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Coupling of AlkynylTMS Derivatives with Vinylic Iodides. An Efficient Route to 1,3-Enynes and Dienes

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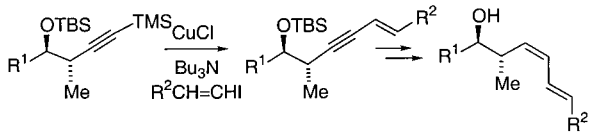
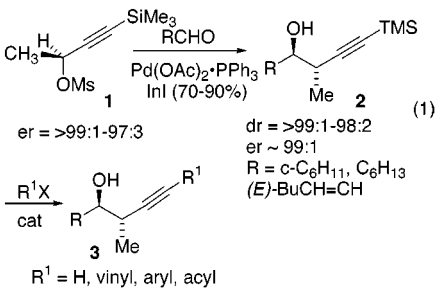
ABSTRACT



CuCl-promoted coupling of alkynylTMS derivatives with vinyl iodides leads to 1,3-enynes in high yield. Enynes prepared from homopropargylic alcohols undergo intramolecular hydrosilylation and subsequent silyl cleavage with TBAF to afford 1,3-dienes.

We recently developed an efficient procedure for the resolution of 4-TMS-3-butyn-2-ol and found that the mesylate derivative (e.g., **1**) can be used for the in situ preparation of allenylindium reagents that undergo facile additions to branched and unbranched achiral and chiral aldehydes to afford adducts **2** in high yield with excellent diastereo- and enantiomeric selectivity (eq 1).[1] Pursuant to our interest in developing seamless integration of this methodology with reactions that further elaborate the alkynyl moiety, we explored the possibility for direct coupling of these adducts with vinylic halides along the lines of **2** → **3**.



Denmark and co-workers have shown that vinylsiloxanes undergo Pd-catalyzed cross-coupling reactions with aryl and vinyl iodides, bromide, and triflates.[2] Alkynylsilanes have also been reported to participate in Pd-catalyzed cross-couplings in the presence of CuCl.[3,4] This latter application seemed to be especially well suited to our objectives, and accordingly, we decided to examine its applicability to various alkynylsilane adducts derived from allenylindium reagents and aldehydes.

Before targeting these applications, we conducted feasibility studies of vinylic cross-coupling with the simple nonvolatile alkynylTMS derivative **4** and *(E)*-1-iodo-1-hexene (Table 1).[5] Adopting the procedure of Nishihara et al.,[3a] but substituting 1,3-dimethylimidazolidin-2-one (DMI) for DMF along the lines of Hosomi and co-workers,[3c] we obtained enyne **6** in 40% yield. Variations in the Pd(0) catalyst or catalyst precursor either caused decomposition or had little

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(4) Couplings of TMSalkynes with vinyl iodides in the presence of $(Et_2N)_3S^+Me_3SiF_2^-$ have been reported (Hatanaka, Y.; Matsui, T.; Hiyama, T. *Tetrahedron Lett.* **1989**, *30*, 2403). Our intended application of the present methodology to silyl-protected polyol derivatives precludes the use of fluoride-assisted silyl cleavage procedures.

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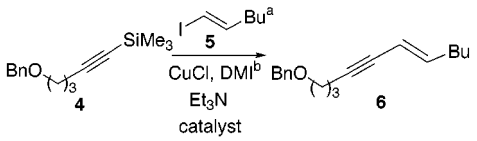
Table 1. Alkynylsilane Cross-Coupling Reactions



CuCl, equiv	Pd catalyst (equiv)	*t*, h	*T*, °C	yield, %
1.1	$Pd(PPh_3)_4$ (0.05)	15	85	40[c]
1.1	$Pd(PPh_3)_2Cl_2$ (0.025)	15	85	dec
1.1	$Pd_2(dba)_3$ (0.025)	15	85	dec
2.0	$Pd(PPh_3)_2Cl_2$ (0.05)	8	85	55[c]
2.2	$Pd(PPh_3)_4$ (0.05)	1.5	85	40[c]
2.2	$Pd_2(dba)_3$ (0.05)	24	85	30[c]
2.2	none	3.5	85	10
2.2	none	40	85	83
2.2	none	20	100	88
2.2	none	6	130	87

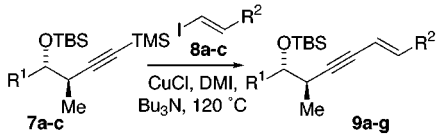
[a] From 1.3 to 1.5 equiv. [b] DMI = 1,3-dimethyl-2-imidazolidinone. [c] From 10 to 20% of the 1,3-diyne product was formed.

effect. In the absence of Pd, addition of 1 equiv of CuCl in DMI to acetylene **4** resulted in a pale yellow-green solution that gave no cross-coupling product with the vinyl iodide. Addition of Et_3N caused the solution to become deep red, but again no coupling was observed. Attempts to force a reaction by increasing the temperature led to decomposition products. However, when 2 equiv of CuCl in DMI were added to acetylene **4**, a yellow precipitate gradually formed. This precipitate is presumed to be the copper acetylide complex.[6] Treatment of the mixture with Et_3N and the vinyl iodide afforded the coupled product in 10% yield after 3.5 h at 85 °C (Table 1). After a reaction time of 40 h, the enyne could be isolated in 83% yield. Increasing the reaction temperature to 100 or 130 °C significantly shortened the reaction time with no decrease in yield. When less than 2 equiv of CuCl were employed, the coupling reactions were markedly slower and decomposition products were produced.

Nishihara et al.[3a] obtained the 1,3-diyne homocoupling product in 80% yield upon treatment of 1-TMS-1-octyne with 1 equiv of CuCl in DMF at 60 °C after 3 h. We observed moderate amounts of homocoupling product from reactions in which Pd(0) catalysts were present (Table 1) but detected no homocoupling of TMSalkyne **4** in their absence. We made one further modification to the procedure by substituting Bu_3N for Et_3N. Results were comparable, but the lower volatility of Bu_3N was more compatible with the higher-temperature procedure. This modification was applied to the racemic adducts **7a**−**c**[1] with excellent results (Table 2).

The homopropargylic alcohol adducts **2** (eq 1) afforded cross-coupled products in low yield. However, TBS ether or acetate derivatives of **2** could be readily converted to enynes as illustrated in Table 2 and eqs 4 and 5. It is possible that the alcohols coordinate with the CuCl promoter in a five-membered alkyne complex (Figure 1, **A** vs **B**) thereby shutting down the formation of Cu acetylide intermediates.

Table 2. Coupling of Alkynylsilanes with Vinyl Iodides



R^1	R^2	*t*, h	yield, %
c-C_6H_{11} (**a**)	C_7H_{15} (**a**)	3	90 (**a**)
c-C_6H_{11} (**a**)	H (**b**)	14	87 (**b**)
i-Pr (**b**)	C_7H_{15} (**a**)	5	73 (**c**)
i-Pr (**b**)	H (**b**)	19	94 (**d**)
$Ph(CH_2)_2$ (**c**)	C_7H_{15} (**a**)	4	97 (**e**)
$Ph(CH_2)_2$ (**c**)	H (**b**)	16	80 (**f**)
$Ph(CH_2)_2$ (**c**)	Bu (**c**)	3.5	91 (**g**)

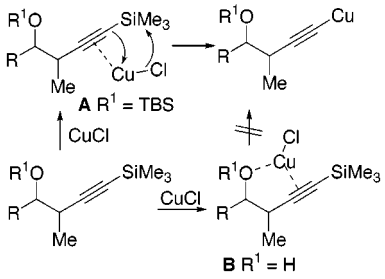
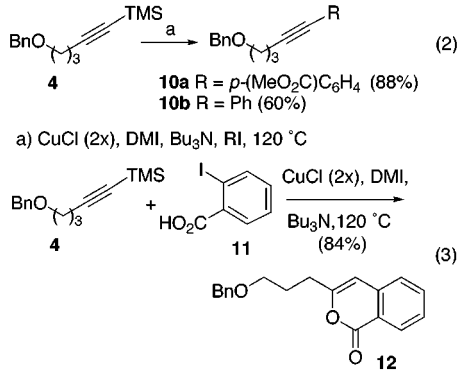


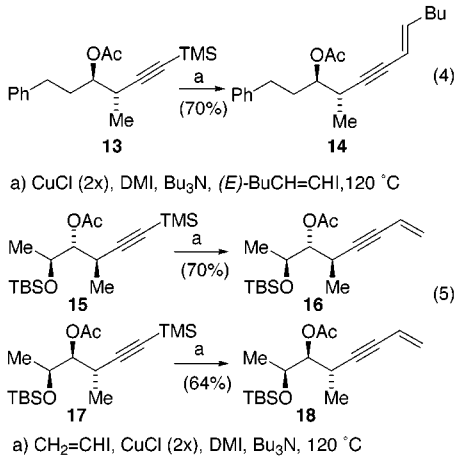
Figure 1. Possible reactivity differences between homopropargylic alcohols and derivatives toward Si−Cu exchange.

Aryl iodide couplings were briefly examined. Methyl *p*-iodobenzoate afforded the coupled product **10a** in high yield but iodobenzene coupling proceeded sluggishly, affording **10b** in 60% yield and the desilylated terminal alkyne as the only other isolated product. *p*-Iodoanisole yielded negligible quantities of coupled product with the TMSalkyne **4** after prolonged reaction times. Interestingly, *o*-iodobenzoic acid (**11**) coupled efficiently to yield the isocoumarin **12**,[7] but *p*-iodobenzoic acid gave the coupled product in only 16% yield along with numerous decomposition products.[8]



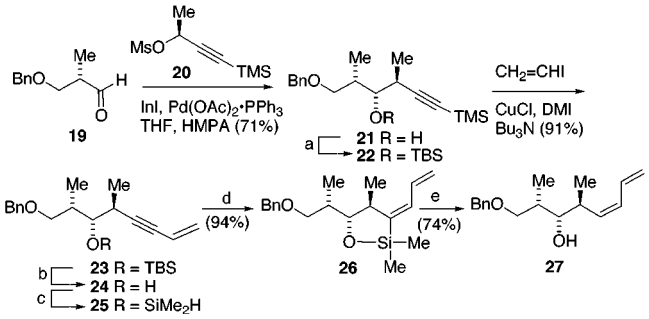
Couplings between homopropargylic acetates and vinylic iodides also proceeded smoothly (eqs 4 and 5). The starting

enantiopure alkynylsilanes were prepared as previously described.[1] The examples in eq 5 show that the methodology can be applied to relatively complex polyfunctional alkynylsilanes. As already stated, both TBS ethers and acetates are superior to the free alcohols as coupling substrates.



We recently disclosed methodology for the conversion of homopropargylic alcohols to β-hydroxy ketones through intramolecular hydrosilylation followed by Tamao oxidation of the intermediate cyclic siloxane (eq 6).[9,10] It was of interest to examine a modification of this sequence on the enynes **23** and **30** as a possible route to the C17−C24 1,3-diene terminus **27** of discodermolide[11] and the analogue **34** (Schemes 1 and 2).

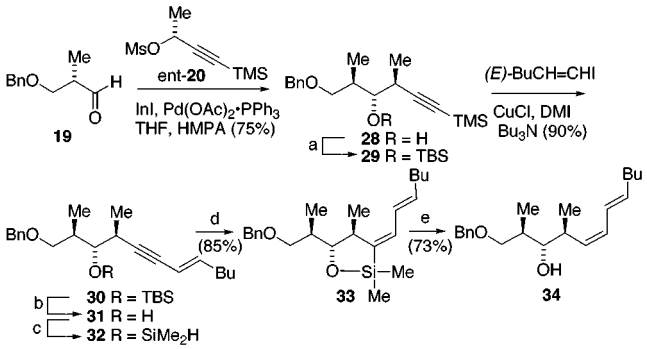
Scheme 1



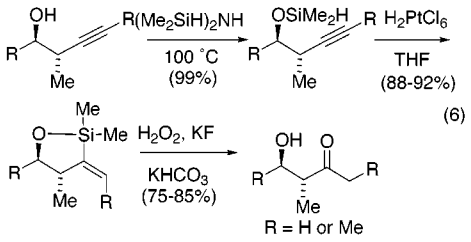
Key: (a) TBSOTf, Et_3N, CH_2Cl_2 (79%); (b) TBAF, THF (91%); (c) $(Me_2SiH)_2NH$, 60 °C; (d) H_2PtCl_6 0.5 mol %, THF (94%, 2 steps); (e) TBAF, THF (74%).

The anti,syn (right-to-left) homopropargylic alcohol **21** was prepared from aldehyde **19** and mesylate **20** via the derived allenylindium reagent.[1] The TBS ether **22** underwent efficient coupling with vinyl iodide to afford enyne **23**. TBS ether cleavage followed by silylation and intramolecular hydrosilylation led to the cyclic siloxane **26**, which was treated without purification with TBAF to afford the pure *(Z)*-1,3-diene **27** in high overall yield.

Scheme 2



Key: (a) TBSOTf, Et_3N, CH_2Cl_2 (87%); (b) TBAF, THF (90%); (c) $(Me_2SiH)_2NH$, 60 °C; (d) H_2PtCl_6 0.5 mol %, THF (85%, 2 steps); (e) TBAF, THF (73%).



The anti,anti homopropargylic alcohol **28** was prepared analogously from aldehyde **19** and mesylate ent-**20** (Scheme 2). CuCl-promoted coupling of the TBS ether derivative **29** with *(E)*-1-iodo-1-hexene afforded the enyne **30**, which was subjected to the foregoing hydrosilylation−TBAF sequence to afford the *(Z,E)*-1,3-diene **34** free of isomeric byproducts.

The methodology described in this report expands the list of useful reactions that can be performed on homopropargylic alcohol derivatives. The ability to prepare the TMSalkyne intermediates through highly diastereo- and enantioselective addition reactions and to seamlessly append vinylic substituents is of particular interest for applications to the polyketide family of natural products. It should be noted that the use of the corresponding 4-butyn-2-ol mesylates as precursors to

(6) The structure of this solid has been formulated as $[Cu_2Cl(C{\equiv}CPh)]_n$: Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, A. *J. Organomet. Chem.* **2001**, *620*, 282. We thank a reviewer for bringing this reference to our attention.

(7) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

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(12) Sonogashira, K. *Comprehensive Organic Synthesis*; Pergamon Press: Elsmford, NY, 1990; Vol. 3, p 521.

the allenylindium reagents leads to mixtures of anti and syn isomers (ca. 90:10−80:20) with unbranched and conjugated aldehydes. Thus, the TMS substituent plays a significant role in the present methodology vis-à-vis the alternative sequence in which a terminal alkyne adduct is converted to the 1,3-enyne through a Sonogashira coupling.[12,13]

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Supporting Information Available: Additional experimental procedures and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Experimental procedures: **(2*S*,3*S*,4*S*)-(+)-1-Benzyloxy-2,4-dimethyl-6-trimethylsilyl-5-hexyn-3-ol (21).** The standard allenylindium addition procedure was followed using aldehyde **19**[1] (120 mg, 0.67 mmol), mesylate **20** (179 mg, 0.81 mmol), InI beads (212 mg, 0.88 mmol), $Pd(OAc)_2$ (9.1 mg, 0.04 mmol), PPh_3 (10.6 mg, 0.04 mmol) in THF (6 mL), and HMPA (2 mL) at 0 °C for 15 min before the solution was warmed to room temperature to give 146 mg (71%) of alcohol **21** and its syn diastereomer as a 99:1 inseparable mixture: $[\alpha]^{20}_D$ +12.2 (c = 2.15, $CHCl_3$); IR (film) υ 3548, 2975, 2162 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 0.96 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 1.62 (d, J = 6.6 Hz, 1H), 1.97 (m, 1H), 2.68 (m, 1H), 3.45 (m, 1H), 3.56 (m, 2 H), 4.52 (s, 2H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.10, 10.7, 17.6, 22.4, 31.8, 36.3, 73.1, 73.7, 75.0, 86.7, 108.4, 127.5, 128.3, 137.9. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 70.84; H, 9.39. **(2*S*,3*S*,4*S*)-(−)-1-Benzyloxy-2,4-dimethyl-7-octene-5-yn-3-ol (24).** To a stirred solution of alcohol **21** (569 mg, 1.87 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (0.52 mL, 3.74 mmol) and TBSOTf (0.60 mL, 2.20 mmol) at room temperature. The reaction was monitored by TLC analysis and quenched with saturated NH_4Cl upon completion. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 615 mg (79%) of silyl ether **22**. The oil was taken on with no further purification and subjected to standard coupling conditions with CuCl (288 mg, 2.94 mmol), DMI (2.0 mL), Bu_3N (630 mg, 4.41 mmol), and vinyl iodide **8b** (294 mg, 1.91 mmol). After 10 h at 120 °C, the mixture was cooled, and the product was isolated and purified by filtration through silica gel affording 498 mg (91%) of enyne **23** as a pale yellow oil that was dissolved in THF and treated with TBAF (2 mL, 2.00 mmol). After 10 h, reaction was judged to be complete by TLC analysis. The mixture was diluted with saturated NH_4Cl and Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (10:1 hexanes/Et_2O) to give 218 mg (91%) of alcohol **24**: $[\alpha]^{20}_D$ −14.0 (c = 1.73, $CHCl_3$); IR (film) υ 3477, 2964, 2229 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 7.5 Hz, 3H), 2.01 (m, 1H), 2.34 (d, J = 4.5 Hz, 1H), 2.78 (m, 1H), 3.47 (m, 1H), 3.57 (m, 2H), 4.51 (d, J = 4.5 Hz, 2 H), 5.41 (dd, J = 2.0, 9.0 Hz, 1H), 5.57 (dd, J = 2.0, 15.5 Hz, 1H), 5.79 (m, 1H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 17.8, 17.6, 31.2, 36.3, 73.2, 73.8, 75.7, 81.6, 91.9, 117.2, 126.3, 127.6, 127.5, 128.3, 138.3. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.11; H, 8.84. **(2*S*,3*S*,4*S*,*Z*)-(+)-1-Benzyloxy-2,4-dimethyl-5,7-octadien-3-ol (27).** Alcohol **24** (218 mg, 0.85 mmol) in $(Me_2SiH)_2NH$ (TMDS) (1.5 mL) was heated to 60 °C. After 12 h, IR analysis indicated complete conversion to silane **25.** The excess TMDS was removed under reduced pressure for 12 h; the residue was taken up in THF (2 mL), and 35 μL (0.5 mol %) of 0.053 M H_2PtCl_6 solution in THF was added. The solution was heated to 60 °C and monitored by IR. After 1 h, conversion to siloxane **26** was complete. The solution was cooled to room temperature, diluted with Et_2O (5 mL), filtered through Celite, and concentrated under reduced pressure to yield 250 mg (94%) of siloxane **26**. A portion of this material (100 mg, 0.32 mmol) in THF (2 mL) was treated with TBAF (1.15 mL, 1.15 mmol). After 7 h, the product was isolated by extraction with Et_2O and purified by chromatography on silica gel (8:1 hexanes/Et_2O) to afford 61 mg (74%) of diene **27**: $[\alpha]^{20}_D$ +21.3 (c = 3.85, $CHCl_3$); IR (film) υ 3477, 2964, 2344 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 2.01 (m, 1H), 2.22 (s, 1H), 2.80 (m, 1H), 3.48−3.57 (m, 3H), 4.52 (d, J = 3.0 Hz, 2H), 5.13 (d, J = 10 Hz, 1 H), 5.23 (d, J = 17 Hz, 1H), 5.38 (t, J = 10.5, 1H), 6.13 (t, J = 10.5 Hz, 1H), 6.62 (m, 1H), 7.34(m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9, 17.2, 17.6, 35.1, 35.7, 35.8, 73.3, 74.6, 76.2, 118.0, 127.6, 128.2, 130.4, 132.2, 135.3, 138.2.