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Deferred Carbonylative Esterification in the Pd-Catalyzed Cyclic Carbometalation–Carbonylation Cascade

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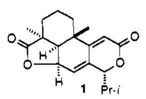
In any cascading carbometalation process, an intricate competition between the propagation and termination steps presents a challenging synthetic problem.[2] On the one hand, the desired cascading propagation steps must take place without premature termination. On the other hand, the termination step is critically important for various purposes, one that pertains to carbopalladation being incorporation of the stoichiometric carbopalladation process into an overall catalytic cycle. We have previously reported examples of cascade termination via the Heck reaction[3,4] involving carbopalladation of an alkene followed by dehydropalladation.[5,6] We have also found that the carbopalladation–cross coupling sequence can be a satisfactory Pd-catalyzed cyclization process provided that the added organometallic reagents for trapping via cross coupling are of sufficiently low relative reactivity.[7,8]

In conjunction with our studies directed toward the development of efficient routes to fused cyclic di- and polyenyl lactones, *e.g.*, nagilactone F (**1**),[9] we sought Pd-catalyzed cyclic carbopalladation–carbonylation cascade that would be applicable to their syntheses. We now report that the catalytic cyclic carbopalladation of alkynes can proceed under the conditions for carbonylation of organopalladiums without premature incorporation of CO and that *in situ* regeneration of a Pd–phosphine catalyst can be accomplished by termination of the carbopalladation cascade via deferred carbonylative esterification, as exemplified by the conversion of **2** to **3**[10] (eq 1) and related conversion of **4–6** to **7–9**[10] in 80, 72, and 73% yields, respectively. In view of a multitude of possible reaction paths that are available to **2** (*vide infra*), its conversion to **3** in 66% yield via one-step pentacyclization[11] is quite remarkable even compared with our recently reported tetracyclization process,[5c] where the number of available paths was much more limited due to the absence of CO, and the results presented herein reveal some striking features and puzzles in the reactions where carbopalladation and carbonylation compete with each other.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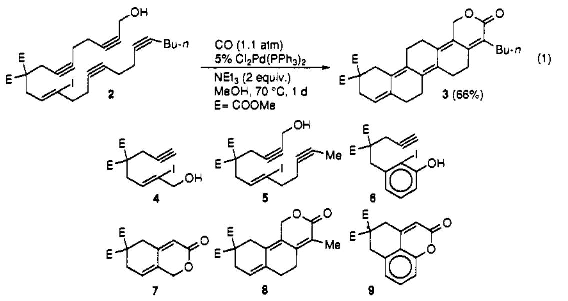
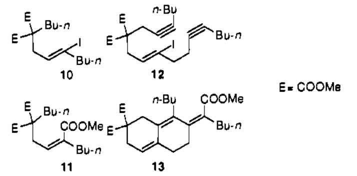
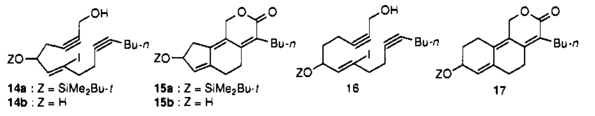


First, the cascade cyclic carbopalladation producing six-membered rings can indeed proceed in good yields despite the fact that carbonylative esterification takes place in the absence of strategically positioned alkyne groups, as exemplifed by the conversion of **10** to **11** in 94% yield. Surprisingly, methanol has proved to be a highly satisfactory solvent which is, in fact, superior to several others employed in this and related previous studies, such as DMF, THF, MeCN, and benzene. The extent of premature esterification in the reaction shown in eq 1 was estimated to be ≤2–3% by NMR analysis of the crude product. In accord with these findings, cascade termination can be satisfactorily effected even with external alcohols, *e.g.*, MeOH, as indicated by the conversion of **12** to **13**[10] in 86% yield in MeOH (100 equiv).[12]



Second, the formation of cyclic ketones via acylpalladation, *i.e.*, addition of acylpalladium bonds to alkenes and alkynes, does not seriously compete with the desired cascade process, even though acylpalladation has been the dominant path in the Pd-catalyzed reaction of iodoalkenes and iodoarenes containing an ω-alkenyl group in the presence of CO in cases where five- or six-membered ketones can be formed.[13] Even in a competition between carbopalladation leading to cyclopentenes and acylpalladation giving five- and/or six-membered ketones, the carbopalladation process is strongly favored, as indicated by the conversion of **14a** into **15a**[10] in 71% yield under essentially the same conditions as in eq 1. This and the closely related transformation of **16** into **17**[10] in 62% yield indicate that the presence of two germinal ester groups in **2**, **4–6**, and **10** is not



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(1) (a) Uehara Memorial Foundation fellow (1992–93). (b) Purdue Research Foundation Graduate Research Fellow (1993–94). (c) National Institutes of Health Postdoctoral Fellow (GM 14176) (1991–92).

(2) For a recent review, see: Negishi, E. *Pure Appl. Chem.* **1992,** *64,* 323.

(3) A tandem sequence of addition of a C—Pd bond to a C=C bond followed by β-dehydropalladation leading to a net substitution of H with a carbon group is referred to as the Heck reaction.

(4) For reviews, see: (a) Heck, R. F. *Org. React.* **1982,** *27,* 345. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985.

(5) (a) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989,** *111,* 3454. (b) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989,** *54,* 2507. (c) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990,** *112,* 8590.

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(8) For related studies reporting similar conversions in modest yields, see: (a) Burns, B.; Grigg, R.; Ratanamukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1988,** *29,* 5565; **1989,** *30,* 1135. (b) Wang, R. T.; Chou, F. L.; Luo, F. T. *J. Org. Chem.* **1990,** *55,* 4846.

(9) Hayashi, Y.; Matsumoto, T.; Nishizawa, M.; Togami, M.; Hyono, T.; Nishikawa, N.; Uemura, M.; Sakan, T. *J. Org. Chem.* **1982,** *47,* 3428.

(10) All isolated cyclization products have been identified by the usual spectroscopic and analytical means.

(11) For some other one-step pentacyclization reactions published recently, see: Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993,** *34,* 7849. See also ref 6d.

(12) (a) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993,** *34,* 7471. (b) After we submitted of this paper, the following paper came to our attention: Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994,** *35,* 4429.

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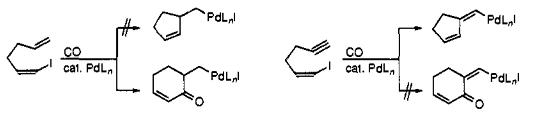
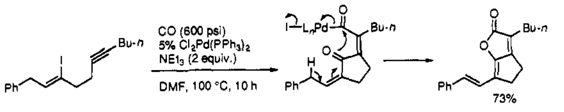
Scheme 1

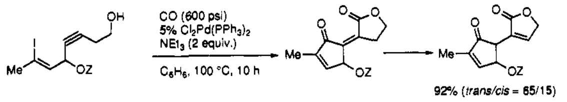


essential to the desired cascade process. We tentatively conclude that, in the competition between cyclic carbopalladation and cyclic acylpalladation of alkynes, the former process producing a five- or six-membered ring is strongly favored over the latter giving a five-, six-, and/or seven-membered ketone. This conclusion is in sharp contrast with the corresponding alkene reaction,[13] as indicated in Scheme 1.

Third, despite the above results, the acylpalladation of alkynes is not an intrinsically disfavored process, as indicated by our recent results[14] on intermolecular reactions of this type. Furthermore, cyclic acylpalladation giving five-membered ketones is indeed faster than carbopalladation giving four-membered rings, as shown by eqs 2 and 3. We have recently demonstrated that



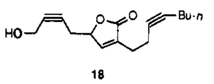
(2)



(3)

trapping of acylpalladiums with enolates as in eq 2 is a viable method of recycling Pd species as catalysts.[15] In eq 3, the exocyclic double bond in the presumed initial product must migrate to alleviate electron repulsion between the two carbonyl groups.

Fourth, since the reaction of PhI with even 1 atm of CO in the presence of 5 mol % of $Cl_2Ph(PPh_3)_2$, 1-octyne (1 equiv), and MeOH (4 equiv) merely gives methyl benzoate in 73% yield without a sign of carbopalladation or acylpalladation, CO insertion is considerably faster than intermolecular carbopalladation. The results also indicate that trapping of acylpalladium species with MeOH (4 equiv) is decidedly faster than intermolecular acylpalladation. On the other hand, the relative rates of CO insertion and intramolecular carbopalladation of alkynes depend on the CO pressure and the ring size of cyclic carbopalladation. Thus, treatment of **14b** with CO (1 atm), NEt_3 (4 equiv), and 5 mol % of $Cl_2Pd(PPh_3)_2$ in MeOH (100 equiv) gave **15b** in 59% yield along with a 19% yield of a premature esterification product **18**.[10] These results indicate that cyclic carbopalladation producing five-membered rings can be faster than CO insertion–lactonization at low pressures of CO and that the butenolide formation via intramolecular alcoholysis of acylpalladium derivatives is at least 10^3 times as fast as methanolysis. At the CO pressure of 20 atm, however, the only monomeric cyclic product was **18** (46% yield), indicating that CO insertion at high CO pressures can be substantially faster than cyclic carbopalladation producing cyclopentenes.



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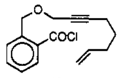

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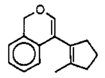

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Fifth, despite the fact that CO insertion is kinetically competitive with and can even be faster than cyclic carbopalladation, the latter process can still be dominant in the absence of a strategically positioned trapping group, *e.g.*, OH, as exemplified by the conversion of **6** into **9** in 73% yield at 10 atm of CO. These results are readily explained in terms of ready reversibility of CO insertion. In accord with this interpretation, treatment of **19** with NEt_3 (2 equiv) and 3 mol % of $Pd(PPh_3)_4$ at 80 °C for 10 h produced **20**[10] in 65% yield. Here again, the formation of the expected exocyclic, tetrasubstituted alkene is avoided via double bond migration.

In conclusion, the present study not only provides a synthetically attractive methodology involving cascade carbopalladation–termination via deferred carbonylative esterification but also permits, for the first time, the following generalization providing reliable predictions of the courses of various competing organopalladium reactions. The relative rates of various processes in the decreasing order of rates are CO insertion (and 5- or 6-membered lactonization) $\simeq$ 5-*exo*- or 6-*exo*-alkyne carbopalladation > 5-*exo*-alkyne acylpalladation > acylpalladium trapping with MeOH > intermolecular carbopalladation or acylpalladation.

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Supplementary Material Available: Characterization data for the compounds described herein (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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