Palladium-Catalyzed Additions of Terminal Alkynes to Acceptor Alkynes

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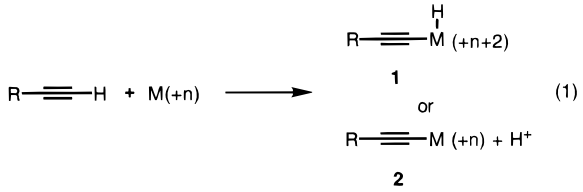
Abstract: The development of addition reactions wherein the product is the simple sum of the reactants plus anything else (only needed catalytically) constitutes an important goal for enhanced synthetic efficiency. The C−H bond of terminal alkynes (the donor alkynes) can be added to either terminal alkynes (self-coupling) or activated internal alkynes (cross-coupling) (the acceptor alkynes) in the presence of a catalytic amount of palladium acetate and an electron rich sterically encumbered ligand, tris(2,6-dimethoxyphenyl)phosphine. The activated internal alkynes for cross-coupling (the acceptor alkyne) include alkynes bearing an ester, sulfone, and ketone. Self-coupling is completely overwhelmed by cross-coupling, even at 1:1 ratios of donor and acceptor alkynes. The reaction exhibits extraordinary chemoselectivity with free carboxaldehydes, alcohols, ketones (saturated and conjugated), esters (saturated and conjugated), sulfones (saturated and conjugated), malonates, and silyl ethers all proving to be compatible. A 1:2 donor/acceptor alkyne adduct can also be optimized. Ethyl propiolate fails as an acceptor but its C-silylated analogue serves with the proper choice of silyl substituent. The products of the latter serve as useful precursors to β-keto esters. An iterative sequence is readily performed and led to a novel conformationally rigid retinoid analogue. The mechanism of this mild method for construction of conjugated enynes, versatile building blocks, is discussed.

Addition reactions constitute an atom economical way to build more complex structures from simpler building blocks.[1] Unfortunately, few of our synthetic reactions fall within this category. The excellent coordinating ability of alkynes for transition metals makes transition metal catalyzed additions of alkynes a promising area for exploration. Two general modes of behavior may be discerned: additions involving the π-system and insertions into the C−H bond of terminal acetylenes. We report a reaction which combines both modes of reaction and provides a general entry to conjugated enynes which represent a novel class of versatile building blocks as well as a key fragment of increasingly populated classes of biologically interesting molecules represented by neocarzinostatin chromophore[2] and calicheamycin.[3,4]

The insertion of a transition metal into a C−H bond (exemplified for the terminal alkynes in eq 1) creates the new complexes **1** or **2** whose potential reactivity profile imparts great interest into such processes.[5] Transition metals, in contrast to main group metals, are characterized by the ability of the C−M or H−M bonds to undergo *cis-syn* additions to relatively unpolarized π-unsaturation like that of unactivated double and triple bonds. In an oxidative addition process, the metal may be simply thought of as a base, wherein complex **1** would result. This complex, in principle, can undergo either a carbametalation or a hydrometalation, for which the latter is normally believed to be kinetically faster.[6] On the other hand, the metal complex **2** may derive from the equivalent of a substitution reaction. In such an event, it may undergo only a carbametalation in subsequent reactions.

In the course of our investigations of the metal-catalyzed cycloisomerization of enynes,[7] we found that the use of an electron rich ligand like tris(2,6-dimethoxyphenyl)phosphine (TDMPP) completely changed the course of the reaction from cycloisomerization to diyne coupling of the type represented generically in eq 2.[8−10] This reaction may be envisioned to involve reactive intermediates like complex **1** or **2**. In order to examine the nature of this reaction, we undertook a more extensive study of its scope. A particularly intriguing question is the feasibility of a "cross-coupling" process, as illustrated in eq 3, which represents a particularly useful synthetic protocol.



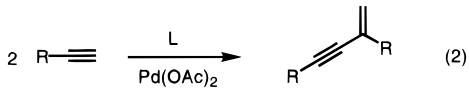


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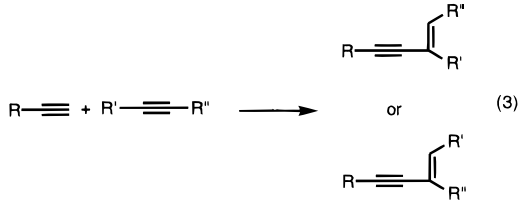
Table 1. Cycloisomerization vs Self-Coupling of Enynes[a]

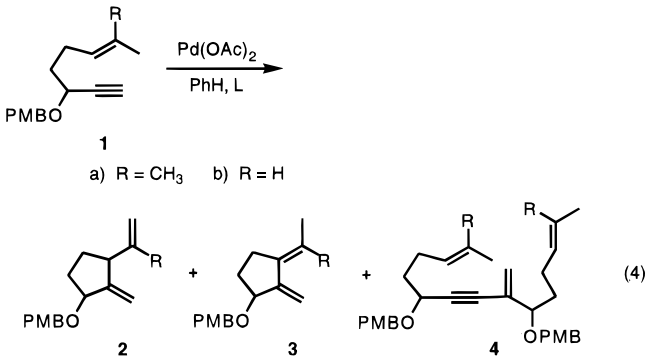
entry	substrate	L	yield cycloisomer (%)	ratio **2**:**3**	ratio diastereomers of **2**	yield self-coupling **4** (%)
1[b]	**1a**	none	23	only **2**	5:4	ND[c]
2	**1a**	Ph_3P	19	6:1	1:2	9−22
3	**1a**	Ph_3As	47	4:1	1:1	9−22
4	**1a**	$(o\text{-}CH_3C_6H_4)_3P$	12	2:1	2:1	66
5[b]	**1b**	none	6	2:1	3:1	ND[c]
6[b]	**1b**	Ph_3P	41	1:1	7:2	ND[c]
7[b]	**1b**	$(o\text{-}CH_3C_6H_4)_3P$	33	1:2	2:1	ND[c]
8	**1b**	TDMPP	4	only **3**		71

[a] All reactions were run with 5 mol % of $Pd(OAc)_2$ in PhH at room temperature unless otherwise noted. [b] Performed at 60 °C. [c] ND = not detected.

We record our observations of the scope of these processes and a few initial mechanistic insights.[11]



Self-Coupling. The reaction of enyne **1a** with palladium acetate in the presence of various ligands produced a mixture of three compounds, the cycloisomerization products **2a** (a mixture of diastereomers) and **3a** and the self-coupling product **4a** (eq 4), as summarized in Table 1. While small amounts of



the self-coupling product **4** were observed with several ligands (entries 2 and 3), the use of a sterically demanding ligand which creates more coordinatively unsaturated palladium, tri-*o*-tolylphosphine,[12] produces **4** in 65% isolated yield (entry 4). With the desmethyl substrate **1b**, even the use of tri-*o*-tolylphosphine as a ligand still produces the cycloisomer (entry 7). Only upon going to TDMPP[10l,13] does the self-coupling product **4b** form satisfactorily, and it is isolated in 71% yield (entry 8).

Spectroscopy confirms the structure of the self-coupling products **4a** and **4b**. Mass spectroscopy establishes their molecular formulae as dimers. The disubstituted alkyne is indicated by the IR absorption at 2050 cm^{-1} and the ^{13}C NMR shifts at δ 80.8 and 83.9. The terminal methylene of the 1,1-disubstituted alkene is indicated by the ^1H NMR absorption at δ 5.53−5.55 and 5.43−5.45.

The presence of the additional double bond is irrelevant to this coupling protocol, as illustrated in Table 2, entries 1−4. These examples illustrate the compatibility of both a free alcohol (entry 4) and a monosubstituted malonate (entry 3). The enyne substrates (entries 5−8) all show good to excellent selectivity for the self-coupling event at the expense of the cycloisomerization. Even an activated acceptor such as an acrylate (entry 8), which promotes the cycloisomerization, produces the homodimer **5f** with the cycloisomer being only a minor product (13% yield). On the other hand, this example ilustrates that such an acrylate does not suffice as an acceptor for the alkynylpalladium intermediate compared to a triple bond, even an unactivated one.

Cross-Coupling. The facility of the homocoupling makes it a challenge to define what may be able to intercept the reactive

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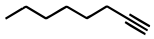
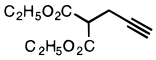
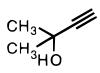
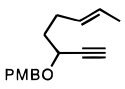
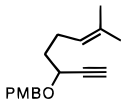
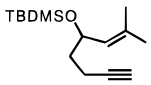
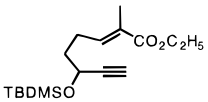
(13) Wada, M.; Higashizaki, S. *J. Chem. Soc., Chem. Commun.* **1984**, 482.

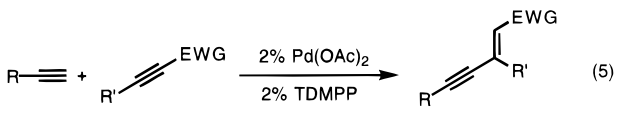
Table 2. Self-Coupling of Terminal Alkynes[a]

entry	starting alkyne	dimer compd no.	isolated yield of dimer (%)
1		**5a**	63
2		**5b**	62
3		**5c**	87
4		**5d**	87
5	 **1b**	**4b**	71
6[b]	 **1a**	**4a**	66
7		**5e**	89
8[b,c]		**5f**	83

[a] All reactions were run with 2 mol % $Pd(OAc)_2$ and mol % of TDMPP in PhH or PhH-d_6 at room temperature unless otherwise noted. [b] Tri-*o*-tolylphosphine employed as ligand. [c] Reaction run at 60 °C.[d] In addition, a 21% yield of trimer was isolated.

intermediate to achieve a cross-coupling event. We previously established that activated allenes can serve this role efficiently and even simple allenes suffice.[10l] Given the above results, it appeared that another alkyne seemed more probable than an alkene if it can be activated. Viewing the carbametalation event as having some characteristics analogous to the Heck reaction,[14] wherein acrylates are particularly good acceptors, our attention turned to alkynoates as candidates.

Methyl butynoate was chosen as an acceptor rather than methyl propynoate because of the high reactivity of the terminal C−H bond of the latter. The dimerization of phenylacetylene, which occurs at room temperature in less than 40 min, is completely eliminated by addition of approximately 1 equiv of methyl butynoate to give a single product (see eq 5 and Table 3).



(5)

Initially, the regioselectivity and alkene geometry were assigned on the basis of ^{1}H NMR shifts. Notably, the absorptions for the vinyl methyl group and the vinylic hydrogen for adducts **6a**−**g** appear at δ 2.26 ± 0.14 and 6.04 ± 0.10, respectively. Thus, the downfield shift of the vinyl methyl group is consistent with its being deshielded by the ester, since it is *cis* and β to this anisotropic group. The high-field shift of the vinylic hydrogen is consistent with its being α to the ester, not

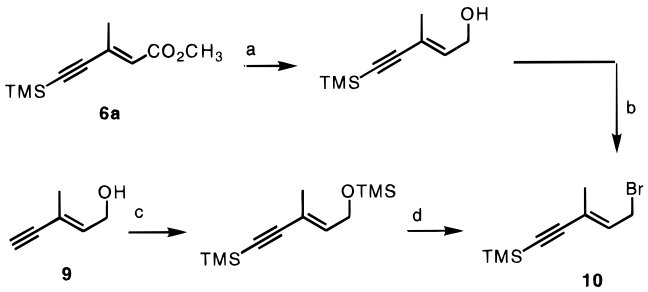
(14) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.3, pp 833−864.

Table 3. Cross-Couplings with Alkyl- and Aryl-Substituted Acceptor Alkynes[a]

entry	donor alkyne R	acceptor alkyne R′	acceptor alkyne EWG	isolated yield (%)	product
1[b]	TMS	CH_3	CO_2CH_3	95	**6a**
2	Ph	CH_3	CO_2CH_3	92	**6b**
3	$HOCH_2$	CH_3	CO_2CH_3	67	**6c**
4	$(CH_3O_2C)_2CHCH_2$	CH_3	CO_{2C2H5}	87	**6d**
5	$PhSO_2CH_2$	CH_3	CO_2CH_3	11	**6e**
6	$OHCCH_2CH_2CH_2$	CH_3	CO_2CH_3	84	**6f**
7	$(PhSO_2)_2CHCH_2CH_2CH_2CH_2$	CH_3	CO_2CH_3	90	**6g**
8	Ph	CH_3	SO_2Ph	91	**7a**
9	*n*-C_4H_9	CH_3	SO_2Ph	68	**7c**
10	$TBDMSOCH_2$	CH_3	SO_2Ph	68	**7c**
11	Ph	Ph	$COCH_3$	72	**8a**
12[c]	Ph	*n*-C_6H_{13}	$COCH_3$	83	**8b**

[a] All reactions were performed with 2 mol % of $Pd(OAc)_2$ and 2 mol % of TDMPP with approximately a 1:1 ratio of donor and acceptor alkyne in benzene at ambient temperature unless otherwise noted. [b] Reaction performed with 3 mol % of catalyst in THF at ambient temperature. [c] Reaction performed with a 2:1 ratio of donor to acceptor alkyne.

Scheme 1.[a] Chemical Correlation of the Structure of Adduct **6a**



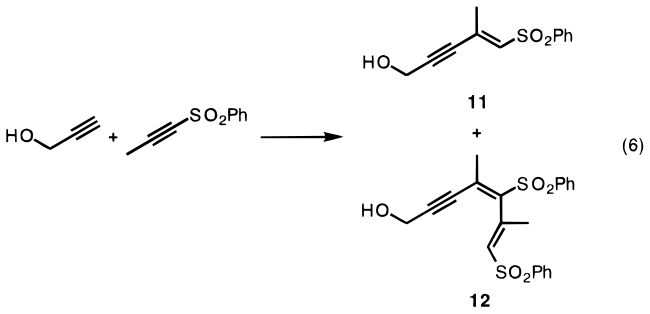
[a] (a) DIBAL-H, $PhCH_3$, 59%; (b) NBS, Ph_3P, CH_2Cl_2, 73%; (c) C_4H_9Li, TMS-Cl, 80%; (d) CBr_4, Ph_3P, CH_3CN, 66%.

β. In conjunction with another project, the structure of the adduct **6a** was proven by correlation with the commercially available enyne **9**, as illustrated in Scheme 1. The allyl bromide **10**, which was used in subsequent alkylation reactions, was identical as prepared by the two routes.

The examples illustrate the high chemoselectivity of the process. It is obvious from the nature of the product that sensitive π-systems, even activated ones, are compatible. Compounds containing acidic protons whose pK_a normally would make them more easily deprotonated than a terminal alkyne such as alcohols (entry 3), malonates (entry 4), bis-sulfonylmethanes (entry 7), etc., participate normally. Perhaps, more remarkably, carbonyl groups including aldehydes (entry 6) and ketones (entries 11, 12), which normally would undergo facile carbonyl additions of acetylide anions, do not interfere.

When 3-decyn-2-one is employed as the acceptor, the reaction using a 1:1 ratio of reactants was incomplete after 24 h at room temperature. Since separation of starting material and products proved difficult, a 2:1 ratio of donor to acceptor alkyne was employed, in which case the reaction went to completion within 18 h at room temperature. It is likely that using elevated temperatures would suffice to enforce full conversion with the 1:1 ratio of reactants.

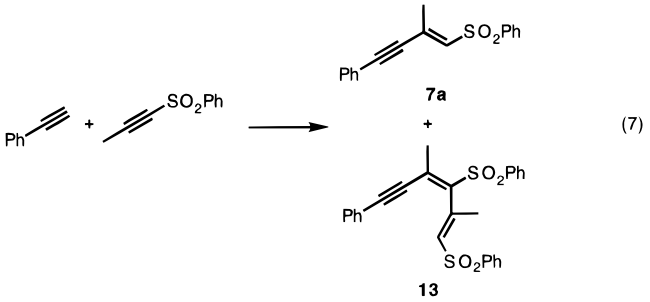
In the addition of propargyl alcohol to 1-(phenylsulfonyl)-1-propyne under the standard conditions, a 1:2 adduct (**12**) formed in addition to the 1:1 adduct **11** (eq 6) in 24% and 40 yields, respectively. Part of the effect derives from the presence of the free OH, since the silyl ether participated without such a complication (Table 3, entry 10) under the same conditions. Adding a protonic medium such as *tert*-butyl alcohol gave a nearly 1:1 ratio of **11** and **12**. Changing from benzene to THF



(6)

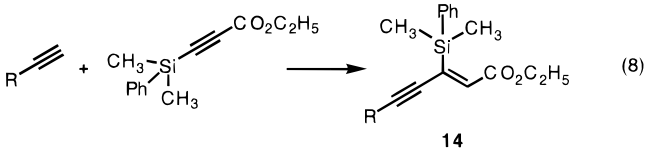
had no effect. The one variable that had a major effect was concentration of the reaction medium. Typically, the reactions were performed at 0.25 M in both reactants. Increasing the concentration of both to 1.0 M led to formation of, predominantly, the 1:2 adduct **12** which was isolated in 48% yield. On the other hand, decreasing the concentration of both to 0.05 M gave only the 1:1 adduct **11** in 88% yield. Changing the ratio of the reactants from 1:1 to 1:2 propargyl alcohol to alkynylsulfone at 1.0 M concentration with respect to the latter gave a 54% yield of the 1:2 adduct **12** and a 38% yield of the 1:1 adduct **11**. Thus, by adjusting concentrations, an excellent yield of the 1:1 adduct and a satisfactory yield of the 1:2 adduct may be obtained.

Since the role of the hydroxyl group in this reaction was not obvious, its requirement was tested by using a non-hydroxyl-bearing alkyne in a cross-coupling reaction at high concentration. As shown in eq 7, a 1:2 ratio of phenylacetylene and the alkynylsulfone at 2.0 M in the latter gave the 1:2 adduct **13** in 59% yield along with 21% of the 1:1 adduct **7a**. This result contrasts with a 91% yield of the 1:1 adduct **7a** under normal conditions (Table 3, entry 8).



(7)

Terminal acetylenic acceptors bearing an electron-withdrawing group were prevented from being employed because of the exceptional reactivity of the acetylenic hydrogen which leads to polymerization. The use of a silyl substituent as a hydrogen surrogate should help resolve this problem. The ethyl propiolate system was chosen as the test system because of the ease of direct silylation of the lithiated species.[15] The trimethylsilyl substituent proved too labile. The triethylsilyl substituent was more satisfactory, but the yields of adducts were still rather low. The dimethylphenylsilyl group ultimately proved satisfactory as summarized in eq 8 and Table 4.



(8)

Initial results using our standard conditions led to a very slow reaction. Raising the temperature to 45 °C, but otherwise keeping all other parameters the same, produced a 33% yield of the desired adduct **14a** (Table 4, entry 1). The low yield was mainly associated with a poor conversion due to the catalyst dying because of the long reaction times required (48 h). Increasing both the mole percent of the catalyst and concentration improved the process immensely (entries 2 and 3). At 3 mol % of catalyst and 0.5 M substrates, the reaction required only 20 h at 45 °C, and at 5 mol %, it was complete within 20 h at room temperature. In both cases, excellent yields of the cross-coupling product **14a** were observed. The reaction with dimethyl propargylmalonate as donor alkyne exhibited lower yields of the 1:1 adduct **14b** at 0.5 M (Table 4, entry 4). In this case, formation of a 1:2 adduct accounts for the diminished yield. As observed before, lowering the concentration of the reactants increased the yield of the normal 1:1 adduct (entry 5). The excellent participation of the aldehyde alkyne as a donor (entry 6) led to smooth reaction, even under the standard conditions. Once again, this example highlights the excellent chemoselectivity of the process.

Table 4. Cross-Coupling with Ethyl 3-(Dimethylphenylsilyl)propiolate[a]

entry	donor alkyne R	TDMPP-Pd(OAc)$_2$ (mol %)	concn	isolated yield (%)	product
1	Ph	2	0.25	33[b]	**14a**
2	Ph	3	0.5	83[b]	**14a**
3	Ph	5	0.5	86	**14a**
4	$(CH_3O_2C)_2CHCH_2$	3	0.5	42	**14b**
5	$(CH_3O_2C)_2CHCH_2$	3	0.05	66	**14b**
6	$OHCCH_2CH_2CH_2$	2	0.25	73	**14c**
7	$AcOCH_2CH_2$	10	0.5	48[b]	**14d**

[a] All reactions were performed in PhH at room temperature using a catalyst derived from a 1:1 ratio of TDMPP and Pd(OAc)$_2$ unless indicated otherwise. [b] Reaction performed at 45 °C.

An Iterative Cross-Coupling Sequence. The ease by which these additions proceed led us to test the ability to use this methodology in an iterative fashion. The retinoids, because of their myriad of biological roles, including cell differentiation, cell proliferation, embryonic development, etc., beyond their well-known role in vision, has been targeted for analoguing.[16,17] In particular, the generation of conformationally rigid analogues haas been quite illuminating concerning the biological activity.[18] Replacing the two disubstituted double bonds with alkynes provides an intriguing rigidification.[19]

Scheme 2 outlines a synthesis of a bis-dehydro derivative, methyl 7,8,11,12-tetradehydroretinoate (**20**). The ability to dehydrate methyl ketones to terminal alkynes[20] led to the exploration of the cross-coupling of alkyne **15**, which is in a 2.5:1 diastereomeric ratio, with 2-pentyn-4-one. In the event, this addition proceeded smoothly to provide **16** (R = CH_3) under standard conditions, but with THF as solvent, in 80% yield. Surprisingly, attempts to continue via this route were thwarted

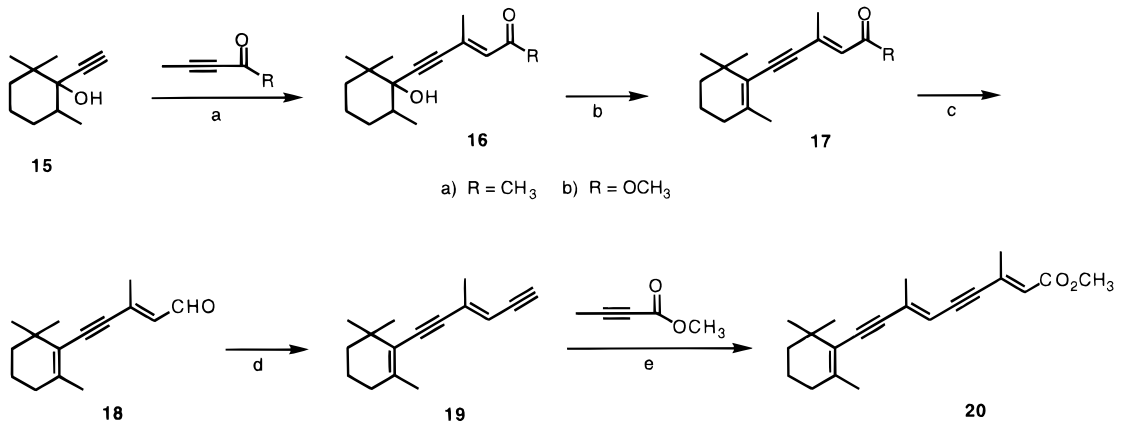
(15) Midland, M. M.; Tramatano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(16) For a few recent overviews, see: *The Retinoids: Biology, Chemistry and Medicine*, 2nd ed.; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven: New York, 1993. Linney, E. *Curr. Top. Dev. Biol.* **1992**, *27*, 309. Bollag, W.; Holdener, E. *Ann. Oncol.* **1992**, *3*, 513. Hashimoto, Y.; Shudo, K. *Cell. Biol. Rev.* **1991**, *25*, 209. *Chemistry and Biology of Synthetic Retinoids*; Dawson, M. I., Okamura, W. H., Eds.; CRC Press: Boca Raton, FL, 1990.

(17) For a few recent leading references, see: Torrado, A.; Iglesias, B.; López, S.; deLera, A. R. *Tetrahedron* **1995**, *51*, 2435. Shimasaki, H.; Kagechika, H.; Fukasawa, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1995**, *43*, 100. Wada, A.; Tode, C.; Hiraishi, S.; Tanaka, Y.; Ohfusa, T.; Ito, M. *Synthesis* **1995**, 1107. Giraud, M.; Andriamialisoa, Z.; Valla, A.; Zennache, S.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 3077. Kim, C. U.; Misco, P. F.; Luh, B. Y.; Mansuri, M. M. *Tetrahedron Lett.* **1994**, *35*, 3017.

(18) Pfahl, M. In *From Molecular Biology to Therapeutics*; Bernard, B. A., Shroot, B., Eds.; Karger: Basel, Switzerland, 1993; pp 83−93. Pfahl, M. In *Retinoids: From Basic Science to Clinical Applications*; Liorea, M. A., Vidali, G., Eds.; Birkhäuser: Basel, Switzerland, 1994; pp 113−126.

Scheme 2.[a] An Iterative Cross-Coupling Sequence



[a] (a) 3% $Pd(OAc)_2$, 3% TDMPP, THF, room temperature, 88% R = OCH_3, 80% R = CH_3; (b) $POCl_3$, C_5H_5N, reflux, 64%; (c) (i) DIBAL-H, $PhCH_2$, −78 °C, 63%; (ii) Dess−Martin periodinane, CH_2Cl_2, 0 °C, Q or NMO, TPAP, 3 Å MS, CH_2Cl_2, rt, 87%; (d) $TMSCHN_2$, LDA, THF, −78 °C to room temperature, 72% or Ph_3P, CBr_4, CH_2Cl_2, 0 °C then *n*-C_4H_9Li, −78 °C to room temperature, 58%; (e) see a, 53%.

by the inability to dehydrate the mono alcohol **16** (R = CH_3) to the dienyne **17** (R = CH_3).

An alternative path to diyne **19** involves direct homologation of an aldehyde to a terminal alkyne via Wittig[21] or Peterson[22] type olefination protocols. For this purpose, the terminal alkyne **15** was added to methyl 2-butynoate to give **16** (R = OCH_3) in 88% yield as a single regioisomer and olefin geometry. Since **15** is a mixture of diastereomers with respect to the ring, a mixture of stereochemical isomers with respect to the ring was isolated. Since this stereochemistry is lost in the next step, the individual stereoisomers were not pursued. This ester undergoes dehydration under classical conditions with phosphorus oxychloride in pyridine to the dienyne **17** (R = CH_3), which is a single isomer confirming the homogeneity with respect to both regiochemistry and alkene geometry.

Access to the diyne **19** was effected by a classical sequence which proceeded efficiently. Reduction with DIBAL-H proceeded readily to the alcohol even at −78 °C. Thus, we chose to oxidize the latter rather than pursue stopping the ester reduction at the stage of the aldehyde. The Dess−Martin periodinane[23] effected oxidation quantitatively. On the other hand, the procedure of Ley employing catalytic tetra-*n*-propylammonium perruthenate (TPAP) with NMO (4-methylmorpholine *N*-oxide) as the stoichiometric reoxidant[24] is more convenient. It effected the same oxidation in somewhat lower but still quite satisfactory yield (87%). Dibromomethylenation with triphenylphosphine and carbon tetrabromide gave the vinyl dibromide in 76% yield. Subjection of the latter to *n*-butyllithium provides the desired terminal acetylene **19** in 76% yield, for an overall 58% yield from aldehyde **18**. A more convenient protocol involved direct treatment of aldehyde **18** with lithiated (trimethylsilyl)diazomethane, wherein the yield increased to 72%. Gratifyingly, the terminal alkyne **19** added smoothly to methyl 2-butynoate to give the conformationally rigid analog **20** in 53% yield.

Discussion

The addition of the C−H bond of terminal alkynes across the π-bond of an internal or terminal alkyne creates a valuable and versatile product, a conjugated enyne. While such reactions have been observed with a variety of transition metal catalysts,[9,10] they frequently produce mixtures arising from the reactivity of the initial adducts toward further additions. In some cases, mixtures of regioisomers result. In other cases, especially those involving lanthanide and actinide catalysts, the reactions are limited to hydrocarbons. Furthermore, the reaction involving some later transition metal catalysts, such as rhodium and ruthenium, involves a mechanism that restricts the reaction to terminal alkynes.

The catalyst system reported herein obviates many, if not all, of these problems and limitations and gives excellent yields of the 1:1 homo- and cross-coupling products. The outstanding chemoselectivity exhibited engenders the notion that any functionality will be compatible with this reaction.

The understanding of the effectiveness of this reacion requires an understanding of the mechanism. The reaction consists of three phases: (1) the activation of the C−H bond of the terminal alkyne, (2) the addition to the π-system of the acceptor alkyne, and (3) the protonation of the vinylpalladium intermediate. In addition, the question of the palladium species responsible for the actual catalytic cycle is not necessarily obvious.

Our initial working hypothesis outlined in Scheme 3 is a modification of our earlier proposal to better take into account the regioselectivity of the process. It invokes the insertion of palladium into the C−H bond of a terminal alkyne that becomes kinetically accessible by coordination of the triple bond with Pd(2+). The beneficial effect of a sterically demanding and electron rich ligand is envisioned to arise from the requirement to maintain a coordinatively unsaturated palladium species that still is electron rich enough to participate in an oxidative addition. While **21** may not be expected to be stable relative to loss of acetic acid, its intermediacy on the way to **22** cannot be excluded. This mechanism accounts for the overall event of a *cis* addition in a Markovnikov fashion for the homocoupling and in a Michael fashion for the cross-coupling.

(19) For chemistry and biology of some dehydroretinoids, see: Khitrina, L. V.; Eremin, S. V.; Khodonov, A. A.; Kaulen, A. D. *Biol. Membr.* **1994**, *11*, 575. Jaeger, E. P.; Jurs, P. C.; Stouch, T. R. *Eur. J. Med. Chem.* **1993**, *28*, 275. Sarkar, R.; Das, S. K. *Neoplasma* **1992**, *39*, 87. Danshina, S. V.; Drachev, A. L.; Drachev, L. A.; Kaulen, A. D.; Mitsner, B. I.; Khitrina, L. V.; Khodonov, A. A. *Bioorg. Khim.* **1989**, *15*, 307. Wuest, H. H.; Janssen, B.; Frickel, F. *Biochem. Soc. Trans.* **1986**, *14*, 933. Niculescu-Duvaz, I.; Simon, Z.; Voiculet, N. *Carcinogenesis* **1985**, *6*, 479. Hopf, H.; Krause, N. *Tetrahedron Lett.* **1985**, *26*, 3323. Gaertner, W.; Oesterhelt, D.; Seifert-Schiller, E.; Towner, P.; Hopf, H.; Boehm, I. *J. Am. Chem. Soc.* **1984**, *106*, 5654. Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413. Lotan, R.; Neumann, G.; Lotan, D. *Cancer Res.* **1980**, *40*, 1097. Olive, J. L.; Mousseron-Canet, M.; Dornand, J. *Bull. Soc. Chim. Fr.* **1969**, 3247.

(20) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1985**, *64*, 44.

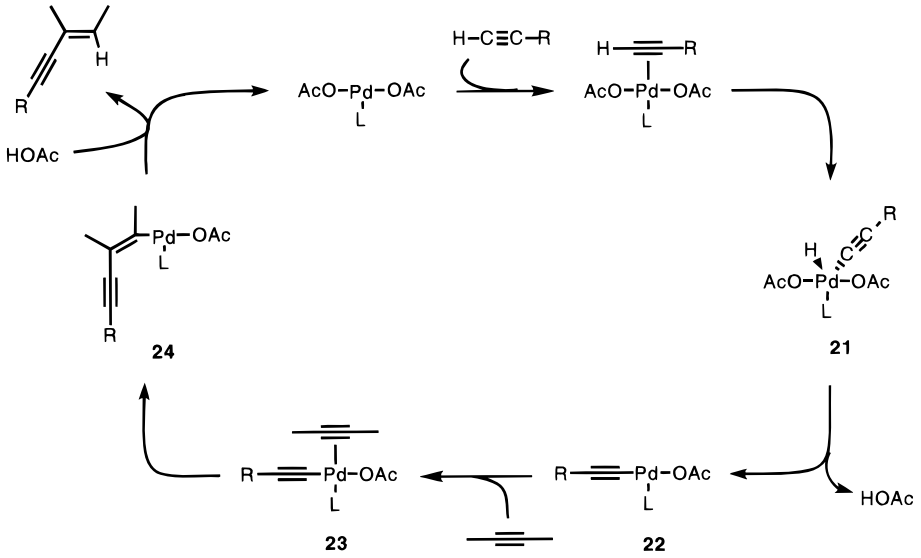
(21) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(22) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107

(23) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(24) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Scheme 3. A Working Hypothesis



However, several features were somewhat discomforting. The formation of the substitution product **22** normally involves a base-catalyzed reaction; however, except for the phosphine, no base is present.[5] Since only a 1:1 ratio of phosphine to palladium is employed, it would seem the phosphine is tied up as a ligand to the palladium and therefore unavailable to serve this function. Invoking the Pd(4+) species **21** is suggested to obviate this problem. The donor ligand then helps stabilize the high oxidation state of palladium.[25] On the other hand, it is less obvious how this route accommodates the cross-coupling event. If the selectivity derives from alkyne coordination of **22**, a Pd(2+) species bearing an electronegative group, such as acetate, would have to preferentially coordinate an electron deficient alkyne over an electron rich alkyne to preclude any homo-coupling, a requirement that appears less likely. Alternatively, this selectivity may derive from the migratory insertion in going from **23** to **24**.[26]

However, we did not seriously question this working hypothesis until we were confronted with the 1:2 adducts **12** and **13**. According to this mechanism, a competition between protonation of the vinylpalladium species **24** and its reaction with another molecule of acceptor alkyne is responsible for the product ratio. However, this competition did not respond to increasing the concentration of protons, even to the extent of using a protonic solvent.

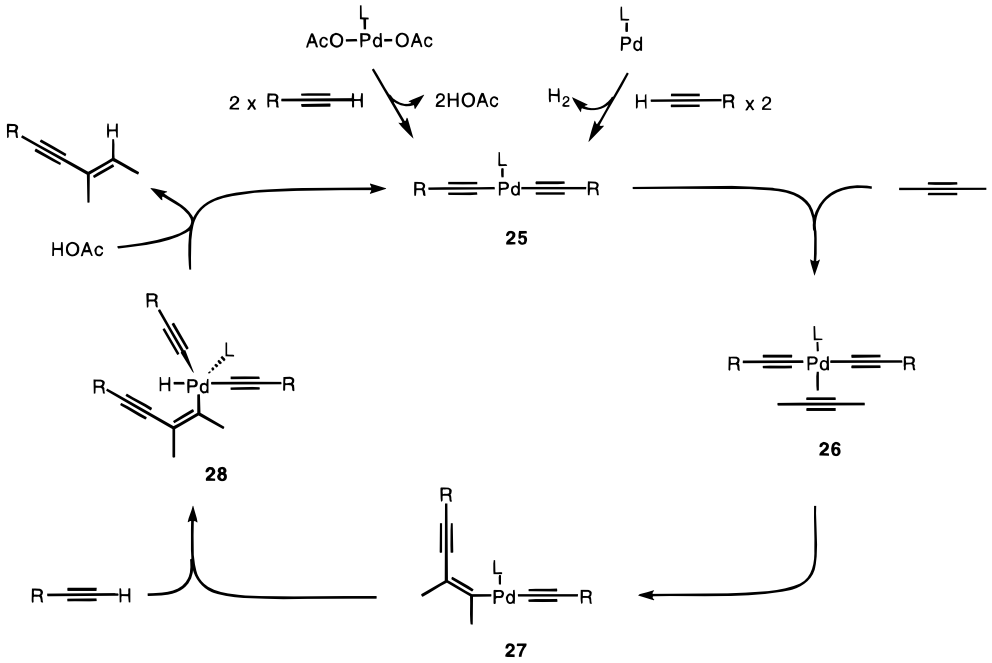
We also explored the question of whether this reaction involves a Pd(0) or Pd(2+) resting state in the catalytic cycle, since palladium acetate is known to be rather easily reduced to Pd(0). We, therefore, examined the feasibility of Pd(0) to catalyze this reaction. Using the self-coupling of diethyl propargylmalonate as an example (Table 2, entry 3), we exposed it to $(dba)_3Pd_2{\cdot}CHCl_3$ in the presence of TDMPP (Pd/P ratio of 1:1) and found that reaction did proceed but somewhat more slowly and incompletely. After 19 h at room temperature, the reaction was 50% complete, and the reaction was stopped at 65% conversion after 27.5 h. In order to keep everything as constant as possible, a Pd(2+) species was generated *in situ* by adding allyl acetate to the above Pd(0) catalyst system. After 17 h, the reaction was 87% complete, and after 23.5 h, it was 94% complete.

The fact that Pd(0) could catalyze the reaction, albeit somewhat less efficiently that Pd(2+), suggests an alternative working hypothesis in which the resting state of the catalyst may be a dialkynylpalladium complex (**25**, see Scheme 4). Formation of such complexes from both Pd(2+) and Pd(0) precursors are documented[5,27] and account for the ability of both to serve as precursors. The strong donor properties of the acetylides predict preferential coordination of an acceptor alkyne with a low-lying antibonding orbital in **26**. Thus, the ability of electron deficient alkynes to compete successfully with the terminal alkyne even at a 1:1 ratio is nicely accommodated by this species. Further, the differential rate of migratory insertion of an electron deficient versus an electron rich alkyne may act synergistically to give the high selectivity observed for cross-coupling. Invoking a migratory insertion in Pd(2+) complex **26** leads to complex **27** and accounts for the 1:1 versus 1:2 adduct formation. The complex **27** may react with another acceptor alkyne in similar fashion to form the 1:2 adduct or another terminal alkyne to give a Pd(4+) complex **28**. The presence of strong donor ligands on palladium as in **26** and **27** should facilitate formation of the higher oxidation state complex. It also accounts for the absence of any effect of an external proton source. Unfortunately, any attempts to establish the terminal alkyne as the source of the vinylic hydrogen in the product in the presence of an external proton source by deuterium labeling is thwarted by a rapid exchange between these protons in the presence of the palladium catalyst. This latter mechanism does not attribute any difference on catalyst precursor, Pd(0) or Pd(2+). While qualitatively they are the same, there appear to be quantitative differences. One way to rationalize the differences is to invoke a hybrid scheme whereby the dummy ligand in Scheme 4 is an acetate, rather than a second acetylide, for the palladium acetate precatalyst as illustrated in Scheme 5. Formation of the active catalyst **22** may occur as outlined in Scheme 3 or via direct deprotonation of the coordinated terminal alkyne to ligated palladium acetate.[28] At present, we cannot differentiate unambiguously among these possibilities.

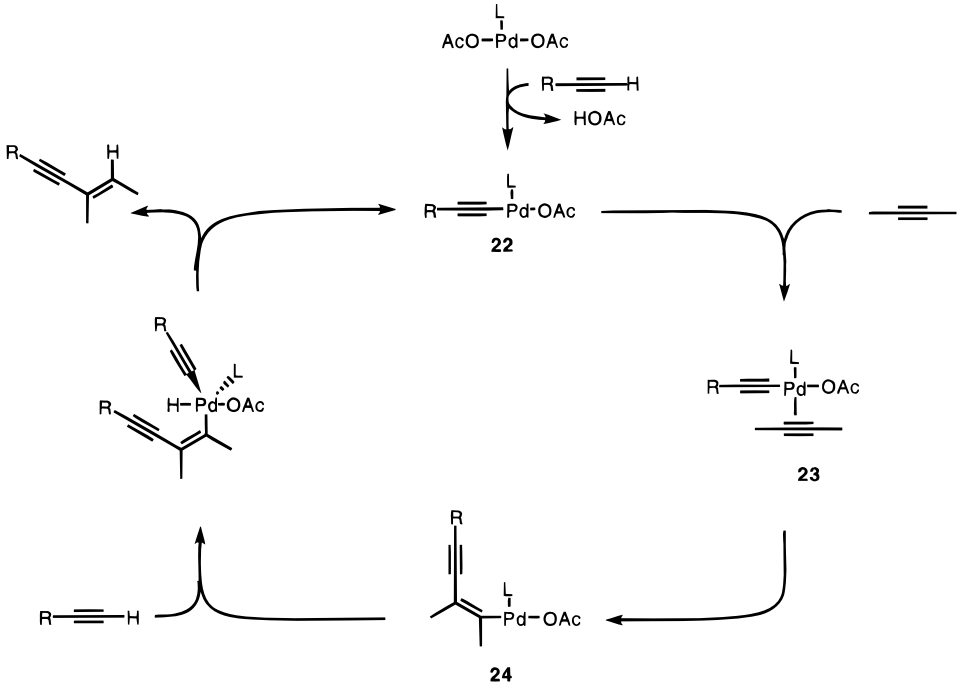
The regiochemistry of the carbametalation of the acceptor alkyne reflects both steric and electronic effects. Thus, the dimerization preferentially involves placing the palladium at the less-substituted carbon, as in **29**, rather than the reverse, as in

(25) Cf.: Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.
(26) Cf.: Yasuda, T.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2888.
(27) Also, see: Nelson, J. H.; Verstuyft, A. W.; Kelley, J. D.; Jonassen, H. B. *Inorg. Chem.* **1974**, *13*, 27. Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291. Sebald, A.; Stader, C.; Wrackmeyer, B.; Bensch, W. *J. Organomet. Chem.* **1986**, *311*, 233.

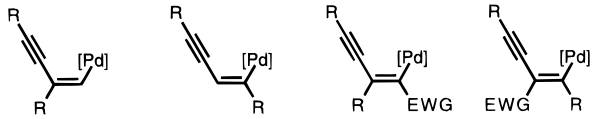
Scheme 4. An Alternative Working Hypothesis



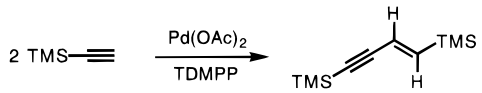
Scheme 5. A Hybrid Mechanistic Rationale



30, both to minimize steric hindrance and to provide the most stable C−Pd bond. The latter presumably dominates in the cross-coupling thereby preferring adduct **31** over **32**. It was not surprising, then, that a preliminary examination of the self-coupling of (trimethylsilyl)acetylene gave the reverse regioselectivity from normal (eq 9), since the trimethylsilyl group is



expected to stabilize the adjacent C−Pd bond in the carbametalation step.



(9)

Synthetically, this reaction appears to hold much promise. The ease of operation and the excellent yields under mild

(28) The details of the activation of the C−H bond of the terminal alkyne remain to be established. The possibility of a series of equilibria as shown in the following equation is also quite reasonable:

$$LPd(OAc)_2 \rightleftharpoons [LPdOAc]^+ {}^-OAc \rightleftharpoons [LPd(\eta^2\text{—}CH{\equiv}CR)OAc]^+ {}^-OAc \rightleftharpoons \mathbf{22} + HOAc$$

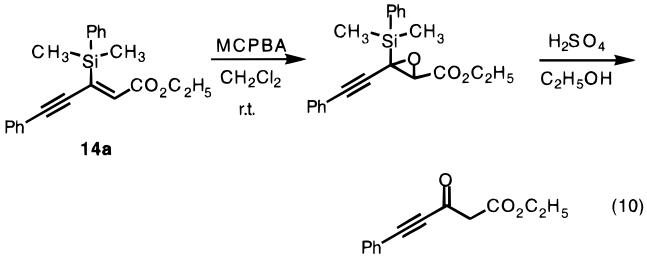
We thank one of the referees for drawing attention to this additional possibility. While this represents one of several possibilities that we have considered, the lack of any experimental data led us not to include details regarding this step in Scheme 5.

Table 5. Experimental Details for Homocoupling

entry	starting alkyne, mg (mmol)	$Pd(OAc)_2$, mg (μmol)	TDMPP, mg (μmol)	PhH, mL	time, h	product, mg, yield (%), R_f (solvent)
1	46.4 (0.42)	1.9 (8.4)	3.7 (8.4)	1.0	64	29.4, 63, 0.44 (hexane)
2	53.8 (0.53)	2.4 (10)	4.7 (10)	1.0	0.67	33.6, 63, 0.18 (hexane)
3	56.1 (0.33)	1.5 (6.6)	3.0 (6.6)	1.0	19	45.5, 81, 0.09 (40% ether/hexane)
4	54.9 (0.65)	2.9 (13)	5.8 (13)	0.65	24	35.3, 64, 0.24 (80% ether/hexane)
5	38.3 (0.16)	1.7 (7.9)	3.5 (7.9)	0.5	0.67	27.2, 71, 0.15 (10% ether/hexane)
6	39 (0.15)	6.3 (7.6)[a]		0.5	43	25.2, 65, 0.06 (10% ether/hexane)
7	41.8 (0.17)	1.9 (8.3)	3.7 (8.3)	0.5	40.75	37.4, 90, 0.67 (10% ether/hexane)
8	16.1 (0.05)	2.2 (2.6)[a]		0.5	16	13.4, 83, N.D.[b] (30% ether/hexane)

[a] Catalyst is preformed bis(tri-*o*-tolylphosphine)palladium acetate. [b] N.D. = not determined.

conditions attest to its practicality. The extraordinary chemoselectivity and excellent regio- and diastereoselectivity enhance its value in organic synthesis. The fact that these reactions constitute simple additions using 1:1 ratio of reactants and anything else being required only catalytically makes them closely approach the ideal in synthetic efficiency. The products are also quite versatile from the point of view of their functionality, since either the double or triple bonds can be selectively manipulated. For example, the adduct of one of the terminal alkynes with ethyl 3-(dimethylphenylsilyl)propynoate undergoes selective epoxidation of the double bond with *m*-chloroperbenzoic acid (MCPBA, eq 10) in 63% yield. Solvolysis of the silyl epoxide effects elimination to produce the β-keto ester in 68% yield. The utility of this reaction for natural products synthesis will be the subject of future investigations.



(10)

Experimental Section

All reactions were performed in a flame-dried flask or test tube under nitrogen as an inert atmosphere. Solvents were distilled prior to use and transferred with syringe to the reaction vessel. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or 300, an XL-400, or a Brucker 270 spectrometer, at the indicated frequencies. IR spectra were recorded either neat or as a film on sodium chloride plates or as potassium bromide pellets. Combustion analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Mass spectra were provided by the UCSF Mass Spectronomy facility employing a Kratos MS-9 instrument with an ionization current of 98 mA and ionizing voltage of 70 eV. For thin layer chromatograhy, Merck precoated glass plates were used and detection was carried out by either a UV lamp, $KMnO_4$ solution, vanillin/sulfuric acid, or ammonium molybdate/ceric sulfate in sulfuric acid. Flash chromatography employed E. Merck silica gel, Kieselgel 60, 230−400 mesh.

Homocoupling. (A) General Procedure. A solution of the alkyne in benzene (1 M) was added to a solution of 2 mol % of palladium acetate and 2 mol % of TDMPP in an equal volume of benzene at room temperature. Stirring was continued until the starting material disappeared as determined by TLC or ^1H NMR spectroscopy (benzene-d_6 employed in such cases). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography to give the product. In some cases, the reaction was directly chromatographed to give the pure product. Table 5 summarizes the results for each of the specific cases.

(B) Specific Example. A solution of dimethyl propargylmalonate (56.1 mg, 0.33 mmol) in 0.5 mL of benzene-d_6 was added to a solution of palladium acetate (1.5 mg, 6.6 μmol, 2 mol %) and TDMPP (3 mg, 6.6 μmol, 2 mol %) in 0.5 mL of benzene-d_6. ^1H NMR spectroscopy revealed reaction was complete after 19 h. Direct chromatography (50% ether−pentane) gave 45.5 mg (81% yield) of 1,1,7,7-tetrakis(carbomethoxy)-5-methylenehept-3-yne (**5c**).

(C) Characterization Data for Homocoupled Products. 4a: IR (neat) 2235, 1605, 1580, 1505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 4H), 6.83 (d, J = 8.5 Hz, 4H), 5.55 (s, 1H), 5.45 (s, 1H), 5.06 (t, J = 7.1 Hz, 2H), 4.70 (d, J = 11.3 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.23 (d, J = 11.3 Hz, 1H), 4.18 (t, J = 6.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (t, J = 7.0 Hz, 1H), 2.13 (q, J = 7.3 Hz, 2H), 2.03 (q, J = 7.4 Hz, 2H), 1.83−1.68 (m, 4H), 1.65 (s, 6H), 1.57 (s, 6H); HRMS calcd for $C_{34}H_{44}O_4$ 516.3239, found 516.3204.

4b: IR (neat) 1608, 1580, 1500 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (d, J = 8.3 Hz, 4H), 6.82 (d, J = 8.3 Hz, 4H), 5.53 (d, J = 1.7 Hz, 1H), 5.43 (d, J = 1.7 Hz, 1H), 5.40−5.34 (m, 4H), 4.68 (d, J = 11.3 Hz, 1H), 4.40 (d, J = 11.3 Hz, 1H), 4.52 (d, J = 11.3 Hz, 1H), 4.21 (d, J = 11.3 Hz, 1H), 4.16 (t, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.75 (t, J = 7.3 Hz, 1H), 2.14−2.00 (m, 4H), 1.83−1.68 (m, 4H), 1.59 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 159.2, 132.2, 130.7, 130.2, 129.6 (3C), 129.4 (3C), 125.5, 125.2, 122.4, 113.8 (4C), 89.9, 83.9, 80.8, 70.1, 70.0, 68.2, 55.3 (2C), 35.6, 34.6, 28.5, 28.4, 17.8 (2C). Anal. Calcd for $C_{32}H_{40}O_4$: C, 78.65; H, 8.25 (MW 488.2926). Found: C, 78.66; H, 8.30 (MW 488.2950).

5a: IR (neat) 2210, 1605, 1455, 885 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.18 (d, J = 2.1 Hz, 1H), 5.10 (d, J = 2.1 Hz, 1H), 2.28 (t, J = 6.9 Hz, 2H), 2.09 (t, J = 7.4 Hz, 2H), 1.6−1.2 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H); HRMS calcd for $C_{16}H_{28}$ 220.2191, found 220.2190.

5b: IR (neat) 2190, 1595, 1570, 1485, 1440, 1330 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.74−7.69 (m, 2H), 7.53−7.50 (m, 2H), 7.41−7.31 (m, 6H), 5.98 (d, J = 1.0 Hz, 1H), 5.75 (d, J = 1.0 Hz, 1H) HRMS calcd for $C_{16}H_{12}$ 204.0939, found 204.0938.

5c: IR (neat) 2220, 1730, 1615, 1433, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.28 (bs, 1H), 5.25 (d, J = 1.2 Hz, 1H), 3.76 (s, 6H), 3.71 (s, 6H), 3.70 (t, J = 7.7 Hz, 1H), 3.59 (t, J = 7.7 Hz, 1H), 2.88 (d, J = 7.4 Hz, 2H), 2.68 (d, J = 7.5 Hz, 2H). Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92 (MW 340.1158). Found: C, 56.58; H, 5.94 (MW 340.1159).

5d: Mp 77−8 °C IR (neat) 3570, 3400 (br), 1600, 1455, 1375, 1360 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.47 (s, 1H), 5.32 (s, 1H), 2.95 (bs, 1H), 2.29 (bs, 1H), 1.52 (s, 6H), 1.38 (s, 6H); HRMS calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1145.

5e: IR (neat) 2205, 1670, 1605 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.19 (s, 1H), 5.11−5.05 (m, 3H), 4.45 (dt, J = 8.1, 5.3 Hz, 1H), 4.30 (q, J = 7.2 Hz, 1H), 2.34−2.25 (m, 2H), 2.16−2.08 (m, 2H), 1.76−1.47 (m, 4H), 1.67 (s, 6H), 1.62 (d, J = 1.0 Hz, 3H), 1.60 (d, J = 1.3 Hz, 3H), 0.86 (s, 18H), 0.025 (s, 3H), 0.005 (s, 3H), −0.008 (s, 3H), −0.02 (s, 3H); HRMS calcd for $C_{26}H_{47}O_2Si_2$ ($M^+ - C_4H_9$) 447.3114. found 447.3092. Anal. Calcd for $C_{30}H_{56}O_2Si_2$: C, 71.36; H, 11.18. Found: C, 71.41; H, 11.27.

5f: IR (neat) 1710, 1650, 1260 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.78−6.71 (m, 2H), 5.48 (d, J = 1.6 Hz, 1H), 5.40 (bs, 1H), 4.49 (t, J = 6.1 Hz, 1H), 4.162 (q, J = 7.1 Hz, 2H), 4.157 (q, J = 7.1 Hz, 2H), 4.16−4.15 (m, 1H), 2.31 (q, J = 7.4 Hz, 2H), 2.16 (q, J = 7.5 Hz, 2H), 1.82 (s, 3H), 1.79 (s, 3H), 1.8−1.7 (m, 4H), 1.27 (t, J = 7.1

Table 6. Experimental Details for Cross-Couplings

entry	donor alkyne mg, mmol	acceptor alkyne mg, mmol	$Pd(OAc)_2$ (mg, μmol)	TDMPP (mg, μmol)	PhH (mL)	time (h)	product, mg, yield (%), R_f (solvent)
1	TMS-≡ 2950, 30	$CH_3C{\equiv}CCO_2CH_3$ 3000, 30	210, 900	250, 900	30[a]	1	**6a**, 5700, 95, 0.5 (90:10 hexane/ethyl acetate)
2	Ph-≡	$CH_3C{\equiv}CCO_2CH_3$	2.3, 10	4.6, 10	0.7[b]	0.5	**6b**, 96, 92, 0.39
3	53.4, 0.523	62.4, 0.63					(10% ether in hexane)
	$HOCH_2C{\equiv}CH$ 606, 10.8	$CH_3C{\equiv}CCO_2CH_3$ 12.72, 13.0	49.9, 220	98.7, 220	10	7	**6c**, 99, 87, 0.28 (70% ether in hexane)
4	$(CH_3O_2C)_2CHCH_2C{\equiv}CH$ 61.3, 0.40	$CH_3C{\equiv}CCO_2CH_3$ 54, 0.48	1.8, 8	3.6, 8	0.7[b]	15.5	**6d**, 99, 87, 0.28 (40% ether in hexane)
5	$PhSO_2CH_2C{\equiv}CH$ 43, 0.24	$CH_3C{\equiv}CCO_2CH_3$ 28, 0.29	1.1, 5	2.2, 5	0.2[b]	25	**6e**, 7.5, 11, 0.13 (40% ether in hexane)
6	$OHC(CH_2)_3C{\equiv}CH$ 1290, 13.4	$CH_3C{\equiv}CCO_2CH_3$ 1580, 16.1	60, 267	120, 272	50	18	**6f**, 2200, 84, N.D.[c] (15% ether in hexane)
7	$(PhSO_2)_2CH(CH_2)_3C{\equiv}CH$ 108.6, 0.3	$CH_3C{\equiv}CCO_2CH_3$ 29.4, 0.3	1.3, 6	2.7, 6	0.5	18	**6g**, 125, 90, N.D.[c] (15% ether in hexane)
8	$PhC{\equiv}CH$ 102.1, 1.0	$CH_3C{\equiv}CSO_2Ph$ 180.2, 1.0	4.5, 20	8.9, 20	4	3	**7a**, 252, 89, N.D.[c] (15:85 ethyl acetate/hexane)
9	n-$C_4H_9C{\equiv}CH$ 82.2, 1.0	$CH_3C{\equiv}CCO_2Ph$ 180.2, 1.0	4.5, 20	8.9, 20	4	24	**7b**, 242, 92, N.D.[c] (20:80 ethyl acetate/hexane)
10	$TBDMSOCH_2C{\equiv}CH$ 170, 1.0	$CH_3C{\equiv}CCO_2Ph$ 180.2, 1.0	4.5, 20	8.9, 20	4	16	**7c**, 236, 68, N.D.[c] (25:75 ethyl acetate/hexane)
11	$PhC{\equiv}CH$ 51.1, 0.5	$CH_3C{\equiv}CCOCH_3$ 72.2, 0.5	2.2, 10	4.5, 10	2	24	**8a**, 88.9, 72, N.D.[c] (25:75 ethyl acetate/hexane)
12	$PhC{\equiv}CH$ 102.2, 1.0	n-$C_6H_{13}C{\equiv}CCOCH_3$ 76.3, 0.5	2.2, 10	4.5, 10	2	18	**8b**, 105.3, 83, N.D.[c] (10:90 ethyl acetate/hexane)
13	$HOCH_2C{\equiv}CH$ 28.0, 0.5	$CH_3C{\equiv}CSO_2Ph$ 90.1, 0.5	2.2, 10	4.5, 10	10	5	**11**, 104.3, 88, N.D.[c] (15:85 ethyl acetate/hexane)
14	$HOCH_2C{\equiv}CH$ 28.0, 0.5	$CH_3C{\equiv}CSO_2Ph$ 180.2, 1.0	2.2, 10	4.5, 10	1	16	**11**, 48.3, 40; 12, 122.6, 59 (25:75 ethyl acetate/hexane)
15	$PhC{\equiv}CH$ 51.1, 0.5	$CH_3C{\equiv}CSO_2Ph$ 180.2, 1.0	2.2, 10	4.5, 10	0.5	24	**7a**, 29.0, 21; 13, 137.0, 59 (20:80 ethyl acetate/hexane)
16	$PhC{\equiv}CH$ 51.1, 0.5	$DMPSC{\equiv}CCO_2C_2H_5$[e] 116.2, 0.50	3.4, 15	6.9, 15	0.5	20[d]	**14a**, 138.2, 83 (5:95 ethyl acetate/hexane)
17	$(CH_3O_2C)_2CHCH_2C{\equiv}CH$ 85.1, 0.5	$DMPSC{\equiv}CCO_2C_2H_5$ 116.2, 0.50	3.4, 15	6.9, 15	10	48	**14b**, 132.6, 66 (5:95 ethyl acetate/hexane)
18	$OHC(CH_2)_3C{\equiv}CH$ 48.2, 0.5	$DMPSC{\equiv}CCO_2C_2H_5$[e] 116.2, 0.50	2.2, 10	4.5, 10	2	16	**14c**, 119.3, 73 (5:95 ethyl acetate/hexane)
19	$AcOCH_2CH_2C{\equiv}CH$ 55.7, 0.497	$DMPSC{\equiv}CCO_2C_2H_5$[e] 133, 0.573	11.3, 50	22.3, 50	1	18	**14d**, 82, 48 (10% ether in hexane)

[a] THF employed as solvent instead of PhH. [b] Benzene-d_6 employed as solvent. [c] N.D. = not determined. [d] At 45 °C. [e] DMPS = $(CH_3)_2PhSi$.

Hz, 6H), 0.88 (s, 18H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); HRMS calcd for $C_{30}H_{51}O_6Si_2$ ($M^+ - C_4H_9$) 563.3225, found 563.3222.

Cross-Coupling. (A) General. A 1:1 mixture of palladium acetate (2 mol %) and TDMPP (2 mol %) in benzene (volume to make reaction 0.5−1.0 M in each reactant alkyne) was stirred 5−15 min at which point the acceptor alkyne was added, all at room temperature. After an additional 5 min, the donor alkyne was added at room temperature. After consumption of starting material, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed to give the pure product. In some cases, the reaction mixture was directly chromatographed to give the pure product. The details for each run are summarized in Table 6.

(B) Specific Example. A mixture of palladium acetate (60 mg, 0.27 mmol) and TDMPP (120 mg, 0.27 mmol) in 45 mL of benzene was stirred 15 min at room temperature. A solution of 5-hexynal (1.29 g, 13.4 mol) and methyl 2-butynoate (1.6 mL, 1.6 g, 16 mmol) in 5 mL of benzene was added. After 18 h of stirring at room temperature, the reaction was concentrated *in vacuo* and the residue was purified by flash chromatography (15% ether−hexane) to give 2.2 g (84% yield) of **6f**.

(C) Characterization Data. 6a: IR (neat) 2150, 1715, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06, (s, 1H), 3.67 (s, 3H), 2.14 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 137.8, 124.4, 106.3, 99.3, 51.2, 19.7, 0.3. Anal. Calcd for $C_{10}H_{16}O_2Si$: C, 61.18; H, 8.21. Found: C, 61.45; H, 7.97.

6b: IR (neat) 2200, 1714, 1612, 1485, 1430 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.47−7.43 (m, 2H), 7.34−7.31 (m, 3H), 6.14 (q, J = 1.5 Hz, 1H), 3.71 (s, 3H), 2.38 (d, J = 1.5 Hz, 3H). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04 (MW 200.0837). Found: C, 78.00; H, 5.94 (MW 200.0837).

6c: IR (neat) 3400 (br), 2220, 1710, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.06 (q, J = 1.5 Hz, 1H), 4.43 (s, 2H), 3.72 (s, 3H), 2.29 (d, J = 1.5 Hz, 3H), 2.18 (s, 1H); HRMS calcd for $C_8H_{10}O_3$ 154.0630, found 154.0623.

6d: IR (neat) 2220, 1750, 1735, 1710, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.95 (q, J = 1.2 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.75 (s, 6H), 3.59 (t, J = 7.7 Hz, 1H), 2.92 (d, J = 7.7 Hz, 2H), 2.20 (d, J = 1.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (2C), 165.9, 137.4, 124.1, 90.0, 84.6, 59.9, 52.8 (2C), 50.8, 19.8, 19.5, 14.2. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.70; H, 6.50.

6e: IR (neat) 2208, 1710, 1615, 1440, 1430, 1160, 1130, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.7, 1.0 Hz, 2H), 7.73−7.56 (m, 3H), 5.95 (d, J = 1.5 Hz, 1H), 4.10 (s, 2H), 3.69 (s, 3H), 2.1 (d, J = 1.5 Hz, 3H); HRMS calcd for $C_{14}H_{14}SO_4$ 278.0613, found 278.0611.

6f: IR ($CDCl_3$) 2725, 2210, 1715, 1620, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, J = 1.3 Hz, 1H), 5.97 (q, J = 1.4 Hz, 1H), 3.68 (s, 3H), 2.58 (td, J = 7.1, 1.3 Hz, 2H), 2.41 (t, J = 6.9 Hz, 3H), 2.24 (d, J = 1.4 Hz, 3H), 1.86 (p, J = 7.0 Hz, 2H); HRMS calcd for $C_{11}H_{14}O_3$ ($M^+ - OCH_3$) 194.0932, found 194.0932.

6g: IR (neat) 2210, 1710, 1620, 1450, 1360 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.04−7.87 (m, 4H), 7.76−7.48 (m, 6H), 5.97 (s, 1H), 4.49 (t, J = 5.4 Hz, 1H), 3.72 (s, 3H), 2.41−2.24 (m, 4H), 2.37 (s, 3H), 1.92−1.84 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.1, 139.0, 138.3, 135.3, 130.2, 129.7, 123.9, 94.1, 84.6, 83.7, 51.8, 27.0, 25.6, 20.7, 19.7. Anal. Calcd for $C_{23}H_{24}S_2O_6$: C, 59.98; H, 5.25 (MW 460.1014). Found: C, 59.88; H, 5.09 (MW 460.1022).

7a: IR ($CHCl_3$) 2190, 1585, 1315 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98−7.93 (m, 2H), 7.65−7.33 (m, 8H), 6.63 (q, J = 1.4 Hz, 1H), 2.38 (d, J = 1.4 Hz, 3H); ^{13}C NMR (300 MHz, C_6D_6) δ 142.0, 135.5,

135.2, 133.6, 132.4, 130.2, 129.7, 129.1, 127.8, 122.3, 96.2, 89.9, 19.1. Anal. Calcd for $C_{17}H_{14}SO_2$: C, 72.31; H, 5.00 (MW 282.0715). Found: C, 72.40; H, 4.82 (MW 282.0724).

7b: IR (neat) 2210, 1585, 1300 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04−7.87 (m, 2H), 7.60−7.51 (m, 3H), 6.43 (q, J = 1.4 Hz, 1H), 2.29 (t, J = 6.5 Hz, 2H), 2.22 (d, J = 0.8 Hz, 3H), 1.47−1.23 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 142.2, 137.4, 133.9, 133.2, 129.8, 127.7, 99.1, 81.4, 30.7, 22.4, 19.9, 19.6, 14.0. Anal. Calcd for $C_{15}H_{18}SO_2$: C, 68.67; H, 6.91 (MW 262.1028. Found: C, 68.42; H, 6.77 (MW 262.1030).

7c: IR (neat) 2216, 1589, 1447, 1372, 1322 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.89 (m, 2H), 7.62−7.56 (m, 3H), 6.50 (s, 1H), 4.42 (s, 2H), 2.27 (s, 3H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 141.9, 135.9, 134.3, 134.0, 128.8, 127.8, 85.5, 84.8, 52.3, 26.2, 19.3, 18.7, −4.7. Anal. Calcd for $C_{18}H_{26}SSiO_3$: C, 61.68; H, 7.48. Found: C, 61.58; H, 7.62.

8a: IR (neat) 2197, 1807, 1688, 1598, 1443, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.49 (m, 4H), 7.48−7.43 (m, 4H), 7.42−7.35 (m, 2H), 6.63 (s, 1H), 2.01 (s, 3H); ^{13}C NMR (300 MHz, C_6D_6): δ 197.6, 137.5, 135.4, 135.0, 132.4, 129.6, 129.5, 129.4, 129.0, 128.8, 123.2, 96.1, 91.3, 30.6. Anal. Calcd for $C_{18}H_{14}O$: C, 87.77; H, 5.73 (MW 246.1045). Found: C, 88.00; H, 5.51 (MW 246.1049).

8b: IR (neat) 2193, 1713, 1685, 1597, 1459, 1311, 1176, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2H), 7.37−7.35 (m, 3H), 6.53 (s, 1H), 2.80 (t, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.64−1.60 (m, 2H), 1.38−1.30 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.2, 142.3, 132.5, 131.1, 129.6, 129.1, 123.0, 95.1, 91.5, 32.9, 32.5, 32.2, 29.6, 29.0, 23.2, 14.7; HRMS calcd for $C_{18}H_{22}O$ (M^+) 254.1093, found 254.1087.

11: IR (neat) 3470, 2210, 1580, 1300 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89−7.84 (m, 2H), 7.65−7.49 (m, 3H), 6.50 (s, 1H), 4.36 (s, 2H), 2.23 (d, J = 1.3 Hz, 3H), 2.15 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 141.6, 136.0, 134.4, 134.2, 129.9, 127.8, 95.0, 85.3, 51.6, 19.3. Anal. Calcd for $C_{12}H_{12}SO_3$: C, 61.00; H, 5.12 (MW 236.0507). Found: C, 60.87; H, 5.19 (MW 236.0503).

12: IR (neat) 3517, 2203, 619, 1583, 1447, 1318 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.68−7.65 (m, 3H), 7.64−7.53 (m, 3H), 7.41−7.35 (m, 1H), 5.85 (s, 1H), 4.26 (s, 2H), 2.61 (s, 3H), 2.35 (s, 3H), 2.20 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.4, 146.1, 141.2, 140,0, 134.5, 134.3, 133.9, 132.8, 129.9, 129.8, 128.5, 127.9, 100.8, 84.7, 51.6, 20.2, 19.1. Anal. Calcd for $C_{21}H_{20}S_2O_5$: C, 60.56; H, 4.84. Found: C, 60.60; H, 5.11.

13: IR (neat) 2188, 1770, 1619, 1583, 1478, 1321, 1178, 1085, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.82 (m, 3H), 7.68−7.34 (m, 12H), 5.96 (s, 1H), 2.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.5, 141.7, 140.2, 134.5, 134.0, 133.2, 132.7, 130.4, 130.2, 129.8, 129.7, 129.2, 128.6, 128.0, 121.9, 101.9, 88.6, 20.7, 19.3; HRMS calcd for $C_{20}H_{17}SO_3$ (M^+ − PhSO) 337.0898, found: 337.0907.

14a: IR (neat) 2207, 1724, 1559, 1443, 1328 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.52−7.50 (m, 2H), 7.40−7.34 (m, 6H), 7.09 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 0.52 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.2, 154.1, 139.5, 134.2, 132.3, 131.4, 129.5, 129.2, 128.4, 123.4, 92.0, 88.2, 62.2, 14.6, −1.3. Anal. Calcd for $C_{21}H_{22}SiO_2$: C, 75.41; H, 6.63 (MW 334.1358). Found: C, 75.34; H, 6.68 (MW 334.1397).

14b: IR (neat) 2260, 2240, 1740, 1440, 1340, 1320 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.35−7.27 (m, 3H), 6.88 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.78 (s, 6H), 3.65 (t, J = 7.8 Hz, 1H), 2.97 (d, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.43 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.8, 165.2, 154.0, 139.4, 134.1, 131.2, 129.4, 128.3, 88.2, 81.3, 62.0, 53.4, 51.5, 20.1, 14.5, −1.3. Anal. Calcd for $C_{21}H_{26}O_6Si$: C, 62.66; H, 6.51 (MW 402.1499). Found: C, 62.47; H, 6.31 (MW 402.1487).

14c: IR (neat) 1722, 1606, 1446, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.55−7.52 (m, 2H), 7.35−7.33 (m, 3H), 6.88 (s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 1.89 (t, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.45 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.3, 165.7, 152.9, 139.5, 134.1, 133.6, 129.4, 128.3, 92.0, 80.7, 62.0, 43.2, 21.5, 19.4, −1.3; HRMS calcd for $C_{19}H_{24}SiO_3$ (M^+) 328.1372, found 328.1355.

14d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.34−7.30 (m, 3H), 6.90 (s, 1H), 4.18 (t, J = 7.0 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.05 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 0.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.7, 153.1, 138.8, 133.5, 130.8, 128.8, 127.7, 87.9, 80.3, 62.1, 61.5, 20.8, 19.9, 13.9, −1.9; HRMS calcd for $C_{19}H_{24}O_4S$ 344.1444, found 344.1449.

Preparation of 16a. Following the general protocol for cross-coupling, terminal alkyne **15** (1.0 g, 6.0 mmol), 3-pentyn-5-one (0.5 g, 6.0 mmol), palladium acetate (42.8 mg, 0.19 mmol), TDMPP (53.1 mg, 0.19 mmol) in 3.2 mL of THF gave, after 5 d at room temperature (rt) and flash chromatography [60:40 hexane−ether, R_f 0.36 (minor), 0.47 (major)], 1.2 g (80% yield) of **16a**. For **16a**: IR (neat) 3600−3200, 2206, 1677, 1586, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.10−1.79 (m, 2H), 1.74−1.14 (m, 6H), 1.15−1.02 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 136.0, 130.5, 95.1, 89.7, 79.0, 39.2, 38.1, 37.1, 32.8, 31.8, 26.9, 21.1, 20.4, 19.8, 16.5. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.50; H, 9.84.

Preparation of 16b. Following the general protocol for cross-coupling, terminal alkyne **15** (700 mg, 4.2 mmol), methyl 2-butynoate (400 mg, 4.2 mmol), palladium acetate (28.2 mg, 0.13 mmol), and TDMPP (34.9 mg, 0.13 mmol) in 2.1 mL of THF gave, after 5 d at room temperature and flash chromatography [60:40 hexane−ether, R_f 0.56 (minor), 0.66 (major)], 1.0 g (88% yield) of **16**. On a 63.2 mmol scale, the reaction yielded 14.4 g of enynoate for an 86% yield. For **16b**, Minor isomer: IR (neat) 3600−3300, 2210, 1720, 1615, 1343 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1H), 3.70 (s, 3H), 2.31 (s, 3H), 2.10 (bs, 1H), 1.95−1.81 (m, 1H), 1.62−1.37 (m, 3H), 1.37−1.13 (m, 3H), 1.10 (s, 3H), 1.00−0.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 137.9, 123.5, 95.0, 89.1, 78.9, 51.2, 39.2, 38.1, 37.0, 32.8, 26.8, 21.1, 20.0, 19.7, 16.5. For **16b**, Major isomer: IR (neat) 3600−3300, 2210, 1720, 1710, 1616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1H), 3.70 (s, 3H), 2.31 (s, 3H), 2.10 (bs, 1H), 1.89 (m, 1H), 1.62−1.39 (m, 4H), 1.38−1.15 (m, 2H), 1.09 (s, 3H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 138.0, 123.5, 96.8, 86.7, 76.4, 51.1, 38.6, 36.1, 33.6, 28.6, 26.3, 23.7, 21.0, 19.9, 17.1. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.60; H, 9.13. Found: C, 72.81; H, 8.96.

Preparation of Methyl 6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-(*E*)-2-penten-4-ynoate (17b). The hydroxyalkynoate **16b** (1.2 g, 4.5 mmol) was added to a solution of phosphorus oxychloride (1.0 g, 6.8 mmol) in pyridine (24 mL) at room temperature. After 15 min of stirring at room temperature and 7 h at reflux, the reaction was cooled to 0 °C and saturated aqueous sodium bicarbonate was added (24 mL). After extraction with ether, the combined organic layers were washed with 10% aqueous hydrochloric acid and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give, after flash chromatography (70:30 hexane−ether, R_f 0.78), 700 mg (64% yield) of dienyne **17b**. For **17b**: IR (neat) 2182, 1717, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 1H), 3.69 (s, 3H), 2.34 (s, 3H), 2.03 (t, J = 6.6 Hz, 2H), 1.87 (s, 3H), 1.64−1.53 (m, 2H), 1.48−1.42 (m, 2H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 144.2, 139.3, 123.6, 121.5, 95.6, 93.9, 51.0, 37.4, 33.8, 32.1, 28.9, 22.7, 20.1, 18.8. Anal. Calcd for $C_{16}H_{22}O_2$: C, 77.90; H, 8.89. Found: C, 78.11; H, 8.73.

Preparation of 5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-(*E*)-2-penten-4-yn-1-ol. To a solution of the unsaturated ester **17b** (61.7 mg, 0.25 mmol) in toluene (0.5 mL) at −78 °C was added DIBAL-H (0.4 mL, 0.62 mmol, 1.5 M in toluene). Reaction was allowed to warm to ambient temperature. Upon completion, the reaction was cooled to 0 °C, and 20% aqueous hydrochloric acid was slowly introduced until the solids were completely dissolved. The mixture was extracted with diethyl ether (2 × 1 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and flash chromatographed (60:40 hexane−ether, R_f 0.33) to yield the desired alcohol (45 mg, 83% yield). On a 10.0 mmol scale, the yield was 1.3 g (63% yield). For title compound: IR (neat) 3600−3200, 2181, 1660, 1615, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (t, J = 6.8 Hz, 1H), 4.24 (d, J = 6.8 Hz, 2H), 2.02 (t, J = 6.1 Hz, 2H), 1.88 (s, 3H), 1.87 (s, 3H), 1.70−1.56 (m, 3H), 1.50−1.44 (m, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 133.2, 123.8, 121.8, 95.3, 87.0, 59.2, 37.6, 33.9, 31.9. 28.8, 22.6, 18.8, 18.7, 17.8; HRMS calcd for $C_{15}H_{22}O$ ($M^{+)}$) 218.1671 found 218.1671.

Preparation of 5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-(*E*)-2-penten-4-yn-al (18). Method A. The Dess−Martin periodinane (400 mg, 0.93 mmol) was added to a solution of the above dienynol

(170 mg, 0.77 mmol) in 1.6 mL of dichloromethane at 0 °C. After 10 min, diethyl ether was added, and the resultant suspension was added to 2 N aqueous sodium hydroxide. The organic layer was washed with additional 2 N aqueous sodium hydroxide and water. After the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, the residue was flash chromatographed (80:20 hexane−ether, R_f 0.50) to give 170 mg (100% yield) of the aldehyde **18**.

Method B. TPAP (112 mg, 0.30 mmol) was added to a mixture of the above dienynol (1.4 g, 6.4 mmol), NMO (1.1g, 94. mmol), and 3 Å MS (3.5 g) in 12 mL of dichloromethane at room temperature. After TLC indicated complete reaction, the mixture was filtered through a short plug of silica gel, concentrated *in vacuo*, and chromatographed as above to give 1.2 g (87% yield) of the same aldehyde: IR (neat) 1737, 1447, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.97 (d, J = 8.0 Hz, 1H), 6.15 (d, J = 8.0 Hz, 1H), 2.30 (s, 3H), 2.03 (t, J = 6.8 Hz, 2H), 1.85 (s, 3H), 1.65−1.50 (m, 2H), 1.50−1.39 (m, 2H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 145.8, 141.7, 132.0, 123.8, 99.5, 95.4, 37.4, 33.8, 32.2, 29.0 (2C), 22.8, 18.7; HRMS calcd for $C_{15}H_{20}$ 216.1515, found 216.1513.

Preparation of Methyl 7,8,11,12-Tetradehydroretinoate (20). (Trimethylsilyl)diazomethane (3.0 mL, 6.0 mmol, 2.0 M in hexanes) was added to a solution of LDA (6.0 mmol) in 40.7 mL of THF at −78 °C. After 30 min of stirring at −78 °C, the aldehyde **18** (1.1 g, 5.0 mmol) was added, and the resultant reaction was kept at −78 °C for an additional 30 min, at which time it was allowed to warm to room temperature. After TLC (hexane, R_f 0.45) indicated completion, the reaction was quenched by addition of water (20 mL). Extraction of the aqueous mixture with diethyl ether (3 × 20 mL) was followed by careful (bath temperature 0 °C) removal of solvent *in vacuo* to give alkyne **18** (780 mg, 72% yield) which was used without further purification: IR (neat) 3311, 2183, 1611, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (s, 1H), 3.35 (s, 1H), 2.10 (s, 3H), 2.03 (t, J = 6.8 Hz, 2H), 1.87 (s, 3H), 1.64−1.52 (m, 2H), 1.50−1.42 (m, 2H), 1.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 134.1, 124.0, 112.2, 94.8, 92.8, 85.3, 81.2, 37.7, 33.9, 32.1, 29.0 (2C), 22.7, 20.6, 18.9.

Following the general protocol, dienediyne **20** (100 mg, 0.47 mmol), methyl 2-butynoate (46.2 mg, 0.47 mmol), palladium acetate (3.2 mg, 14.2 μmol), and TDMPP (3.8 mg, 14.2 μmol) in 0.5 mL of THF gave, after 3 d and flash chromatography (90:10 hexane−ether, R_f 0.33), 77 mg (53% yield) of **20**. On a 3.6 mmol scale, this procedure gave 500 mg (44% yield). For **20**: IR (neat) 2990, 2981, 2865, 2161, 1717, 1611, 1567, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.83 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H), 2.08 (s, 3H), 2.03 (t, J = 6 Hz, 2H), 1.86 (s, 3H), 1.65−1.54 (m, 2H), 1.50−1.43 (m, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 143.0, 138.3, 134.4, 123.9, 122.8, 112.5, 99.8, 95.2, 94.1, 91.8, 51.1, 37.5, 33.9, 32.1, 29.0, 22.8, 20.8, 19.8, 18.8; HRMS calcd for $C_{21}H_{26}O_2$ 310.9334, found 310.9335.

Preparation of Ethyl (*E*)-2,3-Epoxy-3-(dimethylphenylsilyl)-5-phenyl-4-pentynoate. To a solution of silylated enyne **14a** (1.0 g, 3.0 mmol) in 10 mL of methylene chloride was added MCPBA (517.7 mg, 3.0 mmol). After 24 h of stirring at room temperature and 48 h at reflux, concentration *in vacuo* and flash chromatography (5:95 ethyl acetate−hexane) of the residue gave 704.5 mg (67%) of the titled epoxide: IR (neat) 2226, 1751, 1602, 1491, 1307 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.47−7.44 (m, 2H), 7.40−7.38 (m, 3H), 7.32−7.26 (m, 3H), 4.00 (q, J = 7.2 Hz, 2H), 2.98 (s, 1H), 1.23 (t, J = 7.2 Hz), 0.45 (s, 3H), 0.43 (s, 3H); ^{13}C (300 MHz, $CDCl_3$) δ 168.5, 137.2, 135.6, 133.7, 131.3, 130.6, 129.9, 129.6, 123.3, 86.8, 85.2, 63.8, 62.7, 54.5, 15.3, −2.0, −3.3; HRMS: calcd for $C_{21}H_{22}O_2Si$ 350.1338, found 350.1331.

Preparation of Ethyl 3-Oxo-5-phenyl-4-pentynoate. Concentrated sulfuric acid (0.1 mL) was added to a solution of the above epoxide (10.0 mg, 0.029 mmol) in 1 mL of distilled ethanol. After 10 min of heating at 90 °C, potassium carbonate (50 mg) was added. The mixture was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (2:98 ethyl acetate−hexane) to give 4.1 mg (65% yield) of the titled compound: IR (neat) 2203, 1737, 1709, 1671, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54−7.44 (m, 5H), 4.25 (q, J = 7.2 Hz, 2H), 3.71 (s, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 155.7, 134.6, 132.2, 130.2, 121.3, 87.6, 82.3, 63.6, 53.1, 15.5; HRMS calcd for $C_{13}H_{12}O_3$ 216.0936, found 216.0934.

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