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Highly Satisfactory Alkynylation of Alkenyl Halides via Pd-Catalyzed Cross-Coupling with Alkynylzincs and Its Critical Comparison with the Sonogashira Alkynylation[†]

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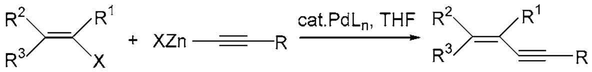
ABSTRACT



R = COOMe, COOEt, COPh, COC$_6$H$_{11}$-*c*, CH=CMeCOOEt,
CH=CHCH=CMeCOOEt, Ph, *n*-Hex.
R^1, R^2, R^3 = C, H, or Br. X = halogens or OTf.

The Pd-catalyzed alkynylation of various alkenyl halides and triflates with alkynylzincs proceeds well even with alkynyl derivatives containing electron-withdrawing groups. The reaction appears to be highly general. Noteworthy is that the corresponding Sonogashira reactions under various reported conditions are significantly less satisfactory in all cases performed in this study.

Over the last quarter of a century, Pd-catalyzed alkynylation[1] has emerged as a highly satisfactory method for the synthesis of alkynes. It has been mainly performed either by Heck-type reactions[1a,2] with terminal alkynes, especially the Sonogashira alkynylation cocatalyzed by Pd and Cu,[1a,2b−e] or with preformed alkynylmetals,[1b] especially with those containing Zn,[3−6] Mg,[3d,4,7] Sn,[4,8] and B[4,9] reported first by the authors' group.[3a,4] Despite the fact that the Sonogashira alkynylation has been the more frequently used of the two, it has also become increasingly clear that this reaction fails partially or totally in a large number of cases. Specifically, it fails to produce terminal alkynes directly in useful yields due to competitive disubstitution of ethyne.[2,5c,d] The use of

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[†] Dedicated to Prof. Marcial Moreno-Mañas on the occasion of his 60th birthday.

(1) For recent reviews, see: (a) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 493−529. (b) Negishi, E.; Xu, C. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 531−549.

(2) (a) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (c) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem Soc., Chem. Commun.* **1977**, 291. (d) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777. (e) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(3) For earlier contributions by the authors, see: (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) King A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358. (c) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. (d) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629.

(4) Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, 1978; pp 285−317. See also: Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(5) For recent papers by the authors, see: (a) Negishi, E.; Ay, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437. (b) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121. (c) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *46*, 209. (d) Kotora, M.; Xu, C.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8957. (e) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. (f) Negishi, E.; Hata, M.; Xu, C. *Org. Lett.* **2000**, *2*, 3687. (g) Negishi, E.; Tan Z.; Liou, S. Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197. (h) Zeng, F.; Negishi, E. *Org Lett.* **2001**, *3*, 719. (i) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.

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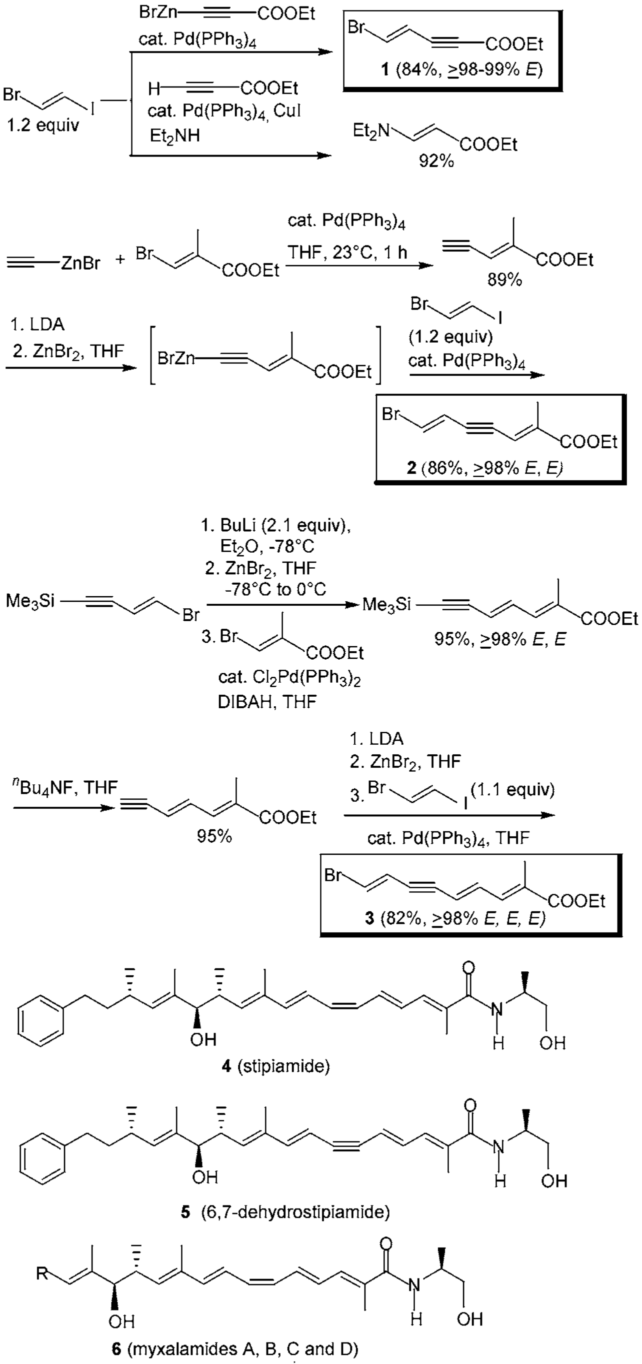
alkynes containing electron-withdrawing substituents has been problematic.[10] There have also been indications that its scope appears to be more limited than that of the alkynylation with preformed alkynylzincs in cases where steric hindrance is significant.[11] Two frequently encountered side reactions in the Sonogashira alkynylation are alkyne homodimerization and Michael-type addition reactions. On the other hand, neither has been serious with preformed alkynylzincs and related alkynylmetals.

Herein reported are some synthetically useful results of Pd-catalyzed alkynylation of alkenyl halides with alkynylzincs that do not appear to be readily achieved by the Sonogashira alkynylation. In conjunction with our recent efforts to synthesize some natural products containing enynes, it became desirable to develop an efficient and selective route to a class of enynes represented by **1**−**3**. The trienyne **3**, for example, may be envisioned as a potentially attractive intermediate for the synthesis of stipiamide (**4**),[12a,b] 6,7-dehydrostipiamide (**5**),[12a,b] and myxalamide (**6**).[12c] As desired, **1**−**3** were prepared in high yields by applying the Pd-catalyzed alkynylation method reported recently by us for the synthesis of alkynylated arenes[5i] (Scheme 1).[13] In none of the steps shown in Scheme 1 was the formation of any stereoisomers detected by ^{1}H and/or ^{13}C NMR spectroscopy, and the overall stereoisomeric purity may be claimed to be ≥98−99%.[14] The three-step synthesis of the C1−C9 moiety (**3**) of 6,7-dehydrostipiamide (**5**) in 74% overall yield and ≥98% isomeric purity from (*E*)-1-iodo-2-bromoethylene, (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne, and ethyl (*E*)-3-bromo-2-methyl-2-propenoate is noteworthy.

Scheme 1



A: R = (*s*)-1-methylpropyl. B: R = ^{i}Pr. C: R = Et. D: R = Me.

In view of highly contrasting results observed in the Pd-catalyzed alkynylation with alkynylzincs on one hand and

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(6) For some other earlier contributions by others, see: (a) Vincent, P.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* **1981**, *22*, 945. (b) Ruitenberg, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 405. (c) Andreini, B. P.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 5533; **1988**, *29*, 2239. (d) Tellier, F.; Sauvêtre, R; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3147. (e) Chen, Q. Y.; He, Y. B. *Tetrahedron Lett.* **1987**, *28*, 2387.

(7) For other early contributions, see: (a) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191. (b) Rossi, R.; Carpita, A.; Lezzi, A. *Tetrahedron* **1984**, *40*, 2773.

(8) For early contributions, see: (a) Kashin, A. N.; Bumagina, I. G.; Bumagin, N. A.; Beletskaya, I. P.; Reutov O. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 479. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (c) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.

(9) For other recent contributions, see: (a) Soderquist, J. A.; Matos, K.; Rane, A. M.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401. (b) Soderquist, J. A.; Rane, A. M.; Matos, K.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 6847. (c) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (d) Fürstner, A.; Nikolakis, K. *Liebigs Ann. Chem.* **1996**, 2107.

(10) See ref 5i and other pertinent papers cited therein.

(11) See, for example: Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett*. **2001**, *3*, 2419.

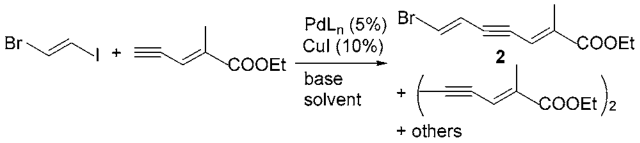
(12) (a) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am Chem. Soc.* **1997**, *119*, 12159. (b) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327. (c) Mapp, K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23.

(13) **Ethyl (*E*,*E*)-2-Methyl-7-bromo-2,6-heptadien-4-ynoate (2)**. **Representative Procedure**. To a solution of commercially available ethynylmagnesium bromide (0.5 M in THF, 4 mL, 2.0 mmol) was added a solution of anhydrous $ZnBr_2$ (450 mg, 2.0 mmol) in THF (2 mL) via *cannula* at 0 °C. The mixture was stirred at 0 °C for 30 min and added via *cannula* to a solution of ethyl (*E*)-3-bromo-2-methyl-2-propenoate (386 mg, 2.0 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in THF (2 mL). The reaction mixture was stirred at 23 °C for 1 h, quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and then with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (pentane/EtOAc = 95/5, v/v) gave 246 mg (89%) of ethyl (*E*)-2-methyl-2-penten-4-ynoate. To a solution of this compound (138 mg, 1.0 mmol) in THF (1 mL) were successively added at −78 °C via *cannula* LDA (1.0 mmol) in THF (3 mL) and a solution of anhydrous $ZnBr_2$ (225 mg, 1.0 mmol) in THF (1 mL). The mixture was stirred at 0 °C for 30 min and added via cannula to a solution of (*E*)-1-iodo-2-bromoethylene (280 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (2 mL). After being stirred at 23 °C for 4 h, the mixture was quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and then with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (pentane/EtOAc = 95/5, v/v) gave 209 mg (86%) of **2**.

(14) For determination of stereoisomeric purities by ^{13}C NMR, see: Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703.

in the Sonogashira alkynylation on the other (vide supra), the preparation of **1** and **2** by the Sonogashira alkynylation was also attempted. However, these compounds were not obtained in more than 28% yield, typical yield being less than a few percent under various conditions reported[15] for the Sonogashira alkynylation. Thus, the reaction of (*E*)-1-iodo-2-bromoethylene with ethyl propynoate in the presence of $Pd(PPh_3)_4$ and CuI in Et_2NH^{2b-e} led to the formation of ethyl (*E*)-3-diethylamino-2-propenoate in 92% yield. In the reaction of (*E*)-1-iodo-2-bromoethylene with ethyl (*E*)-2-methyl-2-penten-4-ynoate under various Sonogashira alkynylation conditions, the major product was always the homodimer of the ethyl (*E*)-2-methyl-2-peten-4-ynoate, as indicated by the results summarized in Table 1. Under the most favorable conditions involving the use of $Pd(PPh_3)_4$ and Cs_2CO_3 in THF,[15c] the yield of **2** was only 28%, the major product being the alkyne homodimer accounting for 57% of ethyl (*E*)-3-bromo-2-methyl-2-propenoate even in the presence of 2,6-di(*tert*-butyl)phenol used as an antioxidant. In some cases, dialkynylation of (*E*)-1-iodo-2-bromoethylene was also observed to the extent of ≤5−10%.

Table 1. Pd-Catalyzed Reaction of (*E*)-1-Iodo-2-bromoethylene with Ethyl (*E*)-2-Methyl-2-penten-4-ynoate



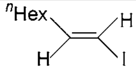
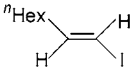
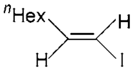
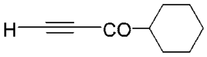
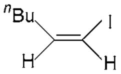
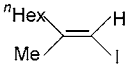
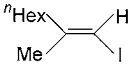
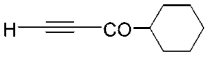
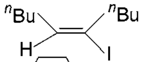
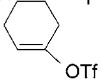
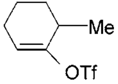
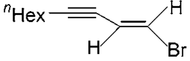
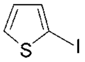
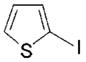
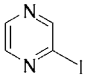
base	solvent	catalyst	temp, °C	time, h	**2**, %[a]	homo-dimer, %[a]
Et_2NH	Et_2NH	$Pd(PPH_3)_4$	23	5	16	41
Et_2NH^b	THF	$Pd(PPH_3)_4$	23	5	trace	72
$K_2CO_3^c$	THF	$PdCl_2(PPH_3)_2$	23	15	trace	*d*
$K_2CO_3^c$	THF	$PdCl_2(PPH_3)_2$	65	5	trace	*d*
K_2CO_3	DMF	$PdCl_2(PPH_3)_2$	23	5	trace	*d*
piperidine[e]	THF	$PdCl_2(PPH_3)_2$	23	2	trace	*d*
$Cs_2CO_3^f$	THF	$Pd(PPH_3)_4$	23	8	28	57

[a] By GLC. [b] 3 molar equiv of Et_2NH used. [c] Reference 15a. [d] The exact amount was not determined, but it was substantial. 1 mol % of BHT added as an antioxidant. [e] Reference 15b. [f] Reference 15c.

It should be noted that the difficulties associated with the synthesis of **1**−**3** by the Sonogashira alkynylation appear to be at least 2-fold. In addition to the previously noted difficulties associated with the use of alkynes containing electron-withdrawing substituents,[5i] the use of (*E*)-1-iodo-2-bromoethylene in the Sonogashira alkynylation must be problematic. Indeed, the reaction of phenylethyne with 1.1 molar equiv of (*E*)-1-iodo-2-bromoethylene in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of CuI in Et_2NH at 23 °C led to the formation of 1,4-diphenyl-1,3-butadiyne in 50% yield without producing the desired product in detectable yield.

The scope of the Pd-catalyzed alkynylation of alkenyl electrophiles with alkynylzincs appears to be very broad, and the reaction is satisfactory even in those cases where the Sonogashira alkynylation is problematic, as can be gleaned from the results summarized in Table 2. No stereoisomerization was detected in any of the reactions with potentially isomerizable alkenyl iodides (entries 1−7 and 10), including

Table 2. Pd-Catalyzed Alkynylation of Alkenyl Halides and Triflates as Well as Heteroaryl and Alkynyl Iodides: Comparison of the Alkynylzinc Reaction and the Sonogashira Reaction[a]

entry	alkenyl electrophile	alkyne	product yield, %[b]	
			alkynylzinc	Sonogashira
1		$H-\equiv-COOMe$	87	53[c]
2		$H-\equiv-COOEt$	89	*d*
3			71	32[c]
4		$H-\equiv-COOEt$	72	*e*
5		$H-\equiv-COOMe$	84	25[c]
6			64	*e*
7		$H-\equiv-COOEt$	76	*e*
8		$H-\equiv-COOMe$	88	*e*
9		$H-\equiv-COOMe$	83	12
10		$H-\equiv-COOEt$	84	31[f]
11		$H-\equiv-COOEt$	82	*e*
12		$H-\equiv-COPh$	81	*e*
13		$H-\equiv-COOEt$	82	37[g]
14	$^nHex-\equiv-I$	$H-\equiv-COOMe$	86	*e*

[a] Unless otherwise indicated, the alkynylzinc reactions were run in THF in the presence of 3 mol % of $Pd(PPh_3)_4$ at 23 °C with alkynylzinc bromides generated in situ by treatment of alkynes with LDA followed by addition of dry $ZnBr_2$. The Sonogashira alkynylation was run by using 3 mol % of $Cl_2Pd(PPh_3)_2$, 6 mol % of CuI, and 2 equiv of K_2CO_3 in THF under reflux. The alkyne-to-alkenyl electrophile ratio was typically 1.2. [b] Isolated yield. All stereodefined products are ≥98% stereoisomerically pure. [c] The yield observed with 3% $Cl_2Pd(PPh_3)_2$, 6% CuI, and Et_2NH was <1%. [d] The yield observed with 3% $Cl_2Pd(PPh_3)_2$, 6% CuI, and Et_3N was <1%. [e] Not performed. [f] Cs_2CO_3 (2.0 equiv) was used in place of K_2CO_3. [g] A yield of 52% was observed with 2 equiv of the alkyne.

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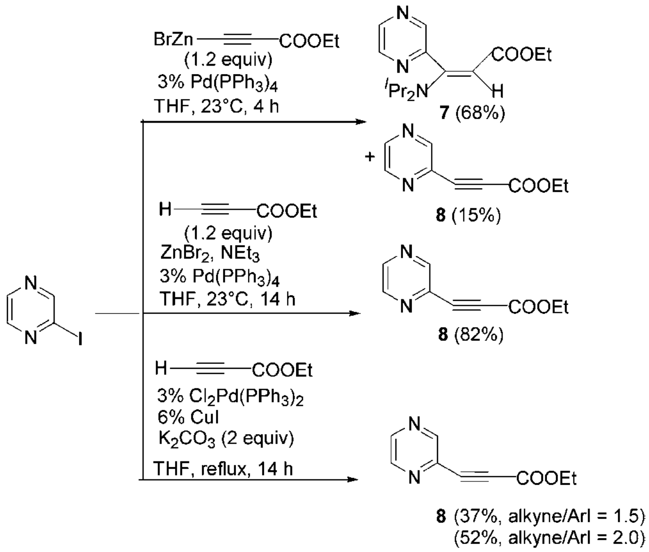
(15) (a) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327. (b) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109. (c) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.

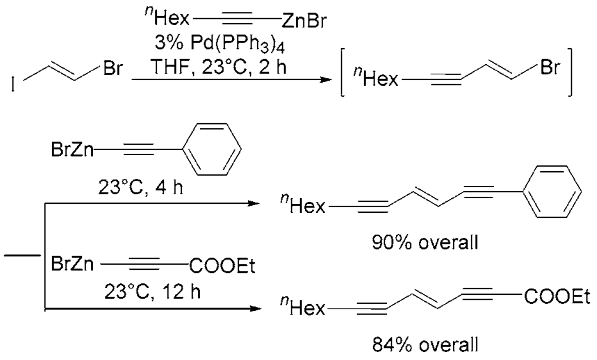
(*Z*)-1-iodo-1-hexene (entry 4). A few examples of the use of heteroaryl and alkynyl halides are also included in Table 2. It should be noted that, in the reaction of iodopyrazine with ethyl 3-bromozincopropynoate, the use of LDA to generate the alkynylzinc reagent led to the formation of **7** in 68% yield along with the desired product **8** obtained only in 15% yield. On the other hand, a recently developed procedure[5i] involving in situ generation of the alkynylzinc reagent by using $ZnBr_2$ (1.2 equiv) and Et_3N (4.8 equiv) led to clean formation of **8** in 82% yield (Scheme 2). The corresponding Sonogashira reaction with 1.5 equiv of the alkyne provided **8** in 37% yield, which was elevated to 52% by the use of 2 equiv of the alkyne. The Pd-catalyzed reaction of 1-iodo-1-octyne with 3-bromozincopropynoate led to clean formation of the desired diyne in 86% yield. However, the corresponding reaction of 1-bromozinco-1-octyne with ethyl 3-iodo-2-propynoate gave a mixture of the same diyne (45%) and the two symmetrically substituted diynes formed in 29% and 15% yield. Thus, as in most of the other alkynyl−alkynyl coupling reactions, the "pair"-selectivity must be strongly substrate dependent.[16]

Scheme 2



With the use of (*E*)-1-iodo-2-bromoethylene as a two-carbon synthon, a clean tandem dialkynylation can be performed in one pot to produce (*E*)-3-ene-1,5-diynes in excellent yields without the use of any reagent in excess, as indicated by the results shown in Scheme 3.

Scheme 3



Efforts are currently being made to apply new findings in the Pd-catalyzed alkynylation reported herein to the synthesis of stereodefined complex natural products and related compounds.

Acknowledgment. We thank the National Science Foundation (CHE-0080795), the National Institutes of Health (GM 36792), and Purdue University for support of this research.

Supporting Information Available: Experimental details of representative reactions as well as spectral and analytical data of isolated products including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030010F

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[16] For strictly "pair"-selective syntheses of conjugated diynes, see: (a) Reference 3d. (b) Kende, A. S.; Smith, C. A. *J. Org. Chem*. **1988**, *53*, 2655. (c) Reference 5e. (d) Reference 5f. (e) Qian, M.; Negishi, E. *Org. Process Res. Dev*. In press. (f) Alami, M.; Ferri, F. *Tetrahedron Lett*. **1996**, *37*, 2763. (g) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett*. **1998**, *39*, 4075.