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# Platinum-Catalyzed Aromatization of Enediynes via a C–H Bond Insertion of Tethered Alkanes

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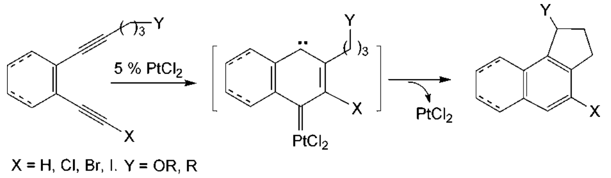
## ABSTRACT



**$PtCl_2$ (5 mol %) is an effective catalyst for aromatization of enediynes via a C–H bond insertion of tethered alkanes. The reaction mechanism of this cyclization is proposed to involve platinum–π-alkyne intermediates. This cyclization works not only for terminal alkynes but also for internal alkynes.**

Bergman aromatization of enediynes[1] has attracted considerable attention because of its useful applications in materials and medicinal chemistry.[2,3] Aromatization of enediynes has been investigated with various approaches, including diradical pathways,[1b,4] electrophilic additions,[5a−c] radical cations,[5d] and nucleophilic addition. The thermal cyclization of unstrained enediynes requires high temperatures, but it can be implemented with metal complexes under ambient conditions.[6−9] In such cases, excess metal reagents are often used to complete the reactions;[6] few examples are known for catalytic cyclization of enediynes.[7−9] Uemura reported[7] rhodium-catalyzed cyclizations of enediynes via a diradical process, which actually mimics the cyclization of 5-allene-3-en-1-ynes (Saito−Myers cyclization) as the terminal alkyne is transformed into a rhodium vinylidene intermediate.[10] The

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(1) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Lockhart, T. P.; Commita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.

(2) Reviews: (a) *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Marcel Dekker: New York, 1995. (b) Xi, Z.; Goldberg, I. H. In *Comprehensive Natural Product Chemistry*; Barton, D. H. R., Nakanishi, K., Eds.; Pergamon: Oxford, 1999; Vol. 7, p 553. (c) Nicolaou, K. C.; Smith, A. L. in *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH Publishers: Weinheim, 1995; Chapter 7, p 203.

(3) Recent reviews: (a) Rawat, D. S.; Zaleski, J. M. *Synlett* **2004**, 393. (b) Basak, A.; Mandal, S.; Bag, S. S. *Chem. Rev.* **2003**, *103*, 4077. (c) Bowles, D. M.; Palmer, G. J.; Landis, C. A.; Scott, J. L.; Anthony J. E. *Tetrahedron* **2001**, 57, 3753. (d) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (e) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.

(4) For cyclization of enediynes via diradical pathways, see ref 1b and: (a) Jones, L. H.; Hartwig, C. W.; Wentworth, P., Jr.; Simeonov, A.; Wentworth, A. D.; Py, S.; Ashley, J. A.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **2001**, *123*, 3607. (b) Grissom, J. W.; Gunawardena, G. U. *Tetrahedron Lett.* **1995**, *36*, 4951. (c) Schottelius, M.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896. (d) Dai, W.-M. *Curr. Med. Chem.* **2003**, *10*, 2265.

(5) (a) Whitlock, H. W. Jr.; Sandvick, P. E.; Overman, L. E.; Reichardt, P. B. *J. Org. Chem. Soc.* **1969**, *34*, 879. (b) Whitlock, H. W., Jr.; Sandvick, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 4525. (c) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 5757. (d) Schmittel, M.; Kiau, S. *Liebigs Ann/Recueil* **1997**, 1391.

(6) (a) Zaleski, J. M.; Rawat, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 9675. (b) Warner, B. P.; Millar, S. P.; Broene, R. D.; Buchwald, S. L. *Science* **1995**, *269*, 814. (c) Konig, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2538. (d) Landis, C. A.; Payne, M. M.; Eaton, D. L.; Anthony, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 1338. (e) Wang, Y. S.; Finn, M. G. *J. Am. Chem. Soc.* **1995**, *117*, 8045. (f) O'Connor, J. M.; Friese, S. J.; Tichenor, M. *J. Am. Chem. Soc.* **2002**, *124*, 3506.

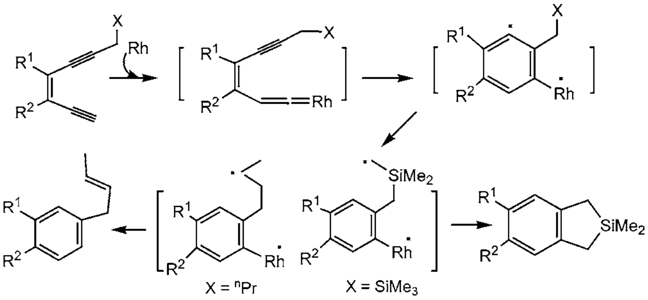
(7) For metal-catalyzed cyclization of enediynes, see refs 7−9: (a) Ohe, K.; Kojima, M.-a.; Yohehara, K.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1823. (b) Manabe, T.; Yanagi, S.-I.; Ohe, K.; Uemura, S. *Organometallics* **1998**, *17*, 2942.

(8) (a) Odedra, A.; Wu, C.-J.; Pratap, T. P.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S., *J. Am. Chem. Soc.* **2005**, *127*, 3406. (b) O'Connor, J. M.; Friese, S. J.; Rodgers, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 16342.

(9) In further recent experiments, we found that $PtCl_2$ (5 mol %) was catalytically active for aromatization of enediynes via regioselective HX addition (X = Cl, Br, I); see: Lo, C.-Y.; Kumar, M. P.; Chang, H.-K.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2005**, *70*, 10482

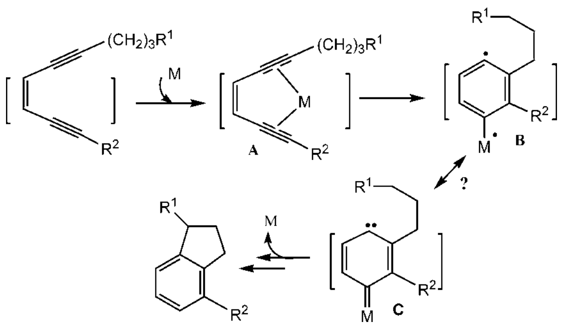
10.1021/ol052962m CCC: $33.50

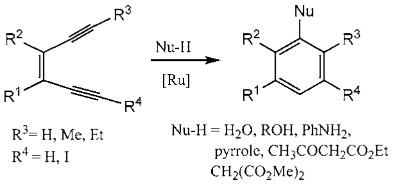
## Scheme 1



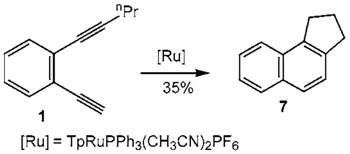
scope of such a cyclization is strictly limited to enediynes bearing one terminal alkyne (Scheme 1). In seeking to accomplish a new catalytic aromatization of enediynes via metal−π-alkyne intermediates, we envisage that a suitable π-activator may coordinate with enediynes to form bis-π-alkyne species **A** (Scheme 2), thus effecting a closer C(1)−C(6) distance, and to facilitate the cyclization.[6] Compared to Uemura's system, one distinct feature is the possible generation of carbenoid species **C** given from the conjugation of diradical intermediate **B** for which the radical character resides at both the metal and C(6) carbon positions. One obvious advantage of this protocol is its applicability to cyclization for both terminal and internal alkynes. This study reports realization of this new catalytic reaction using $PtCl_2$, achieving aromatization of enediynes via an alkane C−H bond insertion (Scheme 2).

## Scheme 2





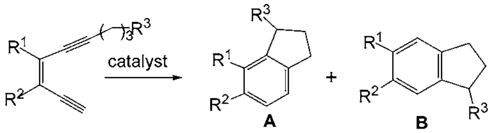
(1)



(2)

We previously reported[8a] catalytic aromatization of enediynes via nucleophilic additions using $TpRuPPh_3(CH_3CN)_2PF_6$ (10 mol %, eq 1), and the mechanism has been elucidated to involve a π-alkyne intermediate. In one instance, we accidentally found that a C−H alkane insertion occurred for enediyne **1** bearing a propyl group and gave benzene **7** in 35% yield (eq 2).[8a] Uemura's mechanism fails to rationalize the formation of this product. We sought to improve this cyclization efficiency using $PtCl_2$ (5 mol %), which is known as an efficient π-activator for alkynes.[9,11] Table 1 shows our results for aromatization of enediynes **1**−**6** using these two catalysts to compare their catalytic efficiency and chemoselectivity; the reactions were performed in hot toluene (100 °C, 10 h). As shown in entries 1−3, $PtCl_2$ (5 mol %) is more efficient than $TpRuPPh_3(CH_3CN)_2PF_6$ (10 mol %) in the aromatization of enediynes **1**−**3** despite a lower loading of $PtCl_2$. For acyclic enediynes **4**−**6**,

**Table 1.** Cyclization of Enediynes with Platinum and Ruthenium Catalysts



| enediynes[a] | catalyst[b] | products[c] |
|---|---|---|
| $R^1, R^2$ =  | | |
| (1) $R^3$ = H (1) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **7** ( **A**, 35%) |
| (**1**) | $PtCl_2$ | **7** ( **A**, 48%) |
| (2) $R^3$ = Me (2) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **8** ( **A**, 54%) |
| (**2**) | $PtCl_2$ | **8** ( **A**, 75%) |
| (3) $R^3$ = ${}^nPr$ (**3**) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **9** ( **A**, 61%) |
| (**3**) | $PtCl_2$ | **9** ( **A**, 79%) |
| (4) $R^1$ = Me, $R^2$ = H, $R^3$ = ${}^nPr$ (**4**) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **10** ( **A**, 54%)<br>**10** ( **B**, 16%) |
| (**4**) | $PtCl_2$ | **10** ( **A**, 71%) |
| (5) $R^1$= ${}^nC_6H_{13}$, $R^2$ = H, $R^3$ = Me (**5**) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **11** ( **A**, 67%)<br>**11** ( **B**, 18%) |
| (**5**) | $PtCl_2$ | **11** ( **A**, 81%) |
| (6) $R^1, R^2$ =  $R^3$ = ${}^nPr$ (**6**) | $TpRuPPh_3(CH_3CN)_2PF_6$ | **12** ( **A**, 58%)<br>**12** ( **B**, 20%) |
| (**6**) | $PtCl_2$ | **12** ( **A**, 85%) |

[a] [Substrate] = 1.0 M toluene, 100 °C, 10 h. [b] 5 mol % $PtCl_2$ and 10 mol % $TpRuPPh_3(CH_3CN)_2PF_6$. [c] Yields were given after purification on a silica column.

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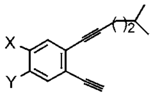
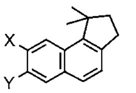
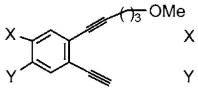
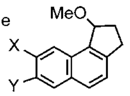
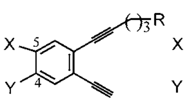
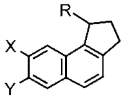
(10) Catalytic reactions via metal-vinylidene intermediates; see: (a) Bruneau, C. *Top. Organomet. Chem.* **2004**, *11*, 125. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Bruneau, C.; Dixneuf, P. *Acc. Chem. Res.* **1999**, *32*, 311. (d) Puerta, M. C.; Valerga, P. *Coord. Chem. Rev.* **1999**, *193*−*195*, 977.

(11) Recent reviews for $PtCl_2$-catalyzed reactions: (a) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

we found that the ruthenium species produced two cyclized benzenes **10**−**12**(**A**) (54−67%) and **10**−**12**(**B**) (16−20%); this information indicates the generation of two active intermediates in this catalytic reaction. Formation of benzenes **10**−**12**(**B**) can be rationalized on the basis of a metal-vinylidene pathway according to Uemura's mechanism.[7] The use of $PtCl_2$ catalyst, however, gives only cyclized benzenes **10**−**12**(**A**) in good yields (71−81%), which seems to favor a $\pi$-alkyne intermediate.

As $PtCl_2$ shows better efficiency and chemoselectivity than $TpRuPPh_3(CH_3CN)_2PF_6$ in the preceding cyclizations, we examined the generality of $PtCl_2$-catalyzed reactions with various enediynes bearing a terminal alkyne as reported in Table 2. Entries 1 and 2 demonstrate two instances of formation of a tertiary carbon through aromatization of enediynes **13** and **14**, which gave corresponding benzenes **24-25** in 46−73% yields. The 4-methoxyphenyl group of species **14** greatly enhanced this cyclization efficiency. A similar phenomenon was observed for compounds **15** and **16** bearing 4-methoxy- and 4,5-dimethoxyphenyl groups, respectively (entries 3 and 4), which produced benzenes **26** and **27** in respective yields of 70% and 86%, better than that (45%) of its unsubstituted enediyne **1** (Table 1, entry 1). This aromatization maintains the same catalytic efficiency on electron-rich benzenes **17** and **18** bearing methoxy groups at the C(4) and C(5) phenyl carbons (entries 5 and 6) relative to its parent benzene derivative **3** (Table 1, entry 3). In contrast, cyclization of benzene **19** bearing a fluoro substituent is less efficient, giving benzene product **30** in 55% yield (entry 7). Notably, this C−H bond insertion failed to work with enediyne **20** bearing a $CH_2$ fragment adjacent to a methoxy group (entry 8); in this case, a complicated reaction mixture was obtained. Nevertheless, the methoxyl groups of enediynes **21**−**23** show a surprisingly activating effect, giving cyclized products **31**−**33** in 81−85% yields.

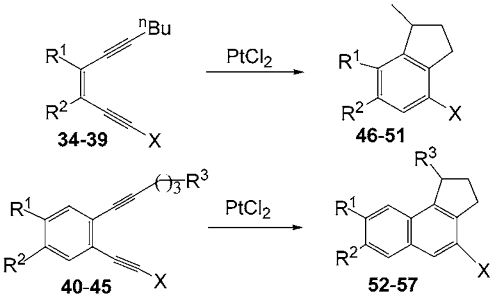
**Table 2.** $PtCl_2$-catalyzed Cyclization of Enediynes Bearing a Terminal Alkyne

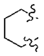
| enediynes[a] | products (yields)[b] | enediynes | products (yields) |
|---|---|---|---|
|  |  | R = $^n$Pr | |
| | | (5) X = H, Y = OMe (**17**) | **28** (78%) |
| | | (6) X = Y = OMe (**18**) | **29** (83%) |
| (1) X = Y = H (**13**) | **24** (46%) | (7) X = H, Y = F (**19**) | **30** (55%) |
| (2) X = H, Y = OMe (**14**) | **25** (73%) |  |  |
|  |  | (8) X = Y = H (**20**) | — |
| R = H | | (9) X = H, Y = OMe (**21**) | **31** (81%) |
| (3) X = H, Y = OMe (**15**) | **26** (70%) | (10) X = OMe, Y = H (**22**) | **32** (67%) |
| (4) X = Y = OMe (**16**) | **27** (86%) | (11) X = Y = OMe (**23**) | **33** (85%) |

[a] 5 mol % $PtCl_2$, [substrate] = 1.0 M toluene, 100 °C, 12 h. [b] Yields of products are given after purification on a silica column.

The value of this cyclization is reflected by its applicability to enediynes bearing two internal alkynes; the results are presented in Table 3. Entries 1−6 show the cyclization of acyclic enediynes **34**−**39** using $PtCl_2$ catalyst (5 mol %); these substrates produced cyclized benzenes **46**−**51** following the same protocol. Such cyclizations work also well for 1,2-bis(alkynyl)benzenes **40**−**42**, and the corresponding naphthalenes **52**−**54** were obtained in 60−69% yields. The structures of **53** and **56** were determined by $^1H$-NOE spectra. The catalytic cyclization is also efficient for cyclization of 1,2-bis(alkynyl)benzenes **43**−**45** bearing one or two methoxy groups at the C(4) and C(5) carbons, giving resulting 2-iodonaphthalenes **55**−**57** in 76−81% yields. The fact that these cyclizations proceed without a 1,2-halogen shift suggests a platinum−$\pi$-alkyne reaction intermediate.[12]

**Table 3.** $PtCl_2$-catalyzed Cyclization of Enediynes Bearing an Internal Alkynes



| enediynes[a] | products[b] | enediynes | products |
|---|---|---|---|
| $R^1$, $R^2$ =  | | $R^1$ = $R^2$ = H<br>$R^3$ = Me | |
| (1) X = Cl (**34**) | **46** (75%) | (7) X = Cl (**40**) | **52** (60%) |
| (2) X = Br (**35**) | **47** (78%) | (8) X = Br (**41**) | **53** (69%) |
| (3) X = I (**36**) | **48** (74%) | (9) X = I (**42**) | **54** (66%) |
| $R^1$, $R^2$ =  | | $R^3$ = $^nC_3H_7$, X = I | |
| (4) X = Cl (**37**) | **49** (77%) | (10) $R^1$ = H, $R^2$ = OMe (**43**) | **55** (81%) |
| (5) X = Br (**38**) | **50** (76%) | (11) $R^1$ = OMe, $R^2$ = H (**44**) | **56** (76%) |
| (6) X = I (**39**) | **51** (74%) | (12) $R^1$ = $R^2$ = OMe (**45**) | **57** (76%) |

[a] 5 mol % $PtCl_2$, [substrate] = 1.0 M toluene, 100 °C, 12 h. [b] Yields of products are given after purification on a silica column.

We have performed deuterium-labeling experiments to study the nature of cyclization using $PtCl_2$ catalyst. We found that the alkynyl deuterium of species **2** located at the same carbon with a loss of 25% deuterium content. In the presence of $D_2O$ (1.0 equiv), the C(4)-deuterium content is up to 58%. This information indicates that $PtCl_2$-catalyzed cyclization

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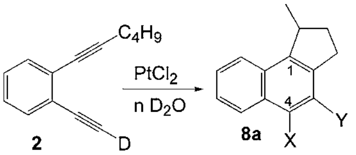
[12] (12) Alkynyl iodide undergoes 1,2-shift with metal species to form 2-iodovinylidene intermediates in several catalytic reactions, see: (a) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518. (b) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745. (c) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556.

**Scheme 3**

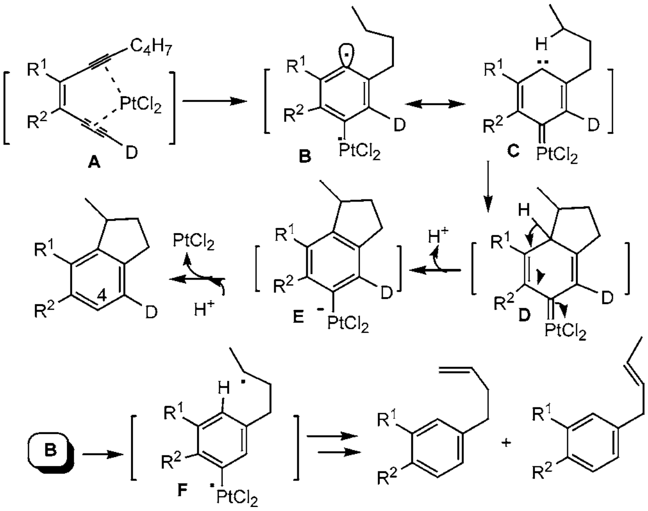


| n D$_2$O | 8a |
|---|---|
| n = 0 | X = H, Y = 0.75 D |
| n = 1 | X = 0.58D, Y = 0.90 D |

of enediyne **2** is consistent with platinum $\pi$-alkyne mechanism because of the absence of 1,2-hydrogen shift for the alkynyl deuterium.

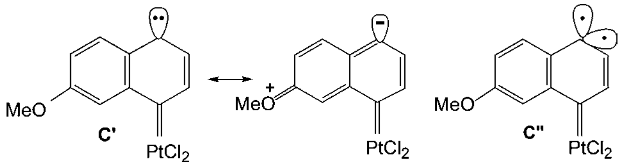
Scheme 4 shows a proposed mechanism for the C−H alkane insertion of enediynes using PtCl$_2$ catalyst. We envisage that PtCl$_2$ activates the cyclization of enediynes via PtCl$_2$−$\pi$-alkyne species **A** and forms diradical species **B** or its resonance form **C**. The observed alkane insertion indicates the role of carbenoid intermediate **C**, which forms cyclopentyl species **D**. This species subsequently loses a proton to generate species **E** and ultimately gives the desired benzene product. In such a mechanism, the C(4)-deuterium content of species **2** will be enriched in the presence of external D$_2$O, consistent with our observation in Scheme 3.

**Scheme 4**



This cyclization is unlikely to arise from the pure diradical species **B**, because its subsequent intermediate **F** is prone to loss of a hydrogen radical, ultimately giving benzene with a pendant 2- or 3-butene. The participation of carbene intermediates **C** is also supported by the enhancing effect of 4-methoxyphenyl substituent, which can stabilize singlet state carbenoid **C′** through resonance (Scheme 5). In this mechanism, we do not exclude the role of triplet state platinum−carbene species **C″**.

**Scheme 5**



In summary, we have demonstrated that PtCl$_2$ (5 mol %) efficiently catalyzed aromatization of enediynes bearing both terminal and internal alkynes; the reaction mechanism has been proposed to involve platinum−$\pi$-alkyne intermediates. The product analysis and deuterium-labeling experiment are consistent with a platinum-stabilized benzene carbenoid being responsible for the alkane C−H bond insertion in the course of aromatization. This work offers a new example for generation of carbenoid reaction intermediates via metal-catalyzed activation of alkynes.[13]

**Acknowledgment.** We thank the National Science Council, Taiwan, for support of this work.

**Supporting Information Available:** Mechanistic discussion,[14] experimental procedures for the synthesis of enediynes, PtCl$_2$-catalyzed cyclization, NMR spectra, and spectral data for compounds **1**−**57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For selected examples, see: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167 (a review article). (b) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (c) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (d) Miki, K.; Nishino, F.; Ohe, K.; Uemura, A. *J. Am. Chem. Soc.* **2002**, *124*, 5260.

(14) One reviewer suggests that this catalytic reaction likely occurs with initial coordination of PtCl$_2$ to a single alkyne group; see the Supporting Information for details of this proposed mechanism.