Chemical Science

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Cite this: *Chem. Sci.*, 2013, **4**, 3538

# Palladium-catalyzed heteroallylation of unactivated alkenes – synthesis of citalopram†

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Received 3rd May 2013
Accepted 24th June 2013

DOI: 10.1039/c3sc51222c

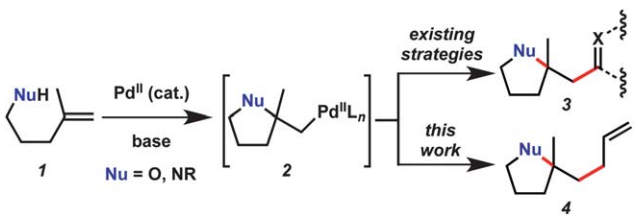
www.rsc.org/chemicalscience

A palladium-catalyzed difunctionalization of unactivated alkenes with tethered nucleophiles is reported. The versatile reaction occurs with simple allylic halides and can be carried out under air. The methodology provides rapid access to a wide array of desirable heterocyclic targets, as illustrated by a concise synthesis of the widely prescribed antidepressant citalopram.

## Introduction

Palladium-catalyzed heterocyclization onto alkenes holds particular importance for synthetic chemists because of the complexity formed, the generally tolerant reaction conditions, and the prevalence of the heterocyclic products in bioactive targets.[1] The σ-alkyl Pd(II) intermediate formed by heterocyclization can participate in a range of subsequent transformations including β-hydride elimination (Wacker-type reaction), alkoxycarbonylation, Heck reaction, or protodemetallation.[1j] In addition to these pathways, when the heterocyclization is preceded by oxidative addition, a reductive elimination can complete the catalytic cycle.[2] Recently, strategies have emerged that involve oxidation of the σ-alkyl Pd(II) intermediate formed by heterocyclization (particularly with hypervalent iodine reagents)[3] as a means of subsequently forming new C–halogen,[4] C–O,[5] C–N,[6] and C–C[6f,7] bonds.

When a Pd(II)-induced heterocyclization onto an unactivated alkene is followed by C–C bond formation, the new C–C bond is typically to an $sp^2$-hybridized carbon (*e.g.* **2** → **3**, Scheme 1).[8,9] Extending this methodology to form $sp^3$–$sp^3$ C–C bonds would constitute a significant advance, in part because increasing the $sp^3$-C content of preclinical drug candidates has been identified as a potential strategy to improve clinical success rates.[10] Pd-catalyzed allylation is a powerful method for C–C bond formation that has seen widespread use in the construction of an impressive array of complex targets;[11] however, this method has never been coupled to the Pd(II)-induced heterocyclization onto unactivated alkenes. In this communication, we report the catalyzed reaction of unactivated alkenes with tethered oxygen or nitrogen nucleophiles and allylic halides to generate a new fully substituted carbon center and a new $sp^3$–$sp^3$ C–C bond. Furthermore, we demonstrate the utility of this method with a synthesis of the widely prescribed selective serotonin reuptake inhibitor (SSRI) citalopram.




**Scheme 1** Pd-induced heterocyclization followed by C–C bond formation.

## Results and discussion

### Optimization

The combination of alkenyl phenol **5** with the commercially available catalyst Pd(hfacac)$_2$ was selected for initial screening of the planned heteroallylation based on precedent in other oxypalladation reactions (Table 1).[7b] Gratifyingly, benzofuran **6** was observed when the reaction with allyl bromide was conducted in THF, though conversion was relatively low after 72 h (entry 1). Solvent screening revealed that *ca.* 80% conversion could be achieved in PhMe after 16 h (entry 2). Attempting to use alternative Pd catalysts (entries 3–6), or allylic electrophiles (entries 7, 8) resulted in substantially lower conversions. By replacing allyl bromide with allyl chloride,[9] full conversion was observed in 6 h (entry 9). Decreasing catalyst loading to 5 mol% resulted in increased reaction time, but full conversion was still observed after 16 h (entry 10).[12] It should be noted that the optimized conditions can be conducted under ambient atmosphere using solvent directly as procured.[13] From a mechanistic point of view, it is noteworthy that only trace amounts of dihydrobenzofuran **6** formed when using a Pd(0) catalyst (entry 11, *vide infra*).

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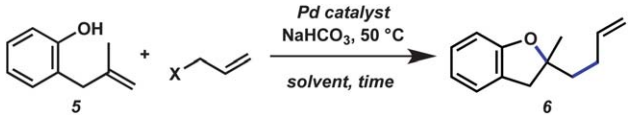
† Electronic supplementary information (ESI) available: Detailed experimental procedures and compound characterization data. See DOI: 10.1039/c3sc51222c

**Table 1** Optimization of the Pd-catalyzed heteroallylation




| Entry[a] | Pd cat. (loading) | X | Solvent | Time | 5 : 6[b] |
|---|---|---|---|---|---|
| 1 | $Pd(hfacac)_2$ (10 mol%) | Br | THF | 72 h | 2 : 1 |
| 2 | $Pd(hfacac)_2$ (10 mol%) | Br | PhMe | 16 h | 1 : 4.3 |
| 3 | $Pd(OAc)_2$ (10 mol%) | Br | PhMe | 22 h | 19 : 1 |
| 4 | $Pd(acac)_2$ (10 mol%) | Br | PhMe | 22 h | 12 : 1 |
| 5 | $Pd(TFA)_2$ (10 mol%) | Br | PhMe | 22 h | N. R.[c] |
| 6 | $PdCl_2$ (10 mol%) | Br | PhMe | 28 h | 1 : 2 |
| 7 | $Pd(hfacac)_2$ (10 mol%) | OAc | PhMe | 18 h | N. R.[c] |
| 8 | $Pd(hfacac)_2$ (10 mol%) | I | PhMe | 18 h | 5 : 1 |
| 9 | $Pd(hfacac)_2$ (10 mol%) | Cl | PhMe | 6 h | <1 : 20 |
| 10 | $Pd(hfacac)_2$ (5 mol%) | Cl | PhMe | 16 h | <1 : 20 |
| 11 | $Pd_2(dba)_3$ (10 mol%) | Br | PhMe | 18 h | N. R.[c] |

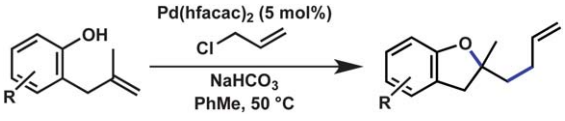
[a] *Reaction conditions*: **5** (1 equiv.), allyl-X (5 equiv.), Pd cat., $NaHCO_3$ (2 equiv.), 50 °C, solvent (0.25 M). [b] Determined by $^1H$ NMR integration of crude reaction mixtures. [c] No reaction. **5** : **6** 20 : <1.

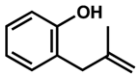
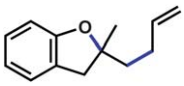
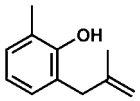
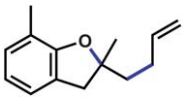
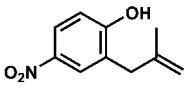
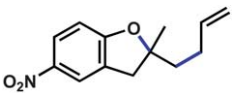
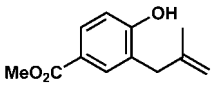
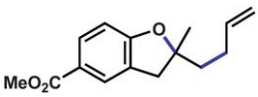
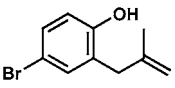
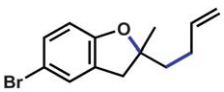
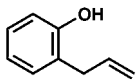
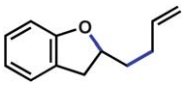
## Substrate scope

With these optimized conditions in place, we sought to examine the scope of this heteroallylation reaction to make substituted dihydrobenzofurans (Table 2). The unsubstituted case provided the allylation product in 70% isolated yield (entry 1). Substitution *ortho* to the reacting oxygen and inclusion of electron-withdrawing substituents were tolerated without decrease in yield (entries 2–4).[14] Of particular importance is the successful heteroallylation in the presence of an aryl bromide (entry 5), which can serve as a handle for the subsequent introduction of a vast array of functionality. When attempting to utilize a monosubstituted alkene, only trace oxyallylation product was detected, with the major product arising from β-hydride elimination from the putative σ-alkyl Pd(II) intermediate (entry 6, *vide infra*).[15]

Next, we chose to further probe the scope of the heteroallylation reaction by examining the formation of heterocycles other than dihydrobenzofuran (Table 3). Use of the previously optimized reaction conditions with a benzylic alcohol led to a relatively low overall yield (entry 1).[16] Fortunately, recourse to allyl bromide resulted in a cleaner reaction profile, with the desired isobenzofuran being obtained in 77% isolated yield (entry 2). Steric hindrance about the unactivated alkene did not prove to be an impediment to the hetroallylation reaction (entry 4). The dihydroisobenzopyran ring system could also be assembled using this methodology (entry 5).[17] Use of a substrate containing an unprotected hydroxyl group that was not involved in the heterocyclization resulted in low conversion with allyl bromide; however, using allyl chloride for this substrate resulted in a synthetically viable yield (entries 7, 8). Secondary and tertiary alcohols, as well as benzoic acids also performed well in the reaction (entries 9–14). It should be highlighted that substitution on the unactivated alkene can include $sp^3$-C (including a sterically encumbering *t*-Bu group), or an aromatic ring.[18] Once again, when attempting the oxyallylation with a monosubstituted alkene, cyclization followed by β-hydride elimination occurred in relatively low conversion, with none of the allylated lactone being observed (entry 15).[15]

**Table 2** Pd-catalyzed heteroallylation using phenols




| Entry[a] | Substrate | Product | Time | Yield[b] |
|---|---|---|---|---|
| 1 |  |  | 16 h | 70% |
| 2 |  |  | 24 h | 75%[c] |
| 3 |  |  | 23 h | 74% |
| 4 |  |  | 24 h | 67% |
| 5 |  |  | 16 h | 71% |
| 6 |  |  | 20 h | n.d.[d] |

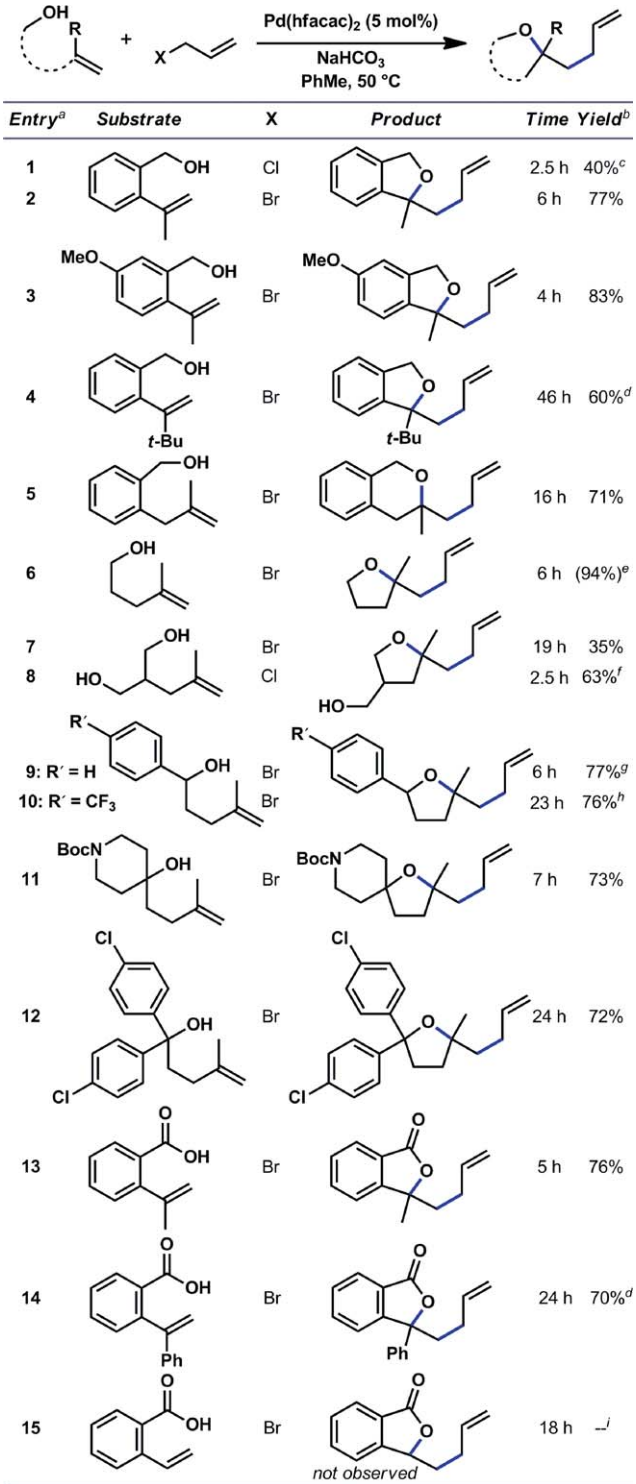
[a] *Reaction conditions*: substrate (1 equiv.), allyl chloride (5 equiv.), $Pd(hfacac)_2$ (5 mol%), $NaHCO_3$ (2 equiv.), PhMe (0.25 M), 50 °C. [b] Isolated yield. [c] Reaction carried out on 0.9 g scale. [d] Yield not determined.

We then attempted to extend the method to an aminoallylation by cyclization of tosyl amides onto unactivated alkenes (Scheme 2). These efforts were initially plagued by low conversion on *gem*-disubstituted alkene precursors even at prolonged reaction times with 10 mol% catalyst loading. However, we were successfully able to access the isoquinolone (**8b**) and pyrrolopyrazinone (**8c**) ring systems from monosubstituted alkene precursors without significant β-hydride elimination.[15] Modification of the base to $KH_2PO_4$ was required for these aminocyclizations in order to suppress *N*-allylation.

## Mechanistic hypothesis

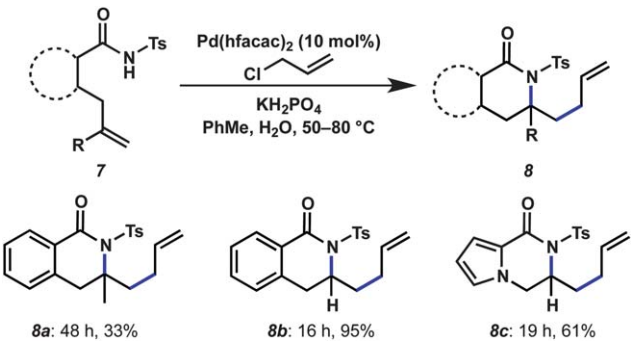
Although the precise mechanism for this heteroallylation reaction is yet to be fully elucidated, we have carried out preliminary studies designed to test the possible intermediacy of a π-allyl species. An experiment using dideuteroallyl bromide labelled at the allylic position resulted in exclusive formation of a product with two vinyl deuterons (Scheme 3).[15]

**Table 3** Pd-catalyzed alkene heteroallylation of unactivated alkenes

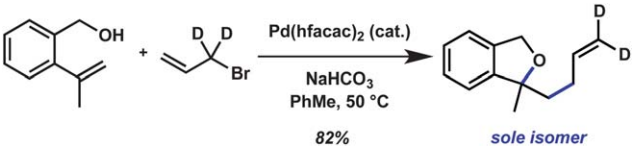



| Entry[a] | Substrate | X | Product | Time | Yield[b] |
|---|---|---|---|---|---|
| 1 | | Cl | | 2.5 h | 40%[c] |
| 2 | | Br | | 6 h | 77% |
| 3 | | Br | | 4 h | 83% |
| 4 | | Br | | 46 h | 60%[d] |
| 5 | | Br | | 16 h | 71% |
| 6 | | Br | | 6 h | (94%)[e] |
| 7 | | Br | | 19 h | 35% |
| 8 | | Cl | | 2.5 h | 63%[f] |
| 9: R′ = H<br>10: R′ = $CF_3$ | | Br<br>Br | | 6 h<br>23 h | 77%[g]<br>76%[h] |
| 11 | | Br | | 7 h | 73% |
| 12 | | Br | | 24 h | 72% |
| 13 | | Br | | 5 h | 76% |
| 14 | | Br | | 24 h | 70%[d] |
| 15 | | Br | not observed | 18 h | –[i] |

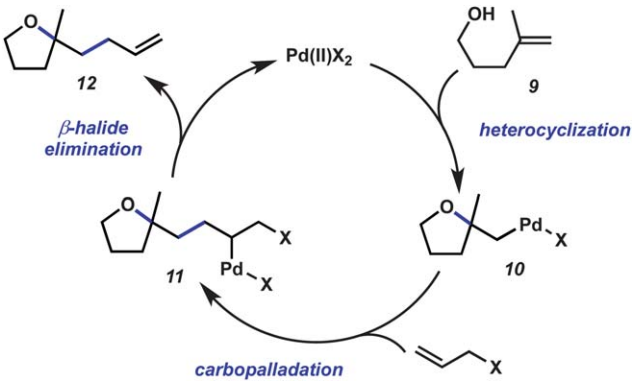
[a] *Reaction conditions*: substrate (1 equiv.), allyl-X (5 equiv.), $Pd(hfacac)_2$ (5 mol%), $NaHCO_3$ (2 equiv.), PhMe (0.25 M), 50 °C. [b] Isolated yield except where noted. [c] Yield at full conversion based on $^1H$ NMR integration, compound contaminated with additional impurities. [d] An additional 5 mol% catalyst was added. [e] Carried out in $d_8$-toluene; yield based on $^1H$ NMR integration *vs.* internal standard. [f] d.r. = 1.4 : 1 see ESI for all assignments. [g] d.r. = 1.3 : 1. [h] d.r. = 1.5 : 1. [i] Low conversion to a mixture of products, see ESI.




**Scheme 2** Aminoallylation substrates and conditions.




**Scheme 3** Deuterium labelling study.

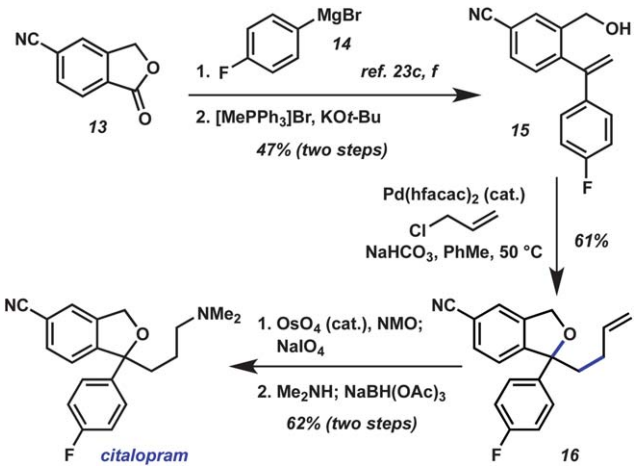



**Scheme 4** Postulated catalytic cycle.

Furthermore, while not definitive, the lack of reactivity using $Pd_2dba_3$, coupled with the fact that precipitation of Pd(0) was not observed during the course of the reactions and the tolerance of the process for aryl halides (which might have undergone oxidative addition to an *in situ*-generated Pd(0) species) suggests that Pd(0) intermediates are not involved.[13] These factors lead us to propose the following catalytic cycle (Scheme 4): Pd(II)-induced heterocyclization (**9** → **10**) might be followed by carbopalladation of the allyl halide to generate Pd(II)-alkyl complex **11**.[1,19] Subsequent β-halide elimination (which has been shown to occur more rapidly than β-hydride elimination in several systems[9,20]) would then afford heteroallylation product **12**, while releasing the Pd(II) catalyst.[21] This mechanistic interpretation is consistent with results obtained in related cyclizations of allenes.[9e,g,h]

## Synthesis of citalopram

In order to demonstrate the utility of the heteroallylation methodology for the preparation of bioactive heterocycles, and




**Scheme 5** Synthesis of citalopram using oxyallylation.

further probe substrate scope, a synthesis of the SSRI citalopram was performed (Scheme 5).[22,23] The reaction of *p*-fluorophenyl Grignard reagent **14** with commercially available cyanophthalide **13** is known from the patent literature.[23c,f] Subsequent Wittig reaction provided the requisite alkenyl alcohol **15**. The pivotal Pd-catalyzed oxyallylation proceeded in good yield to furnish isobenzofuran **16**. Conversion of terminal alkene **16** to citalopram was readily achieved by one-pot dihydroxylation–oxidative cleavage,[24] followed by reductive amination.

## Conclusions

In summary, we have developed a versatile catalytic heteroallylation reaction of unactivated alkenes to form heterocycles that are prevalent in a plethora of targets including natural products and bioactive compounds. The process forms a fully substituted carbon center and a new $sp^3$–$sp^3$ C–C bond in a single step, and occurs using a commercially available catalyst under operationally convenient conditions (*e.g.* under air). The orthogonality of the newly described heteroallylation to standard Pd(0)-catalyzed processes (as illustrated by the tolerance of the reaction for aryl halides, and lack of reactivity with a Pd(0) catalyst) clearly shows the potential for this method to be used in accessing complex targets. Phenols, alcohols, carboxylic acids and tosyl amides are all competent nucleophiles for this transformation, which we have also shown can be employed in a synthesis of the bioactive heterocycle citalopram. Ongoing investigations in our group seek to further expand the scope of the reaction, including ligand-based control of enantioselectivity, and explore the mechanism underpinning the process.

## Acknowledgements

The authors are grateful to the EPSRC, WestCHEM, the University of Glasgow, Pfizer, and AstraZeneca for financial support.

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13 Carrying out the reaction under Ar using degassed solvent did not significantly impact conversion, suggesting that $O_2$ is not involved in the process.

14 A side product resulting from heterocyclization followed by Heck reaction onto the product alkene was isolated from the reaction shown in entry 2 accounting for the majority of the mass balance. See ESI for further details.†

15 See ESI for details.†

16 No trace of aldehyde resulting from Pd(II)-promoted alcohol oxidation was observed for any reaction in Table 3. See T. Nishimura and S. Uemura, *Synlett*, 2004, 201 and references therein for examples of Pd(II)-promoted alcohol oxidation.

17 Extension to ring sizes larger than 6-membered resulted in markedly decreased yields.

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