



An unusual regioselectivity in the Pd-catalyzed cross coupling of alkynes. A correction

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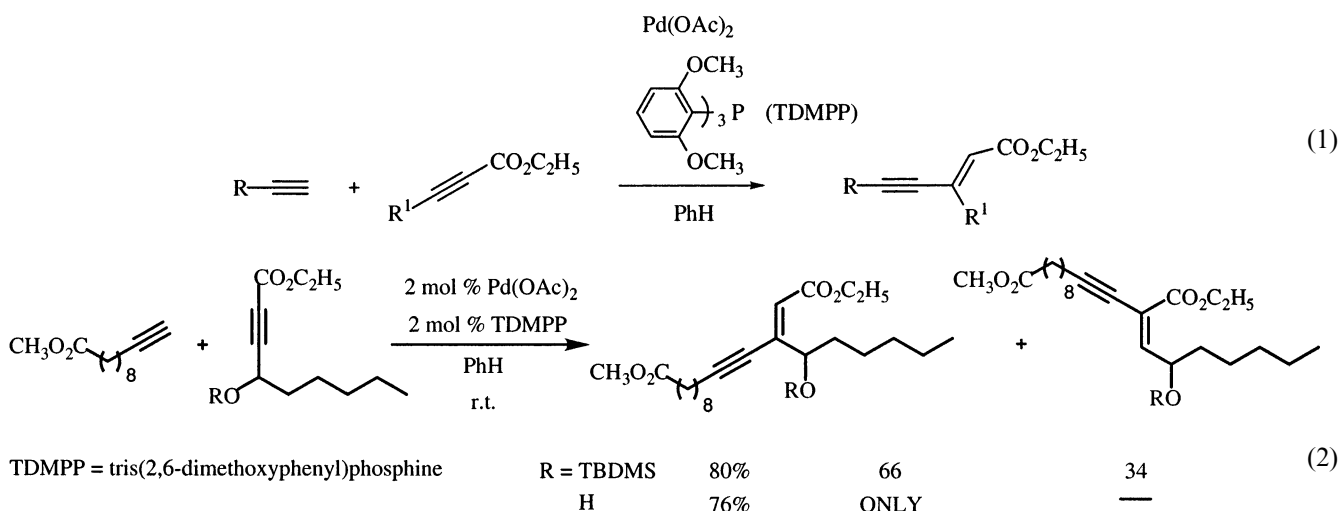
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Abstract—Palladium catalyzed additions of terminal alkynes to alkynoates can lead from preferential to exclusive C–C bond formation at the α -carbon and, in the case of ethyl 3-dimethylphenylsilylpropiolate, complete selectivity for α -attack, an unprecedented regioselectivity that requires revision of the earlier assignment of regioselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

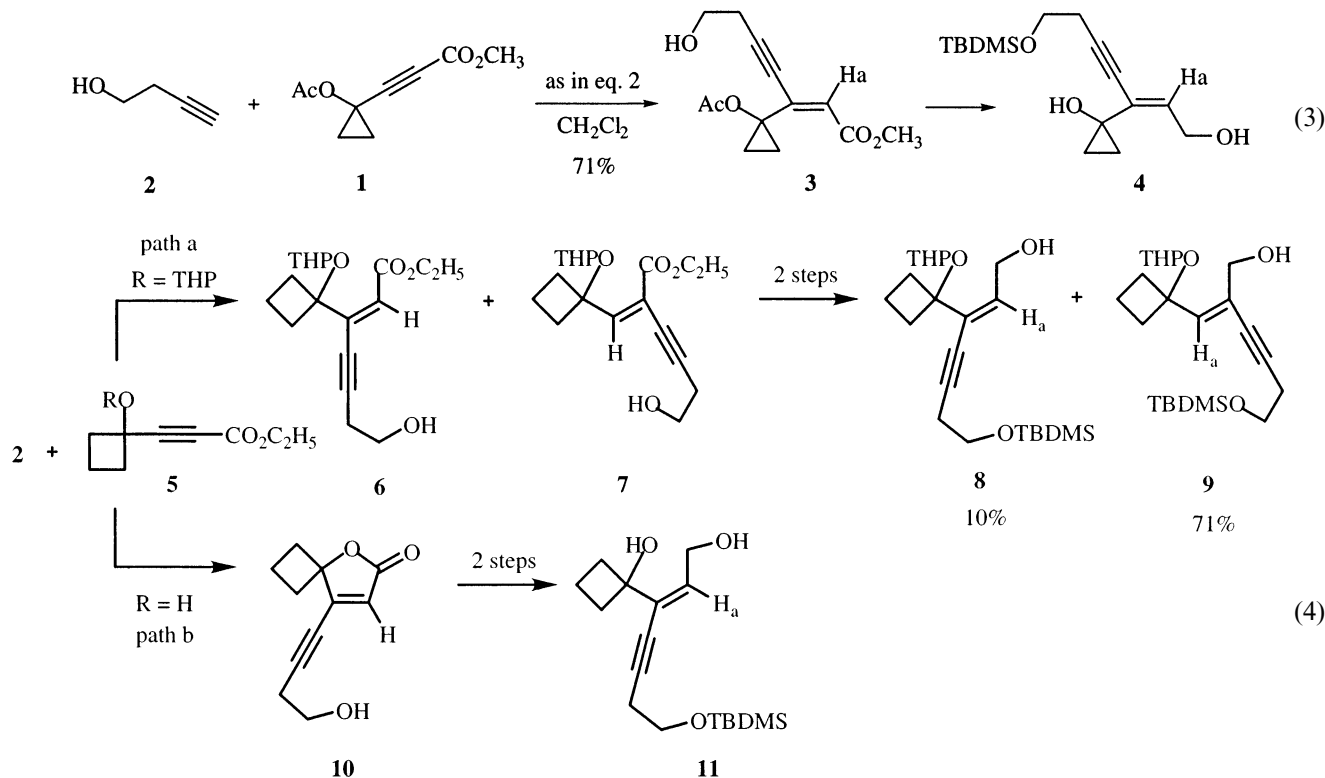
The palladium catalyzed additions of terminal alkynes to internal alkynes activated by an electron-withdrawing group (Eq. (1)) is a very simple, high yielding atom economic way to effect the equivalent of a conjugate addition of a terminal alkyne to an alkynoate or alkynone.^{1–3} The activation afforded by the ester in the disubstituted alkyne acceptor is quite noteworthy since it completely suppresses the homocoupling of the terminal alkyne, itself, a very efficient process in the absence of the alkynoate.^{2,4} This dramatic divergence from homocoupling to cross coupling even employing only 1:1 ratios led us to view the reaction as a conjugate addition-type process which should lead to formation of the ‘conjugate type’ adducts, as depicted in Eq. (1). A clue that this viewpoint was suspect arose in an

observation of the addition of Eq. (2). By using either a PMB or silyl ether derivative of the substrate, significant quantities of the product of α rather than the expected β -attack formed.^{1b} On the other hand, the free alcohol gave only the product of β -C–C bond formation. In conjunction with other projects under way in our laboratories, we have re-examined the factors affecting the regioselectivity of the reaction.

The reaction of equivalent amounts of alkynoate **1** with 3-butyne-1-ol (**2**) under the conditions of Eq. (2), except that methylene chloride was used as solvent, gave the expected adduct **3**⁵ (H_a δ 6.17). Confirmation of this regioselectivity derived after reduction to alcohol **4**, which shows the vinyl proton H_a (δ 6.17) as a triplet



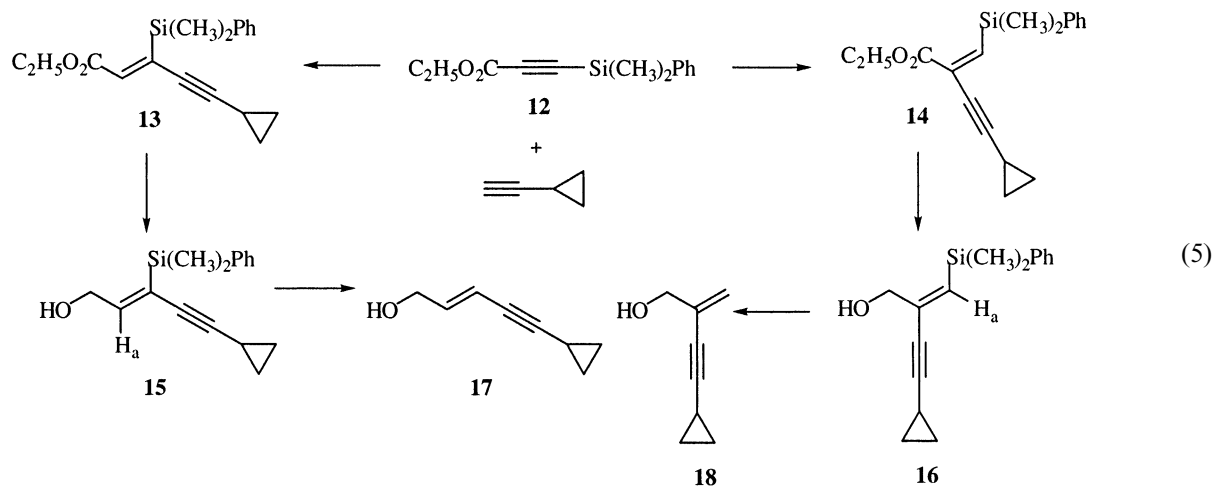
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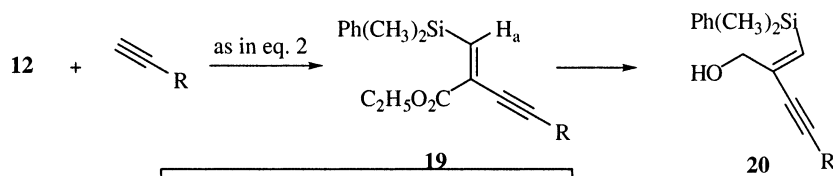




($J=6.6$ Hz). Performing the same reaction with the cyclobutane derivative **5** (Eq. (4), path a) gave a 7:1 ratio of two 1:1 adducts. Reduction of the ester (DIBAL-H) after silylation (TBDMS-Cl, imidazole, DMF) gave the two primary alcohols in **10** and 71% overall yields. The minor adduct showed the vinyl proton H_a (δ 6.17) as a dd ($J=9.0, 6.1$ Hz); whereas the major adduct showed this proton H_a (δ 6.25) as a singlet. Structures **8**⁵ and **9**⁵ corresponding to **6** and **7** for the initial adducts, can therefore be assigned to the minor and major alcohols, respectively. Thus, the major product derived from C–C bond formation to the α -carbon rather than the expected β -carbon. Switching to the free alcohol **5** (R=H) gave a 90% yield of the lactone **10**⁵. That it derives from the ‘expected’ regioselectivity was easily discerned in the reduced product **11**⁵, which exhibited ($J=6.8$ Hz) at δ 6.11 for the vinyl proton H_a .

In conjunction with an effort directed at the total synthesis of callipeltoside, we examined the addition shown in Eq. (5) with the expectation of obtaining **13** in accordance with our earlier reports. Using the same conditions as in Eq. (2), a single adduct was obtained in 93% yield. Reduction led to the primary alcohol in which the vinyl proton appeared as a singlet (δ 6.20). This is consistent with **16**⁵ not **15** and thus, the initial adduct must be **14**⁵ not **13**. This regioselectivity was further confirmed by independent synthesis of **17**⁵ and comparison to the protodesilylated product **18**⁶ (TBAF, 95% yield) obtained from alcohol **16**⁵.

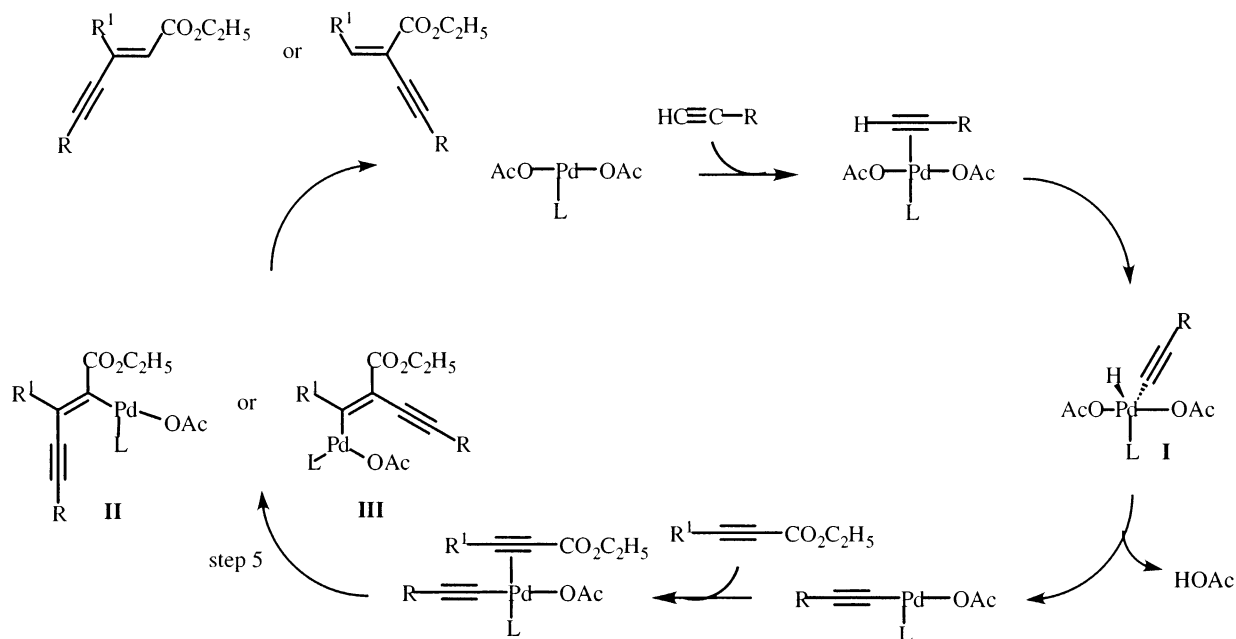
This unprecedented contra-Michael-type regioselectivity was simultaneously exciting and depressing. It was exciting since it corresponds to a new type of regioselectivity not normally accessible by a Michael-type process. It was depressing because we previously recorded^{1a}





R	%	δH_a
Ph	86	7.09
$\text{CH}_2\text{CH}(\text{CO}_2\text{CH}_3)_2$	66	6.88
$(\text{CH}_2)_3\text{CHO}$	73	6.88
$\text{CH}_2\text{CH}_2\text{OAc}$	48	6.90
	99	6.88
	93	6.81

(6)

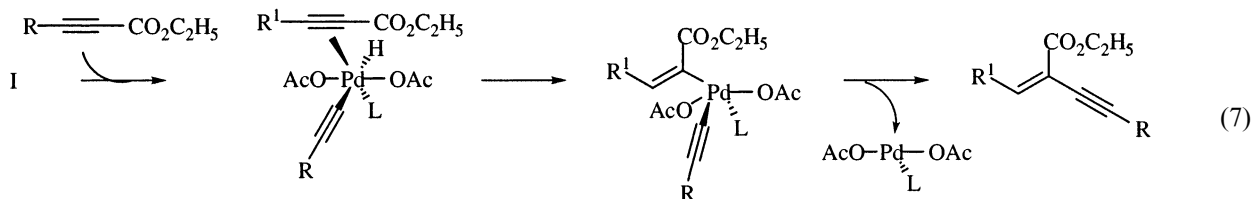


Scheme 1. A mechanistic rationale.

the adducts of the type that would correspond to **13**. Thus, we re-examined our earlier work. Subjecting **19** (R=Ph) and **19** (R=1-cyclohexenyl) to reduction produced the corresponding primary alcohols **20**, which showed the vinyl proton as a singlet. The chemical shift of H_a for the remaining examples agree well for this proton being β to the ester in contrast to when it is α (~δ 6.2). Thus, in all cases of the silylalkynoate **12** only C–C bond formation to the α-carbon is detected (Eq. (6)).

There may be several reasons for this reversal of regioselectivity. Scheme 1 depicts the current working hypothesis. The regioselectivity determining step is the

migratory insertion, step 5. In the absence of any unusual effects, the polarization of the transition state during migration favors placing the metal at the α-carbon, thereby favoring II. However, in the cases where R' of the alkynoate is very sterically bulky, migration of the carbon to the β-carbon of the alkynoate to form II is sterically disfavored over migration to form III. The subtlety that can be seen is exemplified by Eqs. (3) and (4). Simply tying back a ring as in **1** compared to **5** or changing the size of an alcohol by adding a protecting group as in Eq. (4) (path a) versus Eq. (4) (path b) alters the regioselectivity dramatically. Apparently, the tertiary nature of the silyl groups also lead to a similar steric effect.⁷ In this case, the ability of silicon to



stabilize an α -C–Pd bond may also be invoked to reinforce the steric effect and, therefore, account for the completeness of the regioselectivity. However, the α -selectivity of Eq. (4) speaks to the steric effect as the dominant one. An alternative explanation envisions a change in mechanism.⁸ Intermediate I can be envisioned to initiate the reaction by a hydropalladation followed by reductive elimination, as depicted in Eq. (7). While this switch in mechanism cannot be excluded, applying Achim's razor leads us to favor the simplest explanation, as depicted in Scheme 1. In any event, this simple addition allows an unprecedented C–C bond formation at the α -carbon of an alkynoate. A simple illustration of the utility is also demonstrated by the three-step formation of **18** from cheap readily available starting materials.

Acknowledgements

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