Palladium-Mediated Carbon−Carbon Bond Forming Reactions as a New Method for the Synthesis of Peroxides and Hydroperoxides

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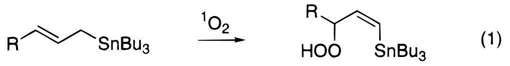
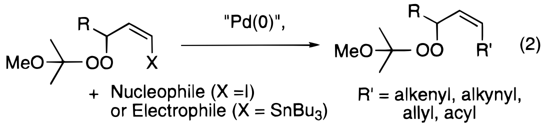
Continuing progress in the isolation of biologically active peroxide natural products has brought growing awareness of the need for improved tools for peroxide synthesis.[1,2] Addition of singlet oxygen ($^1O_2$) to alkenes is a traditional and efficient method for synthesis of unsaturated hydroperoxides.[3,4] However, the utility of this transformation is often limited by poor regioselectivity.[5] We recently described a method for the regio- and stereoselective synthesis of (*Z*)-3-tributylstannyl-2-alkenyl hydroperoxides based upon oxygenation of allylstannanes (eq 1).[6,7] Alkenylstannanes and the corresponding halides are ubiquitous substrates for transition-metal-mediated coupling reactions and we became interested in the possibility of an unprecedented modular approach to peroxide synthesis.[8−11] In this paper, we describe the successful use of functionalized peroxides in palladium-mediated carbon−carbon bond forming reactions (eq 2).

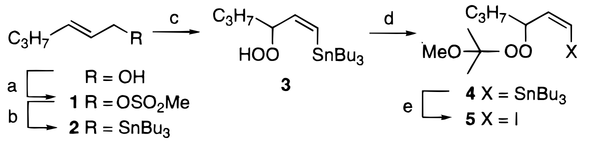




The synthesis of initial substrates, vinylstannane **4** and vinyl iodide **5**, began with formation of allylstannane **2** through nucleophilic addition of tributylstannyllithium to mesylate **1** (Scheme 1). Although oxygenation of allylstannanes has been reported to produce a variety of products depending upon reaction conditions and the nature of substituents on tin,[12,13] our previous investigations demonstrated predominant conversion of 3-tributylstannyl-4(*E*)-alkenoates to hydroperoxy alkenylstannanes via anti-S_E2' addition of $^1O_2$ to form a perepoxide followed by transfer of the proton on the tin-bearing carbon (H-ene).[6] In accordance with these observations, allylstannane **2** underwent photooxygenation to yield 1(*Z*)-tributylstannyl-3-hydroperoxy-1-hexene (**3**) as the major product. Protection of the hydroperoxide with 2-methoxypropene produced stannyl peroxyketal **4**. Vinyl iodide **5** was obtained upon oxidation of **4** with *N*-iodosuccinimide.

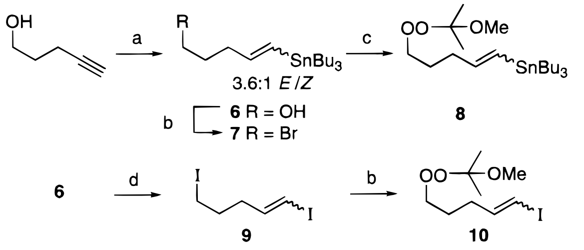
Substrates **8** and **10** were prepared via an alternative strategy (Scheme 2). Radical hydrostannylation of 4-pentyn-1-ol produced an *E*/*Z* mixture of stannylalkenols **6**. Displacement of the corresponding bromide (**7**) with the anion of 2-methoxyprop-2-yl hydroperoxide produced peroxide **8**.[14,15] Iodination of the stannylalkenol **6** with iodine/triphenylphosphine directly furnished diiodide **9**,[16] which underwent displacement with 2-methoxyprop-2-yl hydroperoxide to produce peroxyiodoalkene **10**.

Scheme 1[a]



[a] (a) $ClSO_2Me$, Et_3N, ether; (b) $LiSnBu_3$, THF (69%); (c) TPP, O_2, $h\nu$, CH_2Cl_2 (36%); (d) 2-methoxypropene, PPTs, CH_2Cl_2 (95%); (e) NIS, THF (97%).

Scheme 2[a]



[a] (a) $HSnBu_3$, AIBN (78%); (b) CBr_4, PPh_3, imidazole (94%); (c) 2-methoxyprop-2-yl hydroperoxide, CsOH, DMF (52%); (d) 2 equiv of I_2, PPh_3, imidazole (92%); (e) 2-methoxyprop-2-yl hydroperoxide, CsOH, DMF (65%).

The cross-coupling of alkenylstannanes with acid chlorides or allylic halides is an efficient route to enones and skipped dienes, respectively.[8,17,18] We were particularly interested in 4-peroxy-enones as precursors for alkoxydioxine natural products.[19,20] Coupling of **4** and **8** with benzoyl chloride in the presence of the complex formed from $Pd(dba)_3$ and tri-2-furylphosphine[21] proceeded stereospecifically to produce 4-peroxy-2,3-enones **11** and **12** in good yield (Table 1, entries 1 and 2). Pd-mediated coupling of **4** with cinnamyl bromide proceeded stereospecifically to produce diene **13** in moderate yield. However, coupling of **8** with cinnamyl bromide produced diene **14** as a 2:1 mixture of *E* and *Z* isomers at the reacting alkene. Although this result could imply preferential consumption of the *Z*-alkenylstannane, it more likely represents a nonstereospecific reaction pathway.

We next investigated reactions of the corresponding alkenyl iodides. Oxidative addition of Pd(0) is known to activate vinyl halides and triflates toward nucleophilic displacement as well as carbonylation. Vinyl iodides **5** and **10** underwent Stille reaction with vinytributyltin (Table 2a) to produce conjugated diene peroxides **15** and **16** in good yield;[9] a slight loss of stereochemical integrity was observed for the reaction of **5**. The nearly stereospecific formation of *Z*,*E*-dienes provides a potential route to otherwise inaccessible analogues of fatty acid diene hydroperoxides.

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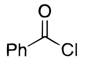
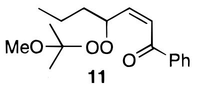
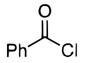
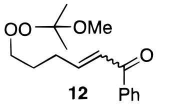
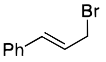
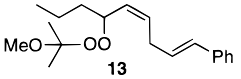
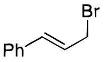
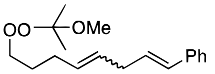
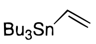
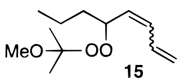
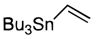
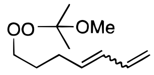
Table 1. Palladium-Mediated Coupling of Vinylstannanes with R−X[a]

Entry	Substrate	R-X	Product	Yield[b] ratio *E*:*Z*
1	**4**		 **11**	69%
2	**8**		 **12**	96% (3.6:1)[c]
3	**4**		 **13**	55%
4	**8**		 **14**	62% (2:1)[d]

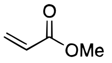
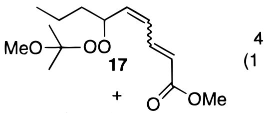
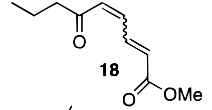
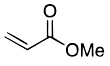
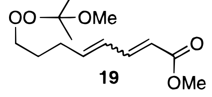
[a] Specific conditions: 5 mol % $Pd_2dba_3CHCl_3$, 10 mol % tri-2-furylphosphine (1.05 equiv of halide 0.04−0.09 M in THF), entries 1 and 2 at 23 °C, entries 3 and 4 at 60 °C for 4−14 h. [b] All yields based on isolated material. [c] Ratio determined by isolation. [d] Ratio determined by ^1H NMR.

Table 2. Stille Reactions, Heck Reactions, and Carbonylations of Vinyl Iodides

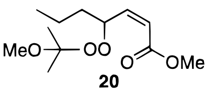
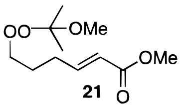
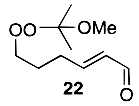
(a) Stille Reactions of Vinyl Iodides[a]

Substrate	Reactant	Product	Yield[b] (ratio *E*:*Z*)[c]
5		 **15**	77% (1:9)
10		 **16**	49% (3.5:1)

(b) Heck Reactions of Vinyl Iodides[d]

Substrate	Reactant	Product	Yield[b] (ratio *E*:*Z*)[c]
5		 **17** +	46% (1 : 5.8)
		 **18**	22% (3.5:1)
10		 **19**	86% (9:1)

(c) Carbonylations of Vinyl Iodides

Substrate	Conditions[e]	Product	Yield[b] (ratio *E*:*Z*)[c]
5	CO/MeOH (A)	 **20**	37% (all Z)
10	CO/MeOH (A)	 **21**	60% (3.5: 1)
10	CO, $HSnBu_3$ (B)	 **22**	17% (3.5:1)

[a] Specific conditions: 10−20 mol % $Pd(PPh_3)_2Cl_2$, 1.05−1.50 equiv of vinyltin, THF, 45 °C, 2−16 h. [b] Based upon isolated material. [c] Ratios determined by ^1H NMR. [d] Specific conditions: 10−15 mol % $Pd(OAc)_2$, 1−1.50 equiv of K_2CO_3, 1−1.5 equiv of *n*-Bu_4NBr, 8−10 mL of methyl acrylate, 23 °C, 6−16 h. [e] Specific conditions: A = 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2 equiv of Et_3N, 1 atm of CO, 2.3:1 DMF/MeOH, 60 °C, 1−3 h; B = 8 mol % $Pd(PPh_3)_4$, 1 atm of CO, THF, addition of 1.1 equiv of $HSnBu_3$ in THF over 4 h at 60 °C.

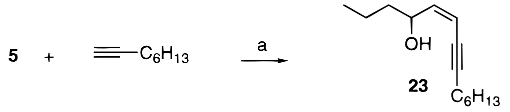
The palladium-mediated alkenylation of vinyl halides (Heck reaction) is a valuable complement to the Stille reaction for preparation of functionalized dienes.[11] Heck couplings of **5** and **10** were attempted at room temperature under phase transfer conditions (Table 2b).[22] Addition of methyl acrylate to peroxy vinyl iodide **5** produced dienoate **17**, predominantly as the *Z*,*E* isomer, accompanied by an oxodienoate (**18**) resulting from base-catalyzed decomposition of the coupled peroxide. Addition of methyl acrylate to peroxide **10** furnished peroxydienoate **19** in high yield as a 9:1 mixture of 2*E*,4*E* and 2*E*,4*Z* isomers.

The palladium-mediated carbonylation of vinyl halides was investigated as an approach to peroxyenoates and peroxyenals, synthetically valuable intermediates.[23] Carbonylation of **5** in the presence of methanol provided a modest yield of *Z*-peroxyenoate **20** while reaction of **10** produced **21** in better yield (Table 2c). Synthesis of the corresponding peroxyenal **22** was achieved in low yield through carbonylation of **10** in the presence of tributyltin hydride.[24] In each case, carbonylation was stereospecific. All reactions were conducted under 1 atm of CO and it is likely that higher yields could be obtained at increased pressures.

The palladium-mediated coupling of terminal alkynes with vinyl electrophiles seemed to offer an attractive entry to peroxy-2-alkene-4-ynes, which would be useful intermediates in the synthesis of polyene hydroperoxides.[25] However, reaction of **5** with 1-octyne under standard conditions[26] furnished only the alcohol corresponding to the coupled product (Scheme 3). The lack of similar byproducts in other reactions involving Pd(0) would seem to support the efficacy of catalytic Cu(I)/stoichiometric alkyne as a reducing agent for peroxides.

In summary, we have demonstrated that functionalized peroxides successfully participate in a wide variety of palladium-catalyzed carbon−carbon bond forming reactions, allowing an efficient synthesis of peroxyenones, peroxydienes, peroxyenoates, and peroxyenals. This new methodology, offering the first modular approach to peroxide synthesis, holds great potential for the synthesis of peroxide-containing natural products.

Scheme 3[a]



[a] (a) $Pd(PPh_3)_4$, CuI, $^nBuNH_2$, benzene (49%).

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C spectra for **2**−**23** (54 pages, print/PDF format). See any current masthead page for ordering information and Web access instructions.

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