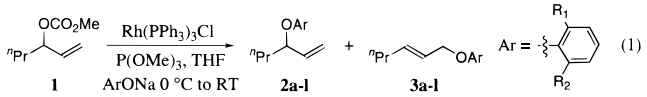
Regioselective and Enantiospecific Rhodium-Catalyzed Intermolecular Allylic Etherification with Ortho-Substituted Phenols

P. Andrew Evans* and David K. Leahy

Brown Laboratory
Department of Chemistry and Biochemistry
University of Delaware, Newark, Delaware 19716

Received February 1, 2000

Aryl ethers are ubiquitous to a variety of biologically important molecules, thus the development of new methods for their construction has become a topic of considerable synthetic interest.[1] The transition metal-catalyzed cross-coupling of aryl halides with alcohols provides an excellent method for the preparation of this important structural motif.[2] However, we anticipated that ortho-disubstituted aryl halides would provide poor substrates for this transformation, due to the difficulties associated with the oxidative addition of a metal into a sterically encumbered environment of this type. The metal-catalyzed allylic etherification provides a complementary approach to this problem, in which the cross-coupling reaction generally occurs at ambient temperature and facilitates the introduction of a new stereogenic center.[3−5] Despite some excellent preliminary work the etherification of unsymmetrical allylic alcohol derivatives, particularly sterically demanding ortho-disubstituted phenols, remains problematic in terms of both the regio- and enantioselective outcome.[4,5] In a program directed toward controlling regioselectivity in metal-catalyzed allylic substitution reactions, we have recently demonstrated that the rhodium-catalyzed reactions proceed with excellent selectivity.[6,7] Herein, we describe the first rhodium-catalyzed allylic etherification reaction using the sodium salt of ortho-substituted phenols to afford the aryl allyl ethers **2/3a**−**l** in excellent yield, favoring the secondary derivative **2** (eq 1). The ability to utilize highly substituted phenols in this manner is expected to provide a useful cross-coupling reaction for organic synthesis.

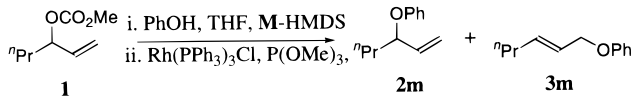


1 2a-l 3a-l (1)

Preliminary studies demonstrated that the etherification using phenol was subject to a similar counterion effect (K, Na, and Li)[8] that had proven crucial in the development of the corresponding rhodium-catalyzed allylic amination.[6c,d] Treatment of the allylic carbonate **1** with the alkali metal-salt (Li, Na, and K) of phenol and Wilkinson's catalyst *modified* with trimethyl phosphite at 30 °C furnished the corresponding alkylation products **2m/3m** with the yields and selectivities outlined in Table 1 (entries 1−3). Hence, although the lithium and potassium counterions favored the formation of **2m**, poor turnover and selectivity prompted the optimization of the alkylation using the sodium salt of the phenol. To improve the selectivity further, we decided to examine the effect of temperature on regioselectivity. *Contrary to earlier studies with carbon and nitrogen nucleophiles that demonstrated 30 °C was crucial for obtaining good selectivity and turnover rates, the rhodium-catalyzed allylic etherification proceeds smoothly at lower temperature affording the aryl allyl ether* ***2m*** *with significantly improved regioselectivity (entry 5).*

Table 2 summarizes the results for the application of the optimized reaction conditions to a series of ortho-substituted phenols, as outlined in eq 1. The etherification appears to tolerate

Table 1. Counterion and Temperature Effect on Regioselectivity in the Rhodium-Catalyzed Allylic Etherification Reaction



1 2m 3m

entry	counterion **M**[a]	temp	ratio **2m/3m**[b]	yield (%)[c]
1	Li	30 °C	38:1	11
2	Na	30 °C	20:1	97
3	K	30 °C	12:1	97
4	Na	RT	30:1	87
5	Na	0 °C to RT	70:1	96

[a] All reactions were carried out on a 0.5 mmol reaction scale at the designated temperature for *ca.* 4 hours. [b] Ratios determined by capillary GLC on crude reaction mixtures. [c] Isolated yields.

Table 2. Regioselective Rhodium-Catalyzed Allylic Etherification with Ortho-Substituted Phenols

	ArONa[a]				
entry	R_1	R_2		ratio of **2/3**[b,c]	yield (%)[d]
1	Me	H	**a**	39:1	94
2	*i*Pr	H	**b**	56:1	95
3	Ph	H	**c**	44:1	90
4	NHAc	H	**d**	≥99:1	95
5	OMe	H	**e**	11:1	82
6	Br	H	**f**	25:1	88
7	Me	Br	**g**	36:1	94
8	*i*Pr	Br	**h**	57:1	90
9	Ph	Br	**i**	36:1	90
10	Me	Me	**j**	36:1	94
11	*i*Pr	*i*Pr	**k**	14:1	80
12	Ph	Ph	**l**	25:1	92

[a] All reactions were carried out on a 0.5 mmol reaction scale.[9] [b] Ratios of regioisomers were determined by HPLC or Capillary GC on crude reaction mixtures. [c] The primary products **3** were prepared independently *via* Pd(0) catalysis.[3] [d] Isolated yields.

(1) For a recent review on transition metal-catalyzed aryl ether formation, see: Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046 and pertinent references therein.

(2) For leading references on intra- and intermolecular metal-catalyzed aryl ether formation from aryl halides and alcohols, see: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395. (d) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413. (e) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L *J. Am. Chem. Soc.* **1997**, *119*, 6787. (f) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224 and pertinent references therein.

(3) For recent reviews on the metal-catalyzed allylic substitution reaction, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Sons: New York, 1996; p 290. For an example of a highly regio- and enantioselective palladium-catalyzed allylic etherification, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

(4) For a working model that highlights the challenges of the regio- and enantioselective metal-catalyzed allylic etherification reactions with *unsymmetrical* substrates, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545 and pertinent references therein.

(5) For an example of the problems associated with obtaining selectivity in the metal-catalyzed allylic etherification reaction, see: Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585 and pertinent references therein.

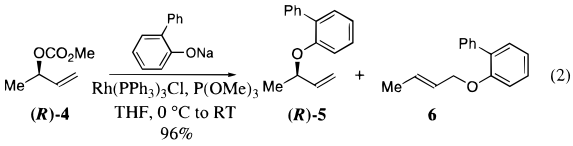
(6) (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *38*, 1725. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (c) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (d) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929.

(7) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. (b) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269. (c) Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, 695.

(8) The rhodium-catalyzed allylic alkylation of **1** with phenol at 30 °C furnished the aryl allyl ethers **2/3m** in only 9% yield, as a 33:1 mixture of regioisomers favoring **2m**. Hence, the deprotonated nucleophile appears to be crucial for smooth turnover.

10.1021/ja0003831 CCC: $19.00 © 2000 American Chemical Society
Published on Web 05/04/2000

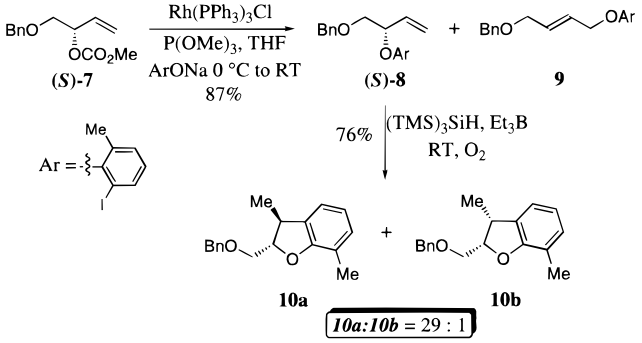
alkyl, including branched alkanes (entries 1−2), aryl substituents (entry 3), heteroatoms (entries 4 and 5), and halogens (entry 6). These results prompted the examination of ortho-disubstituted phenols, which were expected to be more challenging substrates for this type of reaction. Remarkably, the ortho-disubstituted phenols furnished the secondary aryl allyl ethers **2g**−**l** with similar selectivity (entries 7−12). *The excellent regioselectivities obtained with the rhodium-catalyzed reaction, and tolerance of heteroatoms and halogens, provides a unique solution to the metal-catalyzed allylic etherification reaction.* Furthermore, the ability to employ halogen-bearing ortho-disubstituted phenols will facilitate substitutions that would have proven extremely challenging for conventional cross-coupling protocols.



The enantiospecific rhodium-catalyzed etherification was also examined, in which the reaction proceeds with net overall retention of absolute configuration, as outlined in the alkylation of the chiral nonracemic allylic carbonate **(*R*)-4**. Treatment of **(*R*)-4** (95% ee) with the trimethyl phosphite *modified* Wilkinson's catalyst and the sodium salt of *o*-phenyl phenol furnished the aryl allyl ether **(*R*)-5** in 96% yield (2°:1° = ≥99:1), and with 98% cee (eq 2).[10,11] This reaction is consistent with a double inversion process proceeding through an *enyl* ($\sigma + \pi$)[12] organorhodium intermediate analogous to that of stabilized carbon and nitrogen nucleophiles.[6b−d]

The preparation of highly substituted enantiomerically enriched dihydrobenzo[*b*]furan derivatives remains an important synthetic undertaking.[13] Herein, we describe a two-step sequence for the preparation of enantiomerically enriched oxygen containing heterocycles (Scheme 1). The rhodium-catalyzed allylic etherification of **(*S*)-7** (≥99% ee), with the sodium anion of 2-iodo-6-methylphenol, furnished the corresponding aryl allyl ether **(*S*)-8/9** in 87% yield, as a 28:1 mixture of regioisomers favoring **(*S*)-8** (92% cee). Treatment of the aryl iodide **(*S*)-8** with tris(trimethylsilyl)silane[14] and triethylborane at room temperature, in the presence of air, furnished the dihydrobenzo[*b*]furan derivatives **10a/b** in 76% yield, as a 29:1 mixture of diastereoisomers in favor of **10a**.

Scheme 1



In conclusion, we have developed the first regioselective and enantiospecific rhodium-catalyzed allylic etherification reaction. In the course of this study we also demonstrated that the alkylation is tolerant to alkyl, aryl, and heteroatom substituents. Furthermore, the ability to utilize ortho-halogenated phenols provides a direct route to substituted aryl ethers that would prove difficult to construct using conventional cross-coupling protocols. Hence, the ability to prepare substituted aryl allyl ethers in this manner is likely to gain prominence as a useful synthetic method for target directed synthesis.

Acknowledgment. We sincerely thank the National Institutes of Health (GM58877) for generous financial support. We also thank Zeneca Pharmaceuticals for an Excellence in Chemistry Award, Eli Lilly for a Young Faculty Grantee Award, Glaxo Wellcome for a Chemistry Scholar Award, and the Camille and Henry Dreyfus Foundation for a Camille Dreyfus Teacher−Scholar Award (PAE).

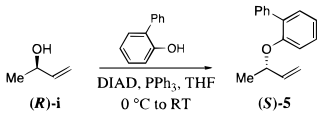
Supporting Information Available: Spectral data for **2a**−**m**, **(*R*)-5**, **(*S*)-8**, and **10a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0003831

(9) **Representative experimental procedure**: Trimethyl phosphite (24 μL, 0.20 mmol) was added directly to a red solution of Wilkinson's catalyst (43.7 mg, 0.047 mmol) in anhydrous THF (2.0 mL) at 30 °C, under an atmosphere of argon. The catalyst was allowed to form over *ca*. 15 min resulting in a light yellow homogeneous solution. Sodium hexamethyldisilyl azide (475 μL, 0.95 mmol, 2.0 M solution in THF) was added to *o*-phenyl phenol (0.184 g, 1.1 mmol) in anhydrous THF (3.0 mL) and the anion allowed to form over *ca*. 10 min. The catalyst and the sodium phenoxide solutions were then cooled with stirring to 0 °C. The optically active allylic carbonate **(*R*)-4** (65.7 mg, 0.5 mmol; 95% ee by capillary GLC analysis) was then added *via* a tared 100 μL syringe to the preformed rhodium catalyst. The sodium phenoxide solution was then added *via* Teflon cannula to the catalyst/carbonate mixture, and the resulting reaction mixture allowed to slowly warm to room temperature over *ca*. 4 h (tlc control). The reaction mixture was then quenched with 30% H_2O_2 solution (1 mL) and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The organic layers were combined, washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with a 3% ethyl acetate/hexane) furnished the *allyl aryl ether* **(*R*)-5** (0.108 g, 96%) as a colorless oil, with 93% enantiomeric excess by chiral GLC analysis.

(10) The term conservation of enantiomeric excess {cee = (product ee/starting material ee) × 100} provides a convenient method of describing the enantiopecificity of the reaction.[6c]

(11) The retention of absolute configuration in the rhodium-catalyzed etherification was assigned by the comparison of **(*R*)-5** prepared from **(*R*)-4** (eq 2) with **(*S*)-5** prepared *via* Mitsunobu inversion of the allylic alcohol **(*R*)-i** with 2-phenylphenol.



(12) Enyl complexes can be defined as those having a discrete σ- and π-metal carbon component within a single ligand. For definitions and examples, see: (a) Sharp P. R. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Chapter 2, p 272. (b) Lawson, D. N.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1733. (c) Tanaka, I.; Jin-no, N.; Kushida, T.; Tsutsui, N.; Ashida, T.; Suzuki, H.; Sakurai, H.; Moro-oka, Y.; Ikawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 657 and pertinent references therein.

(13) For recent examples of approaches to dihydrobenzo[*b*]furans, see: (a) Bernard, A. M.; Cocco, M. T.; Onnis, V.; Piras, P. P. *Synthesis* **1997**, 41. (b) Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem.* **1997**, *62*, 6978. (c) Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 237. (d) Olivero, S.; Rolland, J.-P.; Duñach, E. *Organometallics* **1998**, *17*, 3747. (e) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391 and pertinent references therein.

(14) For a recent review on this reagent, see: Chatgilialoglu, C. *Chem. Rev.* **1995**, *60*, 3826.