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Highly Selective Synthesis of (*E*)-3-Methyl-1-trialkylsilyl-3-en-1-ynes via *trans*-Selective Alkynylation Catalyzed by $Cl_2Pd(DPEphos)$ and Stereospecific Methylation with Methylzincs Catalyzed by $Pd(^tBu_3P)_2$

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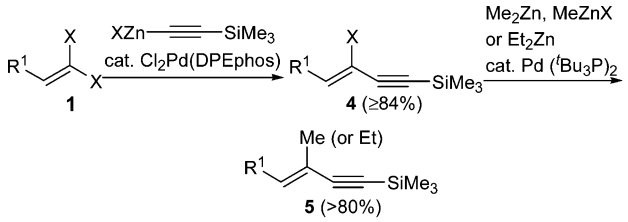
ABSTRACT

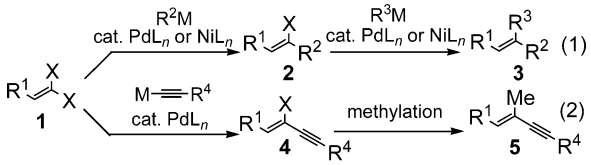


R^1 = *n*-Nonyl, *n*-Hexyl, Ph, $Me_3SiC{\equiv}C$, (*S*)-EtCHMe, (*R*)-TBSOCH$_2$(Me)CH, or (*R*)-(*n*-C_7H_{13})CH(Me)CH$_2$,
X = Br or Cl

***trans*-Selective (≥98%) monoalkynylation of 1,1-dibromo-1-alkenes and 1,1-dichloro-1-alkenes catalyzed by $Cl_2Pd(DPEphos)$ followed by stereospecific methylation with Me_2Zn or MeZnX (X= Cl or Br) catalyzed by $Pd(^tBu_3P)_2$ provides an efficient and stereoselective (≥98%) route to 5, convertible to a wide variety of enynes and conjugated dienes. In the cases of 1,1-dibromo-1-alkenes, the Sonogashira alkynylation may also be satisfactory, but it is distinctly less satisfactory than the alkynylzinc reaction in cases where 1,1-dichloro-1-alkenes are used.**

Reported herein is a highly selective synthesis of (*E*)-3-methyl-3-en-1-ynes via two-stage Pd-catalyzed cross-coupling[1] of 1,1-dihalo-1-alkenes (**1**) containing Br or Cl (eq 2 in Scheme 1, where M is a Zn group and R^4 is a Si group). Although various protocols for the *trans*-selective substitution of **1** to **2** and/or **3** have been known since 1987,[2−7] selective conversion of **1** to **5** via **4** appears to be unprecedented, the only reported example of Pd- or Ni-catalyzed methylation of **2** to produce **3** being that of (*Z*)-bromostilbene with Me_4Sn.[5c] In more recent papers,[7a,b] *trans*-selective Sonogashira alkynylation[7c] of $PhCH_2CH_2CH{=}CBr_2$ with $HC{\equiv}CSiMe_3$

Scheme 1



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(2) For papers involving Grignard reagents, see: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Bryant-Friedrich, A.; Neidlein, R. *Synthesis* **1995**, 1506. (c) Braun, M.; Rahematpura, J.; Bühne, C.; Paulitz, T. C. *Synlett* **2000**, 1070.

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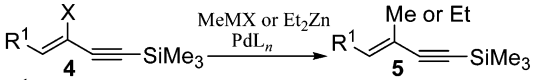
followed by alkylation with a couple of alkylmagnesium chlorides catalyzed with $Cl_2Ni(dppp)$[2a] was reported, but methylation was not achieved. Also known are a few alkylation reactions of (*Z*)-3-bromo-3-en-1-ynes not involving Pd or Ni catalysts.[8] Interestingly, these reactions predominantly produced the stereoinverted (*Z*)-3-alkyl-3-en-1-ynes.

Conjugated oligoenes and oligoenynes containing stereo- and regiodefined methyl-branched trisubstituted alkenes represent a large number of natural products and related compounds of biological and medicinal significance. We recently reported an efficient and selective "head-to-tail" (H-to-T)[9] route to carotenoids involving Zr-catalyzed carboalumination and Pd-catalyzed alkenyl−alkenyl coupling.[10] However, it is also very desirable to develop complementary "tail-to-head" (T-to-H)[9] routes to cope with various structural features, including the presence of proximal asymmetric carbon and heterofunctional groups. One such protocol[11] that has been used with considerable success involves regioselective hydrozirconation of 2-alkynes followed by Pd-catalyzed cross-coupling, and the required alkynes are often prepared via Corey−Fuchs reaction[12] of aldehydes followed by elimination and methylation. In such cases, however, stereoselective two-stage substitution of 1,1-dihaloalkenes would be more straightforward.

Table 1. Methylation or Ethylation of (*Z*)-3-Halo-1-trimethylsilyl-3-en-1-ynes with Me_2Zn, MeZnX (X = Cl or Br), or Et_2Zn in the Presence of Pd Catalysts



R^1 = *n*-Nonyl (**a**); *n*-Hexyl (**b**); Ph (**c**); $Me_3SiC{\equiv}C$ (**d**); (*S*)-EtCHMe (**e**); (*R*)-TBSOCH$_2$CHMe (**f**). M = Zn or Mg.

R^1	X	MeMX or Et_2Zn	PdL_n	temp °C	time h	prod.	yield,[a] % 5*E*	5*Z*
n-Nonyl	Br	MeMgBr	$Cl_2Ni(dppp)$	23	1	**5a**	2[b]	22
n-Nonyl	Br	MeMgBr	$Pd(PPh_3)_4$	23	3	**5a**	5[b]	18
n-Nonyl	Br	MeMgBr	$Pd(P^tBu_3)_2$	23	1	**5a**	31[b]	21
n-Nonyl	Br	Me_2Zn	$Cl_2Ni(dppp)$	23	1	**5a**	8	10
n-Nonyl	Br	Me_2Zn	$Cl_2Pd(TFP)_2$	50	6	**5a**	9	71
n-Nonyl	Br	Me_2Zn	$Cl_2Pd(DPEphos)$	50	8	**5a**	18	43
n-Nonyl	Br	Me_2Zn	$Pd(PPh_3)_4$	50	3	**5a**	47	54
n-Nonyl	Br	Me_2Zn	$Cl_2Pd(dppf)$	50	12	**5a**	70	27
n-Nonyl	Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**5a**	(93)	<2
n-Nonyl	Br	MeZnCl[c]	$Pd(^tBu_3P)_2$	0	1	**5a**	>95	<2
n-Nonyl	Br	MeZnX[d]	$Pd(^tBu_3P)_2$	0	1	**5a**	>95	<2
n-Hexyl	Br	Me_2Zn	$Pd(^tBu_3P)_2$	23	1	**5b**	(91)	<2
n-Hexyl	Br	Et_2Zn	$Pd(^tBu_3P)_2$	23	1	**5g**	(93)	<2
n-Hexyl	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**5b**	>95	<2
Ph	Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**5c**	(95)	<2
Ph	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**5c**	>95	<2
Ph	Cl	Et_2Zn	$Pd(^tBu_3P)_2$	50	3	**5h**	(91)	<2
Me_3Si	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**5d**	(94)	<2
Et	Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**5e**	(94)	<2
ZO	Br[e]	Me_2Zn	$Pd(^tBu_3P)_2$	23	1	**5f**	(95)	<2
ZO	Br[e]	Et_2Zn	$Pd(^tBu_3P)_2$	23	1	**5i**	(99)	<2

[a] By GLC with isolated yields in parentheses. [b] Two other byproducts were formed. [c] From MeLi and $ZnCl_2$. [d] From MeMgBr and $ZnCl_2$. [e] Z = *tert*-butyldimethylsilyl.

As implied by a related investigation mentioned above,[8] stereospecific methylation of (*Z*)-3-halo-3-en-1-ynes (**4**) proved to be very challenging. Methylation of (*Z*)-(*n*-C_9H_{19})-CH=C(Br)C≡CSiMe_3(**4a**) with MeMgBr in the presence of either 5 mol % $Cl_2Ni(dppp)$ or 5 mol % $Pd(PPh_3)_4$ was not clean in our hands. It was hence not a practically useful reaction. On the other hand, the Pd-catalyzed reaction of **4a** with Me_2Zn proceeded to give the methylated product in high yields. As indicated by the results summarized in Table 1, however, all catalysts tested except $Pd(^tBu_3P)_2$,[13,14] namely, $Pd(PPh_3)_4$, $Cl_2Pd(dppf)$, $Cl_2Pd(DPEphos)$ [DPEphos = bis-(2-diphenylphosphinophenyl) ether],[15] and $Cl_2Pd(TFP)_2$ [TFP

(3) For papers involving organoboranes, see: (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett*. **1990**, *31*, 6509. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. J. *Am. Chem. Soc*. **1996**, *118*, 7502 and pertinent references therein. (c) Wong, L. S. M.; Sharp, L. A.; Xavier, N. M. C.; Turner, P.; Sherburn, M. S. *Org. Lett*. **2002**, *4*, 1995.

(4) For papers involving organozincs, see: (a) ref 2a. (b) Minato, A. *J. Org. Chem*. **1991**, *56*, 4052. (c) Xu, C.; Negishi, E. *Tetrahedron Lett*. **1999**, *40*, 431. (d) Ogasawara, M.; Ikeda, H.; Ohtsuki, K.; Hayashi, T. *Chem. Lett*. **2000**, 776. (e) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed*. **2000**, *39*, 1042.

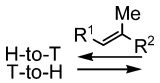
(5) For papers involving organotins, see: (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem*. **1996**, *61*, 5716. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem*. **1998**, *63*, 8965 and pertinent references therein. (c) Shen, W.; Wang, L. *J. Org. Chem*. **1999**, *64*, 8873. (d) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed*. **2000**, *39*, 2732.

(6) For a paper involving organozirconium derivatives, see ref 4c.

(7) For papers involving Sonogashira alkynylation, see: (a) Uenishi, J.; Matsui, K. *Tetrahedron Lett*. **2001**, *42*, 4353. (b) Uenishi, J.; Matsui, K.; Ohmaya, H. *J. Organomet. Chem*. **2002**, *653*, 141. (c) For a recent review of the Sonogashira alkynylation, see: Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 493.

(8) (a) Miller, J. A.; Leong, W.; Zweifel, G. *J. Org. Chem*. **1988**, *53*, 1839. (b) For a synthesis of (*E*)-3-methyl-1-trimethylsilyl-3-decen-1-yne by Cu-promoted methylation of (*Z*)-(*n*-Hex)CH=C(AlBu$_3$Li)C≡CSiMe_3 with MeI, see: Miller, J. A.; Zweifel, G. *J. Am. Chem. Soc*. **1983**, *105*, 1383.

(9) "Head-to-tail" (H-to-T) and "tail-to-head" (T-to-H) directions in methyl-branched trisubstituted alkenes may be conveniently defined as shown below (Negishi, E.; Liou, S. Y.; Xu, C.; Huo, S. *Org. Lett*. **2002**, *4*, 261).



(10) (a) Zeng, F.; Negishi, E. *Org. Lett*. **2001**, *3*, 719. (b) See also: Hoye, T.; Tennakoon, M. A. *Org. Lett*. **2000**, *2*, 1481, for a H-to-T stereocontrolled alkylation of a *β*-methylalkenyl derivative.

(11) For a few representative papers, see: (a) Panek, J. S.; Hu, T. *J. Org. Chem*. **1997**, *62*, 4912. (b) Panek, J. S.; Hu, T. *J. Org. Chem*. **1997**, *62*, 4914. (c) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc*. **1999**, *121*, 456. (d) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett*. **2001**, *3*, 3281. (e) For a seminal paper on regioselective hydrozirconation, see: Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc*. **1975**, *97*, 679.

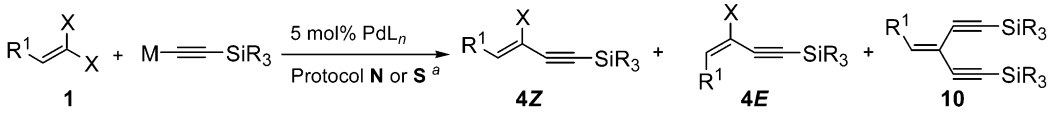
(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, 3769.

(13) For the use of $Pd(^tBu_3P)_2$ in the Pd- or Ni-catalyzed C−C cross coupling, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed*. **1998**, *37*, 3387. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed*. **1999**, *38*, 2411. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc*. **2000**, *122*, 4020. (d) Dai, C.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 2719. (e) Littke, A. F.; Schwarz, L.; Fu, G. C. J. *Am. Chem. Soc*. **2002**, *124*, 6343.

(14) For *trans*-selective alkylation of 1,1-dichloro-1-alkenes with Pd (^{t}Bu$_3$P)$_2$ as a catalyst, see: Tan, Z.; Negishi, E. Manuscript in preparation.

(15) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje *J. Organometallics* **1995**, *14*, 3081. (b) Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem*. **1998**, 155 (c) Frid, M.; Perez, D.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9469.

Table 2. Pd-Catalyzed Alkynylation of 1,1-Dihalo-1-alkenes with M−≡−SiR_3



entry	R^1	X	protocol [a]	M	SiR_3	PdL_n	temp °C	time h	prod.	yield, % [b] 4Z	4E	10 [c]
1	Ph	Br	N	ZnCl	$SiMe_3$	$Pd(PPh_3)_4$	23	24	**4c**(Br)	84	<1	14
2	Ph	Br	N	ZnCl	$SiMe_3$	$Cl_2Pd(TFP)_2$	23	1	**4c**(Br)	87	<1	8
3	Ph	Br	N	ZnCl	$SiMe_3$	Cl_2Pd(dppf)	0	1	**4c**(Br)	89	<1	3
4	Ph	Br	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4c**(Br)	90(84)	<1	8
5	Ph	Br	S	H	$SiMe_3$	$Pd(PPh_3)_4$	23	20	**4c**(Br)	15	<1	18
6	Ph	Br	S	H	$SiMe_3$	$Cl_2Pd(TFP)_2$	23	1	**4c**(Br)	18	<1	43
7	Ph	Br	S	H	$SiMe_3$	Cl_2Pd(dppf)	0	1	**4c**(Br)	78	<1	3
8	Ph	Br	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4c**(Br)	89	<1	8
9	Ph	Cl	N	ZnCl	$SiMe_3$	$Pd(PPh_3)_4$	50	12	**4c**(Cl)	61	<1	12
10	Ph	Cl	N	ZnCl	$SiMe_3$	Cl_2Pd(dppf)	23	6	**4c**(Cl)	87(84)	<1	10
11	Ph	Cl	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	23	6	**4c**(Cl)	84	<1	13
12	Ph	Cl	S	H	$SiMe_3$	$Pd(PPh_3)_4$	60	24	**4c**(Cl)	3	67(61)	21
13	Ph	Cl	S	H	$SiMe_3$	Cl_2Pd(dppf)	23	24	**4c**(Cl)	33	16	10
14	Ph	Cl	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	23	24	**4c**(Cl)	56	3	4
15	*n*-Nonyl	Br	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4a**(Br)	94(87)	<1	3
16	*n*-Nonyl	Br	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4a**(Br)	92	<1	6
17	*n*-Hexyl	Br	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4b**(Br)	95(88)	<1	5
18	*n*-Hexyl	Cl	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	50	24	**4b**(Cl)	65(65)	<1	8
19	*n*-Hexyl	Cl	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	60	36	**4b**(Cl)	26	6	2
20	Me_3Si−≡	Cl	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	23	6	**4d**(Cl)	91(88)	<1	7
21	Me_3Si−≡	Cl	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	23	18	**4d**(Cl)	84	3	12
22		Br	N	ZnCl	$SiMe_3$	Cl_2Pd(DPEphos)	0	1	**4e**(Br)	96(94)	<1	2
23	TBSO 	Br	N	ZnBr	$SiMe_3$	Cl_2Pd(DPEphos)	0	6	**4f**(Br)	87(77)	<1	13
24	TBSO 	Br	S	H	$SiMe_3$	Cl_2Pd(DPEphos)	23	1	**4f**(Br)	90(74)	<1	10
25	TBSO 	Br	S	H	$SiMe_3$	Cl_2Pd(dppf)	23	1	**4f**(Br)	89(73)	<1	11
26	TBSO 	Br	N	ZnBr	$SiPh_3$	Cl_2Pd(DPEphos)	0	6	**4g**(Br)	99(99)	<1	<1
27	TBSO 	Br	N	ZnBr	$SiPr^i_3$	Cl_2Pd(DPEphos)	0	6	**4h**(Br)	99(86)	<1	<1

[a] N = Negishi alkynylation in THF. S = Sonogashira alkynylation in benzene with CuI (5 mol %) and $^iPr_2NH$ (2 equiv). [b] By GLC. Isolated yields in parentheses. [c] Formation of 1% of this product requires 2% of the starting alkyne.

= tris(2-furyl)phosphine],[16] led to stereoisomerization to extents ranging from 28 to 89%. It is also noteworthy that the reaction of **4a** with Me_4Sn[5c] in the presence of $Pd_2(dba)_3$ and TFP also led to extensive stereoisomerization. *Thus, the use of Pd($^tBu_3P$)$_2$ was crucial in achieving stereospecific methylation in high yields with nearly 100% retention of configuration.*

The results summarized in Table 1 also indicate the following. (1) Methylzinc derivatives generated in situ by treating either MeMgBr or MeLi with dry $ZnCl_2$ or $ZnBr_2$ in a molar ratio of 1:1 to 2:1 are comparably satisfactory. (2) On the other hand, MeMgBr without the addition of a Zn salt converted **4a** into a mixture of (*E*)-**5a** and its (*Z*)-isomer in 31 and 21% yields, respectively, along with a byproduct produced in a significant amount even in the presence of Pd($^tBu_3P$)$_2$. (3) The methylation of 1,1-dichloro-1-alkenes with methylzincs in the presence of Pd($^tBu_3P$)$_2$ is slower than but as satisfactory as the corresponding reaction of the dibromo derivatives. (4) The methylation procedure appears to be of wide scope with respect to R^1 in **4**. Thus, not only alkyl groups, e.g., *n*-Hex, *n*-C_9H_{19}, and TBSOCH$_2$-(Me)CH− but also aryl groups, e.g., Ph, and alkynyl groups, e.g., $Me_3SiC{\equiv}C-$, can serve satisfactorily as the R^1 group in **4**. Although the current scope of our investigation is largely limited to methylation, the use of Et_2Zn was similarly satisfactory with little or no complication due to the presence of β hydrogens.

Having developed a highly selective and high-yielding methylation of **4** to give **5**, we then focused our attention on the *trans*-selective alkynylation of **1** to produce the requisite **4**. Prior to our study, this transformation was achieved exclusively by Pd-catalyzed alkynylation of 1,1-dibromo-1-alkenes with alkynylmetals containing Mg or Zn[2b,4d] and with terminal alkynes[7a,b] only in modest yields (≤68%).[17]

In view of these results, an extensive study was undertaken to develop superior procedures. Two main side reactions, i.e., competitive dialkynylation and formation of (*E*)- and

(16) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, 29, 6043.

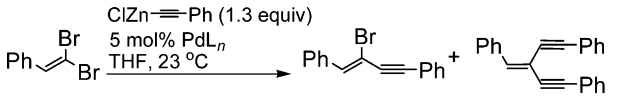
(17) In an earlier paper,[7a] the alkynylation with HC≡CSiMe$_3$ in the presence of Cl_2Pd(dppf) was reported to give the desired product in 87% yield, but a subsequent full paper[7b] changed the yield to 68%.

(*Z*)- stereoisomeric mixtures, were observed. The results summarized in Table 2 indicate the following. First, the reaction of either 1,1-dibromo- or 1,1-dichloro-1-alkenes with $ClZnC{\equiv}CSiMe_3$ in the presence of 5 mol % Cl_2Pd-(DPEphos)[15] proved to be the most satisfactory procedure, leading to the desired monoalkynylation products in ≥84% yields except in the reaction of 1,1-dichloro-1-octene, where the product yield was 65%. Second, the reaction of 1,1-dibromo-1-alkenes is nearly 100% stereoselective. The extent of dialkynylation in each case is <10%, corresponding to the consumption of 0.2 molar equiv of $ClZnC{\equiv}CSiMe_3$ relative to the dibromide.

On the other hand, alkynylation of 1,1-dichloro-1-alkenes displays more widely varied results. Even with Cl_2Pd-(DPEphos), the Sonogashira alkynylation using $HC{\equiv}CSiMe_3$ (1.2−1.3 molar equiv), CuI (5 mol %), Cl_2Pd(DPEphos) (5 mol %), and $^iPr_2NH$ (2 equiv) proceeded slowly at 23 °C and was accompanied by detectable formation of the (*E*)-isomer. Third, dppf may be nearly as effective as DPEphos in some cases but is at least somewhat inferior to the latter, while PPh_3, TFP, dppb, and $^tBu_3P$ are distinctly inferior to DPEphos with some exceptions. Fourth, the use of bulky silyl groups, e.g., Ph_3Si and $^iPr_3Si$, is effective in avoiding dialkynylation, even with highly demanding substrates such as **4f**.

Despite the favorable results presented above, the *trans*-selective monoalkynylation protocol reported herein is still of limited scope with respect to R^4 in **4** and **5**. In contrast, with the favorable results observed with silyl-substituted alkynes, extensive dialkynylation has been observed with other alkynes and their zinc derivatives, including those containing Me, Ph, PhCH═CH, and $TBSOCH_2$ under various conditions, even though favorable results such as those shown in Scheme 2 were also observed in some exceptional cases.

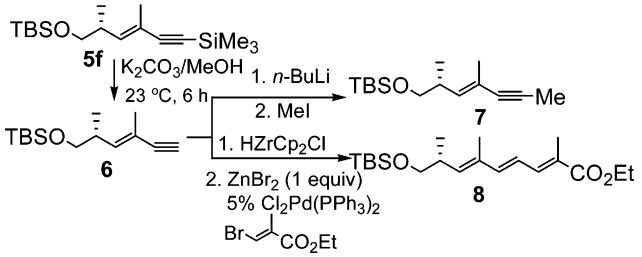
Scheme 2



PdL_n	**monoalkynylation**, %	dialkynylation, %
$Pd(PPh_3)_4$	81	6
Cl_2Pd(dppf)	35	40
Cl_2Pd(DPEphos)	66	26

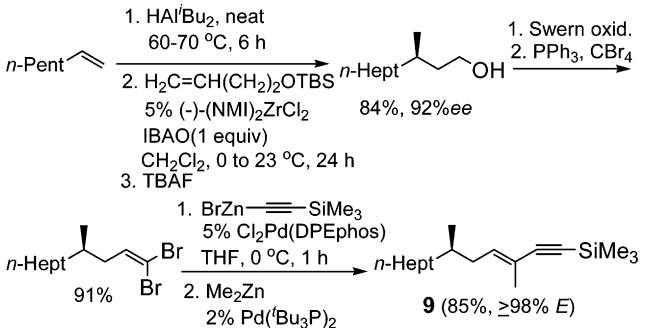
Further development is clearly desirable. In the meantime, however, various 3-bromo- and 3-methyl-substituted 1-trialkylsilyl-3-en-1-ynes preparable by the process reported herein may be desilylated and further converted into a wide variety of their derivatives, as exemplified by the conversion of **5f** to **6** via desilylation with K_2CO_3−MeOH and then to **7** via lithiation with *n*-BuLi and methylation with MeI both in nearly quantitative yields. Conversion of **6** into a trienonic ester **8** in one pot in 94% yield as a single stereoisomer (≥98%) is also noteworthy (Scheme 3). The potential

Scheme 3



synthetic value of the method reported herein is further demonstrated by the five-step synthesis of enyne **9** (≥98% (*E*)- and 92% ee) from 1-heptene in 65% overall yield (Scheme 4). This enyne can potentially serve as a convenient

Scheme 4



intermediate for the synthesis of a recently reported potent topoisomerase inhibitor, topostatin.[18]

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Supporting Information Available: Experimental procedures, spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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