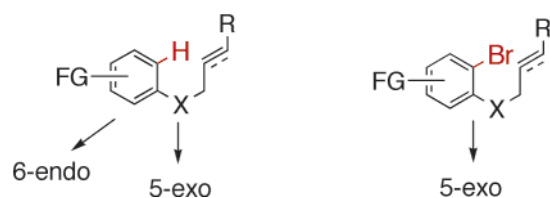


Figure 1. Hydroarylation vs Heck reaction.

include arene metalation–Heck-type addition,<sup>1</sup> multiple bond activation–electrophilic substitution,<sup>2</sup> and metal-catalyzed Claisen rearrangement (Figure 2).<sup>3,4</sup>

We focused our initial efforts in this area on the cyclization of alkyne substrates, specifically propargylic aryl ethers.

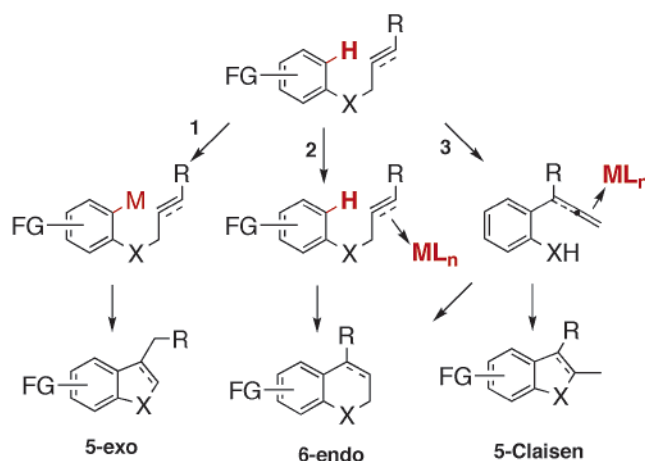


Figure 2. Intramolecular hydroarylation of alkynes and alkenes. Alternative mechanistic possibilities: (1) metalation–alkene/alkyne insertion, (2) alkene/alkyne activation–electrophilic substitution, (3) metal-mediated Claisen rearrangement. X = O, S, NR.

Propargyl ether **1**, the parent member of this class, was selected as the first substrate for screening of a broad spectrum of metal salts and complexes. We assured that reagents and catalysts, reported previously to either promote reactivity of alkenes and alkynes toward nucleophiles or facilitate metalation of arenes, were included in the screen. The experiments were conducted in parallel in a reaction block and analyzed by automated HPLC. Thirty metal salts and complexes were evaluated under approximately 80 reaction conditions in total (Table 1, for complete data, see the Supporting Information).

**Table 1.** Selected Data from a Systematic Screening

catalyst	solvent	yield of <b>2</b> ( <b>1</b> ) <sup>a</sup>	ref
AgBF <sub>4</sub>	CHCl <sub>3</sub>	0 (96)	3
AuCl <sub>3</sub>	toluene	6 (82)	8
GaCl <sub>3</sub>	toluene	3 (103)	9
Pd(OAc) <sub>2</sub> /NaOAc	HCO <sub>2</sub> H	18 (25)	4
Pd(OAc) <sub>2</sub>	TFA	0 (0)	5
Pd(CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub>	CH <sub>3</sub> CN	0 (56)	6
PtCl <sub>2</sub>	toluene	3 (74)	2
<b>PtCl<sub>4</sub></b>	<b>CH<sub>2</sub>Cl<sub>2</sub></b>	<b>32 (7)</b>	<b>11</b>
	toluene	19 (30)	
	THF	18 (36)	

<sup>a</sup> Conditions: 5 mol % catalyst, substrate **1** (0.2 M), rt, 12 h. The yield was determined by HPLC in the presence of an internal standard. Thirty metal salts/complexes were examined under 80 experimental conditions in total. For complete data see the Supporting Information.

Such a matrix rapidly unveiled the incompetence of many known methods for alkyne activation, as low or no yields of **2** were observed (<6%, Table 1) in nearly all experiments. A notable exception was the method based on the use of Pd(OAc)<sub>2</sub>, NaOAc, and formic acid, which has previously been developed for the synthesis of coumarins via coupling of alkynoate esters and electron-rich phenols.<sup>4</sup> In our screen, this protocol showed a promising yield of 18%; however, upon closer examination, it showed limited substrate scope and low isolated yields (<23%, see the Supporting Information). A related method for the preparation of coumarins via

(1) (a) Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 111–112. (b) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692–9693. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905.

(2) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913–4918.

(3) Koch-Pomeranz, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981–3004.

(4) (a) There is yet another mechanistic possibility involving hydro-metalation of triple carbon–carbon bond, generating an alkenylmetal species, followed by intramolecular substitution of the arene ring. Hydro-palladation has been proposed to be the first step in the intermolecular cyclization of alkynoate esters and phenols. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305–6306. (b) See also: Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536–7537.

intramolecular cyclization of aryl alkynoate esters had previously been disclosed, utilizing a catalytic amount of Pd(OAc)<sub>2</sub> in TFA–CH<sub>2</sub>Cl<sub>2</sub>.<sup>5</sup>

Surprisingly, no desired product **2** was formed under these conditions. The use of Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>, recently reported to catalyze the intramolecular reaction between unactivated alkenes and 1,3-diketones, also failed to promote the cyclization (Table 1).<sup>6</sup>

Historically, silver and mercuric salts have been known to mediate the cyclization of propargylic aryl ethers, but only by employing a stoichiometric quantity of the heavy metal.<sup>7</sup> Under the catalytic conditions of our screening, AgBF<sub>4</sub> gave poor yields of chromene **2** (<5%, Table 1).

In more recent disclosures, AuCl<sub>3</sub>, GaCl<sub>3</sub>, and PtCl<sub>2</sub> have been reported to promote the coupling of alkynes with arenes and heteroarenes. Specifically, AuCl<sub>3</sub> has been shown to catalyze intramolecular reactions of alkynes and furans to provide substituted phenols,<sup>8</sup> while GaCl<sub>3</sub><sup>9</sup> and PtCl<sub>2</sub><sup>10</sup> have hitherto been the most efficient catalysts for intramolecular electrophilic hydroarylation of terminal alkynes. Again, all three salts proved ineffective in the cyclization of **1** as only low yields of **2** were observed (<6%, Table 1).

We were delighted to uncover an exciting lead, which unambiguously stood out in the array of experiments owing to the highest yield of the product. Remarkably, PtCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> furnished chromene **2** in 32% HPLC yield (other solvents also yielded promising results, Table 1). In contrast, PtCl<sub>2</sub> showed no or very low activity under the same conditions (<3%). This result prompted us to investigate both the efficiency and scope of Pt(IV)-catalyzed hydroarylation reactions and to compare PtCl<sub>4</sub> with PtCl<sub>2</sub>.<sup>11</sup>

First, we proceeded to examine the scope of PtCl<sub>4</sub> in terms of the alkyne substituent. Thus, terminal alkyne **1**, methyl derivative **3**, phenyl derivative **5**, and alkynoate ester **7** were prepared and subsequently examined (Table 2). Consistent with the results described above, PtCl<sub>4</sub> was the only catalyst that afforded acceptable isolated yields of product **2** from terminal alkyne **1** (55%). In the case of methyl substrate **3**, the desired product **4a** was isolated in 66% isolated yield using dichloroethane as solvent and increased to 92% yield in dioxane. In contrast, PtCl<sub>2</sub> produced only 25% yield of **4a**, and Pd(OAc)<sub>2</sub> according to the Fujiwara<sup>5</sup> protocol

(5) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516–7522 and references therein.

(6) Pei, T.; Wiedenhofer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290–11291.

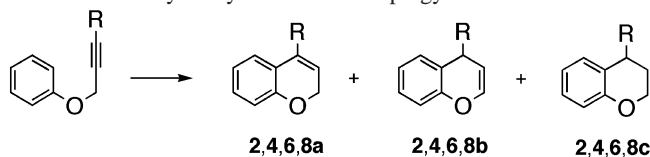
(7) (a) Reference 3. (b) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218–4227.

(8) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.

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(10) (a) Reference 2. (b) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754–4757. (c) Füstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264–6267.

(11) In cycloisomerization of enynes, PtCl<sub>2</sub> showed reactivity similar to that of PtCl<sub>4</sub>, the former being more efficient in many cases. (a) Füstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. (b) Méndez, M.; Paz Muñoz, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520. (c) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567–5569. (d) PtCl<sub>4</sub>-catalyzed addition of carbamates to enones. Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319–1322.

**Table 2.** Catalytic Cyclization of Propargyl Ether Substrates

substrate	PtCl <sub>4</sub> <sup>a</sup> a:b:c (SM)	PtCl <sub>2</sub> <sup>b</sup> a:b:c (SM)	Pd(OAc) <sub>2</sub> <sup>c</sup> a:b:c (SM)
<b>1</b> , R = H	55:0:0 (0) <sup>d</sup>	6:0:0 (23) <sup>e</sup>	9:0:0 (40)
<b>3</b> , R = Me	92:0:0 (0) <sup>f</sup>	25:0:0 (23) <sup>e</sup>	0:0:10 (41)
<b>5</b> , R = Rh	50:5:0 (0)	51:5:0 (30)	0:0:67 (0)
<b>7</b> , R = CO <sub>2</sub> Me	54:0:0 (0) <sup>d</sup>	<1:0:0 (85)	59:0:0 (0) <sup>g</sup>

<sup>a</sup> Conditions: 5 mol % PtCl<sub>4</sub>, (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>, 70 °C, 24 h. <sup>b</sup> Conditions: 5 mol % PtCl<sub>2</sub>, toluene, 80 °C, 24 h. <sup>c</sup> Conditions: 1 mol % Pd(OAc)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/TFA, 3:1, rt, 1 h. <sup>d</sup> Conditions: 3 mol % PtCl<sub>4</sub>, (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>, rt, 24 h. <sup>e</sup> Reaction conducted at room temperature. <sup>f</sup> In dioxane, rt, 2 h. 66% yield was obtained in (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>. <sup>g</sup> Reaction conducted at 50 °C. Isolated yields are given in the table.

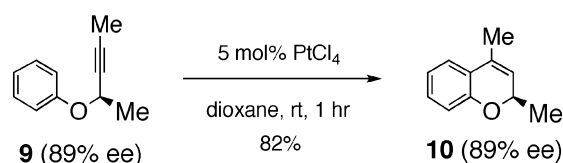
provided none of the chromene. The phenyl substrate **5** turned out to be particularly interesting. In this case, PtCl<sub>4</sub> and PtCl<sub>2</sub> were equally effective in providing 50% yield of desired compound **6a**, while Pd(OAc)<sub>2</sub> in TFA generated saturated benzopyran **6c** as the only isolated product in 67% yield. Subsequently, we found that this compound was formed by the reduction of chromene product **6a** under the reaction conditions. Furthermore, TFA itself was able to reduce **6a** to **6c** in 80% isolated yield as demonstrated by a control experiment.<sup>12</sup> In the case of ester **7**, the greater electrophilicity of Pt(IV) vs Pt(II) became apparent as PtCl<sub>4</sub> yielded 54% of desired chromene **8a**, while only a trace of this product was detected in the presence of PtCl<sub>2</sub>. The highly electrophilic conditions of Pd(OAc)<sub>2</sub> in TFA proved marginally superior to PtCl<sub>4</sub>, furnishing **8a** in 59% yield. Thus, in the case of alkynoate esters, PtCl<sub>4</sub> provides a mild and neutral alternative to the Fujiwara method.

Noteworthy is the fact that PtCl<sub>4</sub> is more soluble in organic solvents than PtCl<sub>2</sub>. Also, PtCl<sub>4</sub>-catalyzed cyclization of alkyne substrates occurs at faster rates in solvents that solubilize the catalyst to a greater extent as demonstrated in the case of substrate **3** (dioxane vs dichloromethane, see above and also the Supporting Information). This may suggest that the higher reactivity of PtCl<sub>4</sub> (in comparison to PtCl<sub>2</sub> and other metal salts) may be related not only to the higher oxidation state of the platinum metal but also to the solubility of the catalyst.<sup>13</sup>

The next issue was whether a stereogenic center in chiral propargyl ethers would be compromised during the cyclization. We were delighted to find that chiral propargyl ether **9** afforded chromene **10** in 82% yield while no racemization was observed (Scheme 1). This finding significantly expands the scope of this hydroarylation methodology.<sup>14</sup>

(12) Apparently, TFA functions at the reductant in this case. It appears that formation of a stabilized cation via protonation of the chromene product is the prerequisite for the subsequent reduction (ester **8a** is stable in TFA). We have not been able to find precedent for this transformation.

(13) Degner, M.; Holle, B.; Kamm, J.; Pilbrow, M. F.; Thiele, G.; Wagner, D.; Weigel, W.; Woditsch, P. *Transition Met. Chem.* **1975/76**, *1*, 41–47.

**Scheme 1**

We continued to elucidate the scope of the new methodology, this time in terms of the benzene ring substitution. This method demonstrated good compatibility with various functional groups, including alkyl groups, protected amines, and halides (Table 3). It was found that electron-releasing groups

**Table 3.** Catalytic Cyclization of Selected Substrates

substrate	major Product	conditions/yield
<b>11</b>	<b>12</b>	<sup>a</sup> PtCl <sub>4</sub> , 86% <sup>a</sup> PtCl <sub>2</sub> , 87%
<b>13</b>	<b>14a/14b</b>	<sup>b</sup> PtCl <sub>4</sub> , 69%, p/-o- = 9:1 <sup>d</sup> PtCl <sub>2</sub> , 70%, p/-o- = 9:1
<b>15</b>	<b>16a/16b</b>	<sup>c</sup> PtCl <sub>4</sub> , 34%, p/-o- = 1:1 <sup>d</sup> PtCl <sub>2</sub> , 30%, p/-o- = 63:47
<b>17</b>	<b>18a/18b</b>	<sup>c</sup> PtCl <sub>4</sub> , 68%, p/-o- = 96:4 <sup>d</sup> PtCl <sub>2</sub> , 58%, p/-o- = 96:4
<b>19</b>	<b>20a/20b</b>	<sup>c</sup> PtCl <sub>4</sub> , 82%, p/-o- = 78:22 <sup>d</sup> PtCl <sub>2</sub> , 66%, p/-o- = 82:18
<b>21</b>	<b>22</b>	<sup>c</sup> PtCl <sub>4</sub> , 78% <sup>d</sup> PtCl <sub>2</sub> , 13%
<b>23</b>	<b>24</b>	<sup>c</sup> PtCl <sub>4</sub> , 73% <sup>d</sup> PtCl <sub>2</sub> , 28%
<b>25</b>	<b>26a/26b</b>	<sup>c</sup> PtCl <sub>4</sub> , 57%, E/Z = 1:1 <sup>d</sup> PtCl <sub>2</sub> , 29% (Z)
<b>27</b>		no reaction

<sup>a</sup> Conditions: 1 mol % PtCl<sub>4</sub>, dioxane, rt. 10% of 4*H*-chromene was also formed. <sup>b</sup> Conditions: 5 mol % PtCl<sub>4</sub>, (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>, rt. <sup>c</sup> Conditions: 5 mol % PtCl<sub>4</sub>, (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>, 70 °C. <sup>d</sup> Conditions: 5 mol % PtCl<sub>2</sub>, toluene, 80 °C. Reaction times differ for each substrate; see the Supporting Information.

generally increased the reactivity of these substrates and as such higher yields of the corresponding products were obtained. For example, substrate **11** bearing two methyl groups on the benzene nucleus was converted to chromene

**12** in 86% isolated yield in the presence of only 1 mol % of PtCl<sub>4</sub> (Table 3). Boc-protected aniline **13** was converted to the chromenes **14a** and **14b** in 69% yield as a 9:1 mixture. Conversion was also observed with free aniline **15**; however, the yield dropped to 34%. Note that in the case of electron-rich arenes the less electrophilic PtCl<sub>2</sub> gave results comparable to PtCl<sub>4</sub> (substrates **11**, **13**, and **15**). Substrate **17**, containing an electron-withdrawing bromine substituent, afforded a 68% yield of desired products **18a/18b** (96:4) under the action of PtCl<sub>4</sub>. In addition to propargyl ethers, propargyl aniline **19** was also a good substrate as it furnished an 82% yield of dihydroquinoline **20a/20b** (78:22). For both of these substrates (**18** and **19**), PtCl<sub>4</sub> afforded higher yields in comparison to PtCl<sub>2</sub>. The higher electrophilicity of PtCl<sub>4</sub> became particularly advantageous in the case of electron-poor alkynes. Alkynoate esters **21**, **23**, and **25** were converted to the corresponding chromene **22**, coumarin **24**, and fused furo-dihydropyran **26**, respectively, in good yields in the presence of PtCl<sub>4</sub>. PtCl<sub>2</sub> was ineffective with these substrates, producing low yields (13–29%) of the corresponding products. It appears that the presence of at least one electron-donating substituent on the benzene ring was required for the cyclization to proceed. For example, the simple arylbutyne **27** was unreactive in the presence of either PtCl<sub>2</sub> or PtCl<sub>4</sub>, providing only recovered starting material.

In summary, we have developed a mild and neutral method for hydroarylation of arene–yne substrates with promising efficiency and scope. PtCl<sub>4</sub> demonstrated consistent performance with arene–yne substrates of diverse structural

features, including propargyl ethers, propargylamines, and alkynoate esters, providing good to excellent yields of the 6-endo products. In contrast, Pt(II) and Pd(II) salts were shown to be sensitive to the substitution on the alkyne moiety.

The greater reactivity and scope of PtCl<sub>4</sub> (vs PtCl<sub>2</sub>) may stem not only from the higher oxidation state of the platinum metal but also from the greater solubility of PtCl<sub>4</sub> in organic solvents. Faster rates of PtCl<sub>4</sub>-catalyzed cyclization reactions in dioxane in comparison to dichloromethane may also be ascribed to better solubility of the catalyst in dioxane. These reactions were also compatible with a small amount of water (0.5%); however, the rates were reduced (see the Supporting Information).

It appears that PtCl<sub>4</sub> possesses a special blend of reactivity and selectivity, as it selectively activated the triple bond toward one class of nucleophiles, namely the arenes.<sup>15</sup> Thus, the competing processes, including the interception of activated alkynes (and alkenes) by other nucleophiles (alkene, alkyne, H<sub>2</sub>O, functional groups), must be considerably slower. It is precisely the rate differences of these competing processes that ultimately determine the distribution of products that are obtained.

**Acknowledgment.** Generous support for this work was provided by GlaxoSmithKline and Johnson & Johnson Pharmaceutical R&D. D.S. is a recipient of the Cottrell Scholar Award of Research Corporation, Alfred P. Sloan Fellowship, and the Camille Dreyfus Teacher–Scholar Award. We thank Dr. J. B. Schwarz for editorial assistance.

**Supporting Information Available:** The entire Experimental Section, complete data for systematic screening, experimental details, and compound spectral characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Direct cycloaddition of propargyl alcohols with phenols have been reported. However, these methods do not provide access to chiral chromenes with asymmetric control: (a) Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Sartori, G. *J. Org. Chem.* **1997**, *62*, 7024–7027. (b) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 77900–7901. For other synthetic approaches to chromenes, see: (c) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4*, 3679–3681 and references therein. For syntheses of fused polycyclic arenes via cyclization of 2-alkynylbiaryls, see: (d) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578–4593 and references therein. (e) Reference 11c.

(15) Chisholm, M. H.; Clark, H. C. *Acc. Chem. Res.* **1973**, *6*, 202–209.