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PMHS-Mediated Couplings of Alkynes or Benzothiazoles with Various Electrophiles: Application to the Synthesis of (−)-Akolactone A

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Polymethylhydrosiloxane (PMHS) in combination with CsF facilitates the cross-coupling of alkynes or benzothiazoles with an array of vinyl, styryl, and aryl halides or nonaflates as well as acid chlorides. Experimental and spectroscopic evidence indicates that these reactions involve the in situ generation of a siloxyl intermediate. These cross-couplings proceed relatively quickly at room temperature and under amine-free conditions. To demonstrate the applicability of the method, a total synthesis of the cyctotoxic butanolide (−)-akolactone A was carried out.

The competence of alkynylsilanes in Sonogashira-type[1,2] reactions is well established. Such species are commonly reacted with vinyl or aryl electrophiles using a fluoride (e.g., TASF)[3] or other additive activators.[4] Most recently, Pale[5] and co-workers developed a Pd/Ag-catalyzed coupling of alkynylsilanes facilitated by K_2CO_3/MeOH or TBAF, while Nishihara and Mori have demonstrated the cross-coupling of alkynylsilanes under Pd/Cu catalysis in DMF at 80 °C.[6] The use of alkynylsilanes in Sonogashira reactions is sometimes a matter of expediency as silyl groups can protect alkynes from synthetic steps that occur prior to the coupling reaction. However, alkynylsilanes can also improve reaction efficiency. For example, Nolan[7] has disclosed that the employment of alkynylsilanes can minimize unwanted side products (homocoupling) during Sonogashira couplings.

Despite these prior studies and those of DeShong[8] and Denmark[9] who have shown that organosiloxanes and organosilanols are superior to the corresponding silanes in sp^2-sp^2 couplings,[10] alkynyl siloxanes have received little attention with respect to $sp-sp^2$ couplings. To the best of our knowledge, Chang's Pd-catalyzed cross-coupling of alkynylsilanols with iodobenzenes[11] stands as the only example of its kind. Thus, we were intrigued by our discovery that adding polymethylhydrosiloxane (PMHS) and CsF to a mixture of alkyne, electrophile, CuX, and Pd facilitated Sonogashira coupling (Scheme 1).[12]

Experimentally, when an alkyne such as **1** was treated with CsF (5 equiv) and PMHS (2 equiv) in NMP followed by addition of $PdCl_2(PPh_3)_2$ (2 mol %), CuX and an electrophile such as (*E*)-*β*-bromostyrene, the corresponding Sonogashira product was obtained at room temper-

(1) For Sonogashira reviews, see: (a) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46−49. (c) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (d) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, 1998; Chapter 10. (e) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127−160.

(2) For recent advances in the Sonogashira reaction, see: (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566−1568 and references cited. (b) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056−1058. (c) Braga, A. L.; Ludtke, D. S.; Vargas, F.; Donato, R. K.; Silveira, C. C.; Stefani, H. A.; Zeni, G. *Tetrahedron Lett.* **2003**, *44*, 1779−1781. (d) Karpov, A. S.; Rominger, F.; Muller, T. J. J. *J. Org. Chem.* **2003**, *68*, 1503−1511. (e) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71−74. (f) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571−1574. (g) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691−1694. (h) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756−757. (i) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118−1122. (j) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365−9368. (k) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679−3681. (l) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731.

(3) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845−853.

(4) (a) TBAF: Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* **2001**, 649−651. (b) DBU/H_2O: Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199−3202. (c) CuCl/Bu_3N: Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107−4110. (d) Ag_2CO_3: Koseki, Y.; Omino, K.; Anzai, S.; Nagasaka, T. *Tetrahedron. Lett.* **2000**, *41*, 2377−2380. (e) AgO: Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935−2937. (f) Triarylantimony(V) diacetates: Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans.* 1 **2001**, 736−739.

(5) (a) Halbes, U.; Pale, P. *Tetrahedron Lett.* **2002**, *43*, 2039−2042. (b) Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, *42*, 8641−8644. (c) Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem.* **2001**, 4391−4393. Also see (d) Shultz, D. A.; Gwaltney, K. P.; Lee, H. *J. Org. Chem.* **1998**, *63*, 4034−4038.

(6) (a) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780−1787. (b) Nishihara, Y.; Ando, J.-i.; Kato, T.; Mori, A.; Hiyama, T. *Macromolecules* **2000**, *33*, 2779−2781. (c) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075−4078. (d) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233−1234.

(7) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020−1022.

(8) Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159−7165.

(9) (a) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541 and references cited. (b) Denmark S. E.; Sweis R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846.

(10) For cross-couplings with polyl(alkenyl)methylsiloxane, see: Mori, A.; Suguro, M. *Synlett* **2001**, 845−847.

(11) Chang, S.; Yang, S. H.; Lee, P. H. *Tetrahedron Lett.* **2001**, *42*, 4833−4835.

(12) Gallagher, W. P.; Maleczka, R. E., Jr. *Synlett* **2003**, 537−541.

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Published on Web 07/31/2003

SCHEME 1

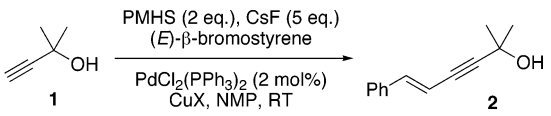
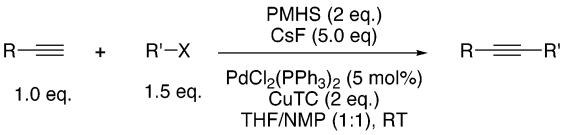


TABLE 1. Copper Effect in Scheme 1

entry	CuX (equiv)	time (h)	yield (%)
1	CuTC (2)	2	99
2	CuTC (0.02)	24	2
3	CuCl (1.5)	2	95
4	CuCl (0.02)	24	2
5	CuI (0.02−1.5)	24	<1
6	CuBr (0.02−1.5)	24	<1
7	CuCN (0.02−1.5)	24	<1

TABLE 2.



entry	alkyne	R'−X	time	product (yield)[a]
1	R = HO(Me)$_2$C- (**1**)	*E*-(β)-bromostyrene	2 h	**2** (99%)
2	R = HO(Me)CH- (**3**)	I-(CH$_2$)$_8$-≡ (**4**)	5 h	**5** (93%)
3	R = HO(Me)$_2$C- (**1**)	*p*-iodoacetophenone	5 h	**6** (87%)
4	R = HO(Me)$_2$C- (**1**)	*p*-bromoacetophenone	5 h	**6** (80%)

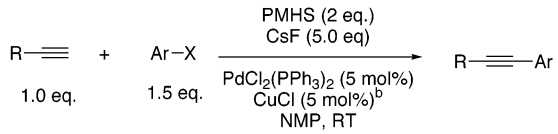
[a] Average isolated yield of two runs.

ature. Without PMHS, CsF, Pd, or Cu the reaction failed. Lowering the amount of CsF to 2 equiv slowed the reaction; however, 1.5 equiv of fused CsF/CsOH (2:1) worked well.[13] In contrast, KF proved ineffective under our conditions. Furthermore, Table 1 illustrates how the choice and amount of Cu(I) catalyst are crucial to the reaction's success. Couplings proceeded efficiently with stoichiometric amounts of copper thiophenecarboxylate (CuTC) or CuCl, but not with catalytic quantities of Cu(I) salts. The use of either catalytic or stoichiometric amounts of CuI, CuBr, or CuCN completely curbed the reaction.

These trends held over the couplings of a variety of aryl or vinyl halides (Table 2). While CuCl or CuTC[14] (2 equiv) were both effective in such reactions, experimentation revealed 2 equiv of CuTC in THF/NMP (1:1) as optimal for the coupling of vinyl or aryl bromides and iodides. Bromobenzene, *p*-bromoanisole, and aryl chlorides did not participate in the reaction. Though disappointing, the reluctance of these electrophiles to couple was not fully unexpected given the general sluggishness of unactivated aryl bromides and aryl chlorides toward Sonogashira reactions.[1c,2j]

Nishihara and Mori[6a,d] noted a dependence on the nature and stoichiometry of the Cu(I) salts during reactions of alkynylsilanes that was similar to our observations in Tables 1 and 2. They concluded that either CuCl or a "CuO" species is needed to affect the transmetalation between silicon and copper. Thus we hypothesized that our couplings might initially involve a reaction between the alkyne and PMHS generating an

TABLE 3.



entry	alkyne	Ar–X	time	product (yield)[a]
1	R = Ph (**7**)	Ac-C$_6$H$_4$-ONf (**8**)	4 h	**9** (96%)
2	R = HO(Me)$_2$C- (**1**)	(**8**)	4 h	**6** (96%)
3	R = HO(Me)CH- (**3**)	(**8**)	5 h	**10** (82%)
4	R = HO(CH$_2$)$_2$CH$_2$- (**11**)	(**8**)	6 h	**12** (86%)
5	R = CH$_3$(CH$_2$)$_2$- (**13**)	(**8**)	8 h	**14** (73%)
6	R = CH$_3$(CH$_2$)$_{13}$CH$_2$- (**15**)	(**8**)	8 h	**16** (95%)
7	R = HO(Me)(Ph)C- (**17**)	MeO-C$_6$H$_4$-ONf (**18**)	6 h	**19** (52%)
8	R = HO(Me)(Et)C- (**20**)	Br-C$_6$H$_4$-ONf (**21**)	6 h	**22** (73%)
9	R = HO(Me)(Et)C- (**20**)	NfO-C$_6$H$_4$-ONf (**23**)	6 h	**24** (76%)
10	R = HO(Me)$_2$C- (**1**)	Ac-C$_6$H$_4$-OTf (**25**)	5 h	**6** (86%)
11	R = HO(Me)CH- (**3**)	C$_6$H$_9$-ONf (**26**)	5 h	**27** (82%)

[a] Average isolated yield of two runs. [b] 5 mol % of CuTC proved to be equally effective.

alkynyl siloxane. To test this hypothesis we explored nonaflate and triflate electrophiles so that the reaction would to produce "CuO" species. The aryl nonaflates were readily prepared from their corresponding phenols by treatment with NfF and NEt_3 in CH_2Cl_2.[15] As anticipated, these electrophiles responded well to our conditions employing *catalytic* amounts of CuCl. A variety of alkynes coupled in good to excellent yields (Table 3), although attempts to react acetylene failed. An aryl nonaflate could be selectively reacted in the presence of an aryl bromide (entry 8) and a bisnonaflate efficiently coupled at both positions (entry 9). An aryl triflate was also worked well (entry 10) as did a vinyl nonaflate (entry 11).

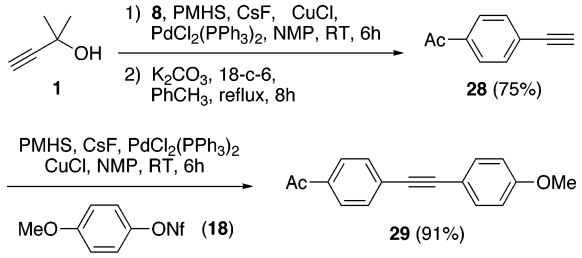
Iterative application of our protocol could be used to synthesize unsymmetric internal alkynes (Scheme 2). 2-Methyl-3-butyn-2-ol (**1**) is a convenient and cheap source of acetylene. Once **1** was coupled with **8**, heating in the presence of K_2CO_3 eliminated acetone and fur-

(13) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729−6730.

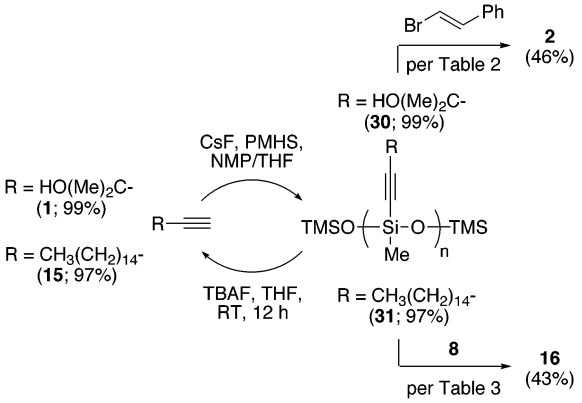
(14) CuTC = copper(I) thiophene carboxylate. See the Supporting Information for a preparation. Alternatively, CuTC can be purchased from Frontier Scientific. CuTC is sufficiently stable and does not require any special handling when dry (Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749), whereas CuCl must be stored and used under N_2 to work efficiently.

(15) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203−208. For a review of the preparation of alkenyl triflates, see: Lyapkalo, I. M.; Webel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015−1025.

SCHEME 2



SCHEME 3



nished the corresponding aryl alkyne **28**. Subjecting **28** and aryl nonaflate **18** to our protocol afforded internal aryl alkyne **29** in 68% yield from 2-methyl-3-butyn-2-ol (**1**).

The ability to use catalytic amounts of CuCl or CuTC with nonaflates, while halides demand stoichiometric quantities of these Cu(I) salts, and the lack of reactivity of CuBr, CuI, or CuCN was consistent with a process that involves a transmetalation between copper and silicon.[6a,d] This copper salt dependence and the necessity of PMHS supported our hypothesis of an alkynyl siloxane intermediate. Seeking additional confirmation of such a species, **1** and **15** were reacted with PMHS and CsF. In both instances a solid product formed (**30** and **31** respectively). The ^{1}H NMR of these crude products showed that each had lost an alkynyl proton (∼2.42 ppm) and that the Si−H from PMHS (∼4.85 ppm) was missing. Subjecting **30** and **31** to our coupling conditions produced the expected cross-coupled products (**2** and **16**, respectively, Scheme 3) albeit in diminished yields relative to reacion of the parent alkynes (Table 2, entry 1, and Table 3, entry 6). The original alkynes could also be regenerated upon treatment with TBAF.

ReactIR monitoring of the alkyne C−H stretch at 3231 cm^{-1} provided further evidence for the putative alkynyl siloxane. An initial measurement was made following admixture of CsF and either **1** or **15**. PMHS was then slowly added via syringe pump.[16] As shown in Figure 1, the alkyne C−H stretch diminished over the course of the PMHS addition. Efforts at elucidating the mechanism of this C−H actvation/silylation are ongoing[17] and will be reported separately, however it would appear that CsF

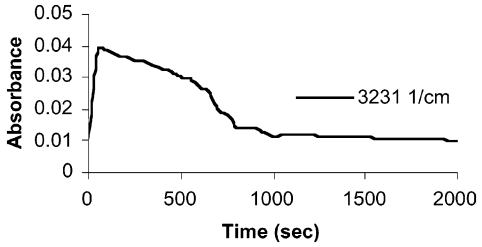
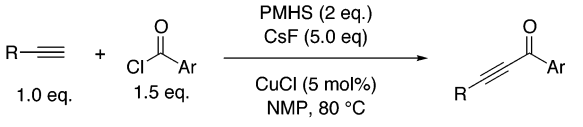


FIGURE 1. ReactIR monitoring of the alkyne C−H stretch during the reaction of **15**.

TABLE 4.



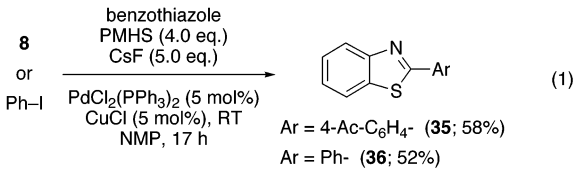
entry	alkyne	ArC(O)Cl	time	product (yield)[a]
1	R = HO(Me)$_2$C- (**1**)	benzoyl chloride	5 h	**32** (47%)
2	R = Ph (**7**)	benzoyl chloride	5 h	**33** (68%)
3	R = Ph (**7**)	*p*-methoxybenzoyl chloride	7 h	**34** (73%)

[a] Average isolated yield of two runs.

deprotonation of the alkyne can be ruled out as ReactIR showed that the acetylenic C−H stretch diminished little when the CsF/alkyne mixture (no PMHS) was monitored over time. We can also rule out silyl ether formation as the O−H stretch of **1** remains constant throughout the ReactIR experiment.

With the spectroscopic data and our experimental observations establishing the involvement of an in situ generated polymethyl(alkynyl)siloxane, we considered the possibility of applying the protocol to other couplings. For example, acid chlorides, which are known to react with alkynylsilanes[18] coupled under our conditions in moderate yield (Table 4).

Likewise, Hosomi[19] has shown that 2-trimethylsilylthiazole coupled with iodobenzene in the presence of CuI.[20] Given the similar reactivity profile of thiazoles and alkynes,[21] we envisioned that benzothiazole could also participate in or protocol. Indeed iodobenzene or aryl nonaflate **8** could be coupled with benzothiazole in modest yield at room temperature (Equation 1). As with the alkynes, benzothiazole did not couple in the absence of CsF or PMHS.



(1)

To further demonstrate the synthetic applicability of our method we chose to synthesize (−)-akolactone A (**37**),

(16) The reaction took off too quickly to make valid measurements when the alkyne, CsF, and PMHS are added at once.

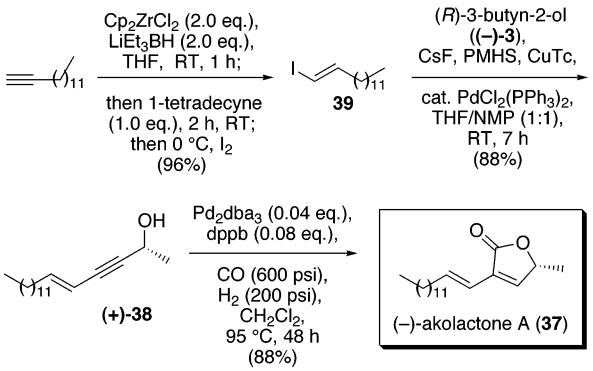
(17) CsF promoted trialkylsilylation of alkynes is known: Ishizaki, M.; Hoshino, O. *Tetrahedron* **2000**, *56*, 8813−8819.

(18) (a) Ito, H.; Sensui, H.-O.; Arimoto, K.; Miura, K.; Hosomi, A. *Chem. Lett* **1997**, 639−640. (b) Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282−286.

(19) Ito, H.; Arimoto, K.; Sensui, H.-o.; Hosomi, A. *Tetrahedron Lett* **1997**, *38*, 3977−3980.

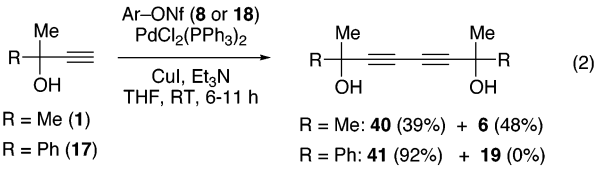
(20) For a complementary benzothiazole coupling see: Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801−802.

SCHEME 4. Synthesis of (−)-akolactone A



a cyctotoxic butenolide from *Litsea Akoensis*.[22] The synthesis began with vinyl iodide **39**, which was easily prepared via hydrozirconation/iodination of 1-tetradecyne with $Cp_2ZrH(Cl)$ (Scheme 4).[23] Our coupling protocol was then applied to (*R*)-3-butyn-2-ol ((−)-**3**). This optically active alkyne was added to a solution of THF/NMP (1:1) containing CsF followed by addition of PMHS, CuTC, vinyl iodide **39**, and $PdCl_2(PPh_3)_2$ to produce enyne (+)-**38** in 88% yield after 7 h at room temperature. The amine free conditions of our method made reaction workup relatively easy. Diluting the reaction with Et_2O and washing with saturated aqueous NH_4Cl and brine was sufficient to prepare the crude material for chromatographic purification. The final step of this short synthesis involved Pd-catalyzed reaction of enyne (+)-**38** in an autoclave charged with 600 psi CO and 200 psi H_2.[24] Under these Pd-catalyzed cyclocarbonylation conditions, (−)-akolactone A (**37**) was obtained in 88% yield after 48 h at 95 °C.

In summary, PMHS in combination with CsF facilitates room-temperature Sonogashira couplings of alkynes with various electrophiles. These reactions can be run amine free, which among other things eases reaction workup. The involvement of an in situ generated alkynyl siloxane intermediate appears likely. Thus, some of the advantages (and disadvantages[25]) of using silylalkynes in Sonogashira couplings can be realized without having to preform such a species in a separate step (usually by deprotonation with an alkyllithium followed by trapping with TMSCl[17]). For example, the use of silylalkynes can limit unwanted homocoupling of the parent alkyne.[7] As shown below, a traditional Sonogashira reaction of 2-methyl-3-butyn-2-ol (**1**) or 2-phenyl-3-butyn-2-ol (**17**) can give significant amounts of homocoupled alkynes **40** and **41** respectively (eq 2). Such homocouplings are promoted by adventitious oxygen, requiring that traditional Sonogashira reactions often be run under inert conditions.[26] In contrast, the corresponding PMHS/CsF mediated Sonogashiras (Table 3, entries 2 and 7) afforded the cross-coupled products exclusively despite being run in air.



Experimental Section[27]

Representative PMHS/CsF-Mediated Coupling of Vinyl or Aryl Halides. Hexadeca-5(*E*),15-dien-3-yn-2-ol (5). To a solution of 3-butyn-2-ol (**3**) (0.16 mL, 2.0 mmol) and PMHS (0.24 mL, 4 mmol) in 60 mL of THF/NMP (1:1) was added CsF (1.52 g, 10.0 mmol). After the initial reaction subsided (∼1 min), CuTC (760 mg, 4.0 mmol), (*E*)-1-iodo-1,11-dodecadiene (**4**) (0.8766 g, 3.0 mmol), and $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol) were added. This mixture was stirred at room temperature until complete by TLC analysis (90/10 hexane/EtOAc). Once complete (7 h), the reaction was diluted with Et_2O and then washed with saturated aqueous NH_4OH. The phases were then separated, and the combined organics were washed with H_2O (2×) and brine (2×), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 80/20) to afford hexadeca-5(*E*),15-dien-3-yn-2-ol[28] (**5**) (400 mg, 93%) as a yellow oil.

Representative Procedure for the Formation of Aryl Nonaflates. 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 4-Acetylphenyl Ester (8). To a solution of *p*-hydroxyacetophenone (6.81 g, 50 mmol) and Et_3N (8.36 mL, 60 mmol) in CH_2Cl_2 (300 mL) at room temperature was added 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (10.8 mL, 60 mmol) in a dropwise fashion. The resulting solution was stirred at room temperature for 10 h. Once complete, the reaction was washed with H_2O (2×) and brine (2×), dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 80/20) to afford 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid 4-acetylphenyl ester (**8**) (19.62 g, 94%) as a white solid: mp 42 °C (lit.[6a] mp 41−42 °C).

Representative PMHS/CsF-Mediated Coupling of Aryl or Vinyl Nonaflates. 1-(4-Phenylethynylphenyl)ethanone (9). To a solution of phenylacetylene (**7**) (0.11 mL, 1.0 mmol) and PMHS (0.12 mL, 2 mmol) in 30 mL of NMP was added CsF (0.7595 g, 5.0 mmol). After the initial reaction subsided (∼1 min), CuCl (5 mg, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid 4-acetylphenyl ester (**8**) (0.6273 g, 1.5 mmol), and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) were added. This mixture was stirred at room temperature until complete by TLC analysis (90/10 hexane/EtOAc). Once complete (4 h), the reaction was diluted with Et_2O and then washed with saturated aqueous NH_4Cl. The phases were then separated, and the combined organics were washed with H_2O (2×) and brine (2×), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90:10) to afford 1-(4-phenylethynylphenyl)ethanone (**9**) (210 mg, 95%) as a light yellow solid: mp 95 °C (lit.[29] mp 94−96 °C).

Representative PMHS/CsF-Mediated Coupling with Acyl Chlorides. 4-Hydroxy-4-methyl-1-phenylpent-2-yn-1-one (32). To 30 mL of NMP were added CsF (1.52 g, 10.0

(21) For a related benzothiazole couplings, see: Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700−1701.

(22) Chen, I.-S.; Lai.-Yaun, I.-L.; Duh, C.-Y.; Tsai, I.-L *Phytochemistry* **1998**, *49*, 745−750.

(23) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257−7260.

(24) Yu, W.-Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684−5687.

(25) Namely, stoichiometric amounts of copper are necessary in the coupling of halides.

(26) Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841−1844 and references cited.

(27) See the Supporting Information for a description of the general materials and methods employed.

(28) For a prior preparation and spectroscopic data, see: Liao, B.; Negishi, E. *Heterocycles* **2000**, *52*, 1241−1249.

(29) For a prior preparation and spectroscopic data, see: Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017−8028.

mmol), 2-methyl-3-butyn-2-ol (**1**) (0.20 mL, 2.0 mmol), and PMHS (0.24 mL, 4.0 mmol). After the initial reaction subsided, CuCl (40 mg, 0.4 mmol) was added followed by benzoyl chloride (0.26 mL, 2.2 mmol). The reaction was then heated to ∼80 °C for 5 h. Once complete, the reaction was diluted with water and then extracted with ether (2×). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90/10) to afford 4-hydroxy-4-methyl-1-phenyl-pent-2-yn-1-one[30] (**32**) (173 mg, 46%) as a yellow oil.

Representative PMHS/CsF-Mediated Coupling of Benzothiazole. 1-(4-Benzothiazol-2-ylphenyl)ethanone (35). To a solution of NMP (20 mL) were added CsF (760 mg, 5.0 mmol), benzothiazole (0.22 mL, 2.0 mmol), PMHS (0.24 mL, 4.0 mmol), CuCl (5.0 mg, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid 4-acetylphenyl ester (**8**) (418 mg, 1.0 mmol), and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol). This mixture was then allowed to stir for 17 h at room temperature. The reaction was then washed with H_2O (20 mL) and separated. The organics were then washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was diluted with a minimum amount of EtOH/$PhCH_3$ (5/2) and cooled to −5 °C to promote crystallization. The solid was then dried under vacuum to afford 1-(4-benzothiazol-2-yl-phenyl)ethanone (**35**) (146 mg, 58%) as an off-white solid solid: mp 181 °C (lit.[31] mp 182−183 °C).

1-Iodotetradec-1-ene (39) (Scheme 4). Super-hydride (51.45 mL of a 1 M THF solution, 51.45 mmol) was added dropwise to a foil-wrapped flask containing a solution of Cp_2ZrCl_2 (15.04 g, 51.45 mmol) in THF (120 mL). After 1 h, 1-tetradecyne (5.0 g, 25.73 mmol) in THF (150 mL) was added dropwise, and stirring continued for 4 h. The reaction was then cooled to 0 °C, and a solution of I_2 (6.53 g, 25.73 mmol) in CH_2Cl_2 (∼200 mL) was added dropwise until a brown-orange color persisted. The mixture was diluted with CH_2Cl_2 (∼100 mL) and washed with aq satd $Na_2S_2O_3$. The phases were separated, and the combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane) to afford 1-iodo-tetradec-1-ene (**39**) (7.95 g, 96%) as a light yellow oil: IR (neat) 2939, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.32 Hz, 3 H), 1.10−1.50 (m, 20 H), 2.06 (q, J = 7.07 Hz, 2 H), 5.99 (d, J = 14.35 Hz, 1 H), 6.53 (dt, J = 7.14, 14.28 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 22.7, 28.4, 28.9, 29.4, 29.54, 29.6, 29.7, 29.7, 29.7, 31.9, 36.1, 74.2, 146.7; HRMS (EI) m/z 322.1158 [(M^+), calcd for $C_{14}H_{27}I$ 322.1156].

(*R*)-3-Butyn-2-ol ((−)-3). TBAF (36.35 mL as a 1 M solution in THF, 36.35 mmol) was added to a 0 °C solution of (*R*)-4-trimethylsilyl-3-butyn-2-ol[32] (4.31 g, 30.3 mmol) in Et_2O (40 mL). The reaction was allowed to warm to room temperature and stir for 2 h. The reaction was then quenched by the addition of satd aqueous NH_4Cl. The phases were separated, and the organics were dried over $MgSO_4$. The Et_2O was distilled off at atmospheric pressure (40 °C). With the majority of the Et_2O removed, the remaining material was distilled at 110 °C to afford (*R*)-3-butyn-2-ol ((−)-**3**) as a 0.49 M solution in THF as judged by ^1H NMR solution in THF (68% yield). This solution was used as is in the next step.

(*R*)-(+)-Octadec-5-en-3-yn-2-ol (38). The representative PMHS/CsF-mediated coupling conditons of vinyl halides shown above were applied to (*R*)-3-butyn-2-ol ((−)-**3**) (24.49 mL of 0.49 M solution in THF, 12.0 mmol) and 1-iodotetradec-1-ene (**39**) (5.80 g, 18 mmol). After 7 h, the reaction was judged complete by TLC analysis (hexanes/EtOAc 90/10). After workup as described above, the resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90/10) to afford (*R*)-(+)-octadec-5-en-3-yn-2-ol (**38**) (2.80 g, 88%) as a solid: mp 32−34 °C; $[\alpha]^{23}_D$ = +12.8, c = 0.392 $CHCl_3$; IR (neat) 3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.11 Hz, 3 H), 1.05−1.41 (m, 20 H), 1.45 (d, J = 6.52 Hz, 3 H), 2.08 (q, J = 6.80 Hz, 2 H), 2.50 (br s, 1 H), 4.62 (q, J = 5.56 Hz, 1 H), 5.47 (d, J = 15.86 Hz, 1 H), 6.13 (dt, J = 7.07, 14.50 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 22.6, 24.3, 28.6, 29.0, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 33.0, 58.6, 82.7, 89.4, 108.7, 145.3; HRMS (EI) m/z 264.2453 [(M^+), calcd for $C_{18}H_{32}O$ 264.2456].

(−)-Akolactone A (37). Under an Ar atmosphere, (*R*)-(+)-octadec-5-en-3-yn-2-ol (**38**) (1.06 g, 4 mmol), Pd_2dba_3 (146.4 mg, 0.16 mmol), and dppb (136.4 mg, 0.32 mmol) were added to an oven-dried stainless steel autoclave. Degassed (∼2 h with N_2) CH_2Cl_2 (40 mL) was added, and the autoclave was sealed under an Ar atmosphere. The vessel was purged 6× with CO (200 psi each time). It was then charged with CO (600 psi) and then H_2 (200 psi). The vessel was placed in oil bath, and the internal temperature was maintained at 95 °C for 48 h. The reaction vessel was cooled to room temperature before opening. Once opened, the reaction was concentrated, and the resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 92/8) to afford (−)-akolactone A (5-methyl-3-tetradec-1-enyl-5*H*-furan-2-one) (**37**) (1.02 g, 88%) as a clear oil: $[\alpha]^{23}_D$ = −12.7, c = 0.4 $CHCl_3$ (lit.[22] $[\alpha]^{23}_D$ = −13.2, c = 0.1 $CHCl_3$); IR (neat) 1767, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.1 Hz, 3 H), 1.16−1.36 (br s, 18 H), 1.42 (m, 5 H), 2.16 (q, J = 6.9 Hz, 2 H), 5.02 (qd, J = 1.7, 7.4 Hz, 1 H), 6.09 (d, J = 17.23 Hz, 1 H), 6.79 (dt, J = 7.1, 15.8 Hz, 1 H), 7.03 (d, J = 1.80 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 19.1, 22.6, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 33.4, 76.9, 118.2, 129.3, 138.7, 146.8, 171.9; HRMS (EI) m/z 292.2402 [(M^+), calcd for $C_{19}H_{32}O_2$ 292.2403].

ReactIR Study. CsF (15.19 g, 100 mmol) was added to a vigorously stirred solution of the alkyne (50 mmol) in NMP (50 mL). An initial IR spectrum was obtained. PMHS (6 mL, 100 mmol) was added dropwise at a rate that kept the reaction under control (∼17 min). Data collection began immediately upon the first addition of PMHS and continued at 45 s intervals for 5.5 h.

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Supporting Information Available: Experimental procedures not described herein and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) For a prior preparation and spectroscopic data: Saimoto, H.; Yasui, M.; Ohrai, S.; Oikawa, H.; Yokoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279−284.

(31) For a prior preparation and spectroscopic data see: Perry, R. J.; Wilson, B. D. *Organometallics* **1994**, *13*, 3346−3350.

(32) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369−3372.