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Palladium-Catalyzed Hydroalkynylation of Alkylidenecyclopropanes

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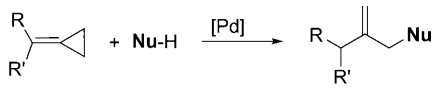
The transition-metal-catalyzed addition of C–H bonds across carbon–carbon multiple bonds is a transformation of high interest due to its potential to increase, in an atom-economical manner, the structural complexity of readily available molecules.[1] While most efforts have been devoted to the addition of C–H bonds of arenes to unsaturated carbon–carbon bonds (hydroarylation reactions),[2] the transition-metal-catalyzed addition of other C–H bonds, such as the sp-C–H bond of terminal alkynes (hydroalkynylation reaction), has only received attention in recent years.

Most processes reported thus far involve a sp-C–H bond activation and its subsequent addition to the same or another alkyne molecules (homo- or cross-hydroalkynylations).[3,4] Catalysts able to promote hydroalkynylations of unsaturated molecules other than alkynes are still quite rare.[5–10] Usually, in these cases, very reactive C–C double bonds such as those of allenes, enones, or strained cyclic alkenes are required.[5–7] Indeed, the first examples involving less reactive alkenes have only been reported very recently, and were achieved by using Ni catalysts.[8,9]

One of these reports deals with a nickel-catalyzed hydroalkynylation of methylenecyclopropanes with trisopropylsilylacetylene,[9] a reaction that provides cyclopropane derivatives. While the transformation is of undoubted synthetic interest, related processes in which the hydroalkynylation reaction is accompanied by opening of the cyclopropyl ring might be even more appealing.

Herein, we report the discovery of a palladium-catalyzed intermolecular hydroalkynylation of alkynylidenecyclopropanes, a reaction that provides an entry to a variety of 1,4-enynes. We also report some mechanistic data, and demonstrate that the presence of a coordinating heteroatom in the cyclopropylidene substrate allows complete control of the regioselectivity of the process.

Alkylidenecyclopropanes (ACPs) are strained but readily accessible molecules that have proven very useful in the development of new synthetic methodologies.[11] In particular, the presence of a strained ring attached to a coordinating double bond has allowed the development of a variety of novel transition-metal-catalyzed rearrangements as well as [3+n+(m)] cycloaddition processes[12–15] Relevant to the current work are the Pd-catalyzed hydrofunctionalizations of ACPs (Scheme 1), mostly developed by Yamamoto and co-workers.[16] These reactions, which generally lead to allylic derivatives, have been reported to proceed with several types of pronucleophiles such as amides, alcohols, heteroaromatic rings (i.e. furans), and malonates. In most cases the reaction requires relatively stringent conditions: high temperatures, long reaction times, and high concentration of reactants.



Nu-H = R_2NH, ROH, furan, active methynes
[Pd] : $[Pd(PPh_3)_4]$, $[Pd(PPh_3)_4]$ / P(o-tolyl)$_3$, or $[Pd(PPh_3)_4]$ / P(O)R_3,
100-120 °C, 12 h- 4 days

Scheme 1. Previous Pd-catalyzed hydrofunctionalizations of ACPs with different pronucleophiles.[16]

Our research on this topic began when exploring the feasibility of performing selective Pd-catalyzed [3C+2C] intermolecular cycloadditions between the 2-pyridyl derivative **1a** and ethynyltrimethylsilane (**2a**, Scheme 2). We designed ACP **1a** expecting that a hypothetical coordination of the Pd complex to the nitrogen atom of the pyridine could direct the oxidative insertion into the cyclopropane ring, and thereby provide a regioselective [3C+2C] cycloaddition to the alkyne.[17] Surprisingly, when a mixture of **1a** and **2a** was treated under conditions previously shown to be effec-

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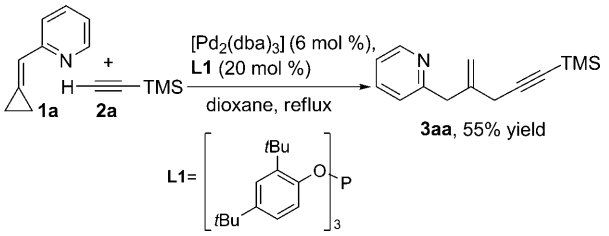


Scheme 2. Hydroalkynylation of **1a**.

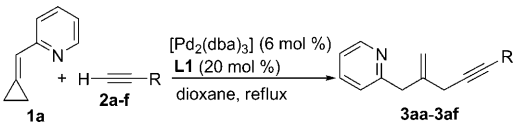
tive for the Pd-catalyzed cycloaddition of alk-5-ynylidenecyclopropanes,[13j–l] instead of the [3C+2C] cycloadducts, we isolated the 1,4-enyne **3aa** in 55% yield.

This result led us to analyze the performance of other metal complexes previously shown to be effective in either the hydrofunctionalization of ACPs,[9,16] or in Pd-catalyzed hydroalkynylations of different unsaturated C–C bonds. However, the formation of enyne **3aa** was not observed when the reaction was performed with $Pd(OAc)_2$/TDMPP (TDMPP = tri(2,6-dimethoxyphenyl)phosphane),[4b] $Pd(OAc)_2$/dppe (dppe = bis(diphenylphoshanyl)ethane),[4e] or $Pd(OAc)_2$/P(*o*-tolyl)$_3$.[6a,16] Instead, the homo-alkynylated dimer **6a** and/or the 1,3-diene **7a**,[18] itself arising from a Pd-catalyzed rearrangement of **1a** (vide infra), were observed in the crude reaction mixtures, together with unreacted **1a**. Using $[Pd(PPh_3)_4]$, or a mixture of $[Pd(PPh_3)_4]$ (5 mol%) and $P(O)Bu_3$ (10 mol%), catalysts previously reported for the hydrofunctionalization of ACPs with amines and heteroaromatic pronucleophiles such as furans,[16b,d,f,g,i] we only observed the formation of traces of product **3aa**. Low reaction rates, scarce reproducibility, and the competitive formation of conjugated diene **7a** led us to discard these catalysts for the current process. On the other hand, Ni catalysts recently employed in the hydroalkynylation of conjugated dienes[8] and methylenecyclopropanes,[9] failed to catalyze the ring opening-coupling process, and mainly led to unreacted **1a** and homodimeric product **6a**.[18] Therefore, the choice of the transition metal (Pd vs. Ni) as well as the nature of the ligand seems to play an essential role in the current hydroalkynylation reaction; the combination leading to the best results being the bulky triarylphosphite ligand **L1** and tris(dibenzylideneacetone)dipalladium ($[Pd_2(dba)_3]$).

With these conditions in hand, we next analyzed the scope of the new hydroalkynylation process using **1a** as the alkylidene coupling partner. As can be seen in Table 1, the reaction can be performed with different terminal alkynes, affording the corresponding 1,4-enynes (**3aa**–**3af**) in moderate to good yields. Interestingly, in contrast to the previous Ni-promoted alkynylations,[8,9] the presence of a bulky silyl group at the alkyne terminus (Table 1, entries 1 and 2) is not strictly required for the success of the process. Thus, both linear and branched aliphatic groups (Table 1, entries 3–5), as well as aromatic substituents are tolerated; the corresponding products are obtained in comparable yields.

Curiously, use of (cyclopropylidenemethyl)benzene (**1b**) instead of the pyridine derivative **1a**, in the coupling reaction with ethynyltrimethylsilane (**2a**), in addition to providing the expected 1,4-enyne **3ba**, gave its isomer **4ba** and a small proportion of **5ba** (6:3:1). Isomers **3ba** and **4ba** could be isolated from the mixture in an excellent combined yield of 89%.[19] The different outcomes for **1a** and **1b** must be attributed to the presence of the nitrogen atom in the 2-position of the aryl group in **1a**, since the reaction of related 3- and 4-pyridyl derivatives **1c** and **1d** led to mixtures of enynes **3**–**5** in comparable ratios to those obtained from phenyl derivative **1b** (Table 2, entries 2 and 3).

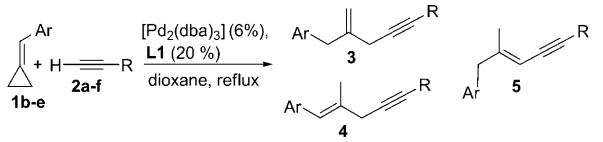
Table 1. Pd-catalyzed hydroalkynylations of **1a** with different terminal alkynes.



Entry	Alkyne, **2**	R	Product, **3**	Yield [%][b]
1	**2a**	TMS	**3aa**	55
2	**2b**	TIPS	**3ab**	51
3	**2c**	*n*Bu	**3ac**	52
4	**2d**	*t*Bu	**3ad**	41
5	**2e**		**3ae**	44
6	**2f**	Ph	**3af**	65

[a] Reactions carried out with $[Pd_2(dba)_3]$ (6 mol%), **L1** (20 mol%), **1a** (1 equiv), and **2a**–**f** (2.5 equiv) in refluxing dioxane for 3 h. [b] Yield of isolated product.

Table 2. Pd-catalyzed hydroalkynylations of **1b**–**e**.[a]

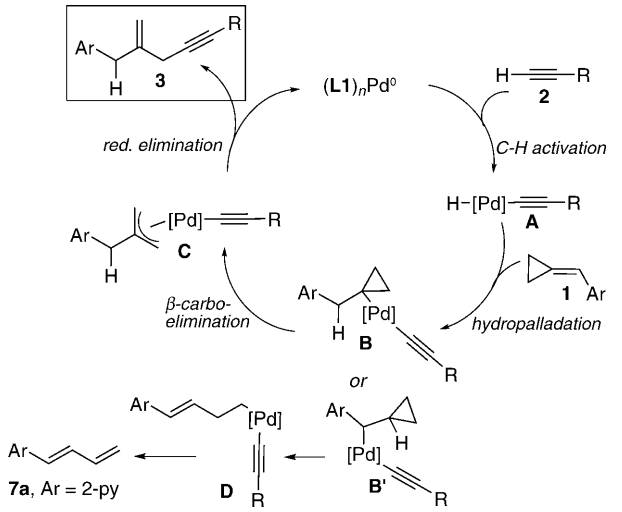


Entry	Ar (**1**)	R (**2**)	**3**:**4**:**5** (ratio)[b]	Yield **3**+**4** [%][c]
1	Ph (**1b**)	TMS (**2a**)	**ba** (58:32:10)	89
2	3-pyridyl (**1c**)	TMS (**2a**)	**ca** (40:44:16)	81
3	4-pyridyl (**1d**)	TMS (**2a**)	**da** (62:30:8)	33
4	Ph (**1b**)	TIPS (**2b**)	**bb** (47:53:0)	60
5	Ph (**1b**)	*t*Bu (**2d**)	**bd** (55:36:9)	57
6	Ph (**1b**)	C_6H_9 (**2e**)	**be** (54:46:0)	42
7	Ph (**1b**)	Ph (**2f**)	**bf** (38:46:16)	82
8	*p*-$NO_2C_6H_4$ (**1e**)	TMS (**2a**)	**ea** (88:9:3)	50

[a] Reactions carried out with $[Pd_2(dba)_3]$ (6 mol%), **L1** (20 mol%), **1a** (1 equiv), and **2** (2.5 equiv) in refluxing dioxane for 3 h. [b] Based on ^{1}H NMR spectra of the crude reaction mixtures.[c] Isolated combined yield of **3** and **4**.[19]

Other alkynes, such as **2b**–**f**, also participated in the hydroalkynylation of **1b**, preferentially providing enynes **3** and **4** (Table 2, entries 4–8). The electronic characteristics of the phenyl group might partially influence the regioselectivity, as the reaction with the *p*-nitro derivative **1e** afforded a major proportion of isomer **3** (Table 2, entry 8).

A potential mechanism that explains the formation of 1,4-enynes of type **3**, is shown in Scheme 3. The reaction path-

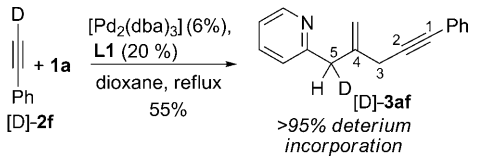


Scheme 3. Plausible mechanism for the formation of product **3**. Diene **7a** was observed in the reactions of **1a** and **2a** with $Pd(OAc)_2$/TDMPP or with other related catalysts (vide supra and Supporting Information).

way probably involves an initial oxidative addition of the sp-C–H bond of the terminal alkyne to the Pd^0 catalyst, leading to the generation of a (hydro)(alkynyl)palladium(II) intermediate **A**. Insertion of the ACP into the Pd–H bond generates intermediate **B**, which might undergo a β-carboelimination with concomitant distal opening of the cyclopropane ring to afford a π-allyl–Pd species of type **C**. A final reductive elimination provides the 1,4-enyne **3**, with regeneration of the Pd^0 catalysts. The detection of alkyne homodimerization products such as **6a** as minor components in the crude reaction mixtures, is consistent with the participation (hydro)(alkynyl)metal intermediate **A**.[20]

As discussed above, in presence of Pd reagents other than $[Pd_2(dba)_3]$/**L1**, we observed, the formation of minor amounts of diene **7a**, in the hydroalkynylation of **1a** with **2a**. This product might arise from the regioisomeric hydrometallation intermediate **B′**, which could evolve through a β-carboelimination followed by β-hydride elimination.

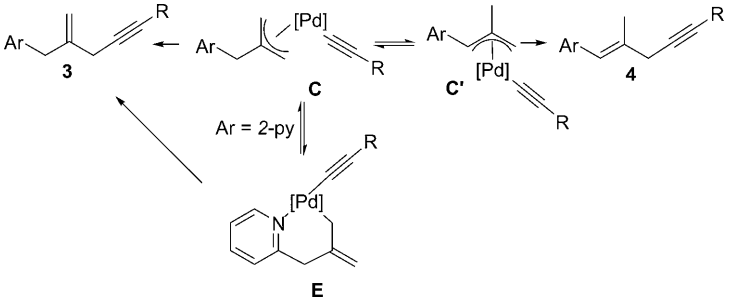
Consistent with the mechanistic proposal, when deuterated phenylacetylene ([D]-**2f**) was allowed to react with **1a**, the monodeuterated product [D]-**3af**, in which the deuterium isotope is only incorporated at the C-5 position (deuterium content > 95%), was obtained (Scheme 4). Moreover, when the same reaction was not allowed to reach full conversion (reaction time of 1 h), the recovered ACP (**1a**) did not show any incorporation of deuterium into the double



Scheme 4. Hydroalkynylation of **1a** with deutarated phenylacetilene [D]-**2f**.

bond. Thus, the insertion of the ACP into the Pd–H bond is most likely irreversible, as well as completely regioselective.

The formation of regioisomeric enynes of type **4** (and the minor isomers **5**), when ACPs other than **1a** are employed, is more difficult to explain. Hypothetically, these enynes could arise from an in situ isomerization of **3** through a hydropalladation/β-hydride elimination sequence, promoted by a Pd–hydride species. However, treatment of a mixture of **3bf** and **4bf** (ratio = 62:38) with $[Pd_2(dba)_3]$ (6%), **L1** (20%), and **2a** (2.5 equiv) in refluxing dioxane did not promote any modification of the initial isomeric ratios, making quite unlikely such an isomerization pathway. The formation of isomer **4** could be explained in terms of a hypothetical isomerization of the π-allyl–Pd species of type **C** to **C′** (Scheme 5),[21] albeit other alternatives cannot be discarded.



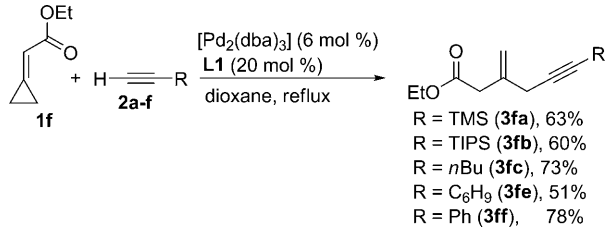
Scheme 5. Mechanistic hypotheses.

In the case of the 2-pyridyl derivative **1a**, such an isomerization process is probably prevented by the coordination of the pyridine nitrogen atom to the Pd center, which facilitates the accumulation of a σ-complex like **E**, which upon reductive elimination would provide **3**, the only isomer observed.

The obvious relevance of the 2-pyridyl nitrogen in controlling the regioselectivity of the hydroalkynylation process suggested that other cyclopropane substrates containing topologically comparable heteroatoms might provide similar outcomes. In particular, we considered assessing the performance of easily accessible ACP **1f**, which features a carboxylate substituent as a potential directing group.[1–2] In the event of a successful reaction the synthetic scope of the methodology would be considerably expanded owing to the versatility of the ester functional group.

Gratifyingly, the reaction of **1f** with ethynyltrimethylsilane (**2a**), in the presence of catalytic amounts of ligand **L1** and $[Pd_2(dba)_3]$, proceeded very efficiently, exclusively providing the desired enyne **3fa** in 63% yield (Scheme 6). The reaction can be extended to other alkynes so that a variety of enynes (**3fa**–**3ff**) could be obtained in good yields. Notably, α,β-unsaturated regioisomers of type **4**, or enynes of type **5**, were never detected in the crude mixtures (or after flash chromatography on silica gel), confirming the directing effect of the carboxylate of **1f**.

In summary, we have shown that a Pd^0 catalyst generated from $[Pd_2(dba)_3]$ and a sterically encumbered phosphite



Scheme 6. Hydroalkynylation of **1f** with several terminal alkynes.

ligand (**L1**) is capable of promoting a tandem ring-opening coupling process involving terminal alkynes and alkylidenecyclopropanes. Importantly, we have demonstrated that the presence of an appropriate directing group, such as a 2-pyridyl unit or a carboxylate moiety, leads to a regioselective hydroalkynylation, most probably due to a direct coordination of the sp^2-heteroatom to the palladium catalyst. Crescent interest in C–H activation chemistry of alkynes and in atom-economical C–C coupling reactions between partners lacking heteroatom groups at the coupling positions, warrants further studies to increase the efficiency and potential of the described chemistry.

Experimental Section

Procedure for the Pd-catalyzed hydroalkynylations of 1a with 2a–f (exemplified for 1a and 2a): $[Pd_2(dba)_3]$ (21.0 mg, 6%) and phosphite **L1** (50.0 mg, 20%) were mixed in a dried Schlenk tube under argon. Dioxane (3 mL) was added and the solution was deoxygenated (three vacuum–argon cycles) and stirred for 5 min at room temperature. A solution of **1a** (50 mg, 0.382 mmol) in dioxane (1 mL) was then added and the resulting mixture was further deoxygenated (one vacuum–argon cycle). Alkyne **2a** (0.13 mL, 0.954 mmol) was added and the reaction mixture was heated under reflux for 2.5 h, allowed to cool to room temperature, diluted with Et_2O (8 mL), and filtered through a short pad of Fluorisil (elution with Et_2O). The filtrate was concentrated and purified by flash chromatography on silica gel [deactivated with 2% NEt_3/hexanes (20–30% Et_2O/hexanes)] to afford **3aa** as a colorless oil (47.7 mg, 55%).

Acknowledgements

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Keywords: alkylidenecyclopropanes · alkynes · C–C coupling · C–H activation · palladium

[1] a) *Handbook of C-H Transformations*, (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; b) F. Kakiuchi, S. Murai in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Heidelberg, **1999**, p. 48; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770; d) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949–957.

[2] For recent reviews on C–H activation/hydroarylation, see: a) L. Ackermann, *Top. Organomet. Chem.* **2008**, *24*, 35–60; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; c) D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35–41; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.

[3] For representative homo-hydroalkynylations (self-couplings of terminal alkynes), see: a) E. Bustelo, P. H. Dixneuf, in *Handbook of C-H Transformations*, (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, p 62; b) Y. Nishibayashi, M. Yamanashi, I. Wakiji, M. Hidai, *Angew. Chem.* **2000**, *112*, 3031–3033; *Angew. Chem. Int. Ed.* **2000**, *39*, 2909–2911; c) M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2001**, *123*, 11107–11108; d) M. Nishiura, Z. Hou, Y. Wakatsuki, T. Yamaki, T. Miyamoto, *J. Am. Chem. Soc.* **2003**, *125*, 1184–1185; e) S. Ogoshi, M. Ueta, M. Oka, H. Kurosawa, *Chem. Commun.* **2004**, 2732–2733; f) W. Weng, C. Guo, R. Çelenligil-Çetin, B. M. Foxman, O. V. Ozerov, *Chem. Commun.* **2006**, 197–199; g) R. Ghosh, X. Zhang, P. Achord, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *J. Am. Chem. Soc.* **2007**, *129*, 853–856.

[4] For cross-hydroalkynylations (additions of a terminal alkyne to a different alkyne molecule), see: Pd-catalyzed: a) B. M. Trost, M. C. McIntosh, *Tetrahedron Lett.* **1997**, *38*, 3207–3210; b) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms, G. Rühter, *J. Am. Chem. Soc.* **1997**, *119*, 698–708; c) U. Lücking, A. Pfaltz, *Synlett* **2000**, 1261–1264; d) L. Chen, C.-J. Li, *Tetrahedron Lett.* **2004**, *45*, 2771–2774; e) S. Kamijo, Y. Sasaki, C. Kanazawa, T. Schüßeler, Y. Yamamoto, *Angew. Chem.* **2005**, *117*, 7896–7899; *Angew. Chem. Int. Ed.* **2005**, *44*, 7718–7721; f) N. Tsukada, S. Ninomiya, Y. Aoyama, Y. Inoue, *Org. Lett.* **2007**, *9*, 2919–2921; Rh-catalyzed: g) T. Katagiri, H. Tsurugi, A. Funayama, T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 830–831; h) T. Nishimura, X.-X. Guo, K. Ohnishi, T. Hayashi, *Adv. Synth. Catal.* **2007**, *349*, 2669–2672; i) T. Katagiri, H. Tsurugi, A. Funayama, T. Satoh, M. Miura, *Chem. Commun.* **2008**, 3405–3407; Ir-catalyzed: j) T. Hirabayashi, S. Sakaguchi, Y. Ishii, *Adv. Synth. Catal.* **2005**, *347*, 872–876; Ru-catalyzed: k) C. S. Yi, N. Liu, *Organometallics* **1998**, *17*, 3158–3160; l) H. Katayama, H. Yari, M. Tanaka, F. Ozawa, *Chem. Commun.* **2005**, 4336–4338; Ni-catalyzed: m) K. Ogata, H. Murayama, J. Sugasawa, N. Suzuki, S. Fukuzawa, *J. Am. Chem. Soc.* **2009**, *131*, 3176–3177.

[5] For hydroalkynylations of allenes, see: a) B. M. Trost, G. Kottirsch, *J. Am. Chem. Soc.* **1990**, *112*, 2816–2818; b) M. Yamaguchi, K. Omata, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 5689–5692; c) D. Bruyere, R. Grigg, J. Hinsley, R. K. Hussain, S. Korn, C. O. de La Cierva, V. Sridharan, J. Wang, *Tetrahedron Lett.* **2003**, *44*, 8669–8676; d) M. Rubin, J. Markov, S. Chuprakov, D. J. Wink, V. Gevorgyan, *J. Org. Chem.* **2003**, *68*, 6251–6256.

[6] For norbornadienes, see: a) A. Tenaglia, L. Giordano, G. Buono, *Org. Lett.* **2006**, *8*, 4315–4318; b) K. Kohno, K. Nakagawa, T. Yahagi, J-C. Choi, H. Yasuda, T. Sakakura, *J. Am. Chem. Soc.* **2009**, *131*, 2784–2785; c) T. Nishimura, E. Tsurumaki, T. Kawamoto, X-X. Guo, T. Hayashi, *Org. Lett.* **2008**, *10*, 4057–4060.

[7] For cyclopropenes and enones, see: a) J. Yin, J. D. Chisholm, *Chem. Commun.* **2006**, 632–634; b) L. Chen, C.-J. Li, *Chem. Commun.* **2004**, 2362–2364; c) R. V. Lerum, J. D. Chisholm, *Tetrahedron Lett.* **2004**, *45*, 6591–6594; d) T. Nishimura, Y. Washitake, Y. Nishiguchi, Y. Maeda, S. Uemura, *Chem. Commun.* **2004**, 1312–1313; e) T. Nishimura, X-X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 1576–1577.

[8] For addition to 1,3-dienes, see: a) M. Shirakura, M. Suginome, *J. Am. Chem. Soc.* **2008**, *130*, 5410–5411; for styrenes, see: b) M. Shirakura, M. Suginome, *Org. Lett.* **2009**, *11*, 523–526.

[9] M. Shirakura, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 5060–5061.

[10] For the catalytic addition of terminal alkynes to carbon-heteroatom bonds, such as imines and aldehydes, see: a) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275 and references therein; b) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268–269; c) Y. Kuninobu, Y. Inoue, K. Takai, *Chem. Lett.* **2006**, *35*, 1376–1377; d) J.-X. Ji, J. Wu,

L. Xu, C.-W. Yip, K. H. Lam, A. S. C. Chan, *Pure Appl. Chem.* **2006**, *78*, 267–274 and references therein.

[11] For recent reviews, see: a) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; b) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213–1270.

[12] For a review on transition-metal-catalyzed reactions of methylenecyclopropenes, see: I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, *344*, 111–129.

[13] For examples on [3+2] cycloadditions, see: a) R. Noyori, T. Odagi, H. Takaya, *J. Am. Chem. Soc.* **1970**, *92*, 5780–5781; b) P. Binger, U. Schuchardt, *Chem. Ber.* **1981**, *114*, 3313–3324; c) P. Binger, Q.-H. Lü, P. Wedemann, *Angew. Chem.* **1985**, *97*, 333–334; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 316–317; d) P. Binger, H. M. Buech, *Top. Curr. Chem.* **1987**, *135*, 77–152; e) M. Lautens, Y. Ren, P. Delanghe, P. Chiu, S. Ma, J. Colucci, *Can. J. Chem.* **1995**, *73*, 1251–1257; f) I. Nakamura, B. Ho Oh, S. Saito, Y. Yamamoto, *Angew. Chem.* **2001**, *113*, 1338–1340; *Angew. Chem. Int. Ed.* **2001**, *40*, 1298–1300; g) A. Delgado, J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2003**, *125*, 9282–9283; h) F. López, A. Delgado, J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2004**, *126*, 10262–10263; i) A. I. Siriwardana, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 3202–3204; j) J. Durán, M. Gulías, L. Castedo, J. L. Mascareñas, *Org. Lett.* **2005**, *7*, 5693–5696; k) B. Trillo, M. Gulías, F. López, L. Castedo, J. L. Mascareñas, *Adv. Synth. Catal.* **2006**, *348*, 2381–2384; l) M. Gulías, R. García, A. Delgado, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2006**, *128*, 384–385.

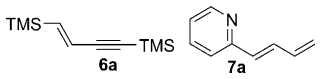
[14] For examples on [3+4] cycloadditions, see: a) M. Gulías, J. Durán, F. López, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2007**, *129*, 11026–11027; b) S. Saito, K. Takeuchi, *Tetrahedron Lett.* **2007**, *48*, 595- 598.

[15] For examples on [3+2+2] cycloadditions, see: a) P. Binger, U. Schuchardt, *Chem. Ber.* **1980**, *113*, 1063–1071; b) S. Saito, M. Masuda, S. Komagawa, *J. Am. Chem. Soc.* **2004**, *126*, 10540–10541; c) L. Zhao, A. de Meijere, *Adv. Synth. Catal.* **2006**, *348*, 2484–2492; d) S. Komagawa, S. Saito, *Angew. Chem.* **2006**, *118*, 2506–2509; *Angew. Chem. Int. Ed.* **2006**, *45*, 2446–2449; e) S. Saito, S. Komagawa, I. Azumaya, M. Masuda, *J. Org. Chem.* **2007**, *72*, 9114–9120; f) K. Maeda, S. Saito, *Tetrahedron Lett.* **2007**, *48*, 3173–3176; g) P. A. Inglesby, P. A. Evans, *J. Am. Chem. Soc.* **2008**, *130*, 12838–12839; h) R. Yamasaki, I. Sotome, S. Komagawa, I. Azumaya, H. Masu, S. Saito, *Tetrahedron Lett.* **2009**, *50*, 1143–1145.

[16] a) Y. Yamamoto, U. Radhakrishnan, *Chem. Soc. Rev.* **1999**, *28*, 199–207; b) N. Tsukada, A. Shibuya, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 8123–8124; c) D. H. Camacho, I. Nakamura, S. Saito, Y. Yamamoto, *Angew. Chem.* **1999**, *111*, 3576–3578; *Angew. Chem. Int. Ed.* **1999**, *38*, 3365–3367; d) I. Nakamura, S. Saito, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 2661–2662; e) D. H. Camacho, I. Nakamura, S. Saito, S. Yamamoto, *J. Org. Chem.* **2001**, *66*, 270–275; f) I. Nakamura, A. I. Siriwardana, S. Saito, Y. Yamamoto, *J. Org. Chem.* **2002**, *67*, 3445–3449; g) D. H. Camacho, I. Nakamura, B. Ho Oh, S. Saito, Y. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 2903–2907; h) M. Shi, Y. Chem, B. Xu, *Org. Lett.* **2003**, *5*, 1225–1228; i) A. I. Siriwardana, M. Kamada, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 5932–5937.

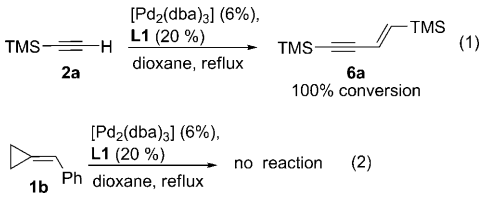
[17] The [3C+2C] intermolecular cycloadditon of ACPs with alkynes has only been reported under Ni catalysis.[13c,d] However, intramolecular versions, are very efficient with Pd catalysts.[13g,h,j]

[18] See Supporting Information for a list of results with other catalysts employed.



[19] Regioisomers **3** and **4** were isolated together after standard chromatography. The minor isomer of type **5** could be separated from the mixture of **3** and **4** but it turned out to be slightly contaminated by **L1** and other very minor reaction components. Therefore, yields refer to the mixture of the major components, **3** and **4**.

[20] The reaction of **2a** with $[Pd_2(dba)_3]$ (6%) and **L1** (20%), in the absence of **1b**, exclusively provided 1,2-enyne homodimerizations adduct **6a** [Eq. (1)]. On the other hand, treatment of **1b** with $[Pd_2(dba)_3]$ (6%) and **L1** (20%), in the absence of **2a**, led to the recovery of **1b** [Eq. (2)].



[21] This type of isomerization process has been previously proposed in a related hyfrofunctionalization os ACPs, see reference [16e].

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