

ChemComm

This article is part of the

New advances in catalytic C–C bond formation via late transition metals web themed issue

Guest editor: Professor Michael Krische

All articles in this issue will be gathered together online at
[www.rsc.org/catalytic CC](http://www.rsc.org/catalytic_CC).



Cite this: *Chem. Commun.*, 2012, **48**, 609–611

www.rsc.org/chemcomm

Synthesis of chromans *via* Pd-catalyzed alkene carboetherification reactions†‡

Amanda F. Ward, Yan Xu and John P. Wolfe*

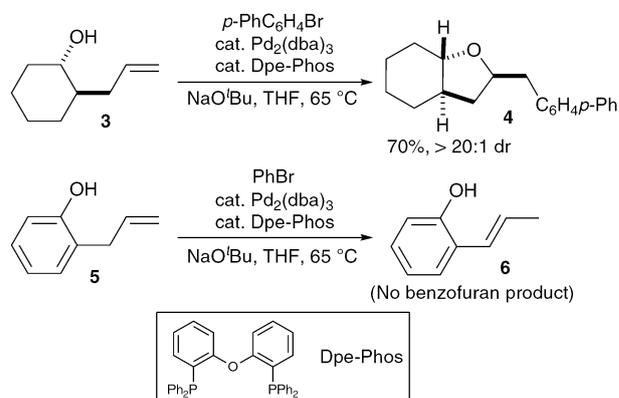
Received 22nd September 2011, Accepted 11th November 2011

DOI: 10.1039/c1cc15880e

A new method for the construction of 2-substituted and 2,2-disubstituted chromans *via* Pd-catalyzed carboetherification reactions between aryl/alkenyl halides and 2-(but-3-en-1-yl)phenols is described. These reactions effect formation of a C–O bond and a C–C bond to afford the chroman products in good yield, and also provide stereoselective access to tricyclic chroman derivatives.

Chromans and other benzo-fused oxygen heterocycles are displayed in a number of biologically active natural products,¹ including α -tocopherol^{2a} and polyalthidin.^{2b} In addition, 2-benzylchroman derivatives such as englitazone (**1**, antidiabetic activity)^{3a} and molecules with general structure **2** (β -secretase inhibitory activities)^{3b} have been explored as pharmaceutical leads (Fig. 1).

Over the past several years we have developed a new approach to the construction of substituted tetrahydrofurans *via* palladium-catalyzed carboetherification reactions between aryl or alkenyl halides and alcohols bearing pendant alkenes.^{4–6} For example, treatment of alcohol **3** with 4-bromobiphenyl, NaO^tBu, and a catalyst composed of Pd₂(dba)₃/Dpe-Phos provided **4** in 70% yield with >20:1 dr (Scheme 1). We envisioned that this method could provide a concise and convergent approach to benzofurans or chromans^{7,8} from simple starting materials (phenols bearing pendant alkenes).⁹ However, although the Pd-catalyzed carboetherification reactions were quite effective for the generation of tetrahydrofurans, our efforts to employ Pd-catalyzed carboetherification reactions for the synthesis of 6-membered heterocycles (*e.g.* tetrahydropyrans) failed to afford satisfactory results.¹⁰ In addition, the scope of our



Scheme 1 Palladium-catalyzed carboetherification reactions of alcohols vs. phenols.

carboetherification method appeared to be limited to aliphatic alcohol substrates, as efforts to couple 2-allylphenol **5** with bromobenzene failed to generate the desired substituted benzofuran product.¹¹ Instead, the formation of 2-(prop-1-en-1-yl)phenol **6** *via* double bond isomerization was observed.

We have previously illustrated that the mechanism of Pd-catalyzed carboetherification reactions, such as those shown in Scheme 1, involves suprafacial insertion of the substrate alkene into the Pd–O bond of an intermediate palladium alkoxide complex.^{4,5a} Recent mechanistic studies conducted by our group and others have shown that the rate of alkene insertion into Pd-heteroatom bonds is highly dependent on the nucleophilicity of the heteroatom, and the insertion likely occurs from an intermediate Pd-complex that bears a single phosphine ligand.¹² These results suggest that two factors may be responsible for the poor reactivity of phenols such as **5** in Pd/Dpe-Phos-catalyzed carboetherifications: (a) the relatively low nucleophilicity of phenols as compared to aliphatic alcohols; and (b) use of the chelating bis-phosphine Dpe-Phos, which may disfavor generation of the reactive monophosphine intermediate. These factors apparently slow the catalytic reaction to the point that alkene isomerization of **5** to **6** occurs more rapidly than the desired transformation.

The hypothesis outlined above suggests that use of catalysts bearing monodentate phosphine ligands may provide improved results in carboetherification reactions of phenol derivatives, as these ligands could potentially facilitate the key alkene insertion step. In addition, we also anticipated that the conversion of

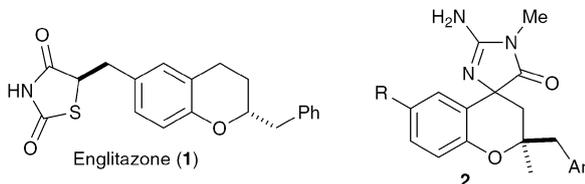


Fig. 1 Biologically active 2-benzylchroman derivatives.

University of Michigan, Department of Chemistry, 930 N. University Ave., Ann Arbor, MI 48109-1055, USA. E-mail: jpwolfe@umich.edu; Tel: +1 734-763-3432

† This article is part of the *ChemComm* ‘Advances in catalytic C–C bond formation via late transition metals’ web themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures and spectral data for all new compounds reported in the text. See DOI: 10.1039/c1cc15880e

Table 1 Optimization of ligand for the coupling of **7** with bromobenzene^a

Entry	Ligand	Yield ^b (%)
1	S-Phos	84 (75)
2	RuPhos	76
3	Me-Phos	31
4	Dave-Phos	12
5	Brett-Phos	47
6	Dpe-Phos	30

^a Conditions: 1.0 equiv. **7**, 2.0 equiv. PhBr, 2.0 equiv. NaO^tBu, 2 mol% Pd₂(dba)₃, 4 mol% ligand, toluene (0.25 M), 110 °C. ^b Yield were determined by ¹H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. The yield in parentheses is an isolated yield of the pure product.

2-(but-3-en-1-yl)phenol (**7**) to chroman **8** (Table 1) may be more straightforward than the analogous transformation of 2-allylphenol (**5**) to a benzofuran derivative, as **7** should be much less prone to base-mediated alkene isomerization than **5**. Thus, we elected to initially examine the coupling of **7** with bromobenzene using the biaryl monophosphine ligand S-Phos. We had previously found that this ligand provided good results in other challenging carboetherification reactions,^{5e} and we were gratified to discover that these conditions afforded the desired product **8** in 86% isolated yield. A quick survey of related biaryl phosphines did not lead to any further improvement in yield (entries 2–5), and Dpe-Phos produced **8** in only 30% yield (entry 6).

In order to examine the scope of the phenol carboetherification reactions, a number of substrates with different substitution patterns were synthesized and subjected to the optimized reaction conditions. As shown in Table 2, substrates **7**, **9**, and **10** were converted to 2-substituted- or 2,2-disubstituted chromans in moderate to good yield (entries 1–9). In addition, cyclopentane- and cyclohexane-derived substrates **11–12** were transformed into tricyclic products **22–24** with high diastereoselectivity (entries 10–12). However, stereocontrol was poor in the reaction of **13** with 4-bromo-*tert*-butylbenzene (2:1 dr), and a significant amount (*ca.* 25%) of an inseparable unidentified low molecular

Table 2 Pd-catalyzed carboetherification reactions of phenols bearing pendant alkenes^a

Entry	Substrate	RBr	Product	Yield ^b
1				75%
2	7			57%
3	7			51%
4				87%
5	9			71%
6	9			83%
7	9			68%
8				54%
9	10			56%
10				59% >20:1 dr
11				71% >20:1 dr
12	12			63% >20:1 dr
13				<i>ca.</i> 47% ^c 2:1 dr
14				37%

^a Conditions: 1.0 equiv. phenol substrate, 2.0 equiv. R-Br, 2.0 equiv. NaO^tBu, 2 mol% Pd₂(dba)₃, 4 mol% S-Phos, toluene (0.25 M), 110 °C. ^b Isolated yield (average of two experiments). ^c The two inseparable stereoisomeric products were isolated in 63% yield and *ca.* 75% purity. The remaining 25% of the mixture was primarily composed of an unidentified low molecular weight side product that appears to be derived from the phenol substrate.

weight side product was also formed (entry 13). In addition, substrates bearing internal alkenes failed to undergo the

desired transformation; no reaction was observed at temperatures up to 140 °C. Although these new reaction conditions were generally effective for the preparation of chromans, efforts to transform **5** into substituted benzofuran **26** were still only modestly successful; the desired product was generated in 37% yield (entry 14).

A range of different electrophiles were examined in the carboetherification reactions of **7**, **9**, and **10**. As shown in Table 2, aryl halides bearing chloride, fluoride, methoxy and diaryl ketone functionality were successfully converted to the desired products. Alkenyl halides were also effective coupling partners in these reactions (entries 6–7), and the coupling of **9** with the heteroaryl halide 3-bromopyridine also proceeded smoothly (entry 4). However, the scope of carboetherification reactions involving **11** and **12** was not as broad, and the use of aryl halides that were relatively electron rich or electron deficient led to poor reactivity or low yields.

In conclusion, we have developed a new method for the construction of 2-substituted chroman derivatives *via* Pd-catalyzed carboetherification reactions. These transformations employ simple substrates, and provide access to a number of different derivatives in a straightforward manner. In addition these are the first examples of Pd-catalyzed alkene carboetherification reactions between aryl bromides and alkenyl phenols, and are also rare cases in which six-membered oxygen heterocycles are generated *via* 1,2-alkene carboheterofunctionalization processes. Future studies will be directed towards the development of catalysts for enantioselective variants of these transformations.

Notes and references

- 1 H. C. Shen, *Tetrahedron*, 2009, **65**, 3931.
- 2 (a) J.-M. Zingg and A. Azzi, *Curr. Med. Chem.*, 2004, **11**, 1113 and references cited therein; (b) M. C. Zafra-Polo, M. C. Gonzalez, J. R. Tormo, E. Estornell and D. Cortes, *J. Nat. Prod.*, 1996, **59**, 913.
- 3 (a) F. J. Urban and B. S. Moore, *J. Heterocycl. Chem.*, 1992, **29**, 431 and references cited therein; (b) K. W. Hunt, J. P. Rizzi and A. Cook, *PCT Int. Appl.*, WO 2011072064A1, 2011.
- 4 For reviews, see: (a) J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571; (b) J. P. Wolfe, *Synlett*, 2008, 2913.
- 5 (a) M. B. Hay and J. P. Wolfe, *J. Am. Chem. Soc.*, 2005, **127**, 16468; (b) J. P. Wolfe and M. A. Rossi, *J. Am. Chem. Soc.*, 2004, **126**, 1620; (c) M. B. Hay and J. P. Wolfe, *Tetrahedron Lett.*, 2006, **47**, 2793; (d) M. B. Hay, A. R. Hardin and J. P. Wolfe, *J. Org. Chem.*, 2005, **70**, 3099; (e) A. F. Ward and J. P. Wolfe, *Org. Lett.*, 2009, **11**, 2209.
- 6 For recent, complementary alkene difunctionalization reactions of unsaturated alcohols that generate disubstituted tetrahydrofurans with formation of both a C–C and a C–O bond, see: (a) P. Fries, D. Halter, A. Kleinschek and J. Hartung, *J. Am. Chem. Soc.*, 2011, **133**, 3906; (b) Z. Chen and J. R. Falck, *Angew. Chem., Int. Ed.*, 2011, **50**, 6626; (c) G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474; (d) S. Protti, D. Dondi, M. Fagnoni and A. Albin, *Eur. J. Org. Chem.*, 2008, 2240; (e) X. Yang, X. Fang, X. Yang, M. Zhao, Y. Han, Y. Shen and F. Wu, *Tetrahedron*, 2008, **64**, 2259.
- 7 For recent reviews on the synthesis of chromans, see: (a) ref. 1; (b) Y. Tang, J. Oppenheimer, Z. Song, L. You, X. Zhang and R. P. Hsung, *Tetrahedron*, 2006, **62**, 10785; (c) S. B. Ferreira, F. de C. da Silva, A. C. Pinto, D. T. G. Gonzaga and V. F. Ferreira, *J. Heterocycl. Chem.*, 2009, **46**, 1080; (d) Y.-L. Shi and M. Shi, *Org. Biomol. Chem.*, 2007, **5**, 1499.
- 8 For selected recent syntheses of chroman derivatives, see: (a) D. Enders, X. Yang, C. Wang, G. Raabe and J. Runkik, *Chem.–Asian. J.*, 2011, **6**, 2255; (b) Z. Xin, Y. Zhang, H. Tao, J. Xue and Y. Li, *Synlett*, 2011, 1579; (c) G. Hernandez-Torres, M. C. Carreno, A. Urbano and F. Colobert, *Eur. J. Org. Chem.*, 2011, 3864; (d) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 8379; (e) M. Leibeling, D. C. Koester, M. Pawliczek, S. C. Schild and D. B. Werz, *Nat. Chem. Biol.*, 2010, **6**, 199.
- 9 Two other Pd-catalyzed alkene carboetherification methods have successfully been employed for synthesis of benzofurans or chromans from phenols bearing pendant alkenes. However, these transformations appear to be limited to alkenes bearing a substituent on the internal carbon atom. For Pd-catalyzed oxyalkynylation reactions between unsaturated phenols and hypervalent iodoalkyne reagents, see: (a) S. Nicolai, S. Erard, D. F. Gonzalez and J. Waser, *Org. Lett.*, 2010, **12**, 384. For Pd-catalyzed domino Wacker/Heck reactions between unsaturated phenols and α,β -unsaturated esters or ketones, see: (b) L. F. Tietze, D. A. Spiegel, F. Stecker, J. Major, C. Raith and C. Große, *Chem.–Eur. J.*, 2008, **14**, 8956; (c) L. F. Tietze, J. Zinngrebe, D. A. Spiegel and F. Stecker, *Heterocycles*, 2007, **74**, 473; (d) L. F. Tietze, F. Stecker, J. Zinngrebe and K. M. Sommer, *Chem.–Eur. J.*, 2006, **12**, 8770; (e) L. F. Tietze, K. M. Sommer, J. Zinngrebe and F. Stecker, *Angew. Chem., Int. Ed.*, 2005, **44**, 257.
- 10 Only a single example of a Pd-catalyzed alkene difunctionalization reaction that generates a tetrahydropyran product has been reported. See ref. 6c.
- 11 M. B. Hay, A. F. Ward, J. P. Wolfe, unpublished results.
- 12 (a) J. D. Neukom, N. S. Perch and J. P. Wolfe, *Organometallics*, 2011, **30**, 1269; (b) J. D. Neukom, N. S. Perch and J. P. Wolfe, *J. Am. Chem. Soc.*, 2010, **132**, 6276; (c) P. S. Hanley, D. Markovic and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 6302; (d) P. S. Hanley and J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 15661.