Organic LETTERS

Letter

pubs.acs.org/OrgLett

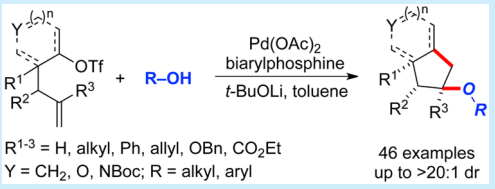
Palladium-Catalyzed Alkene Carboalkoxylation Reactions of Phenols and Alcohols for the Synthesis of Carbocycles

Derick R. White, Madeline I. Herman, and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055, United States

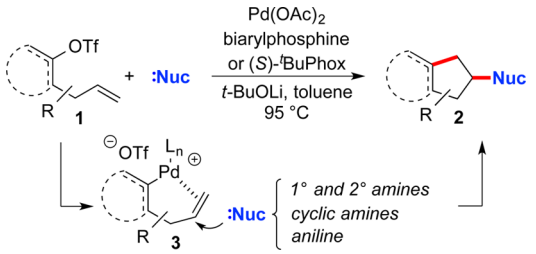
Supporting Information

ABSTRACT: Intermolecular alkene difunctionalization reactions between terminal alkenes bearing a pendant aryl or alkenyl triflate electrophile and exogenous alcohol or phenol nucleophiles are described. These transformations afford substituted indanyl or alkylidenecyclopentyl ethers in high yield with excellent diastereoselectivity. The transformations proceed through intermolecular capture of an intermediate [Pd(II)-alkene]$^+$[OTf]$^-$ complex by the alcohol or phenol nucleophile.



Alkene difunctionalization reactions represent a powerful synthetic tool for the rapid construction of two new bonds and up to two new stereocenters via 1,2-addition to an alkene.[1] We recently reported a Pd-catalyzed alkene carboamination reaction between 2-allylphenyl triflates **1** and exogenous amine nucleophiles that affords cyclopentylamine derivatives **2** in good yield and high stereoselectivity (Scheme 1).[2] During the course

Scheme 1. Pd-Catalyzed Intermolecular Carboheterofunctionalization Reactions



of those studies, we observed that weak nucleophiles such as amides or sulfonamides were not effectively coupled, whereas more nucleophilic amines such as pyrrolidine or morpholine afforded products in excellent yield. These effects are not surprising, as the mechanism of these reactions involves capture of cationic Pd–alkene complex **3** by the nucleophile, and the rate of that process relative to that of potential competing side reactions should be nucleophile dependent.

Due to the dependency of reaction efficiency on substrate nucleophilicity, we were curious as to whether oxygen nucleophiles could be employed in analogous carboalkoxylation reactions. We felt that these reactions may be challenging to develop since alcohols and phenols are considerably less nucleophilic than aliphatic amines. In addition, Pd-catalyzed oxidation of alcohols to aldehydes or ketones is well established,[3] and competing cross-coupling of the aryl/alkenyl triflate with the alcohol to afford an enol ether or aryl ether may also be problematic.[4] Aryl and alkenyl triflates can also undergo transesterification reactions with alkoxides that would lead to destruction of substrates such as **1**.[5]

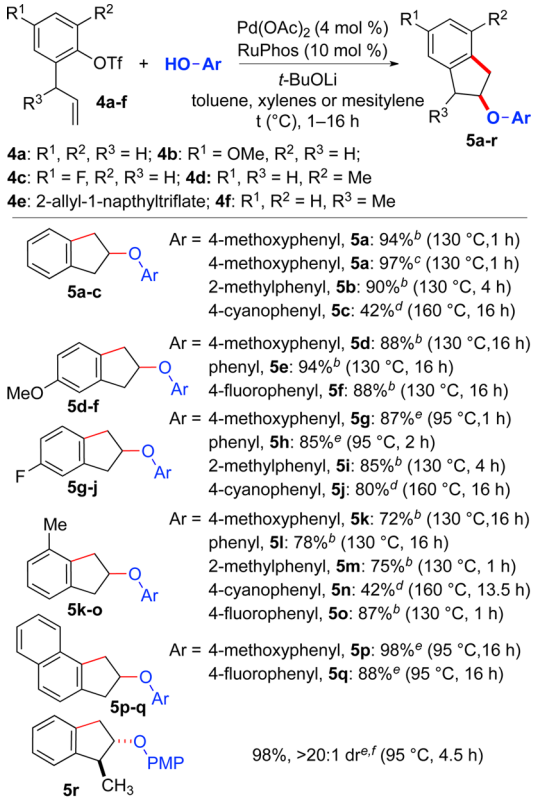
Despite these potential challenges, the development of a coupling reaction between **1** and alcohols/phenols would provide rapid access to *O*-substituted indanes and cyclopentenoid derivatives, which are useful synthetic intermediates[6] that are prevalent in pharmaceuticals,[7] natural products,[8] fragrances,[9] agrochemicals,[10] and materials.[10] In addition, this approach may have significant advantages over existing methods for the construction of alkylidenecyclopentyl ether derivatives. The most common methods for the synthesis of these compounds involve substitution reactions of cycloalkyl halides or Mitsunobu reactions of cyclic secondary alcohols.[11] Substitution reactions between alcohols or alkoxides and secondary alkyl electrophiles often require harsh reaction conditions and suffer from (a) competing elimination reactions and (b) competition between S_N1 and S_N2 pathways that leads to mixtures of stereoisomers.[12] The synthesis of ethers bearing 3°-alkyl groups are particularly challenging since 3° alkyl halides do not participate in S_N2 reactions, and substitution reactions of tertiary alcohols are often slow due to steric hindrance.[13,14]

In our preliminary studies, we investigated the reactivity of 2-allylphenyl triflate derivatives **4a–f** with phenol nucleophiles, which we reasoned would be completely deprotonated under the reaction conditions to provide nucleophilic phenoxides. The aryl triflate substrates were prepared in three steps from the corresponding phenols via *O*-allylation, aromatic Claisen rearrangement, and then treatment with triflic anhydride. We initially examined conditions that we previously developed with amine nucleophiles,[2] and we were pleased to discover that a minor modification to these conditions (use of RuPhos[15] as ligand in place of BrettPhos)[16] provided products in good to excellent yield for most transformations.[2,17] As shown in Scheme 2, electron-donating or -withdrawing substituents in the 4-position of the aryl triflate (R^1 = H, F, OCH_3; **5a–j**) were

Received: June 28, 2017

DOI: 10.1021/acs.orglett.7b01975
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Alkene Carboalkoxylation Reactions between *o*-Allylphenyl Triflates and Phenols[a]



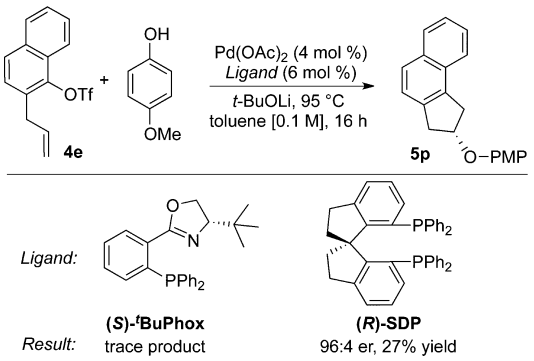
[a]Reaction conditions: $Pd(OAc)_2$ (4 mol %), RuPhos (10 mol %), Ar-OH (1.2 equiv), *t*-BuOLi (1.4 equiv), **4a–f** (1.0 equiv, 0.1 mmol), [0.1 M]. Yields are isolated yields. [b]Xylenes was used as solvent. [c]The reaction was conducted on a 1.0 mmol scale. [d]Mesitylene was used as solvent. [e]Toluene was used as solvent. [f]RuPhos (6 mol %) and *t*-BuONa (1.4 equiv) base were used as ligand and base.

tolerated, as were substituents adjacent to the $C_{(aryl)}$–OTf bond (**5k–q**), although in some cases lower yields were obtained with these more hindered substrates. A substrate (**4f**) bearing an allylic substituent was efficiently converted to **5r** in 98% yield and >20:1 dr.[18]

As expected, the combined nucleophilicity of the phenol and electrophilicity of the aryl triflate had a significant impact on reactivity and chemical yield. In general, couplings between electron-poor aryl triflates and electron-rich phenol nucleophiles proceed at lower reaction temperatures and shorter reaction times (e.g., **5g**, 95 °C/1 h) than are required for the coupling of electron-rich aryl triflates and electron-poor phenol nucleophiles (e.g., **5f**, 130 °C/16 h and **5n**, 160 °C/13.5 h). This is likely due to the influence of the arene substituent on the electrophilicity of the metal center in intermediate **3** (Scheme 1), as electron-donating groups will diminish the electrophilicity of the metal, but electron-withdrawing groups increase the electrophilicity of the metal and thereby increase the reactivity of the coordinated alkene toward nucleophilic attack.[19]

We have previously shown that Pd-catalyzed couplings of substituted 2-allylphenyl triflate derivatives with amines proceed with high levels of enantioselectivity (up to 99:1 er) when (*S*)-^{t}BuPhox is used as the ligand.[2a] As such, we examined an analogous asymmetric carboalkoxylation reaction between 2-allyl-1-naphthyl triflate (**4e**) and 4-methoxyphenol. Unfortunately, only a trace amount of product was generated (Scheme 3). After screening several other chiral ligands, the (*R*)-SDP ligand was found to deliver **5p** with high enantioselectivity (96:4 er) but modest chemical yield (27%), and these conditions did not prove to be general as efforts to employ other phenol nucleophiles have thus far produced very low yields of the desired products. Thus, the asymmetric transformations, although feasible, will require further catalyst development to increase scope and efficiency.

Scheme 3. Asymmetric Alkene Carboalkoxylation

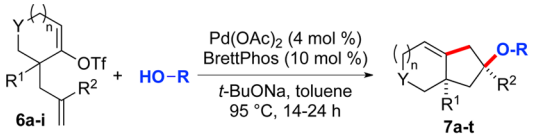


Our prior studies with amine nucleophiles suggested that alkenyl triflates may also function as electrophiles in the alkene carboalkoxylation reactions.[2b] As such, we prepared a series of both cyclic and acyclic alkenyl triflates bearing pendant alkenes in two to four steps from ketones via alkylation followed by subsequent *O*-triflation of the kinetic enolate. As shown in Schemes 4 and 5, the coupling reactions of the alkenyl triflate substrates with a variety of phenols were highly efficient and afforded the desired products with excellent diastereoselectivity. For some specific substrate combinations one of two ligands (BrettPhos and RuPhos) and one of two bases (*t*-BuONa and *t*-BuOLi) proved to be superior to the other. But in many cases, the two ligands or bases could be interchanged without substantial impact on chemical yield or stereoselectivity. Phenols bearing chloro or fluoro groups were viable coupling partners, as was the heterocyclic phenol 5-hydroxyquinoline. Primary and secondary aliphatic alcohols were coupled without significant competing oxidation to the corresponding aldehydes or ketones. The isolated yields of **7e–g**, which derive from ethanol, hexanol, or cyclopentanol, were low, but this is mainly due to the volatility of these products, as ^{1}H NMR yields (shown in parentheses) were significantly higher. Moreover, the coupling of the heavier 3-phenylpropanol with **6a** afforded **7h** in 74% yield. Although the transformations were effective with a variety of alcohol nucleophiles, efforts to employ hydroxide as the nucleophile were unsuccessful due to competing hydrolysis of the triflate.[20]

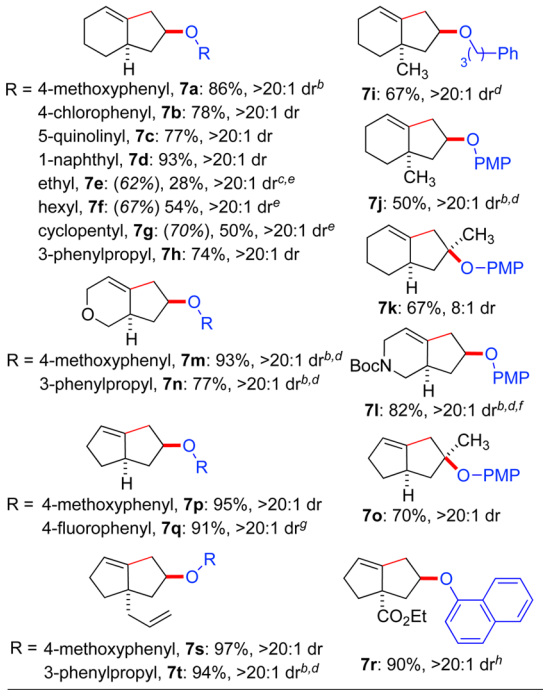
The scope of this method with respect to the alkenyl triflates is also quite broad, as substrates bearing fused dihydropyran (**6e**) or dihydropyridine (**6d**) groups were transformed to **7l–n** in high yield and >20:1 dr. Reactions of cyclohexenyl and cyclopentenyl triflates **6b**, **6h**, and **6i** that contain a substituent in the homoallylic position also proceeded smoothly to afford **7i–j**, **7r**, and **7s–t** in good yield with excellent diastereoselectivity (>20:1). Gratifyingly, tertiary-substituted ethers **7k** and **7o** were also formed in good yield with 8:1 and >20:1 dr, respectively, from substrate **6c** or **6g** that contains a 1,1-disbustituted alkene.[21] These latter results stand in stark contrast to our previous investigations using amine nucleophiles, as efforts to couple 1,1-disubstituted alkenes with amines led to very low

DOI: 10.1021/acs.orglett.7b01975
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Alkene Carboalkoxylation Reactions between Cyclic Alkenyl Triflates and Phenols or Alcohols[a]

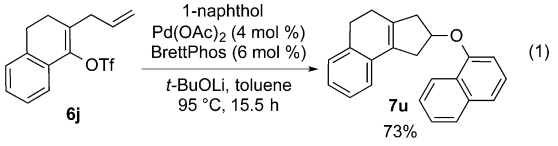


6a: n = 1, R^1, R^2 = H, Y = CH_2; **6b**: n = 1, R^1 = Me, R^2 = H, Y = CH_2; **6c**: n = 1, R^1 = H, R^2 = Me, Y = CH_2; **6d**: n = 1, R^1, R^2 = H, Y = NBoc; **6e**: n = 1, R^1, R^2 = H, Y = O; **6f**: n = 0, R^1, R^2 = H, Y = CH_2; **6g**: n = 0, R^1 = H, R^2 = Me, Y = CH_2; **6h**: n = 0, R^1 = CO_2Et, R^2 = H, Y = CH_2; **6i**: n = 0, R^1 = allyl, R^2 = H, Y = CH_2



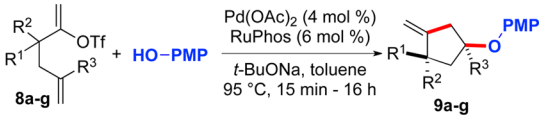
[a]Reaction conditions: $Pd(OAc)_2$ (4 mol %), BrettPhos (10 mol %), *t*-BuONa (1.4 equiv), R–OH (1.2 equiv), **6a–i** (1.0 equiv, 0.1 mmol), toluene (0.1 M), 95 °C, 14–24 h. Yields are isolated yields. [b]*t*-BuOLi (1.4 equiv) was used as base. [c]The reaction was conducted at 70 °C. [d]BrettPhos (6 mol %) was used. [e]Crude yields in parentheses were determined by ^{1}H NMR integration using phenanthrene as an internal standard. [f]Diastereomeric ratio was determined after Boc deprotection. [g]This product contained 4% of an inseparable alkene regioisomer.

yields of the desired products.[2b] The coupling of tetrasubstituted alkenyl triflate **6j** with 1-naphthol afforded **7u** in 73% yield (eq 1).

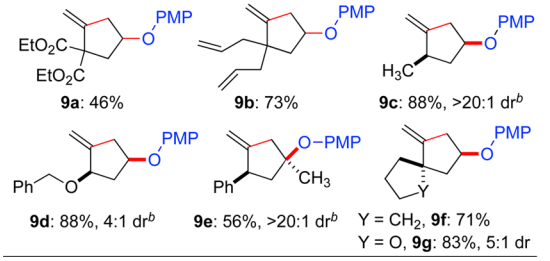


Transformations of dienyl triflates **8a–g** provided ether-substituted alkylidenecyclopentanes **9a–g** in good yields with moderate to excellent stereocontrol. The diastereoselectivities in reactions of **8c–e** were dependent on the size of the substituent adjacent to the triflate, with larger substituents leading to higher selectivities. Substrate **8e** was transformed to tertiary alkyl ether **9e** in moderate yield but with high stereocontrol. In addition, substrates **8f–g** were converted to spirocyclic products **9f–g** in good yield.[22]

Scheme 5. Alkene Carboalkoxylation Reactions between Acyclic Alkenyl Triflates and Phenols or Alcohols[a]



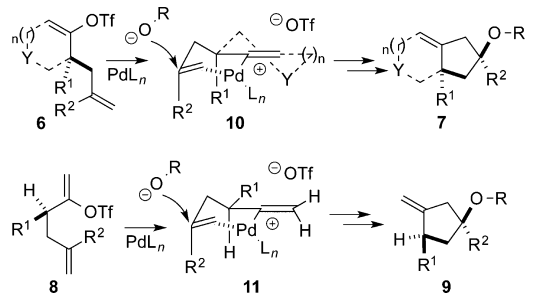
8a: R^1, R^2 = CO_2Et, R^3 = H; **8b**: R^1, R^2 = allyl, R^3 = H; **8c**: R^1 = Me, R^2, R^3 = H; **8d**: R^1 = OBn, R^2, R^3 = H; **8e**: R^1 = Ph, R^2 = H, R^3 = Me; **8f**: R^1 = $(CH_2)_4$ = R^2, R^3 = H; **8g**: R^1 = $(CH_2)_3O$ = R^2, R^3 = H



[a]Reaction conditions: $Pd(OAc)_2$ (4 mol %), RuPhos (6 mol %), *t*-BuONa (1.4 equiv), R–OH (1.2 equiv), **8a–g** (1.0 equiv, 0.1 mmol), toluene (0.1 M), 95 °C, 15 min to 16 h. Yields are isolated yields. [b]CPhos (6 mol %) was used as the ligand.

The mechanism of the alkene carboalkoxylation reactions is likely similar to that of our previously reported carboamination reactions,[2] and involves oxidative addition of the aryl/alkenyl triflate to Pd(0) followed by alkene complexation to afford intermediate **3**. This intermediate can then undergo *anti*-oxypalladation followed by C–C bond-forming reductive elimination to afford the product. The stereochemical outcome of the transformations shown in Schemes 4 and 5 may derive from reaction through a chairlike conformation of this intermediate in the alkene oxypalladation step. As shown in Scheme 6, reaction of substrates **6** through a chair/half-chair

Scheme 6. Stereochemical Model



conformation (**10**) would afford products **7** with the observed stereochemistry. Similarly, substrates **8** are converted to alkylidenecyclopentyl ethers **9** via chairlike conformations **11** in which the larger homoallylic substituent R^1 is positioned in a pseudoequatorial orientation to avoid a 1,3-diaxial interaction with the alkene R^2 group. The modest (4:1) dr obtained in the conversion of **8d** to **9d** may be due to a small difference in energy for equatorial vs axial orientation of the relatively small OBn group. Alternatively, it is also possible that there may be a stereoelectronic preference for axial orientation of the OBn group similar to that observed in additions of nucleophiles to oxocarbenium ions.[23] However, the reasons for the modest dr in conversion of **8g** to **9g** are unclear, as both the steric and

DOI: 10.1021/acs.orglett.7b01975
Org. Lett. XXXX, XXX, XXX–XXX

stereoelectronic effects should be complementary and lead to the formation of **9g** with high selectivity, but this was not observed.

In conclusion, the Pd-catalyzed coupling of aryl or alkenyl triflates bearing pendant alkenes represents a new method for the stereoselective synthesis of a variety of 2-indanyl ethers and ether-substituted alkylidenecyclopentane derivatives. The products are generated in good yields and high diastereoselectivities in most cases, and a number of functional groups, including chloro, fluoro, quinoline, ester, alkene, ether, and carbamate groups, are tolerated. In addition, this method also provides access to 3°-alkyl ethers that are difficult to access in a stereocontrolled fashion. Future studies will be directed toward improving enantioselectivities in reactions of prochiral substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01975.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jpwolfe@umich.edu.

ORCID

John P. Wolfe: 0000-0002-7538-6273

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Michigan for financial support of this work. D.R.W.'s studies were also supported in part by a Bristol-Myers Squibb Graduate Research Fellowship, for which he is grateful. We thank Ms. Janelle Kirsch, University of Michigan Department of Chemistry, for assistance with stereochemical assignments.

■ REFERENCES

(1) For reviews on Pd-catalyzed alkene difunctionalization, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (b) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (c) Garlets, Z. J.; White, D. R.; Wolfe, J. P. *Asian J. Org. Chem.* **2017**, *6*, 636. (d) Yin, M.; Mu, X.; Liu, G. *Acc. Chem. Res.* **2016**, *49*, 2413. (e) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (f) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (g) Muñiz, K.; Martinez, C. *J. Org. Chem.* **2013**, *78*, 2168. For alkene difunctionalization reactions via copper catalysis, see: (h) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727. (i) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009. For hypervalent iodine catalyzed vicinal difunctionalization of alkenes, see: (j) Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. - Asian J.* **2014**, *9*, 972. For other metal-catalyzed 1,2-diamination reactions, see: (k) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269.

(2) (a) White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246. (b) White, D. R.; Wolfe, J. P. *Chem. - Eur. J.* **2017**, *23*, 5419.

(3) (a) Muzart, J. *Tetrahedron* **2003**, *59*, 5789. (b) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685. (c) Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* **2007**, *63*, 4266.

(4) The Pd-catalyzed coupling of aryl triflates with phenols is known to proceed in good yield with Pd/biarylphosphine catalyst systems. See: Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(5) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (b) Green, A. E.; Agouridas, V.; Deniau, E. *Tetrahedron Lett.* **2013**, *54*, 7078.

(6) (a) Toyota, M.; Wada, T.; Matsuura, M.; Fukumoto, K. *Synlett* **1995**, *1995*, 761. (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.

(7) (a) Ogawa, S.; Watanabe, T.; Sugimoto, I.; Moriyuki, K.; Goto, Y.; Yamane, S.; Watanabe, A.; Tsuboi, K.; Kinoshita, A.; Kigoshi, H.; Tani, K.; Maruyama, T. *ACS Med. Chem. Lett.* **2016**, *7*, 306. (b) Martins, T. J.; Fowler, K. W.; Odingo, J.; Kesicki, E. A.; Oliver, A.; Burgess, L.E.; Gaudino, J. J.; Jones, Z. S.; Newhouse, B. J.; Schlachter, S. T. Cyclic AMP-Specific Phosphodiesterase Inhibitors. US Patent 6,423,710 B1, Jul 23, 2002.

(8) (a) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (b) Chanon, M.; Barone, R.; Baralotto, C.; Julliard, M.; Hendrickson, J. B. *Synthesis* **1998**, *1998*, 1559.

(9) Sprecker, M. A.; Weiss, R. A.; Levorse, A. T., Jr.; Heinsohn, H. H., Jr.; Beck, C. E. J.; Hanna, M. R. Carbon Containing Functional Group Substituted 4,5,6,7-Tetrahydro-polyalkylated-4-indanes, Isomers Thereof, Processes for Preparing Same and Uses Thereof. US Patent 6,271,193 B1, Aug 7, 2001.

(10) Baum, J. W.; Alto, P.; Diekman, J. D.; Park, M. Aliphatic Indanyl Ethers. US Patent 3,850,992, Nov 26, 1974.

(11) For recent reviews on the Mitsunobu reaction, see: (a) Fletcher, S. *Org. Chem. Front.* **2015**, *2*, 739. (b) Swamy, K. C.. K; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551. (c) But, T. Y. S.; Toy, P. H. *Chem. - Asian J.* **2007**, *2*, 1340.

(12) (a) Winstein, S.; Roberts, R. M. *J. Am. Chem. Soc.* **1953**, *75*, 2297. (b) Feuer, H.; Hooz, J. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Wiley: New York, 1967; p 445.

(13) (a) Subramanian, R. S.; Balasubramanian, K. K. *Synth. Commun.* **1989**, *19*, 1255. (b) Sankara Subramanian, R. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1989**, *30*, 2297. (c) Shi, Y.-J.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609. (d) Lanning, M. E.; Fletcher, S. *Tetrahedron Lett.* **2013**, *54*, 4624.

(14) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359.

(15) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(16) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

(17) BrettPhos ligand may also be utilized to afford product in good yield, although slightly better results were usually obtained with RuPhos.

(18) The *trans*-1,2-disubstituted indane product stereochemistry matches that of previous investigations utilizing 2-(but-3-en-2-yl)phenyl triflate and pyrrolidine nucleophile; see ref 2b.

(19) For studies on highly electrophilic cationic-Pd activation of alkenes, see: Hahn, C.; Morvillo, P.; Vitagliano, A. *Eur. J. Inorg. Chem.* **2001**, *2001*, 419.

(20) The main side products observed in the transformations described in Schemes 2−5 result from base-mediated cleavage of the triflate to afford the corresponding phenol or ketone (after enol tautomerization), or from reduction of the aryl or alkenyl triflate starting material.

(21) Efforts to employ substrates bearing 1,2-disubstituted alkenes have thus far produced only small amounts of desired products.

(22) Efforts to prepare an unsubstituted analog of **8** (R^1, R^2, R^3 = H) have thus far been unsuccessful due to the formation of inseparable mixtures of enol triflate regioisomers that result from modest regioselectivity during enolate generation.

(23) Electrostatic stabilization for pseudoaxial conformers of oxocarbenium ions by heteroatom substituents in nucleophilic substitution reactions has previously been proposed: Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

DOI: 10.1021/acs.orglett.7b01975
Org. Lett. XXXX, XXX, XXX−XXX