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Herrmann–Beller Phosphapalladacycle-Catalyzed Addition of Alkynes to Norbornadienes

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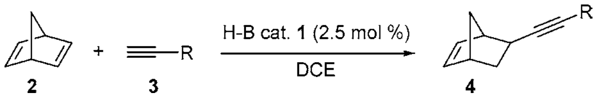
ABSTRACT



Herrmann–Beller (H–B) phosphapalladacycle selectively catalyzed the addition of terminal alkynes across one double bond of norbornadiene to afford *exo*-5-alkynyl-bicyclo[2.2.1]hept-2-enes. The reaction shows general applicability to various functionalized alkynes and bicyclo[2.2.1]-hepta-2,5-dienes. Insights into the mechanism of this reaction are discussed.

Palladacycles are recognized as important key intermediates in numerous carbon−carbon (or carbon−heteroatom) bond-forming processes[1] and, as such, have been extensively utilized as catalysts.[2] Among these, phosphapalladacycles have emerged as powerful catalysts, allowing the reactions to proceed at low catalyst loading and high turnover numbers (TON). For instance, Herrmann−Beller (H−B) phosphapalladacycle **1** (Figure 1), readily available from tri-*o*-tolylphosphine and palladium acetate,[3a] is able to catalyze the Heck or Suzuki couplings with TON up to 1,000,000.[3] Generally, these reactions are performed at high temperatures (>100 °C) and are believed to occur with decomposition of the palladacycle, giving rise to highly reactive, coordinatively unsaturated zerovalent palladium[4] or ligand-free palladium species.[5] In contrast, carbon−carbon bond-forming reactions under mild conditions are less common with palladacycles.

Herein, we describe the first palladium-catalyzed addition of terminal acetylenes **3** across one double bond of norbornadiene (NBD)[6] **2** (and related compounds) achieved under mild conditions in the presence of **1** to afford 5-*exo*-alkynyl-2-norbornenes **4** in fair to good yields.

Initial experiments, focused on the coupling of phenylethyne (**3a**) and alkenes (2 equiv) such as 1-hexene, cyclopentene, or norbornene in the presence of $Pd(OAc)_2$/$P(o\text{-}Tol)_3$ (5/10 mol %) in 1,2-dichloroethane (DCE) at 50 °C, proved disappointing, leading to a mixture of the known linear and branched enynes resulting from the dimerization of **3a**.[7] Since the coordination of an alkene to a metal center in the presence of the alkyne is kinetically disfavored,[8] the coordination of more strained double bonds such as in

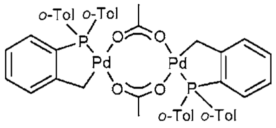


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Figure 1. Structure of Herrmann−Beller phosphapalladacycle

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[1] (a) Dyker, G.; Körning J.; Nerenz, F.; Siemsen, P.; Sostman, S.; Wiegand, A. *Pure Appl. Chem*. **1996**, *68*, 323−326. (b) Dyker, G. *Chem. Ber./Recl.* **1997**, *130*, 1967−1578. (c) Catellani, M. *Synlett* **2003**, 298−313.

[2] (a) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem*. **1999**, *576*, 23−41. (b) Poli, G.; Scolastico, C. *Chemtracts* **1999**, *12*, 643−655. (c) Speicher, A.; Shulz, T.; Eicher, T. *J. Prakt. Chem*. **1999**, *341*, 605−608. (d) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917−1927. (e) Herrmann, W. A.; Öfele, K.; von Preysing, D.; Schneider, S. K. *J. Organomet. Chem*. **2003**, *687*, 229−248. (f) Beller, M.; Zapf, A.; Riemer, T. H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 274−281. (g) Beletskaya, I. P.; Cheprakhov, A. V. *J. Organomet. Chem*. **2004**, *689*, 4055−4082. (h) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev*. **2005**, *105*, 2527−2571.

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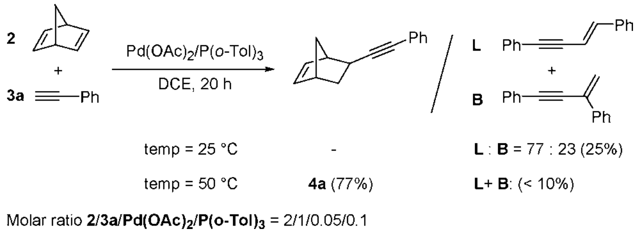
norbornadiene **2**, able to form η^2 and/or η^4 complexes without increasing steric hindrance, was expected to compete favorably. Effectively, transition metal-catalyzed cycloadditions between alkynes and NBD are well-documented.[9,10] Much to our delight, the reaction of norbornadiene **2** and phenylethyne (**3a**) under similar conditions afforded a new adduct **4a** (77%) as a single diastereomer and the self-coupling products of **3a** (≤5−10%), which were easily removed by chromatography (Scheme 1).[11]

Scheme 1. Temperature Dependence of the Reaction of Norbornadiene **2** and Phenylethyne (**3a**) Catalyzed with Pd(OAc)$_2$/P(*o*-Tol)$_3$



In contrast, the reaction performed at room temperature led to only 25% of a 3:1 mixture of linear (**L**) and branched (**B**) enynes in agreement with Trost's observations.[7] The major feature of this new hydroalkynylation reaction rests upon the nature of the catalyst. On performing the reaction at 50 °C, phosphapalladacycle **1** generated in situ was the key catalyst. More interestingly, the reaction carried out without solvent with phosphapalladacycle **1** (2.5 mol %) and a 10-fold molar excess of NBD allowed a quantitative formation of **4a** and the recovery of 60% of the loaded catalyst after addition of petroleum ether and filtration from the crude reaction mixture. The recovered complex proved to be active without loss of efficiency.

The structure of the cycloadduct **4a** was established by ^{1}H and ^{13}C NMR, and the *exo* stereochemistry of the alkynyl group was assigned on the basis of the coupling patterns of H-5 and H-6 protons (Figure 2) and the lowfield shielding of H-6*ex* with respect to H-6*en* as a result of the anisotropy effect of the triple bond.

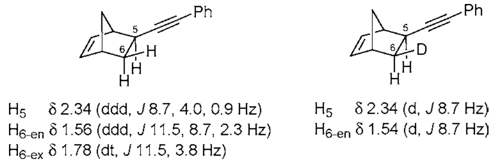


Figure 2. ^{1}H NMR (CDCl$_3$, 500 MHz) Data of **4a** and **D-4a**

The NMR spectra reveal that addition of the terminal alkyne occurred across one double bond of NBD and the *exo* stereochemistry of the carbon−carbon bond formed was deduced from NOESY experiments. One striking feature supporting the stereochemical outcome of the reaction becomes apparent after labeling the alkyne. *exo*-6-D-*exo*-5-phenylethynyl-bicyclo[2.2.1]hept-2-ene **D-(4a)** (see Figure 2) was obtained in 92% yield from an excess of NBD and 2-D-phenylethyne **D-(3a)** under strictly anhydrous solvent-free conditions (Supporting Information).

The hydroalkynylation of NBD **2** with Herrmann−Beller phosphapalladacycle **1** appears to be generally applicable to a variety of alkynes, and the wide tolerance of the reaction to functional groups is illustrated in Table 1. In these conditions, the ^{1}H NMR of the crude reaction mixtures reveals the formation of a single cross-coupling adduct and the alkyne self-coupling byproducts are only observed in few cases.

The presence of functional groups such as ether, including TBDMS ether, ester, carbonate, ketone, sulfone, tertiary alcohol or amine, in the alkyne have no deleterious effects on the reaction. A thiophenyl group at the propargylic position turned out to be moderately tolerable, but the reaction fails to proceed to completion (Table 1, entry 15). Cross-coupling adduct **4o** was obtained in 37% yield along with unreacted **3o** as an unseparable mixture.[12] Whatever the conditions (55 °C, 24 h or room temperature, 3 d), the reaction stopped at about 50% conversion. Alkynes **3q** and **3r** bearing a free hydroxyl group also participate in coupling with moderate yields (Table 1, entry 17 and 18). With prop-2-ynol (**3q**), the self-coupling process competes favorably and hex-2*E*-en-4-yne-1,6-diol (**5**)[13] was obtained in 43% yield along with the expected adduct **4q** (44%) (Table 1, entry 17).[14,15] In contrast, sterically demanding tertiary propargylic alcohols such as **3s** behave similarly to other alkynes,

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(3) (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 4, 1844−1848. (b) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849. (c) Beller, M.; Riermeier, T. H.; Haber, S.; Kleiner, H.-J.; Herrmann, W. A. *Chem. Ber*. **1996**, *129*, 1259−1264. (d) Beller, M.; Riermeier, T. H. *Tetrahedron Lett*, **1996**, *37*, 6535−6538. (e) Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann W. A. *Tetrahedron Lett.* **1997**, *38*, 2073−2074. (f) Riermeier, T.;. Zapf, H. A.; Beller, M. *Top. Catal.* **1997**, *4*, 301−309. (g) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357−1364. (h) Herrmann, W. A.; Böhm, V. P. W. *J. Organomet. Chem*. **1999**, *572*, 141-145.

(4) Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2359−2361.

(5) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288.

(6) Norbornadiene is used for bicyclo[2.2.1]hepta-2,5-diene as a matter of convenience.

(7) (a) Trost, B. M.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486−3487. (b) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698−708.

(8) However, coordination of an alkene is favored when the latter is connected to the alkyne; see: (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987; pp 149−151. (b) L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, 1994.

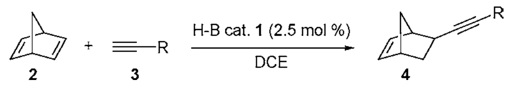
(9) [2 + 2] Cycloaddition: Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580−581.

(10) [2 + 2 + 2] Cycloaddition: Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 5627−5628 and references therein.

(11) Other complexes such as $[PdCl(\eta^3\text{-}(C_3H_5)]_2$, PdCl$_2$(MeCN)$_2$, and Pd$_2(dba)_3$·CHCl$_3$ with or without PPh$_3$ were inefficient.

(12) Attempts to purify **4o** by distillation resulted in decomposition.

Table 1. Palladium-Catalyzed Addition of Alkynes **3** to Norbornadiene **2**[a]



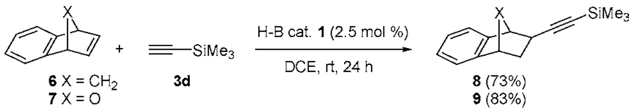
entry	alkyne	temp (°C), time (h)	adduct	yield (%)
1	**3a** R = Ph	55, 20	**4a**[b]	90
2	**3b** R = *n*-C_4H_9	50, 20	**4b**	72
3	**3c** R = 1-cyclohexen-1-yl	45, 16	**4c**[c]	87
4	**3d** R = $SiMe_3$	55, 16	**4d**	93
5	**3e** R = CH_2OPh	50, 16	**4e**	80
6	**3f** R = CH_2OBn	50, 16	**4f**	95
7	**3g** R = $CH_2OTBDMS$	50, 16	**4g**	95
8	**3h** R = CH_2OAc	50, 16	**4h**	67
9	**3i** R = CH(Me)OAc	50, 16	**4i**	63
10	**3j** R = CH_2CH_2OAc	50, 15	**4j**	91
11	**3k** R = CH_2OCO_2Me	50, 16	**4k**	70
12	**3l** R = $CH_2CH(CO_2Me)_2$	55, 16	**4l**	92
13	**3m** R = $CH_2C(CO_2Me)_2$(allyl)	50, 14	**4m**	82
14	**3n** R = $CH_2C(Me)_2CH_2Ac$	50, 16	**4n**	90
15	**3o** R = CH_2SPh	55, 24	**4o**	37 (64)[d]
16	**3p** R = CH_2SO_2Ph	45, 22	**4p**	52
17	**3q** R = CH_2OH	22, 96	**4q**[e]	44
18	**3r** R = CH_2CH_2OH	22, 96	**4r**	52
19	**3s** R = 1-hydroxycyclohexyl	45, 16	**4s**	97
20	**3t** R = $-CH_2Mp$[f]	45, 16	**4t**	69

[a] Reactions were carried out with 2.5% of **1** in 1,2-dichloroethane (0.125 M) based on alkyne, molar ratio **2**/**3**/**H-B** cat. = 2/1/0.025). [b] See text. [c] Enyne **4c** slowly polymerizes on standing in refrigerator. [d] Number in the parenthesis refer to the yield based on recovered starting material (57% conversion of **2o**). [e] Hex-2*E*-en-4-yne-1,6-diol was also formed in 43% yield. No significant change in products ratio was observed at higher temperatures. [f] Mp = morpholinyl (C_4H_8NO).

providing enyne **4s** in excellent yield (Table 1, entry 19). Applying these conditions to tertiary amine **3t** allowed the formation of enyne **4t** in a satisfactory 69% yield (Table 1, entry 20).

Among the selectivity issues, the palladacycle **1** discriminates against unstrained cyclic or acyclic alkenes (see entries 3 and 13, Table 1), and most noteworthy, intramolecular cyclization (cycloisomerization) of 1,6-enyne **3m** is totally precluded in contrast with Trost's observations with electron-deficient palladacycles.[16] The fact that the hydroalkynylation of norbornene fails under our conditions suggested that through space interaction between the two double bonds of norbornadiene is crucial for the coupling.[17] Indeed, the addition of trimethylsilylethyne (**3d**) to benzonorbornadiene **6** or 7-oxa-benzonorbornadiene **7** proceeded smoothly at room temperature affording the expected adducts **8** or **9** in good yields (Scheme 2).

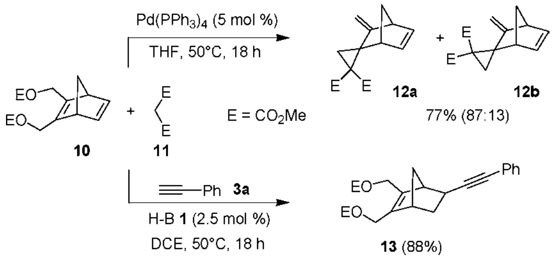
Scheme 2. Hydroalkynylation of Benzonorbornadiene **6** and 7-Oxa-benzonorbornadiene **7** with Trimethylsilylethyne (**3d**)



Molar ratio (**6** or **7**)/**3d**/**H-B 1** = 1.2/1/0.025

Although the mechanisms involving Pd(IV)/Pd(II) or Pd(II)/Pd(0) intermediates from palladacycles as precatalysts are still under debate, recent investigations on Heck-type coupling,[2a,18] amination,[4] and allylic alkylation[19] reactions focused on Pd(0) species generated in situ from palladacycles as active catalysts. It is important to note that these reactions are carried out at high temperatures and require the presence of base which plays a crucial role in generating the active species. In contrast, the hydroalkynylation was performed under neutral and mild conditions (45−55 °C) and even at room temperature (Table 1, entries 17 and 18 and Scheme 2). In addition, the recovery of the phosphapalladacycle from reactions carried out under solvent-free conditions suggest that a Pd(II)/Pd(0) pathway is unlikely for the present reaction. To probe such a pathway, experiments were conducted with bis-allylic dicarbonate **10** able to perform both the hydroalkynylation and/or the allylic alkylation under neutral conditions.[20] First, in the presence of $Pd(PPh_3)_4$ an equimolar mixture of **10** and methyl malonate **11** afforded a 87:13 mixture of vinylcyclopropanes **12a** and **12b** in 77% yield (Scheme 3). Second, an equimolar mixture of dicarbonate **10**, methyl malonate **11**, and phenylethyne (**3a**) was reacted at 50 °C for 18 h in the presence of 2.5 mol % of

Scheme 3. H−B Palladacycle-Catalyzed Hydroalkynylation versus Allylic Alkylation



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(13) Self-coupling of prop-2-ynol (**3q**) affording a mixture of linear and branched conjugated enynes was reported using Wilkinson's complex; see: Schaefer, H.-A.; Marcy, R.; Rueping, T.; Singer, H. *J. Organomet. Chem.* **1982**, *240*, 17−25.

(14) No significant change in products ratio **4q**/**5** was observed at higher temperatures.

(15) The homocoupling of propyn-2-ol (**3q**) needs the presence of NBD, presumably as active ligand to stabilize reaction intermediates. In the absence of NBD, no product was formed as a result of catalyst decomposition.

(16) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753−4755.

(17) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482−6490.

(18) (a) Böhm, P. V. W.; Herrmann, W. A. *Chem. Eur. J.* **2001**, *7*, 4191−4197. (b) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449−7476.

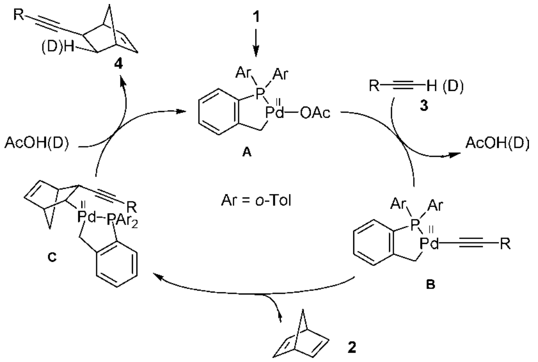
(19) Poli, G.; Giambastiani, G.; Pacini, B. *Tetrahedron Lett.* **2001**, *42*, 5179−5182.

(20) (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361−4401. See also: (b). Brunel, J. M.; Maffei, M.; Muchow, G.; Buono, G. *Eur. J. Org. Chem.* **2000**, 1799−1803. (c) Brunel, J. M.; Maffei, M.; Muchow, G.; Buono, G. *Eur. J. Org. Chem.* **2001**, 1009−1012.

phosphapalladacycle **1** in order to compete the hydroalkynylation with the allylic alkylation. In this experiment, the hydoalkynylation adduct **13** was detected as the sole product by ^{1}H and ^{13}C NMR analyses of the crude reaction mixture and isolated in 88% yield (Scheme 3).

On the basis of these observations, Pd(0) species can be ruled out under our conditions,[21] and we propose a rationale involving Pd(II) intermediates for the hydroalkynylation (Scheme 4). The monomeric palladium(II) acetate **A** could bind the alkyne **3** and undergo a concerted acetate assisted deprotonation and palladium−carbon bond-forming reaction to give alkynylpalladium(II) **B**. This will carbopalladate norbornadiene **2** to form **C**, which undergoes protonolysis to release the adduct **4** and the palladacycle **A**.[22]

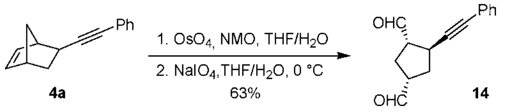
Scheme 4. Proposed Mechanism for the Herrmann−Beller Phosphapalladacycle Catalyzed Hydroalkynylation of Norbornadiene



The acetate ligand of the phosphapalladacycle **1** is crucial to effect the coupling.[23] Indeed, the chloropalladacycle obtained by chlorine to acetate exchange[3g] showed no catalytic activity under the usual conditions.[24] We assume that acetic acid plays an important role in the catalytic cycle and this was demonstrated as follows. When **D-3a** and NBD were reacted in the presence of AcOH (8 equiv with respect to **D-3a**), no deuterium incorporation was detected in the coupling product **4a**, indicating an efficient intermolecular scrambling. Conversely, when **3a** and NBD were reacted in the presence of AcOD (8 equiv with respect to **D-3a**), **4a** incorporated 50% of the deuterium. On the other hand, the addition of a base such as DBU (1 molar equiv with respect to **3a**) or K_2CO_3 (as a 5 M aqueous solution; 1 molar equiv with respect to **3a**) to the reaction media shut down the catalytic reaction.

To demonstrate the synthetic utility of alkynylnorbornenes, compound **4a** was transformed into 1,2,4-trisubstituted cyclopentane **14** by catalytic dihydroxylation followed by cleavage of the diol with $NaIO_4$ in 63% overall yield (Scheme 5).

Scheme 5. Oxidative Cleavage of Adduct **4a** to Trisubstituted Cyclopentane **14**



In summary, the palladium-catalyzed addition of terminal alkynes to one double bond of norbornadienes provides an entry to *exo*-2-alkynyl-5-norbornenes using an operationally simple procedure and a readily accessible catalyst.[25] The reaction exhibits extraordinary generality with respect to the alkyne. This constitutes, to our knowledge, the first addition of a C(sp)-H bond to a nonactivated isolated double bond under neutral conditions.[26] On the basis of the fact that trimethylsilylethyne (**3d**) as well as alkynol **3s** may be used as ethyne equivalent, the opportunity to introduce any side chain in **4** by further alkylation greatly enhances the scope of such couplings. The interesting possibilities to develop an enantioselective version of the hydroalkynylation with chiral palladacycles is underway.

Acknowledgment. The authors would like to thank Dr. I. De Riggi (EGIM, Université P. Cézanne, Marseille) for help with the NMR and the CNRS for financial support.

Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The propensity to form η-1-allenylpalladium(II) complexes from zerovalent palladium and propargyl acetate **3h** or carbonate **3k** also ruled out Pd(0) species as active catalyst from **1**.

(22) We thank one of the referees for useful comments regarding the mechanism.

(23) Similar observations have been reported for the palladium-catalyzed [2 + 1] cycloaddition of terminal alkynes with norbornenes. See: Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753−4757.

(24) For a pertinent review on the halide effects in transition-metal catalysis, see: Fagnou, K,. Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

(25) **Typical Experimental Procedure.** Norbornadiene **2** (184 mg, 2 mmol) and phenylethyne **3a** (102 mg, 1 mmol) in DCE (6 mL) were added to a solution of palladium catalyst **1** (23.5 mg, 0.025 mmol) in DCE (2 mL). The mixture was stirred at 55 °C for 20 h, cooled at room temperature, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (hexanes) to yield 175 mg (90% yield) of *exo*-5-(phenylethynyl)-2-norbornene (**4a**).

(26) To the best of our knowledge, the metal-catalyzed addition of the C*sp*-H bond across the C−C double bond of allenes (a, b), 1, 3-butadiene (c), or bicyclo[2.2.1]hepta-2, 5-diene (d) has been described. (a) **Pd**: Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816−2818. (b) **Rh**: Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5689−5692. (c) **Ru**: Mitsudo, T.; Nakagawa, Y.; Watanabe, H.; Watanabe, K.; Misawa, H.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 496−497. (d) **Rh**: Brunner, H.; Prester, F. *Tetrahedron: Asymmetry* **1990**, *1*, 587−588.