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COMMUNICATION

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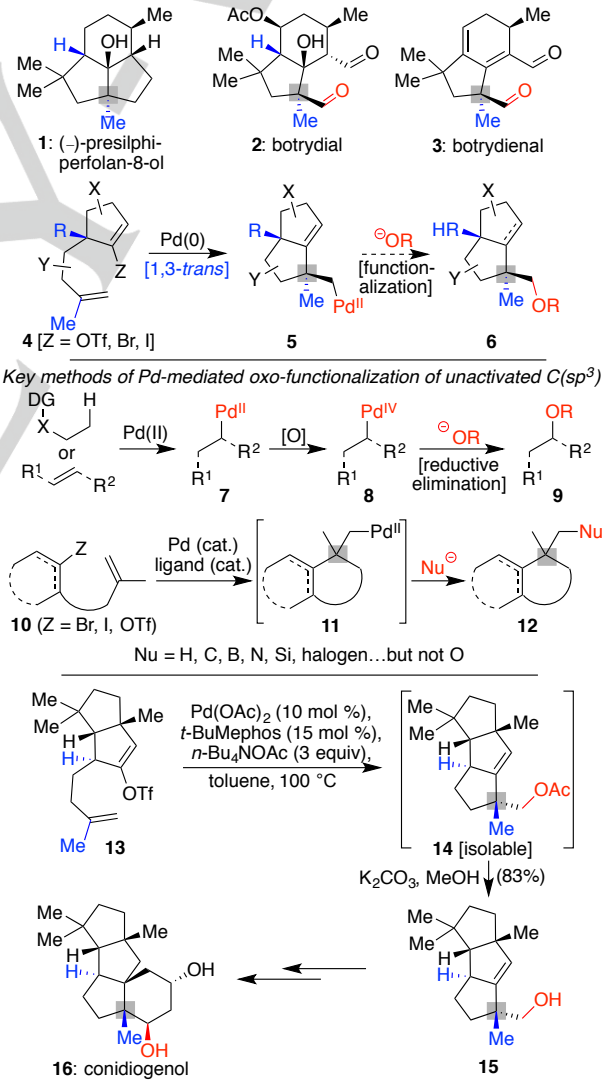
Development and Elucidation of a Pd-based Cyclization/ Oxygenation Sequence for Natural Product Synthesis

Heng Yi,[+] Pengfei Hu,[+] and Scott A. Snyder*[a]

Abstract: Pd-catalyzed sequences involving oxidative addition, cyclization, and termination through intermolecular nucleophile capture have tremendous utlity. Indeed, they can generate a plethora of different polycyclic structures possessing a diverse range of functionality. However, one area of deficiency for Pd(0)/Pd(II) variants is the ability to conclude them with oxygen-based species. Inspired by the recent discovery of one such reaction in the course of a total synthesis program, we delineate herein that it has significant power, both in terms of substrate scope as well as the terminating oxygen nucleophile. As a result, the reaction proved critical in achieving total syntheses of two oxygenated natural products, one of which was prone to over-oxidation. Finally, a mechanistic proposal that accounts for its success is provided.

Among terpene-based natural products, there are a number of triquinanes and related congeners,[1] including (−)-presilphiperfolan-8-ol (**1**),[2] which possess a 1,3-*trans* stereochemical arrangement of substituents at the fusions of their varied ring systems (colored here in blue). Given that structural homology, our group has been interested in developing a cohesive Pd-catalyzed cyclization approach to fashion the diverse targets possessing such patterning. Our previous work on the total synthesis of presilphiperfolan-8-ol (**1**),[3] and other literature precedents,[4] have demonstrated that the desired 1,3-*trans* selectivity could be achieved via a Pd-mediated migratory insertion step (from **4** to **5**). However, further extensions of the process,[5] including an intermolecular oxygen nucleophile terminating functionalization (**5** to **6**), are needed to access molecules such as **2**[6] and **3**[7] that possess an oxygen adjacent to the quaternary center.

While seemingly plausible, reports of C−O bond formation from unactivated C(sp^3)−Pd(II) intermediates are rare. Normally, such processes occur via Pd(IV) intermediates (**7**→**9**),[8] typically requiring the presence of an additional oxidant traditionally incompatible with Pd(0)/Pd(II) catalytic systems. Nevertheless, our hope was that the α-quaternary center in the alkyl-Pd(II) intermediate **5** might enable its interception by an oxygen nucleophile through intermolecular capture by precluding any intramolecular reactions such as β-H elimination; such a strategy has proven successful in promoting other types of challenging reductive eliminations.[5e-n] In fact, we recently achieved one example of such a functionalization as part of a total synthesis of conidiogenol (**16**)[9] and related family members in which **14** was obtained directly from **13** following an initial C–C bond construction via migratory insertion, leading to a similarly situated quaternary center.[10] Herein, we delineate the development and scope of this overall reaction process, one that is capable of affording a range of architectures with a variety of terminating oxygen-based nucleophiles with complete diastereocontrol. Critically, this method also provides general access to the core carbon skeleton of the botrydial family of natural products,[1b] with two members of this class successfully synthesized in a concise fashion. In addition, mechanistic studies provide a sound rationale for the sequence's success.



Scheme 1. Development of a unified approach to varied terpenes of different oxidation states predicated on the development of a unique functionalization of unactivated C(sp^3)–Pd[II] intermediates of type **5**.

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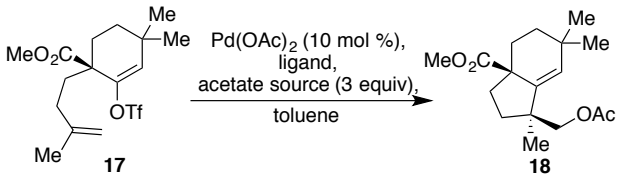
Our investigations commenced using alkenyl triflate **17** as the initial test substrate, searching for competent oxygen nucleophiles and ligands in the presence of catalytic $Pd(OAc)_2$. As shown in Table 1, when Trixiephos[11] was used as the ligand at a 30 mol % loading along with 10 mol % of $Pd(OAc)_2$, only trace product was obtained with NaOAc or KOAc as the oxygen source (entries 1 and 2). By contrast, when the commercially available and highly nucleophilic *n*-Bu_4NOAc[12] was used, **18** was obtained in 61% yield based on NMR analysis (Entry 3). Pleasingly, a decrease in the ligand loading to 15 mol % led to a further increase in yield to 86% (Entry 4); any additional attenuation in loading level resulted in lower conversion, as did efforts to use less than 3.0 equivalents of *n*-Bu_4NOAc. Further ligand screening under these parameters ultimately revealed that *t*-BuMephos[13] afforded the highest yield of **18** (95%, Entry 9). Finally, the reaction temperature could also be lowered to 90 °C with no erosion in material throughput (Entry 10).

Table 1. Condition screening for a Pd-based cyclization/functionalization.[a]

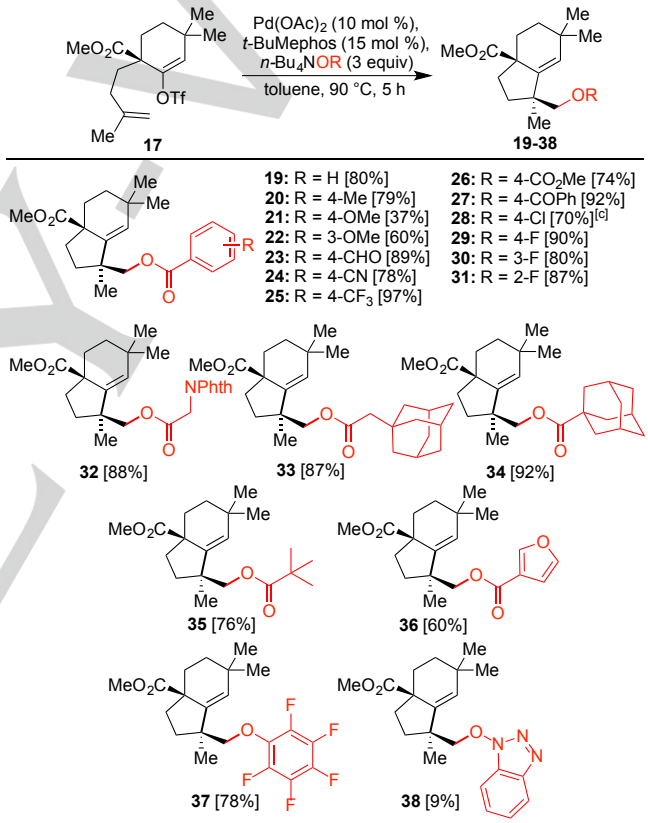


Entry	Ligand (loading)	Acetate source	Yield (%)[b]
1	Trixiephos (30 mol %)	NaOAc	-
2	Trixiephos (30 mol %)	KOAc	4
3	Trixiephos (30 mol %)	*n*-Bu_4OAc	61
4	Trixiephos (15 mol %)	*n*-Bu_4OAc	86
5	Johnphos (15 mol %)	*n*-Bu_4OAc	76
6	*t*-BuDavephos (15 mol %)	*n*-Bu_4OAc	82
7	*t*-BuXantphos (15 mol %)	*n*-Bu_4OAc	52
8	dtbpf (15 mol %)	*n*-Bu_4OAc	22
9	*t*-BuMephos (15 mol %)	*n*-Bu_4OAc	95
10[c]	*t*-BuMephos (15 mol %)	*n*-Bu_4OAc	96 (95)

[a] Reaction conditions unless otherwise noted: **17** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.03 mmol), acetate source (0.6 mmol), toluene (2 mL), 130 °C; [b] Yields were determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard with the yield in parentheses reflecting an isolated yield; [c] Reaction temperature was 90 °C.

Having identified this optimal condition set, we sought next to explore the scope of compatible oxygen nucleophiles using substrate **17** with a range of tetrabutylammonium salts. As shown in Table 2, a wide variety of such salts formed from benzoic acids with electron-donating and -withdrawing substituents proved successful, irrespective of their overall patterning, leading to the formation of products **19**–**31**. In nearly all cases the yields were high (>70%), although they were more modest for the two most electron-rich analogs leading to **21** and **22**. For salts with halogen substituents, only those that were not prone to oxidative addition with Pd(0), such as –F and –Cl, proved competent. Pleasingly, aliphatic acid salts with a tetrabutylammonium counterion worked as well to afford **32**–**36** smoothly in high yield. Finally, investigations with non-carboxylic acid-based nucleophiles revealed that phenols were not competent unless the pK_a of their acidic proton was in the range of a typical carboxylic acid, as is true for pentafluorophenol (pK_a = 5.5 in H_2O).[14] That salt afforded a 78% yield of **37**. 3,5-Ditrifluoromethylphenol (pK_a = 8.26 in H_2O),[15] by contrast, did not lead to any desired product. A very modest yield was observed using the salt of the acidic *N*-oxide HOBt in the reaction leading to **38**. Critical for all these successful cases listed in Table 2 was that the salts (while easily prepared) had to be scrupulously dry, an issue of import, as some proved to be hygroscopic if not stored properly (see SI for detailed procedure).

Table 2. The scope of the oxygen nucleophile in the Pd-based cyclization.[a,b]

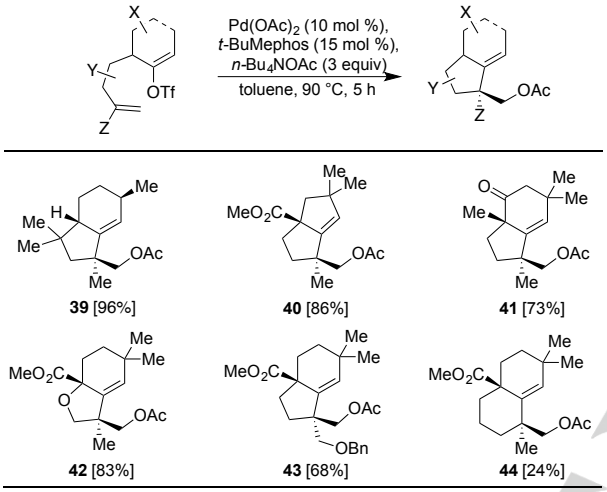


[a] Reaction conditions unless otherwise noted: **17** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *t*-BuMephos (0.015 mol), acetate source (0.3 mmol), toluene (1 mL), 90 °C, 5 h; [b] Isolated yields; [c] Reaction temperature was 130 °C.

We next investigated the scope of the alkenyl triflate. Gratifyingly, starting materials with different core skeletons performed effectively under the optimal conditions using *n*-Bu_4NOAc as the terminating nucleophile to deliver a range of fused bicyclic products in high yields and as single diastereomers. Of note, the ring size of the starting alkenyl triflate and the nature and position of substituents on the periphery of that ring showed no impact on reactivity (**39**–**41**, Table 3). Equally significant, a substrate with an oxygen linkage between the alkenyl triflate and terminating olefin acceptor led to a product (**42**) containing both an acetate group as well as an

ether ring. And, pleasingly, an alkoxymethyl substituted olefin precursor led to the asymmetric formation of a new quaternary center in **43** in which the two oxygen centers were differentiated by the acetate group installed from the reaction. Substrates designed to undergo 6-*exo*-trig cyclization proved to be the most challenging, as the yield for these events, illustrated here for product **44**, were consistently lower than for those formed through 5-*exo*-trig cyclizations. If intramolecular β-hydride elimination was possible, the reaction was unable to deliver product in any useful yield; one example is provided in the Supporting Information section.

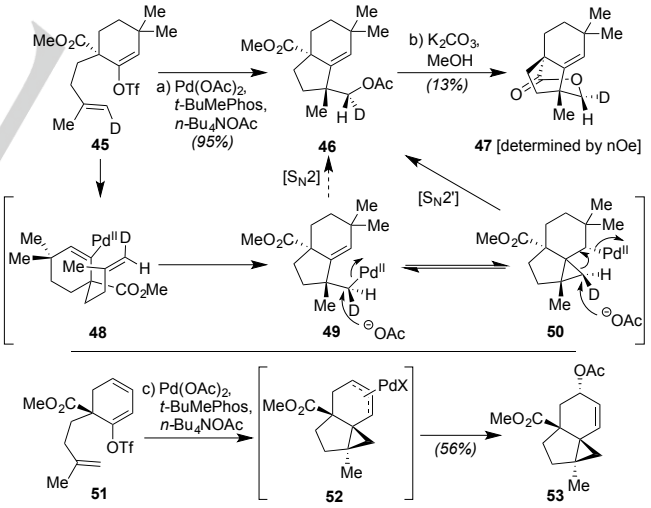
Table 3. The scope of the alkenyl triflate in the Pd-based cyclization.[a]



[a] Reaction conditions unless otherwise noted: substrate (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *t*-BuMephos (0.015 mol), *n*-Bu_4NOAc (0.3 mmol), toluene (1 mL), 90 °C, 5 h.

Given that final set of results, and in an effort to study the mechanism and deduce what parameters might be key for success of the sequence, deuterium-labeled **45** was prepared and subjected to the standard reaction conditions. This transformation led to the formation of **46** in 95% yield as a single diastereomer. As such, the formation of a single product provided evidence that a radical mechanism was not at play. To establish the relative stereochemistry of the deuterium-containing carbon, **46** was subsequently treated with K_2CO_3 in MeOH. That operation afforded lactone **47** in 13% yield along with both recovered starting material and hydrolyzed, but non-cyclized, material. Critically, nOe studies of **47** revealed that the deuterium atom was *trans* to the methyl group, indicating that the new C–O bond within **46** was formed via a stereoinvertive process; therefore, either an S_N2-type substitution on intermediate **49** or an S_N2'-type reaction with its equilibrium congener cyclopropane **50** would be required for its formation.[16] We believe the latter is more likely, with the generation of a strained ring potentially being a critical element for the reactivity needed for oxygen incorporation by giving the intermediate enhanced reactive character.[17] Evidence for the existence of cyclopropane intermediates was provided by substrate **51**, with functionalization of the intermediate π-allyl species (**52**) proving to be more expedient than cyclopropane ring opening.

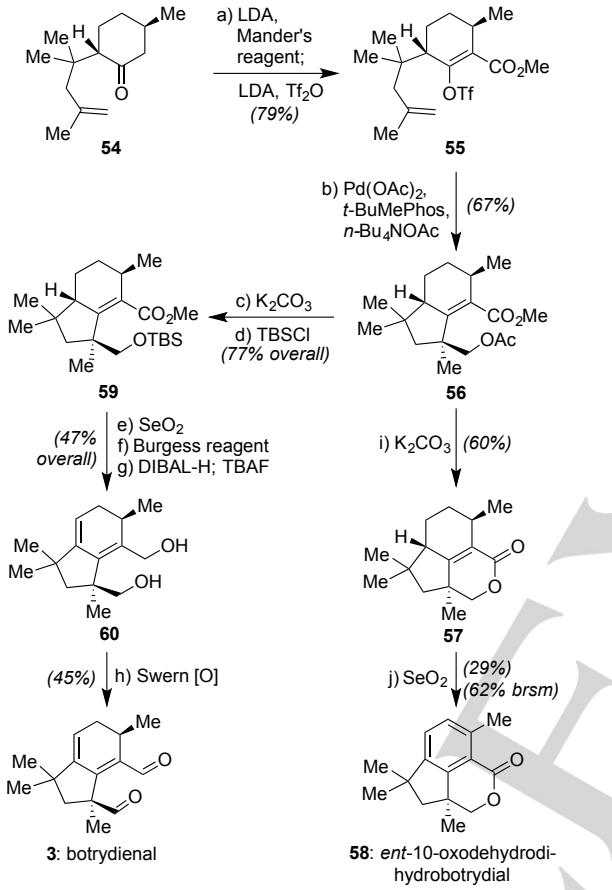
As a final demonstration of the power of the developed reaction, we attempted to utilize it for the preparation of natural products of types **2** and **3** (cf. Scheme 1). As shown in Scheme 3, we were able to access both botrydienal (**3**) as well as an aromatized variant (**58**). Those efforts began with ketone **54**,[3] prepared in one step from (*R*)-pulegone. Subsequent conversion into **55** was achieved in a single pot by effecting oxycarbonylation with Mander's reagent[18] followed by alkenyl triflate formation. With the stage now set for the key Pd-based cyclization, we found that while the reaction proceeded effectively using toluene (35% yield), a superior outcome was obtained using EtOAc instead, with **56** formed as a single diastereomer in 67% yield after 12 h. Subsequent hydrolysis with 1.05 equivalents of K_2CO_3 in MeOH at 23 °C over the course of 10 h afforded **57** in 60% yield; its oxidation with SeO_2 in 1,4-dioxane at 110 °C then completed a 5 step synthesis of the enantiomer of 10-oxodehydrodihydrobotrydial (**58**).[19] Intriguingly, if **56** was treated with an excess of K_2CO_3 (10 equiv) in MeOH under the same conditions, a free alcohol was generated instead which could be smoothly protected as a TBS ether. This specific protecting group proved essential to the subsequent SeO_2-mediated allylic oxidation,[20] as the original acetate or its pivaloate, TIPS, or TMS-protected congeners generally afforded aromatized materials and/or uncharacterized side-products during that oxidation (including attempts with many other oxidants). Finally, dehydration of that newly installed allylic alcohol with the Burgess reagent[21] and standard protecting group and oxidation state changes completed the enantioselective total synthesis of botrydienal (**3**) in 9 steps overall.[22]



Scheme 2. Key mechanistic analysis of the process using deuterated substrate **45**. (a) $Pd(OAc)_2$ (10 mol %), *t*-BuMephos (15 mol %), *n*-Bu_4NOAc (3.0 equiv), toluene, 90 °C, 5 h, 95%; (b) K_2CO_3 (5.0 equiv), MeOH, 12 h, 13%; (c) $Pd(OAc)_2$ (10 mol %), *t*-BuMephos (15 mol %), *n*-Bu_4NOAc (3.0 equiv), toluene, 90 °C, 5 h, 56%.

In conclusion, inspired by the homology of several natural product architectures and aiming to develop a unified approach to access their differentially functionalized variants, we were able to develop a one-pot Pd-catalyzed cyclization/oxygenation reaction featuring C−O bond formation from an unactivated

C(sp^3)−Pd(II) intermediate in a Pd(0)/Pd(II) catalytic cycle. Mechanistic studies have revealed this event to be a stereoinvertive process, with reaction probes revealing wide scope in substrate and nucleophile. Specific applications have ultimately afforded short and enantioselective total syntheses of two sesquiterpenes in the botrydial family. Further efforts to extend this reaction process and apply it to other complex molecules, as well as to develop additional means of terminating functionalization, are the subject of current endeavors.



Scheme 3. Total synthesis of botrydienal (**3**) and *ent*-10-oxodehydrodihydrobotrydial (**58**) via the Pd-catalyzed cyclization cascade. Reaction conditions: a) LDA (3.0 equiv), THF, -78 to 0 °C, 1.5 h, then HMPA (3.0 equiv), Manders' reagent (3.3 equiv), THF, -78 °C, 1 h, then LDA (10 equiv), Tf_2O (10 equiv), -78 °C, 4 h, 79%; b) $Pd(OAc)_2$ (10 mol %), *t*-BuMephos (15 mol %), *n*-Bu_4NOAc (3.0 equiv), EtOAc, 90 °C, 12 h, 67%; c) K_2CO_3 (10 equiv), MeOH, 23 °C, 10 h, 84%; d) TBSCl (1.5 equiv), imidazole (1.6 equiv), DMF, 23 °C, 12 h, 92% e) SeO_2 (4.0 equiv), 1,4-dioxane, 110 °C, 12 h, 49%, and 25% aromatization product; f) Burgess reagent (3.0 equiv), toluene, 80 °C, 12 h, 96%; g) DIBAL-H (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, then TBAF (3.0 equiv), 3 h, 99%; h) $(COCl)_2$ (20 equiv), DMSO (10 equiv), Et_3N (30 equiv), CH_2Cl_2, -78 °C, 3 h, 45%; i) K_2CO_3 (1.05 equiv), MeOH, 23 °C, 10 h, 60%; j) SeO_2 (4 equiv), 1,4-dioxane, 110 °C, 12 h, 29%, 62% b.r.s.m.

Acknowledgements

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Keywords: catalysis • Pd • oxygenation • total synthesis • triquinanes

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those reported here. In addition, their system tolerates halides, which are not compatible in our reaction. The authors proposed a distinct mechanism involving acetoxypalladation, cyclization, and β-Br elimination processes, all as a Pd(II)-based system, not a Pd(0)/Pd(II) cycle; however, it should be noted that since no mechanistic experiments were performed, a pathway akin to that presented here cannot be ruled out: M. Himmelbauer, J.-B. Farcet, J. Gapnepain, J. A. Mulzer, *Org. Lett.* **2013**, *15*, 3098.

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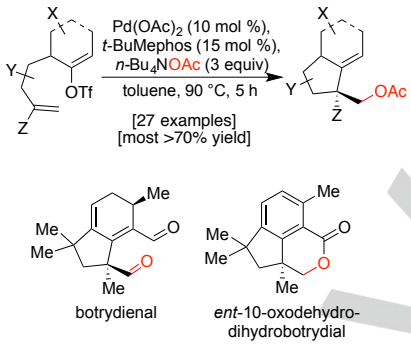
Although Pd-based cyclizations are of tremendous value, certain terminating functionalizations remain challenging. Herein is described the development of a terminating oxygen-based reaction predicated on a Pd(0)/Pd(II) catalytic cycle which has wide substrate scope and works with a range of acidic oxygen-based additives. Mechanistic studies provide key details for the reaction's success, with its power enabling the concise synthesis of two members of the botrydienal family of natural products.



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