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Pd^0/Sn^{II} mediated three-component cascade coupling (3-C^3) approaches☆

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Abstract—The 3-C^3strategy involves (i) Pd(0)/SnX_2 (X = Cl, Br) mediated generation of allyltin(IV) from allyl bromide in anhydrous DCM, (ii) formation of homoallyloxytin(IV) intermediate **I** from allyltin(IV) and an aldehyde, and (iii) coupling of **I** with an aldehyde, an aryl epoxide or an arene as the third partner to afford tetrahydropyrans, benzyl tetrahydropyrans or 4,4-diarylbut-1-enes, respectively.
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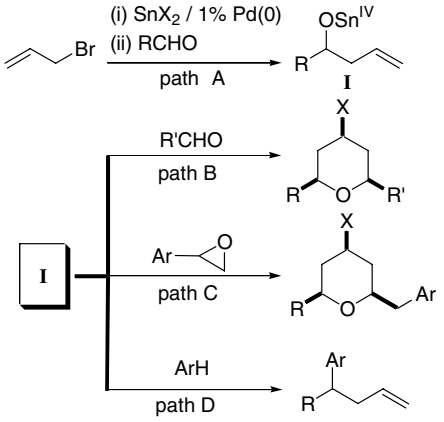
An attractive atom-efficient strategy in organic synthesis is to construct multiple chemical bonds in cascade from one or more substrates in one pot. While the increasing popularity of multicomponent cascade coupling (MCC) approaches is replete in literature,[1] we became interested in those catalyzed by a transition metal, and having at least one organometallic step[2–4] in the cascade. The present work originates from our continued interest on a bimetallic strategy to generate allyl-, allenyl-, and propargyltin reagents in situ from an appropriate organic halide, tin(II) and a transition metal catalyst, and reacting the resulting organotin reagents with aldehydes, ketones, or epoxides in a Barbier fashion. We and others have also stressed the profound influence of transition metal catalysts, and water in these reactions.[5,6] With specific reference to carbonyl allylation reactions, it may be noted that homoallyloxytin(IV) is an important intermediate (Scheme 1, intermediate **I**). The presence of two reactive sites in **I** (nucleophilic terminal alkene, and electrophilic carbon in C–OSn) makes it a potential candidate for further reaction with a suitable third partner. Herein, we delineate such three-component cascade coupling (3-C^3) strategies using **I** as the common intermediate, the third partner being an aldehyde (Scheme 1, path B), an aryl epoxide (Scheme 1, path C), or an arene (Scheme 1, path D).



Scheme 1. 3-C^3 routes involving intermediate **I**; Pd(0) = $Pd_2(dba)_3$·$CHCl_3$, solvent = CH_2Cl_2, for other details see text.

The three-component assembly was first examined using allyl bromide, 4-nitrobenzaldehyde, and benzaldehyde. The allyltin reagent obtained from allyl bromide (2 mmol), $Pd_2(dba)_3$·$CHCl_3$ (0.01 mmol), and anhydrous $SnCl_2$ (1.5 mmol) in dry dichloromethane was reacted with 4-nitrobenzaldehyde (1.2 mmol) at −78 °C to generate the corresponding homoallyloxytin(IV) intermediate, which was further reacted with benzaldehyde (1 mmol, 4 h, −78 °C to room temp.) to provide tetrahydropyran **1** in an 86% isolated yield (Table 1, entry 1). Catalyst screening showed that $Pd_2(dba)_3$·$CHCl_3$ was markedly superior to $Pd(PPh_3)_4$, $Cu(acac)_2$, and $CuCl(SMe_2)$. Further, there was no reaction in the

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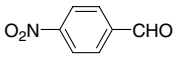
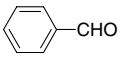
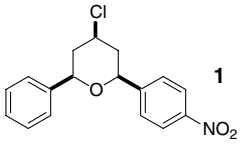
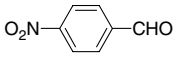
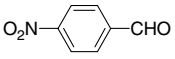
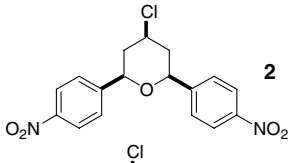
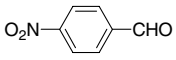
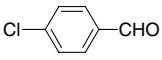
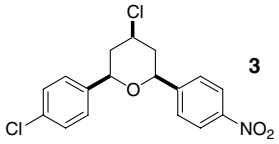
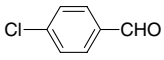
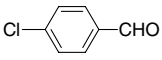
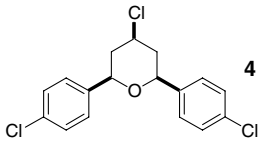
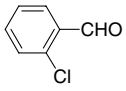
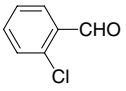
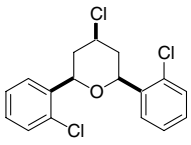
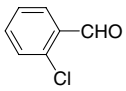
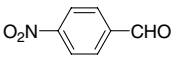
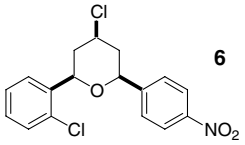
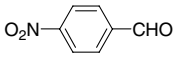
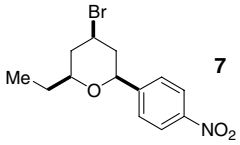
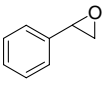
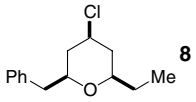
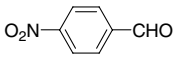
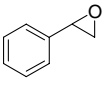
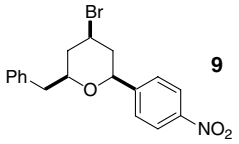
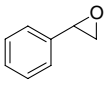
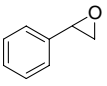
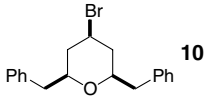
Table 1. Synthesis of 2,4,6-trisubstituted tetrahydropyrans from allyl bromide and the 2nd component and 3rd component[a,b]

Entry	2nd component	3rd component	Product	Time (h)	Yield (%)
1			 **1**	15	86
2			 **2**	21	63
3			 **3**	22	67
4			 **4**	23	54
5			 **5**	13	81
6			 **6**	17	77
7		$MeCH_2CHO$	 **7**	12	89
8	$MeCH_2CHO$		 **8**	13	68
9			 **9**	14	63
10			 **10**	11	57

[a] 1st component: allyl bromide (2 mmol), 2nd component: aldehyde or epoxide (1.2 mmol), 3rd component: aldehyde or epoxide (1 mmol), SnX_2 (1.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol), solvent: dichloromethane; detailed procedures in Supplementary data.
[b] For entries 1–6, 8: X = Cl; for entries 7, 9, 10: X = Br.

absence of the catalyst. Control studies with homoallylic alcohol and aldehyde in the presence of $Pd(0)/SnX_2$ failed to provide tetrahydropyran derivative. The generality of the reaction was tested (Table 1, entries 2–7) by varying the aldehyde partner which indicated that, (i) in all cases the substituents at the 2,4,6-positions in the tetrahydropyran ring maintain an all-cis relationship (X-ray crystallography and NMR),[7] and (ii) reaction with $SnBr_2$ in place of $SnCl_2$ afforded the corresponding bromo derivative (Table 1, entry 7).

It may be noted that tetrahydropyrans are important building blocks in organic synthesis, and the tetrahydropyran core features widely in many natural products.[8] Although the mechanism of coupling between homoallyloxytin(IV) intermediate **I** with the aldehyde in the

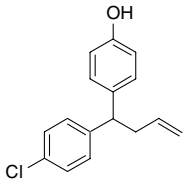
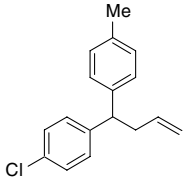
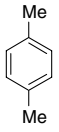
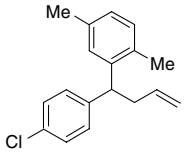
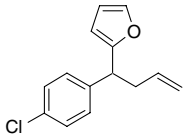
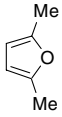
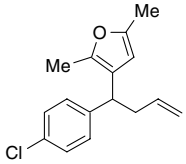
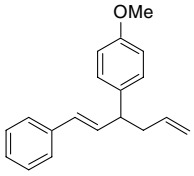
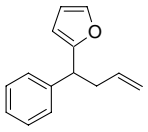
present case has not been established, we assume that it follows a Prins-like cyclization. The formation of tetrahydropyrans from a carbonyl compound and either a homoallyl alcohol or an allyl-metal reagent via Prins cyclization is well known.[9] In comparison, there are only two reports on the direct use of an allyl halide in such a reaction.[3] Li and co-workers reported an indium-mediated tetrahydropyran synthesis[3b] whilst Zhao et al. reported a Prins reaction employing $SnBr_2$/ionic liquid as reagent.[3a]

The second 3-C^3 strategy involved the reaction of an allyl bromide, an aldehyde and an aryl epoxide, leading to an easy formation of the corresponding benzyl tetrahydropyran derivatives. Thus, following the generation of the homoallyloxytin(IV) intermediate from allyl bromide, catalytic $Pd_2(dba)_3{\cdot}CHCl_3$, anhydrous $SnCl_2$, and propionaldehyde in dry dichloromethane, styrene epoxide was added, and the reaction was brought to completion (TLC monitoring for epoxide) to afford tetrahydropyran **8** in a 68% yield (Table 1, entry 8). A similar reaction but with 4-nitrobenzaldehyde and $SnBr_2$ gave tetrahydropyran **9** in a 63% yield (Table 1, entry 9). Based on our previous experience,[5d,e] we believe that aryl epoxides may rearrange to the corresponding benzyl aldehydes under Pd(0)/Sn(II) assistance, and undergo Prins cyclization with intermediate **I**. This assumption gains an additional ground from the fact that a 3-C^3 coupling involving allyl halide–epoxide–epoxide provided a symmetrical dibenzyl-substituted tetrahydropyran **10** (Table 1, entry 10).

In a third 3-C^3 strategy we reacted an allyl bromide, an aldehyde, and an arene leading to a clean formation of the corresponding 4,4-diarylbut-1-enes (Table 2), the reaction can be equated to consecutive Barbier and Friedel–Crafts reactions. Note that 4-arylbut-1-enes are potential substrates for further structural modification via cyclization.[10] While extending the scope of the reaction, we observed that, (i) heteroarenes were equally effective, and (ii) in terms of yield and reaction time, ring deactivated aromatic aldehydes, and ring activated arenes were better (Table 2). An earlier attempt by Shinna et al. to couple homoallyloxy(tributyl)tin with arenes failed, however, the corresponding silyl ether analogue proved to be effective.[4b] We tentatively propose that the mechanism of this 3-C^3 coupling would involve deoxygenative carbon–carbon bond formation at the C–OSn carbon in intermediate **I** under the assistance of the arene as the nucleophile.

In summary, we have presented versatile three-component cascade coupling (3-C^3) approaches based on a common intermediate.[11–13] The notable features of the strategy are, (i) the generation of allytin(IV) from allyl bromide in an anhydrous medium via Pd(0)/$SnCl_2$, (ii) facile transformation of allyltin(IV) in the presence of an aldehyde to a homoallyloxytin(IV) intermediate which served as the common intermediate for coupling with an aldehyde, an aryl epoxide or an arene. Investigations are underway to broaden the scope of the present strategy further, and to include other electrophilic and nucleophilic partners in the 3-C^3 assembly.

Table 2. Synthesis of 4,4-diarylbut-1-enes from allyl bromide, an aldehyde (RCHO)[a] and an arene (ArH)[b]

Entry	Arene	Product		Time (h)	Yield (%)
1			**11**	13	90
2			**12**	11	80
3			**13**	10	90
4			**14**	7	88
5			**15**	13	55
6			**16**	15	75
7			**17**	15	62

[a] R = 4-chlorophenyl (entries 1–5), cinnamyl (entry 6), phenyl (entry 7).
[b] Allyl bromide (2 mmol), aldehyde (1 mmol), ArH (4 mmol), solvent: dichloromethane; detailed procedures in Supplementary data.

Acknowledgements

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Supplementary data

Crystal structure data for compounds **2**, **4**, and **6** has been deposited at CCDC (deposition no. 629088, 629089, and 629090). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.080.

References and notes

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11. *Typical experimental procedure for the preparation of 4-chloro-2-(4-nitro-phenyl)-6-phenyl-tetrahydropyran* **1***:* Allyl bromide (242 mg, 2 mmol, 0.17 mL) and $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mg, 0.01 mmol) were mixed in dry DCM (3 mL) and stirred for 5 min at room temperature. Anhydrous $SnCl_2$ (285 mg, 1.5 mmol) was added to the solution and stirring continued for 6 h at room temperature. The mixture was cooled to −78 °C, 4-nitrobenzaldehyde (181 mg, 1.2 mmol in 1 mL of dry DCM) was added, and stirred at −78 °C for 5 h until the aldehyde was consumed (TLC monitoring on silica gel, eluent: ethyl acetate/hexane 1:9 v/v). Benzaldehyde (106 mg, 0.1 mL, 1 mmol in 1 mL of dry DCM) was then added at −78 °C. Stirring was continued at −78 °C for 1 h, and then at 30 °C for 3 h until complete consumption of benzaldehyde (TLC monitoring on silica gel, eluent: ethyl acetate/hexane 1/9 v/v). Following solvent removal under reduced pressure, water and ammonium fluoride were added, and the mixture was extracted with diethyl ether (3×30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired 4-chloro-2-(4-nitrophenyl)-6-phenyl-tetrahydropyran **1** was obtained from the crude by column chromatography (eluent: *n*-hexane/ethyl acetate 97:3) in an 86% yield (273 mg).
12. *Typical experimental procedure for the preparation of 2-benzyl-4-bromo-6-(4-nitrophenyl)-tetrahydropyran* **9***:* Allyl bromide (242 mg, 2 mmol, 0.17 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mg, 0.01 mmol) and activated molecular sieves 4 Å (100 mg) were mixed in 3 mL of dry DCM and stirred for 5 min at room temperature. Anhydrous $SnBr_2$ (418 mg, 1.5 mmol) was added to the mixture and stirring continued for 6 h at room temperature. The mixture was cooled to −78 °C, 4-nitrobenzaldehyde (181 mg, 1.2 mmol in 1 mL of dry DCM) was added and the mixture was stirred at −78 °C for 5 h until the aldehyde was completely consumed (TLC monitoring on silica gel, eluent: ethyl acetate/hexane 1:9 v/v). Styrene oxide (120 mg, 0.11 mL, 1 mmol in 1 mL of dry DCM) was added at −78 °C and the mixture was stirred at −78 °C for 1 h, and then at 30 °C for 2 h (TLC monitoring on silica gel, eluent: ethyl acetate/hexane 1:9 v/v) until complete consumption of the epoxide. Following solvent removal under reduced pressure, water and ammonium fluoride were added, and the mixture was extracted with diethyl ether (3×30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The desired 2-benzyl-4-bromo-6-(4-nitrophenyl)-tetrahydropyran **9** was obtained from the crude by column chromatography (eluent: *n*-hexane/ethyl acetate 97:3) in a 63% yield (237 mg).
13. *Typical experimental procedure for the preparation of 4-[1-(4-chlorophenyl)-but-3-enyl]-phenol* **11***:* Allyl bromide (242 mg, 2 mmol, 0.17 mL) and $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mg, 0.01 mmol) were mixed in 3 mL of dry DCM and stirred for 5 min at room temperature. Anhydrous $SnCl_2$ (285 mg, 1.5 mmol) was added to the mixture and stirring continued for 6 h at room temperature. Next, phenol (376 mg, 0.35 mL, 4 mmol) and aldehyde (140 mg, 1 mmol in 1 mL dry DCM) were added to the reaction mixture sequentially, which was stirred for 7 h at this temperature until the aldehyde was completely consumed (TLC monitoring on silica gel, eluent: ethyl acetate/hexane 1:9 v/v). Following solvent removal under reduced pressure, water and ammonium fluoride were added, and the mixture was extracted with diethyl ether (3×30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. 4-[1-(4-Chlorophenyl)-but-3-enyl]-phenol **11** was obtained from the crude by column chromatography (eluent: *n*-hexane/ethyl acetate 99:1) in a 90% yield (233 mg).