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Synthesis of 2,3-Dihydrobenzofurans via the Palladium Catalyzed Carboalkoxylation of 2-Allylphenols

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Abstract

A new Pd-catalyzed alkene carboalkoxylation strategy for the preparation of 2,3-dihydrobenzofurans is described. This method effects the coupling of readily available 2-allylphenol derivatives with aryl triflates to generate a wide range of functionalized 2,3-dihydrobenzofurans in good yields and diastereoselectivities (up to >20:1). Use of newly developed reaction conditions that promote *anti*-heteropalladation of the alkene is essential in order to generate products in high yield.

2,3-Dihydrobenzofurans are a valuable structural motif present in numerous naturally occurring and biologically active molecules[i] with notable examples such as the flavaglines,[ii] morphine alkaloids,[iii] and lignans and neolignanans.[iv] The biological importance of this motif has served as inspiration for numerous synthetic approaches to functionalized derivatives.[v] Some examples of these efforts include palladium-catalyzed Wacker-type oxidative cyclizations,[vi] intramolecular palladium-catalyzed allylic alkylations,[vii] copper or nickel catalyzed alkene diarylation or alkylarylation of allylphenyl ethers,[viii] and palladium catalyzed C-H activation/C-O cyclizations.[ix] Despite the attention these compounds have received in the synthetic community, a general cross-coupling approach employing aryl electrophiles and simple 2-allylphenol derivatives has yet to be reported.[x]

Over the past decade our group has developed a series of Pd-catalyzed alkene carboalkoxylation and carboamination reactions as a means of accessing functionalized, stereodefined heterocycles.[xi] Despite the broad substrate scope of these transformations, previous attempts to access the 2,3-dihydrobenzofuran core via Pd-catalyzed alkene carboalkoxylation with aryl or alkenyl halide electrophiles were met with limited success. For example, we have previously reported conditions for the construction of chroman derivatives (e.g., **3a**) via Pd-catalyzed carboalkoxylation of 2-(but-2-enyl)phenols (e.g., **1**), but the analogous generation of **4a** from 2-allylphenol **2a** proceeded in low yield (37%) (Scheme 1).[xii,xiii] The main side product observed in these reactions resulted from base-

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mediated isomerization of the substrate alkene, which appeared to be relatively fast compared to the rate of catalysis.

Our prior studies on the mechanism of related Pd-catalyzed alkene carboamination reactions illustrated the rate of the key carbon-heteroatom bond-forming step, *syn*-aminopalladation of the alkene, was highly dependent on the electronic properties of the nucleophile, with electron-rich amines undergoing relatively fast reactions.[xiv] As such, we reasoned that the challenges associated with Pd-catalyzed alkene carboalkoxylations of 2-allylphenols were due at least in part to the relatively poor nucleophilicity of the aromatic alcohol substrate. We have recently demonstrated that Pd-catalyzed alkene carboamination reactions of electron-poor nucleophiles that fail under typical conditions can be conducted in high yield when reaction conditions that favor an anti-aminopalladation mechanistic pathway are employed.[xv,xvi,xvii] In this communication we describe the application of these conditions to the Pd-catalyzed synthesis of dihydrobenzofurans from 2-allylphenols, which proceeds through a key anti-oxypalladation of the substrate's pendant alkene.[xviii]

We began our studies by exploring the coupling of 2-allylphenol **2a** and phenyl triflate using conditions analogous to those previously employed in Pd-catalyzed alkene carboamination reactions that proceed via *anti*-aminopalladation of the alkene.[xv-xvii] We were pleased to observe that a number of biaryl phosphine ligands provided the desired product **4a**, with CPhos proving optimal to afford 85% yield of **4a**.

With optimized reaction conditions in hand we explored the scope of this transformation (Table 2). We found that the reaction was fairly general with respect to the aryl triflate component, as electron-rich, electron-poor and ortho-substituted electrophiles all provided the desired dihydrobenzofuran products **4a**–**4d** in good yield. However, alkenyl triflates were found to have limited efficacy in this transformation; product **4e** was generated in only 25% yield. Substitution on the aromatic ring of the substrate was generally well-tolerated as substrates bearing halogens, methoxy groups, or fused aromatic rings were all converted to the desired products **4f**–**4l** in good yield. The reactions were also effective with substrates bearing allylic substituents to afford *trans*-2,3-disubstituted products **4m**–**4p**. The diastereoselectivity of these transformations was dependent on the size of the allylic group. Substrates bearing a methyl group were transformed with moderate stereocontrol (5-8:1 dr), whereas substrates that contain an allylic phenyl group were converted with high selectivity (15-29:1 dr). Finally, substitution at the internal alkene carbon atom was also tolerated to generate products **4q**–**4r**. However, larger loadings of CPhos (7.5 mol%) were necessary to obtain reproducible yields. The synthesis of tricyclic rings from exo-methylenecycloalkane derivatives proceeded with excellent stereocontrol to afford **4s**–**4v**. The consecutive double carboalkoxylation of 2,3-diallylbenzene-1,4-diol proceeded to afford **4w** in modest yield, but with low diastereoselectivity.

To probe the mechanism of this transformation by examining the stereochemistry of the alkene addition we carried out the Pd-catalyzed carboalkoxylation reaction of deuterated substrate ***d*-2a** with phenyl triflate (Scheme 2). This reaction afforded ***d*-4a**, which results from *anti*-addition of the oxygen atom and the aryl group to the alkene, in 81% yield and 20:1 dr. Interestingly, when ***d*-2a** was coupled with bromobenzene using the conditions

previously employed for the synthesis of chromans the stereoisomeric product ***d*-4a**, generated via *syn*-addition to the alkene, was formed (albeit in low yield with modest 2:1 dr).[xix] This further illustrates the impact of reaction conditions on the stereochemistry of the heteropalladation step in Pd-catalyzed alkene difunctionalization reactions.[xv–xvii,xx]

Based on the results of the deuterium labelling experiments, the Pd-catalyzed alkene carboalkoxylation reactions of 2-allylphenols likely proceed through the catalytic cycle illustrated in Scheme 3. Oxidative addition of the aryl triflate to the Pd(0)/CPhos complex (generated in situ) affords intermediate palladium(aryl)triflate complex **5**. The cationic Pd-complex then binds to the alkene of substrate **2** to yield **6**. Deprotonation of the phenol followed by *anti*-oxypalladation of the alkene provides intermediate **7**, which undergoes reductive elimination to give the product **4** with concomitant regeneration of the Pd(0) catalyst.

Given the utility of these new conditions for Pd-catalyzed alkene-carboalkoxylation reactions of 2-allylphenols, we elected to briefly survey the utility of these conditions in chroman-forming reactions. As shown in Table 3, our newly developed conditions successfully promoted the coupling of **1** with three different aryl triflates to afford chromans **3a-c**. The yields obtained using the *anti*-aminopalladation conditions with phenyl triflate or *p*-methoxyphenyl triflate as the electrophile were lower than the analogous reactions we have previously reported with aryl bromide electrophiles and *syn*aminopalladation conditions (entries 1-2). However, the *anti*-aminopalladation conditions provided results superior to those obtained using the *syn*-aminopalladation conditions with an electron-poor aryl electrophile (entry 3).

Conclusions

In conclusion, we have developed a new method for the synthesis of 2,3-dihydrobenzofurans via the Pd-catalyzed alkene carboalkoxylation of 2-allylphenols. The reactions proceed in good yields with diastereoselectivities of 5:1 to >20:1 dr, and are effective with a broad range of aryl triflate electrophiles. This provides a new means of rapidly generating many different substituted 2,3-dihydrofurans from the corresponding phenol in a short synthetic sequence. Moreover, this further illustrates the utility of conditions that favor *anti*-aminopalladation pathways in Pd-catalyzed alkene difunctionalization reactions of relatively weak nucleophiles .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

i. a Tamada M, Endo K, Hikino H, Kabuto C. Tetrahedron Lett. 1979; 10:873.b Namikoshi M, Kobayashi H, Yoshimoto T, Meguro S. Chem. Lett. 2000; 29:308.c Li SY, Fuchino H, Kawahara

N, Sekita S, atake MS. J. Nat. Prod. 2002:262. [PubMed: 11908962] d Li Y, Wu C, Liu D, Proksch P, Guo P, Lin W. J. Nat. Prod. 2014; 77:138. [PubMed: 24387683] e Lee J-H, Kim Y-G, Ryu SY, Choo MH, Lee J. J. Nat. Prod. 2014; 77:168. [PubMed: 24456071]

ii. a Thaud F, Bernard Y, Turkeri G, Dirr R, Aubert G, Cresteil T, Baguet A, Tomasetto C, Svitkin Y, Sonenberg N, Nebigil CG, Désaubry L. J. Med. Chem. 2009; 52:5176. [PubMed: 19655762] b Ribeiro N, Thuaud F, Nebigil C, Désaubry L. 2012; 20:1857.c Ribeiro N, Thaud F, Bernard Y, Gaiddon C, Cresteil T, Hild A, Hirsch E, Michel MP, Nebigil CG, Désaubry L. J. Med. Chem. 2012; 55:10064. [PubMed: 23072299]

iii. For recent reviews, see: Bentley KW. Nat. Prod. Rep. 2000; 17:247. [PubMed: 10888012] Blakemore PR, White JD. Chem. Commun. 2002; 11:1159.Zezula J, Hudlicky T. Synlett. 2005; 3:388.

iv. For a recent review, see: Pan J-Y, Chen S-L, Ynag M-H, Wu J, Sinkkonen J, Zou K. Nat. Prod. Rep. 2009; 26:1251. [PubMed: 19779640]

v. For recent reviews, see: Sheppard TD. J. Chem. Res. 2011; 35:10476.Bertolini F, Pineschi M. Org. Prep. Proceed. Int. 2009; 11:385.

vi. a Uozumi Y, Kato K, Hayashi T. J. Am. Chem. Soc. 1997; 119:5063.b Trend RM, Ramtohul YK, Ferreira EM, Stoltz BM. Angew. Chem. Int. Ed. 2003; 42:2892.

vii. Pelly SC, Govender S, Fernandes MA, Schmalz H-G, de Koning CB. J. Org. Chem. 2007; 72:2857. [PubMed: 17375958]

viii. a You W, Brown MK. J. Am. Chem. Soc. 2014; 136:14730. [PubMed: 25303225] b Cong H, Fu GC. J. Am. Chem. Soc. 2014; 136:3788. [PubMed: 24575754]

ix. a Wang X, Lu Y, Dai H-X, Yu J-Q. J. Am. Chem. Soc. 2010; 132:12203. [PubMed: 20715820] b Wang H, Li G, Engle KM, Yu J-Q, Davies HML. J. Am. Chem. Soc. 2013; 135:6774. [PubMed: 23600441]

x. Palladium-catalyzed alkene carboalkoxylation reactions between 2-(2-methylallyl)phenols and allyl chloride have been previously reported. These transformations are postulated to proceed via Pd(II)-mediated oxypalladation of the alkene followed by Heck-type carbopalladation of allyl chloride and subsequent b-chloride elimination. See: Hewitt JF, Williams HL, Aggarwal P, Smith CD, France DJ. Chem. Sci. 2013; 4:3538.

xi. For recent reviews, see: Wolfe JP. Synlett. 2008:2913.Schultz DM, Wolfe JP. Synthesis. 2012; 44:351. [PubMed: 23243321] Wolfe JP. Top. Heterocycl. Chem. 2013; 32:1.

xii. Ward AF, Xu Y, Wolfe JP. Chem. Commun. 2012; 48:609.

xiii. In contrast, analogous transformations of 2-allylanilines are quite facile and efficient. See: Lira R, Wolfe JP. J. Am. Chem. Soc. 2004; 126:13906–13907. [PubMed: 15506735]

xiv. For studies on the mechanism of syn-migratory insertion of alkenes into Pd–N bonds, see: Neukom JD, Perch NS, Wolfe JP. J. Am. Chem. Soc. 2010; 132:6276. [PubMed: 20397666] Hanley PS, Marković D, Hartwig JF. J. Am. Chem. Soc. 2010; 132:6302. [PubMed: 20408534] Neukom JD, Perch NS, Wolfe JP. Organometallics. 2011; 30:1269.Hanley PS, Hartwig JF. J. Am. Chem. Soc. 2011; 133:15661. [PubMed: 21815675] White PB, Stahl SS. J. Am. Chem. Soc. 2011; 133:18594. [PubMed: 22007610]

xv. Fornwald RM, Fritz JA, Wolfe JP. Chem. Eur. J. 2014; 20:8782. [PubMed: 24938206]

xvi. Peterson LJ, Wolfe JP. Adv. Synth. Catal. 2015; 357:2339. [PubMed: 26622222]

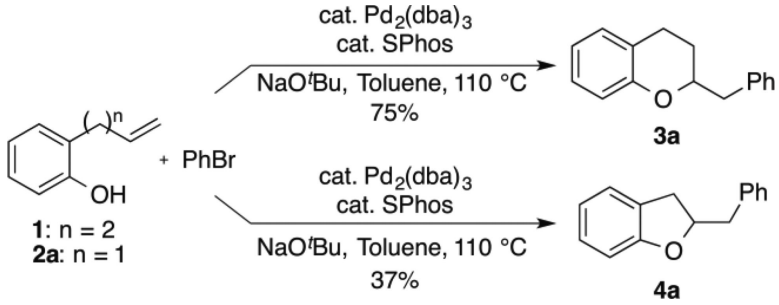
xvii. Babij NR, McKenna GM, Fornwald RF, Wolfe JP. Org. Lett. 2014; 16:3412. [PubMed: 24916343]

xviii. For reviews on stereochemistry of alkene nucleopalladation reactions, see: Kocovsky P, Bäckvall J–E. Chem. Eur. J. 2015; 21:36. [PubMed: 25378278] McDonald RI, Stahl SS. Chem. Rev. 2011; 111:2981. [PubMed: 21428440] Jensen KH, Sigman MS. Org. Biomol. Chem. 2008; 6:4083–4088. [PubMed: 18972034]

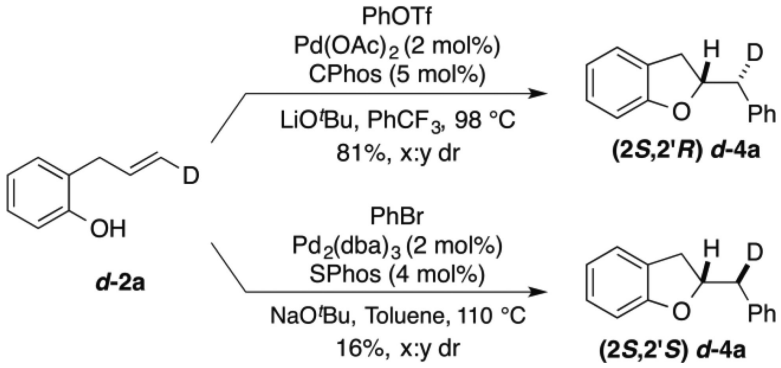
xix. The deuterated 2-allylphenol starting material was completely consumed in the coupling of ***d*-2a** proceeded to completion. The low yield of **(2*S*,2'*S*)-*d*-4a** is the result of the formation of a complex mixture of unidentifiable side products. Efforts to improve yields in reactions of aryl bromides through use of metal triflate additives has thus far been unsuccessful.

xx. a Liu G, Stahl SS. J. Am. Chem. Soc. 2007; 129:6328. [PubMed: 17439217] b Weinstein AB, Stahl SS. Angew. Chem. Int. Ed. 2012; 51:11505.c Ye X, White PB, Stahl SS. J. Org. Chem. 2013;

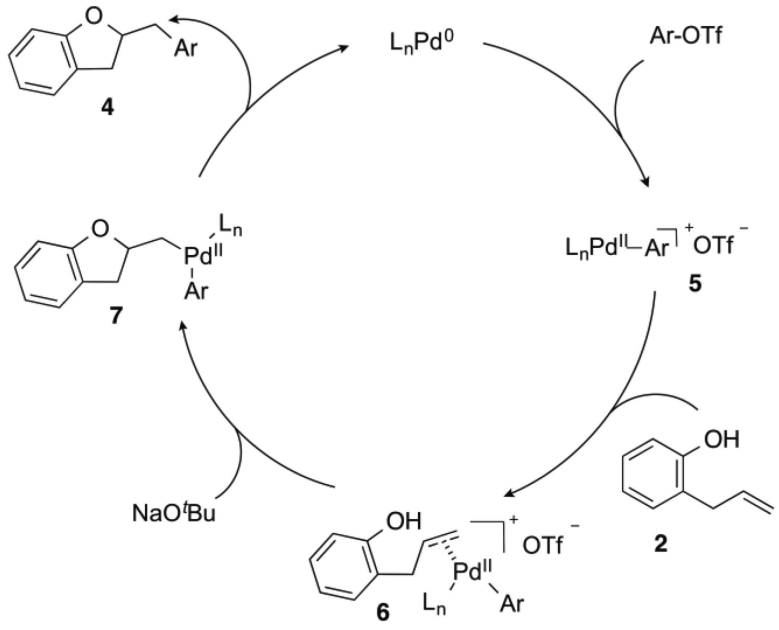
78:2083. [PubMed: 23157332] d Martinez C, Wu Y, Weinstein AB, Stahl SS, Liu G, Muniz K. J. Org. Chem. 2013; 78:6309. [PubMed: 23734834]



Scheme 1.
Pd-catalyzed synthesis of chromans vs dihydrobenzofurans



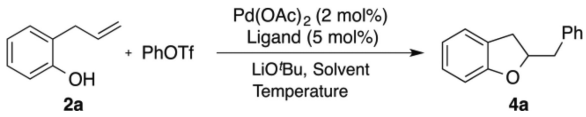
Scheme 2.
Deuterium Labeling Experiments



Scheme 3.
Catalytic Cycle

Table 1

Ligand and solvent optimization[a]



Entry	Solvent	Ligand	NMR Yield[b] (Isolated Yield)
1	$PhCF_3$	SPhos	50
2	$PhCF_3$	XPhos	41
3	$PhCF_3$	RuPhos	73
4	$PhCF_3$	BrettPhos	73
5	$PhCF_3$	CPhos	84 (85)
6	^{t}BuOH	CPhos	46[c]
7	$PhCF_3$	None[d]	0

[a]Reaction Conditions: 1.0 equiv **2a**, 1.2 equiv PhOTf, 1.4 equiv LiO^{t}Bu, 2 mol % $Pd(OAc)_2$, 5 mol % ligand, solvent (0.125 M), 98 °C, 16 h.

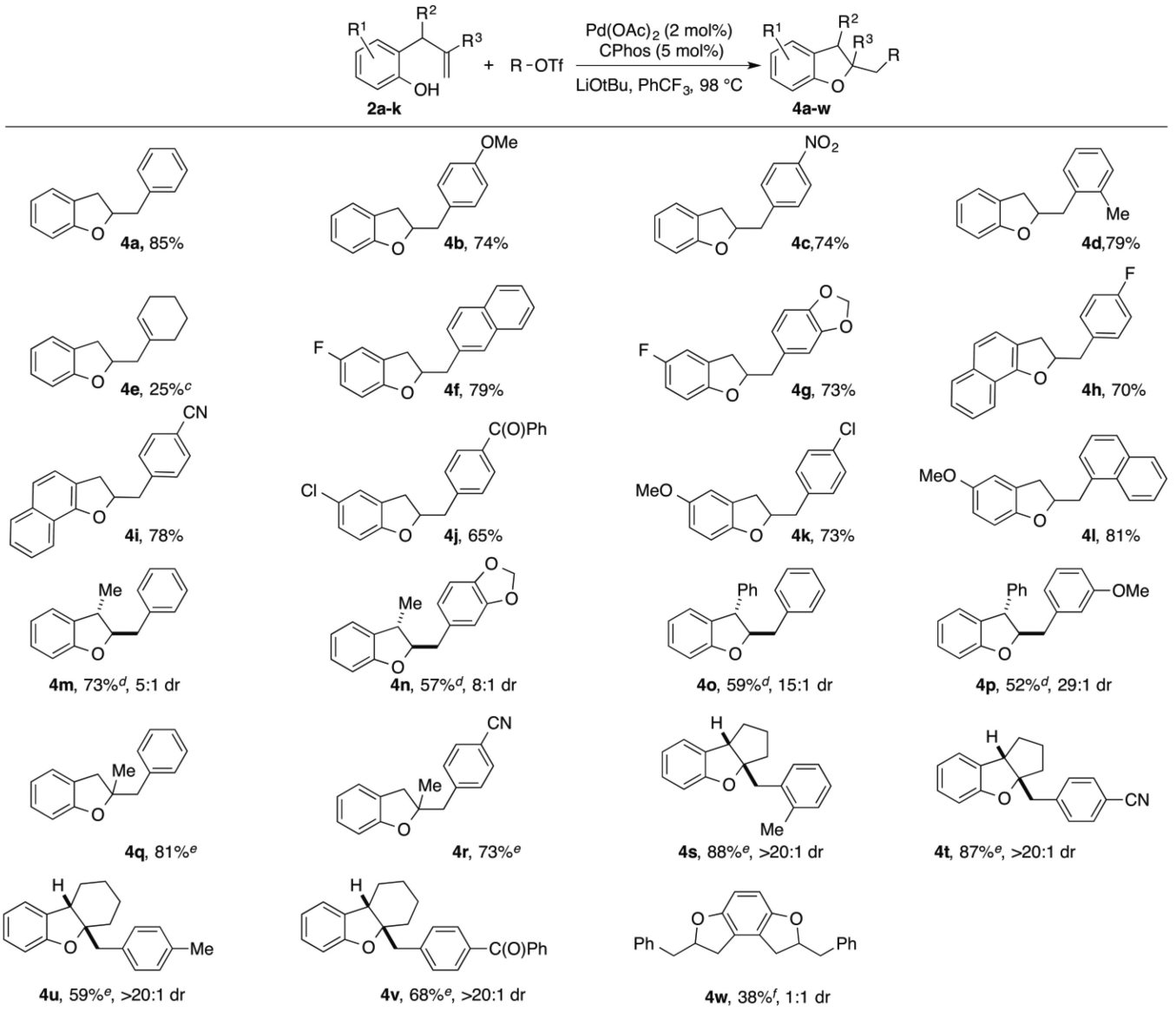
[b]NMR yields were determined using phenanthrene as an internal standard.

[c]The reaction was conducted at 82 °C.

[d]This control reaction was conducted in the absence of $Pd(OAc)_2$ and ligand.

Table 2

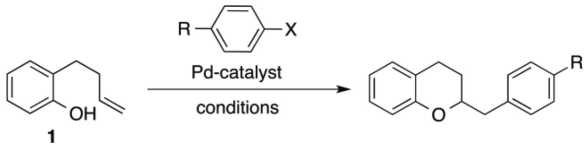
Pd-Catalyzed Synthesis of Dihydrobenzofurans[a]



[a]Reaction Conditions: 1.0 equiv **2**, 1.2 equiv R-OTf, 1.4 equiv LiO^{t}Bu, 2 mol % $Pd(OAc)_2$, 5 mol % CPhos, $PhCF_3$ (0.125 M), 98 °C, 16 h. [b]Yields are isolated yields (average of two or more experiments) of material with >95% purity unless otherwise noted. Diastereomeric ratios were determined by ^{1}H NMR analysis, and diastereomeric ratios of isolated materials were identical to those of the crude products unless otherwise noted in the Supporting Information. [c]The isolated product contained ca. 10% of unidentified impurities. [d]The reaction was conducted using BrettPhos as ligand. [e]The reaction was conducted using a 7.5 mol% loading of CPhos. [f]The reaction was conducted using 2.4 equiv PhOTf and 2.4 equiv LiO*t*Bu in $PhCF_3$ (0.008 M). Diastereomeric ratio determined by GC.

Table 3

Comparison of Conditions for Chroman Synthesis[a]



Entry	R	X	Yield[b]
1	H	OTf	68
2	H	Br	76[c]
3	OMe	OTf	41
4	OMe	Br	57[c]
5	C(O)Ph	OTf	78
6	C(O)Ph	Br	51[c]

[a]Reaction Conditions for X = OTf: 1.0 equiv **1**, 1.2 equiv R-OTf, 1.4 equiv LiO^{t}Bu, 2 mol % $Pd(OAc)_2$, 5 mol % ligand, solvent (0.125 M), 98 °C, 16 h. Reactn Conditions for X = Br: 1.0 equiv **1**, 2.0 equiv R–Br, 2.0 equiv NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % S-Phos, toluene (0.25 M), 110 °C.

[b]Yields are isolated yields (average of two or more experiments) of material with >95% purity.

[c]Yields as reported in reference 12.