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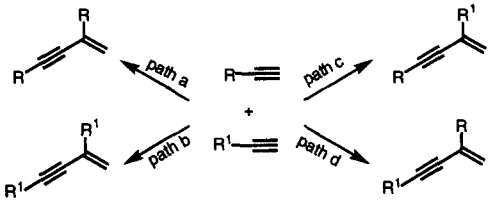
An Unusual Selectivity in Pd Catalyzed Cross-Coupling of Terminal Alkynes with "Unactivated" Alkynes

Barry M. Trost and Matthias C. McIntosh
Department of Chemistry
Stanford University
Stanford, CA 94305-5080

Summary: The previous premise that a conjugating electron withdrawing group is required for the title reaction has been challenged and found to be incorrect. © 1997 Elsevier Science Ltd.

The high affinity of transition metals towards alkynes sets the stage for a myriad of reactions. The challenge involves both the definition of new chemical processes and the exercise of selectivity. In conjunction with our program to develop new addition reactions,[1] we have been examining the palladium catalyzed addition of the C-H bond of a terminal alkyne across the pi unsaturation of another alkyne.[2,3] In considering two different terminal alkynes, the efficiency of the self-coupling reaction (eq. 1, paths a and b) appeared to make it

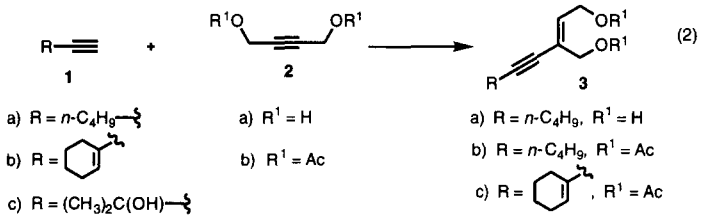


(1)

improbable that the cross-coupling processes (eq. 1, paths c and d) could dominate. As a result, we focused on a cross-coupling reaction in which the acceptor alkyne (i.e., that alkyne partner whose pi system "accepts" the C-H bond) was internal and activated by a conjugating substituent.[4] In this paper, we record our observations on the cross-coupling reaction that establishes that paths c (or d) can be accomplished in a synthetically useful and chemoselective fashion.

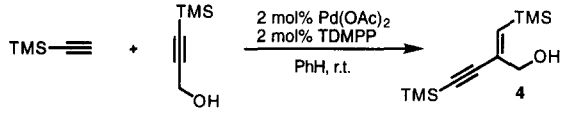
We began our studies with the continued belief that cross-coupling between two different terminal alkynes was not feasible. As a result, we explored the effect of non-conjugating substituents on a disubstituted alkyne acceptor. The efficiency of the self-coupling of propargyl alcohols wherein oligomers beyond the dimer are sometimes seen suggested that the presence of a propargylic oxygen substituent might be a sufficient activator. Thus, the co-dimerization of 1 equiv of 2-butyn-1,4-diol (**2a**) with 2 equiv of 1-hexyne (**1a**) was explored using 2 mol% of palladium acetate and 4 mol% of tris(2,6-dimethoxyphenyl)phosphine (TDMPP) in THF at room temperature (eq. 2). The sensitivity of the product diol **3a** towards cyclization to furans and decomposition during purification on chromatography led us to acylate the adduct *in situ* by simply adding triethyl amine (4 equiv), acetyl chloride (3 equiv), and catalytic 4-dimethylaminopyridine (DMAP) directly to the reaction mixture before work-up. In this way, a 55-62% yield of the adduct **3b**[5] is obtained as a single geometric isomer. The diacetate **2b**, by avoiding product decomposition during reaction, is a more effective acceptor. Co-dimerization of **2b** (1 equiv) 1-ethynylcyclohexene (3 equiv) in benzene for 36 h at room temperature provides **3c**[5] in 88% yield. The sluggishness of the reaction led us to add a second charge of 4 mol% of catalyst after 12 h to the initial 4 mol% to have the reaction go to completion. Thus, a conjugating

substituent is not required in the acceptor alkyne in order to achieve a cross-coupling.



(2)

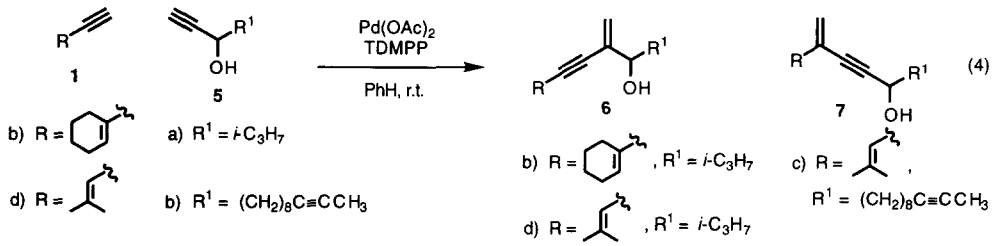
Using silicon as a proton surrogate, the equivalent of cross-coupling of two terminal alkynes was explored as shown in eq. 3. In this case, a ligand to palladium ratio of 1:1 (2 mol% of each) was employed. In



(3)

ancillary studies, varying this ratio from 0.5 to 4.0:1 showed a 1:1 ratio to give good results with some increase in reaction rate by going to 2:1, but no further improvements with additional ligand. For practical purposes wherein minimization of ligand is desirable, a 1:1 ratio was normally employed as in the case here. The cross-coupled product **4**[5] was isolated in 58% yield employing a 5:1 ratio of trimethylsilylacetylene to the propargyl alcohol after 48 h at room temperature. This method should serve as a practical synthesis of stereodefined alkynylvinyl silanes which, themselves, are useful building blocks. Protodesilylation would give the equivalent of the addition of acetylene to propargyl alcohol.

Several observations induced us to explore the cross-coupling of two terminal alkynes. First, the reaction of 3-methyl-1-butyn-3-ol (**1c**) with **2a** led to formation of 2:1 adducts (**1c:2a**) but reaction with **2b** led to a very slow reaction. Second, the reaction of ethynylcyclohexene **1b** led to smooth reaction with both **2a** and **2b**. These results suggested that propargyl alcohols may be good acceptors and vinylalkynes good donors (participate as the C-H "donor").[6] As a result, the reaction of **1b** with propargyl alcohol **5a** was explored (eq. 4). Because of anticipated self-coupling of the vinylalkyne **1b**, a 10:1 ratio of **1** to **5** was employed to screen the



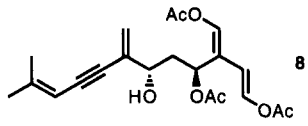
(4)

reaction parameters. The ratio of the two cross-dimerization products **6:7** varied with the ligand (L) to palladium acetate (Pd) ratio increasing from 2.7:1 with a 1:1 L:Pd ratio to 5.3:1 at 2:1 L:Pd and 5.5:1 at 4:1 L:Pd. In this latter case, a 95% yield of this 5.5:1 ratio of cross-dimers **6** (major) and **7** (minor) was obtained. Synthetically, the best protocol employs a syringe pump addition of a solution of a 2:1 ratio of **1b:5a** to 5 mol% of the catalyst (L:Pd 2:1) in benzene at room temperature over 5 h wherein an 81% yield of a 6.7:1 ratio of the cross-dimers **6a** and **7a** was obtained. In this way, only a 2:1 ratio of **1b:5a** was needed to assure complete

conversion of propargyl alcohol.

Switching to the reaction of vinylalkyne **1d** (3 equiv) and propargyl alcohol **5a** (1 equiv) with 2 mol% of a catalyst consisting of a 1:1 L:Pd ratio using syringe pump addition gave a single isomer **6b** in 60% yield with the alternative **7b** not detected. The effect of the propargyl alcohol substituent on the ability of the alkyne to function as an acceptor was examined with diyne **5b** wherein an internal competition between the two types of alkynes exists. Its co-dimerization with vinylalkyne **1d** using the same conditions as for the synthesis of **6b** gave enyne **6c** as the exclusive cross-dimer in 75% yield.

The versatility of these products combined with the increasing number of members of the polyenyne family of natural products, many of which have important biological activity, attaches special significance to the effectiveness of this cross-coupling. For example, the dienyne 7,7-C-didehydro-6-hydroxy-6,7-dihydrocaulerpenyne (**8**) is the most complex and cytotoxic member of a class of highly unsaturated



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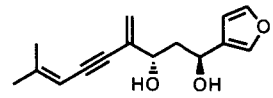
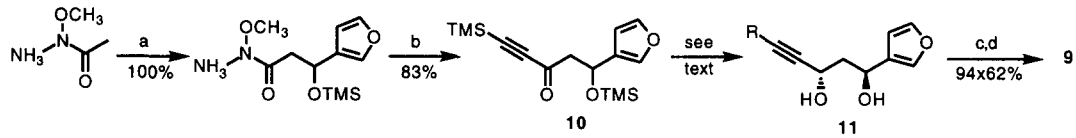


9

sequiterpene constituents isolated from the seaweed *Caulerpa taxifolia*.[7] Its natural abundance is quite low (0.0021% of lyophilyzed weight of seaweed). The dienyne **9** was chosen as a target since it should be a reasonable model for the sensitive dienyne functionality of **8** and also serves as an interesting analogue. Its synthesis is summarized in the Scheme. The reduction of the β-hydroxyketone **10** available via the Weinreb amide[8] with tetramethylammonium triacetoxyborohydride in acetic acid-acetonitrile[9] at -40 °C to room temperature gave a quantitative yield of a 5:1 anti:syn ratio of diols. Considering the stereochemical requirements of the transition state[9] for this reaction suggested increasing the effective steric bulk of the alkyne would increase the diastereoselectivity. The corresponding dicobalt hexacarbonyl complex of **10** formed

Scheme. A Synthesis of Caulerpenyne Analogue

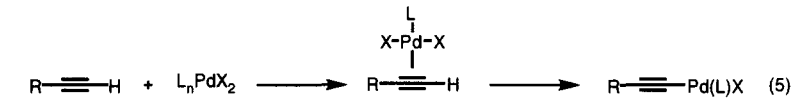


(a) LDA, THF, 3-furaldehyde, TMS-Cl, -78°. (b) TMS-≡-Li, THF, -78°, quench with HOAc. (c) TBAF, CH_3CN, 0°. (d) **1d**, $Pd(OAc)_2$, TDMPP.

smoothly at room temperature in methylene chloride. Reduction as before and oxidative work-up (NMO, CH_2Cl_2, room temperature) gave crystalline diol **11** (R=TMS),[5] mp 87-8 °C, with a >30:1 anti:syn ratio in a 585 overall yield. This protocol should prove to be generally useful for enhanced diastereoselectivity for similar alkynyl ketones.[11] The desilylated alkyne **11** (R=H) undergoes smooth addition under the same conditions as the previous two cross-couplings with enyne **1d** to give the desired product **9**[5] in 62% yield. Again, the alternative cross-coupling product was not detected. The closeness of the ^{13}C NMR signals for comparable carbons in the analogue **9** to the natural product **8** suggest that the ynediene portions of the two are quite similar electronically.

A major question that arises is the source of the chemoselectivity in the cross-coupling of the two terminal alkynes. The ability of 2-butyn-1,4-diol and the propargyl alcohols to serve as good acceptors would

appear to derive from the inductive effect of the alcohol substituents in which only one such substituent is necessary. The fact that the acetate also activates indicates coordination of palladium with the hydroxyl group is not a major factor. As already shown, an electron deficient alkyne is the best acceptor in this reaction.[2,4] On the other hand, the ability of the vinylalkyne to be a better donor is less obvious. A possible explanation derives from consideration of the mechanism of the C-H insertion by palladium where an initial π-complex may provide the kinetic path for the insertion (eq. 5).[3,10] In such a sequence, the ability of the alkyne to be a good ligand to Pd(+2) may affect its participation as a donor. The HOMO-LUMO gap should measure the effectiveness of the alkyne to be a ligand—the smaller the gap, the more effective the alkyne should serve as a



ligand. A MOPAC calculation indicates this gap is 9.6 eV for the conjugated enyne **1d** but 11.0 eV for an unconjuaged isomer, 4-methyl-3-buten-1-yne. This gap for the propargyl alcohol **5a** is 12.3 eV. Indeed, the terminal alkyne having the lowest HOMO-LUMO gap does serve as the best donor. While it may be argued that coordination also plays a role in the carbametallation step as well, that step would have to be less kinetically sensitive to this parameter. While the source of this effect remains to be truly established, the current results clearly indicate this reaction has the potential of much broader scope than previously could be envisioned.

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