

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

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

Joanne F. M. Hewitt, Lewis Williams, Pooja Aggarwal, Craig D. Smith and David J. France*

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), alkoxy-carbonylation, Heck reaction, or protodemetalation.² 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.

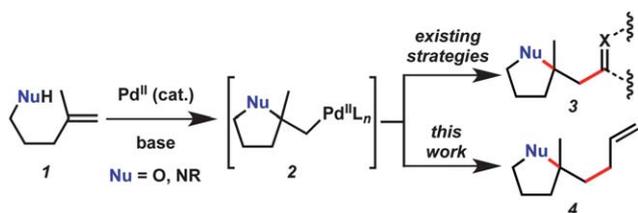
When a Pd(II)-induced heterocyclization onto an unactivated alkene is followed by C–C bond formation, the new C–C bond is typically to an sp^2 -hybridized carbon (e.g. **2** \rightarrow **3**, Scheme 1).^{8,9} Extending this methodology to form sp^3 – sp^3 C–C bonds would

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.

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*).



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

WestCHEM, School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, UK. E-mail: david.france@glasgow.ac.uk; Fax: +44 (0)141 330 6867; Tel: +44 (0)141 330 4708

† 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., NaHCO₃ (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 heteroallylation 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 sp³-C (including a sterically encumbering *t*-Bu group), or an aromatic

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%), NaHCO₃ (2 equiv.), PhMe (0.25 M), 50 °C. ^b Isolated yield. ^c Reaction carried out on 0.9 g scale. ^d Yield not determined.

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

We then attempted to extend the method to an amino-allylation 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 KH₂PO₄ was required for these aminocyclizations in order to suppress *N*-allylation.

Mechanistic hypothesis

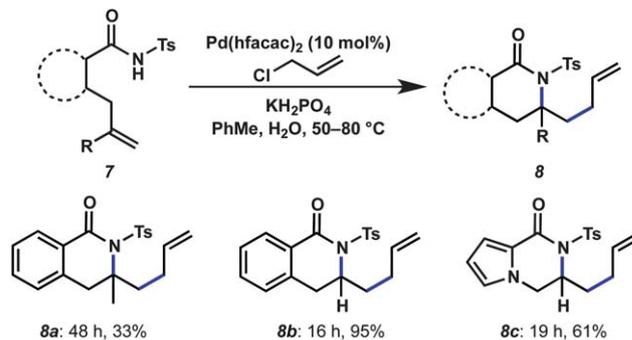
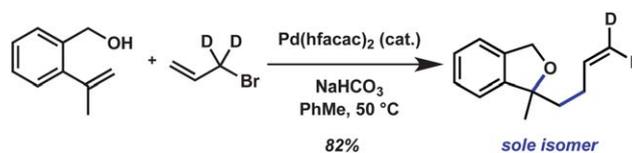
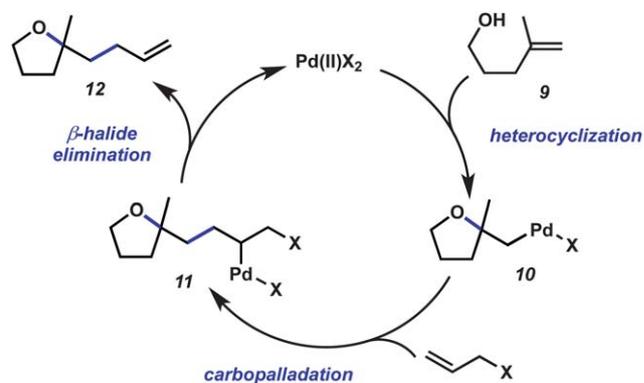
Although the precise mechanism for this heteroallylation reaction is yet to be fully elucidated, we have carried out preliminary studies designed to test the possible intermediacy of a π-allyl species. An experiment using dideuteroallyl bromide labelled at the allylic position resulted in exclusive formation 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		6 h	77% ^g
10: R' = CF ₃		Br		23 h	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		18 h	ⁱ

^a Reaction conditions: substrate (1 equiv.), allyl-X (5 equiv.), Pd(hfacac)₂ (5 mol%), NaHCO₃ (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 d₈-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.

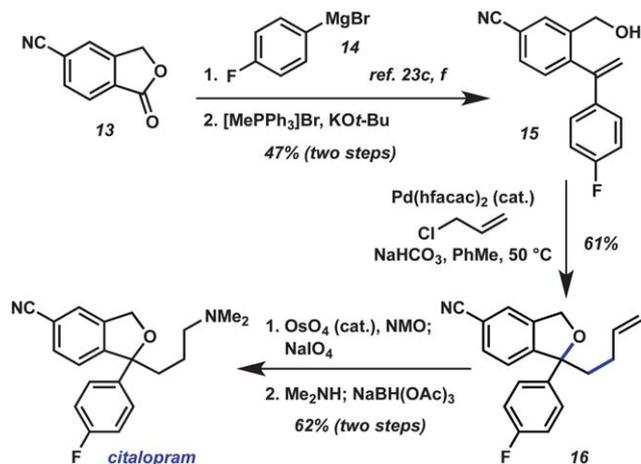
**Scheme 2** Aminoallylation substrates and conditions.**Scheme 3** Deuterium labelling study.**Scheme 4** Postulated catalytic cycle.

Furthermore, while not definitive, the lack of reactivity using Pd₂dba₃, 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.^{9c,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.

Notes and references

- (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley, New York, 2002, vol. 2; (b) G. Balme, D. Bouyssi, T. Lomberget and N. Monteiro, *Synthesis*, 2003, 2115; (c) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (d) L. F. Tietze, H. Ila and H. P. Bell, *Chem. Rev.*, 2004, **104**, 3453; (e) A. Minatti and K. Muñiz, *Chem. Soc. Rev.*, 2007, **36**, 1142; (f) E. M. Beccalli, G. Broggin, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (g) J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571; (h) J. P. Wolfe, *Synlett*, 2008, 2913; (i) K. H. Jensen and M. S. Sigman, *Org. Biomol. Chem.*, 2008, **6**, 4083; (j) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981; (k) D. M. Schultz and J. P. Wolfe, *Synthesis*, 2012, 351; (l) J. P. Wolfe, *Angew. Chem., Int. Ed.*, 2012, **51**, 10224.
- (a) M. F. Semmelhack and W. R. Epa, *Tetrahedron Lett.*, 1993, **34**, 7205; (b) J. P. Wolfe and M. A. Rossi, *J. Am. Chem. Soc.*, 2004, **126**, 1620; (c) J. E. Ney and J. P. Wolfe, *Angew. Chem., Int. Ed.*, 2004, **43**, 3605; (d) R. Lira and J. P. Wolfe, *J. Am. Chem. Soc.*, 2004, **126**, 13906; (e) J. E. Ney, M. B. Hay, Q. Yang and J. P. Wolfe, *Adv. Synth. Catal.*, 2005, **347**, 1614; (f) S. Hayashi, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2009, **131**, 2052; (g) S. Hayashi, H. Yorimitsu and K. Oshima, *Angew. Chem., Int. Ed.*, 2009, **48**, 7224; (h) J. D. Neukom, N. S. Perch and J. P. Wolfe, *J. Am. Chem. Soc.*, 2010, **132**, 6276; (i) D. N. Mai and J. P. Wolfe, *J. Am. Chem. Soc.*, 2010, **132**, 12157; (j) S. G. Newman and M. Lautens, *J. Am. Chem. Soc.*, 2011, **133**, 1778; (k) H. Liu, C. Li, D. Qiu and X. Tong, *J. Am. Chem. Soc.*, 2011, **133**, 6187; (l) S. Nicolai and J. Waser, *Org. Lett.*, 2011, **13**, 6324; (m) S. G. Newman, J. K. Howell, N. Nicolaus and M. Lautens, *J. Am. Chem. Soc.*, 2011, **133**, 14916; (n) D. C. Koester, M. Kobayashi, D. B. Werz and Y. Nakao, *J. Am. Chem. Soc.*, 2012, **134**, 6544; (o) B. A. Hopkins and J. P. Wolfe, *Angew. Chem., Int. Ed.*, 2012, **51**, 9886; (p) S. Nicolai, R. Sedigh-Zadeh and J. Waser, *J. Org. Chem.*, 2013, **78**, 3783; (q) N. Sun, Y. Li, G. Yin and S. Jiang, *Eur. J. Org. Chem.*, 2013, **13**, 2541.
- (a) N. R. Deprez and M. S. Sanford, *Inorg. Chem.*, 2007, **46**, 1924; (b) K. Muñiz, *Angew. Chem., Int. Ed.*, 2009, **48**, 9412; (c) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (d) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824; (e) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177.
- (a) M. R. Manzone, T. P. Zabawa, D. Kasi and S. R. Chemler, *Organometallics*, 2004, **23**, 5618; (b) A. Lei, X. Lu and G. Liu, *Tetrahedron Lett.*, 2004, **45**, 1785; (c) F. E. Michael, P. A. Sibbald and B. M. Cochran, *Org. Lett.*, 2008, **10**, 793; (d) T. A. Doroski, M. R. Cox and J. B. Morgan, *Tetrahedron Lett.*, 2009, **50**, 5162; (e) T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 16354.
- (a) E. J. Alexanian, C. Lee and E. J. Sorensen, *J. Am. Chem. Soc.*, 2005, **127**, 7690; (b) Y. Li, D. Song and V. M. Dong, *J. Am. Chem. Soc.*, 2008, **130**, 2962; (c) D. V. Liskin, P. A. Sibbald, C. F. Rosewall and F. E. Michael, *J. Org.*



- Chem.*, 2010, **75**, 6294; (d) Y.-B. Kang and L. H. Gade, *J. Am. Chem. Soc.*, 2011, **133**, 3658.
- 6 (a) J. Streuff, C. H. Hövelmann, M. Nieger and K. Muñoz, *J. Am. Chem. Soc.*, 2005, **127**, 14586; (b) L. V. Desai and M. S. Sanford, *Angew. Chem., Int. Ed.*, 2007, **46**, 5737; (c) K. Muñoz, *J. Am. Chem. Soc.*, 2007, **129**, 14542; (d) K. Muñoz, C. H. Hövelmann and J. Streuff, *J. Am. Chem. Soc.*, 2008, **130**, 763; (e) P. A. Sibbald and F. E. Michael, *Org. Lett.*, 2009, **11**, 1147; (f) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945; (g) E. L. Ingalls, P. A. Sibbald, W. Kaminsky and F. E. Michael, *J. Am. Chem. Soc.*, 2013, **135**, 8854.
- 7 (a) C. F. Rosewall, P. A. Sibbald, D. V. Liskin and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 9488; (b) S. Nicolai, S. Erard, D. Fernández González and J. Waser, *Org. Lett.*, 2010, **12**, 384; (c) S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 4680.
- 8 Other methods of heterocyclization onto unactivated alkenes with concomitant sp³-sp³ C-C bond formation include use of organomercurials (a-d), radical cyclizations (e-h) including Co-catalyzed reactions (i-k), Pd-catalyzed reactions with other subsequent processes (2p, l-o), or other related pathways (p, q): (a) B. Giese and K. Heuck, *Chem. Ber.*, 1981, **114**, 1572; (b) S. Danishefsky, E. Taniyama and R. R. Webb II, *Tetrahedron Lett.*, 1983, **24**, 11; (c) W. Carruthers, M. J. Williams and M. T. Cox, *J. Chem. Soc., Chem. Commun.*, 1984, 1235; (d) D. R. Adams, W. Carruthers, M. J. Williams and P. J. Crowley, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1507; (e) H. Yorimitsu, K. Wakabayashi, H. Shinokubo and K. Oshima, *Tetrahedron Lett.*, 1999, **40**, 519; (f) H. Yorimitsu, K. Wakabayashi, H. Shinokubo and K. Oshima, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1963; (g) T. W. Liwosz and S. R. Chemler, *J. Am. Chem. Soc.*, 2012, **134**, 2020; (h) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (i) D. Schuch, P. Fries, M. Dönges, B. Menéndez Pérez and J. Hartung, *J. Am. Chem. Soc.*, 2009, **131**, 12918; (j) P. Fries, D. Halter, A. Kleinschek and J. Hartung, *J. Am. Chem. Soc.*, 2011, **133**, 3906; (k) P. Fries, M. K. Müller and J. Hartung, *Org. Biomol. Chem.*, 2013, **11**, 2630; (l) M. A. Arai, M. Kuraishi, T. Arai and H. Sasai, *J. Am. Chem. Soc.*, 2001, **123**, 2907; (m) K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu and D. Yang, *J. Am. Chem. Soc.*, 2006, **128**, 3130; (n) K.-T. Yip, N.-Y. Zhu and D. Yang, *Org. Lett.*, 2009, **11**, 1911; (o) B. M. Trost and J. Rey, *Org. Lett.*, 2012, **14**, 5632; (p) S. Kumar, J.-C. P. Helt, J. Autschbach and M. R. Detty, *Organometallics*, 2009, **28**, 3426; (q) K. Komeyama, Y. Kouya, Y. Ohama and K. Takaki, *Chem. Commun.*, 2011, 47, 5031.
- 9 Heterocyclizations involving allylic electrophiles have been demonstrated for alkynes (a, b) and allenes (c-h): (a) Y. Wakabayashi, Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki, *Tetrahedron*, 1985, **41**, 3655; (b) Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki, *J. Org. Chem.*, 1991, **56**, 5816; (c) M. Kimura, K. Fugami, S. Tanaka and Y. Tamaru, *J. Org. Chem.*, 1992, **57**, 6377; (d) S. Ma and L. Li, *Org. Lett.*, 2000, **2**, 941; (e) S. Ma and W. Gao, *J. Org. Chem.*, 2002, **67**, 6104; (f) S. Ma, F. Yu and W. Gao, *J. Org. Chem.*, 2003, **68**, 5943; (g) S. Ma and Z. Yu, *J. Org. Chem.*, 2003, **68**, 6149; (h) B. Alcaide, P. Almendros, R. Carrascosa and T. Martínez del Campo, *Chem.-Eur. J.*, 2010, **16**, 13243.
- 10 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (b) T. J. Ritchie, S. J. F. Macdonald, R. J. Young and S. D. Pickett, *Drug Discovery Today*, 2011, **16**, 164; (c) A. Nadin, C. Hattotuwigama and I. Churcher, *Angew. Chem., Int. Ed.*, 2012, **51**, 1114.
- 11 (a) R. F. Heck, *J. Am. Chem. Soc.*, 1968, **90**, 5531; (b) R. C. Larock, J. C. Bernhardt and R. J. Driggs, *J. Organomet. Chem.*, 1978, **156**, 45; (c) J. Tsuji, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, WILEY-VCH, New York, 2002, vol. 2, pp. 1669-1767; (d) B. M. Trost and D. L. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (e) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (f) J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846.
- 12 Other combinations of catalyst, ligand, base, and solvent were less successful.
- 13 Carrying out the reaction under Ar using degassed solvent did not significantly impact conversion, suggesting that O₂ 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.
- 18 Substitution on the allyl component is less well tolerated under the present conditions. For example, reaction of a benzylic alcohol with 1-chloro-3-methyl-2-butene provided only a 20% isolated yield of the oxallylation product after 5 d at 50 °C. Use of 1,2-disubstituted alkenes leads to β-hydride elimination.
- 19 See ref. 2a and 8l as well as: (a) L. S. Hegedus, G. F. Allen and D. J. Olsen, *J. Am. Chem. Soc.*, 1980, **102**, 3583; (b) R. C. Larock and N. H. Lee, *J. Am. Chem. Soc.*, 1991, **113**, 7815; (c) L. F. Tietze, K. M. Sommer, J. Zinngrube and F. Stecker, *Angew. Chem., Int. Ed.*, 2005, **44**, 257.
- 20 See ref. 11a and b, as well as: (a) X. Lu, *Top. Catal.*, 2005, **35**, 73; (b) H. Zhao, A. Ariafard and Z. Lin, *Organometallics*, 2006, **25**, 812; (c) J. Le Bras and J. Muzart, *Tetrahedron*, 2012, **68**, 10065.
- 21 An alternative pathway that proceeds via a Pd(IV)-allyl complex may also be possible. See: (a) P. K. Byers and A. J. Canty, *J. Chem. Soc., Chem. Commun.*, 1988, 639; (b) R. Guo, J. L. Portscher, V. W. Day and H. C. Malinakova, *Organometallics*, 2007, **26**, 3874.
- 22 Clinical use: M. B. Keller, *J. Clin. Psychiatry*, 2000, **61**, 896.



- 23 Existing syntheses of citalopram: (a) K. P. Bøgesø and A. S. Toft, *U.S. Pat.* 4,136,193, 1979; (b) K. P. Bøgesø, *U.S. Pat.* 4,650,884, 1987; (c) H. Petersen, K. P. Bøgesø and M. Bech Sommer, *WO Pat.* 98/19511, 1998; (d) H. Petersen, P. Bregnedal and K. P. Bøgesø, *WO Pat.* 98/19512, 1998; (e) H. Petersen, *WO Pat.* 98/19513, 1998; (f) M. H. Rock, H. Petersen and P. Ellegaard, *WO Pat.* 00/12044, 2000; (g) R. Vedantham, P. V. N. K. V. Vetukuri, A. Boini, M. Khagga and R. Bandichhor, *Org. Process Res. Dev.*, 2013, **17**, 798.
- 24 (a) R. Pappo, D. S. Allen Jr, R. U. Lemieux and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478; (b) V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973.

