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Synthesis of Aryl Ethers via a Sulfonyl Transfer Reaction

Neal W. Sach, Daniel T. Richter, Stephan Cripps, Michelle Tran-Dubé, Huichun Zhu, Buwen Huang, Jean Cui, and Scott C. Sutton*

Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, California 92121, United States

scott.sutton@pfizer.com

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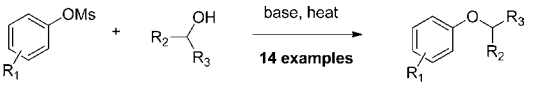
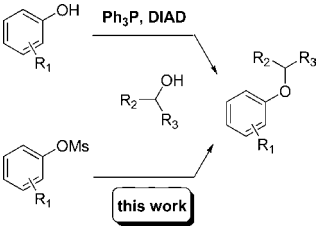
ABSTRACT



A general synthesis of aryl ethers from primary and secondary alcohols and aryl mesylates is presented. The reaction proceeds via a sulfonyl-transfer mechanism. In this paper, we compare the sulfonyl transfer reaction to Mitsunobu ether formation. The reaction can be employed in a multistep synthesis where the aryl mesylate is used as a phenol protecting group and then as an activating group for ether formation. This protecting/activating group strategy is demonstrated using raloxifene as the target.

The Mitsunobu reaction[1] of phenols and aliphatic alcohols is considered an essential reaction for aryl ether formation (Scheme 1). Its popularity arises from the great abundance of low molecular weight, accessible alcohols used as synthons of alkyl halides. The utility of the Mitsunobu reaction has been demonstrated through ether formation using stable synthons (i.e., amino alcohols) equivalent to unstable alkyl halides[2] and for inversion of stereochemistry during ether formation. At the same time, the Mitsunobu reaction suffers from poor atom economy,[3] the necessary removal of byproducts, and the potential explosive properties of azodicarboxylates, such as DEAD, when heated.[4] Because of these drawbacks, alternative methods to the Mitsunobu reaction have received some attention.[5] In this paper, we describe an alternative that reacts primary and secondary alcohols with aryl mesylates under basic conditions to form aryl ethers. Although not as efficient as the Williamson ether synthesis,[6] the utility of this transformation fits a recurrent need to use low molecular weight alcohols from commercial and corporate collections for SAR studies.[7] Although ether formation has been observed as a side product in the deprotection of aryl mesylates in alcohol solvents,[8] the synthetic utility of this transformation has not been systematically studied.

Scheme 1. Activation of Alcohols for Aryl Ether Synthesis



Aryl mesylates have generally been regarded as protected phenols, until recently.[9] Although the use of the aryl triflates for cross coupling is ubiquitous in organic synthesis, aryl mesylates are differentiated because of their excellent stability to acidic and mildly basic conditions, making them a useful phenol protecting group.[10]

(1) (a) Mitsunobu, O. *Synthesis* **1981**, *1*, 1. (b) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551.

(2) For example, free-base β-chloroamines have a propensity to ring close spontaneously to the corresponding aziridinium salts. See: Hickmott, P. W.; Wood, S.; Murray-Rust, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2033.

(3) Li, C-J; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105* (36), 13197.

(4) Berger, A.; Wehrstedt, K. D. *J. Loss Prev. Process Ind.* **2010**, *23*, 734.

(5) (a) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63* (18), 6273. (b) Iranpoor, N.; Firouzabadi, H.; Khalili, D. *Org. Biomol. Chem.* **2010**, *8* (19), 4436. (c) Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2000**, *65* (24), 8379.

(6) Fuhrmann, E.; Talbiersky, J. *Org. Process Res. Dev.* **2005**, *9* (2), 206.

(7) Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X. *J. Med. Chem.* **2007**, *50* (13), 2990.

(8) Bensel, N; Pevere, V; Desmurs, J. R.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43* (23), 4281.

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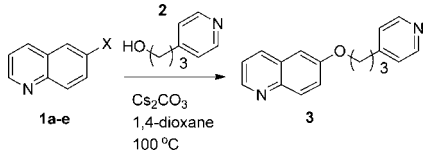
At the same time, aryl mesylates undergo a synthetically useful reaction to form aryl ethers.[11] Our initial investigation studied the nature of four different sulfonates. Using sulfonates derived from 6-hydroxy quinoline (**1b**–**e**) paired with 3-(pyridin-4-yl)propan-1-ol (**2**), we found that methanesulfonate **1c** afforded the highest yield (52%) when using our initial conditions of 1,4-dioxane as solvent and Cs_2CO_3 as base at 100 °C (Table 1).

Table 1. Arylsulfonates Derived from 6-Hydroxyquinoline

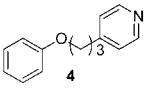
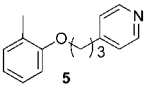
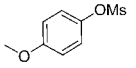
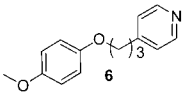
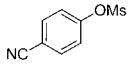
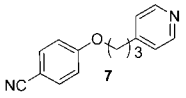
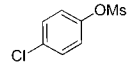
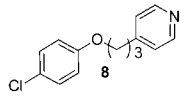
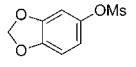
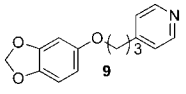


entry	quinoline	X	time (h)	yield
1	1a	Cl	16	0c, 52b
2	1b	OTf	4	22a
3	1c	OMs	16	52a
4	1d	OTs	16	28a
5	1e		16	38a

[a] Isolated, chromatographically purified. [b] 0.05 equiv of $Pd_2(dba)_3$ and 0.1 equiv of BippyPhos added. [c] Based on LCMS analysis

Based on these preliminary results, we used **1c** to further optimize our reaction conditions using microscale techniques to screen a cross of six solvents and seven bases at elevated temperatures (80 and 120 °C) in an effort to improve upon the 52% yield.[12] The screening results and subsequent follow-up work led to identification of four optimal conditions: NaO-*t*-Bu in acetonitrile, at 80 °C (conditions A), Cs_2CO_3 in DMF at 100 °C (conditions B), NaH in DMF at 70 °C (conditions C), and LiO-*t*-Bu in DMSO at 150 °C (conditions D). LiO-*t*-Bu in DMSO led to a 74% yield of the reaction of **1c** with **2** (Figure 1), a significant improvement over the 52% achieved using Cs_2CO_3, and 1,4-dioxane at 100 °C. When the A and B conditions were applied to a variety of aryl mesylates while keeping the alcohol constant, several interesting features were noted (Table 2). Conditions A using NaO-*t*-Bu in acetonitrile at 80 °C was the most general affording 63–77% isolated yields for five of the six reactions. The hindered *o*-methyl substrate (entry 2) furnished a 77% yield under the NaO-*t*-Bu in acetonitrile conditions, while the electron-rich *p*-OMe mesylate (entry 3) afforded a 77% yield under the same conditions. The example affording a higher yield using the weaker base, Cs_2CO_3, was entry 4 where a CN group para to the mesylate led to a 32% yield when conditions A was used and a 61% yield for conditions B.

Table 2. Mesylate Transfer Using Alcohol **2** and Various ArOMs[a]

entry	ArOMs	product	condition	yield
1		 **4**	A B	67% 37%
2		 **5**	A B	77% 58%
3		 **6**	A B	77% 23%
4		 **7**	A B	32% 61%
5		 **8**	A B	63% 41%
6		 **9**	A B	73% 11%

[a] Conditions A: NaO*t*-Bu, CH_3CN, 80 °C, 16 h. Conditions B: Cs_2CO_3, DMF, 100 °C, 3 h. Yields represent isolated material on 1 mmol scale.

These results suggested that the mesylate-transfer reaction can tolerate a variety of aryl mesylates including electron-rich, electron-poor, and ortho-substitution[13] when paired with a primary alcohol. The results also indicated that the nature of the aryl mesylate substrate can be sensitive to the strength of the base used. With this information in hand, we turned our

(9) (a) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.* **2011**, *40* (10), 4963. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17* (6), 1728. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111* (3), 1346. (d) Molander, G. A.; Shin, I. *Org. Lett.* **2012**, *14* (12), 3138. (e) Leowanawat, P.; Zhang, N.; Safi, M.; Hoffman, D. J.; Fryberger, M. C.; George, A.; Percec, V. *J. Org. Chem.* **2012**, *77* (6), 2885. (f) Chang, J. W. W.; Chia, E. Y.; Chai, C. L. L.; Seayad, J. *Org. Biomol. Chem.* **2012**, *10* (11), 2289. (g) Chung, K. H.; So, C. M.; Wong, S. M.; Luk, C. H.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Chem. Commun. (Cambridge, U. K.)* **2012**, *48* (14), 1967. (h) Leowanawat, P.; Zhang, N.; Percec, V. *J. Org. Chem.* **2012**, *77* (2), 1018. (i) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134* (1), 169. (j) Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2011**, *76* (24), 9946. (k) Shen, C.; Yang, G.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10* (17), 3500. (l) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50* (42), 9943. (m) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132* (33), 11592. (n) Naidu, A. B.; Jaseer, E. A.; Sekar, G. *J. Org. Chem.* **2009**, *74* (10), 3675. (o) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73* (1), 284. (p) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129* (12), 3490. (q) Dooleweerdt, K.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2010**, *12* (10), 2350. (r) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130* (41), 13552.

(10) Looker, J. H.; Thatcher, D. N. *J. Org. Chem.* **1954**, *19*, 784.

(11) Sach, N. W.; Sutton, S. C.; Richter, D. T.; Cripps, S.; Zhu, H.; Tran-Dubé, M.; Cui, J. Abstracts of Papers, 239th ACS National Meeting, San Francisco, CA, United States, Mar 21–25, 2010, ORGN-74.

(12) Results from this microscale screen are presented in the Supporting Information.

(13) Using 2,6-dimethylphenyl methanesulfonate was attempted but led to only trace amounts of product.

(14) (a) Hughes, D. L. *Org. React. (Hoboken, NJ)* **1992**, 42. (b) Bisi, A.; Rampa, A.; Budriesi, R.; Gobbi, S.; Belluti, F.; Ioan, P.; Valoti, E.; Chiarini, A.; Valenti, P. *Bioorg. Med. Chem.* **2003**, *11* (7), 1353. (c) Kiesewetter, D. O.; Eckelman, W. C. *J. Labelled Compd. Radiopharm.* **2004**, *47* (13), 953. (d) Miko, T.; Ligneau, X.; Pertz, H. H.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. *J. Med. Chem.* **2003**, *46* (8), 1523. (e) Inversion and determination of ee were confirmed using chiral SFC with the appropriate standards. Kaufman, T. S. *Tetrahedron Lett.* **1996**, *37* (30), 5329. (f) The control Mitsunobu reaction was ran at Pfizer-LJ.

attention to benchmark this transformation alongside the Mitsunobu reaction in an effort to evaluate the synthetic utility of this reaction. Comparison of mesylate transfer to the Mitsunobu reaction is shown in Figure 1. Mitsunobu yields from the literature[14] or from control reactions[14f] are tabulated adjacent to yields using mesylate transfer. Although formation of the aryl mesylate, itself, needs to be considered in the overall yield of this two-step process, a straightforward comparison of the yields starting with the ArOMs precursors is listed in Figure 1 along with the Mitsunobu yields.

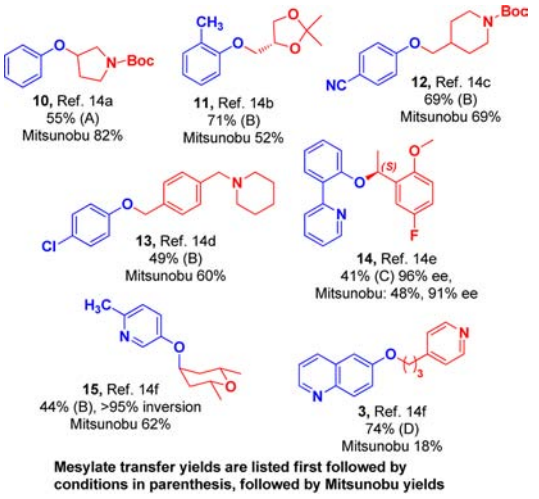
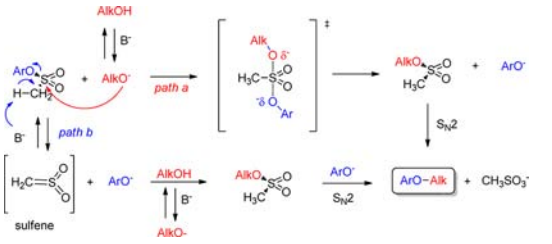


Figure 1. Comparison to Mitsunobu ether formation.

For compounds **3**, **11**, and **12** equal or improved yields were obtained using the mesylate transfer method. On the other hand, the Mitsunobu reaction led to higher yields for compounds **10**, **13**, and **15**. For compound **14**, the use of NaH in DMF at 70 °C (conditions C) afforded inversion of the chiral secondary alcohol to the inverted aryl ether in 41% yield and 96% ee compared to the Mitsunobu reaction leading to a 48% yield and 91% ee. Kaufman demonstrated that benzylic alcohols with *o*-methoxy groups are known to undergo partial racemization during Mitsunobu inversion thought to arise from a S_N1 reaction pathway which could explain the slight difference in ee results here.[14e]

Scheme 2 shows two reasonable mechanisms for the reaction, both going through S_N2 inversion as the final step. For sulfonyl transfer, Gordon and co-workers examined a variety of potential mechanisms[15] and concluded that a concerted bimolecular displacement at the sulfonyl group (path a, Scheme 2) is the dominant pathway. On the other hand, path b involving E2 elimination of the phenolate to form sulfene[16] cannot be ruled out.[17] In Table 1, we observed lower yields when the sulfonyl group lacks a hydrogen on the carbon alpha to the sulfur. These arylsulfonates are unable to go through path b. However, there are too many other factors involved to infer any mechanistic details from this observation. In Table 2 and Figure 1, we observed the weaker base, Cs_2CO_3, to give improved yields for the more stabilized 4-cyanophenolate and 4-chlorophenolate leaving groups (entry 4, Table 2 and compounds **12** and **13** of Figure 1). These observations led to a hypothesis that path b is in play for ArOMs bearing an electron-withdrawing group para to the sulfonate. It was hypothesized that both paths a and b are possible, depending on the nature of the aryl mesylate and the base employed.

Scheme 2. Proposed Mechanisms



To study the mechanism further, we studied the intermediacy of the alkyl mesylate which was believed to form with retention of alcohol stereochemistry during the transfer step. To prove this, we used a stereochemical probe substrate, namely *meso*-(2*R*,4*R*,6*S*)-2,6-dimethyltetrahydro-2*H*-pyran-4-ol having all-cis stereochemistry[18] as the starting alcohol in the synthesis of compound **15** (Figure 1). Interception of the secondary mesylate intermediate with retention of configuration was accomplished by observing the reaction, in progress, using ^{1}H NMR.[19,20] Having established that the mesylate-transfer step goes with retention of configuration, we then considered the second step of the mechanism. Since Gordon and co-workers provided evidence covering a concerted bimolecular displacement at the sulfonyl group (path a),[15] we sought a method to examine path b, especially in the context of the p-CN substrate (entry 4, Table 2) which was an outlier giving higher yields under conditions that are unlikely to form the fully deprotonated alcohol. After conducting a literature search around the keywords "sulfene trap", a paper by Pregel and Buncel[21] was found that fully supported

(15) Gordon, I. M.; Maskill, H.; Ruasse, M.-F. *Chem. Soc. Rev* **1989**, *18*, 123.

(16) King, J. F.; Lee, T. S. *J. Am. Chem. Soc.* **1969**, *91* (23), 6524.

(17) For reactions of sulfene with alcohols via 1,2-addition, see: (a) Skrypnik, Y. G.; Bezrodnyi, V. P.; Panov, V. P.; Baranov, S. N. *Katal. Sint. Org. Soedin. Sery.* **1979**, 197. (b) Langendries, R.; De Schryver, F. C.; De Mayo, P.; Marty, R. A.; Schutyser, J. *J. Am. Chem. Soc.* **1974**, *96* (9), 2964. (c) Reich, M. F.; Lee, V. J.; Ashcroft, J.; Morton, G. O. *J. Org. Chem.* **1993**, *58* (19), 5288. (d) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35* (9), 3195.

(18) Gelin, S.; Gelin, R.; Henry, R. *Bull. Soc. Chim. Fr.* **1975**, *1*–*2* (Part 2), 302.

(19) The ^{1}H NMR data for this experiment is shown in the Suporting Information section.

(20) *cis*-2,6-Dimethyltetrahydro-2*H*-pyran-4-yl methanesulfonate: ^{1}H NMR (400 MHz, DMF) δ ppm 4.79–4.92 (m, 1H), 3.49–3.60 (m, 2H), 3.27 (s, 3H), 2.06–2.17 (m, 2H), 1.28 (q, J = 11.37 Hz, 2H), 1.13–1.18 (m, 6H). *trans*-2,6-Dimethyltetrahydro-2*H*-pyran-4-yl methanesulfonate: ^{1}H ^{1}H NMR (400 MHz, DMF) δ ppm 5.13 (t, J = 2.91 Hz, 1H), 3.77 (ddd, J = 1.52, 6.19, 11.49 Hz, 2H), 3.27 (s, 3H), 1.93 (dd, J = 2.78, 14.91 Hz, 2H), 1.49 (ddd, J = 2.65, 11.62, 14.27 Hz, 2H), 1.11 (d, J = 6.32 Hz, 6H).

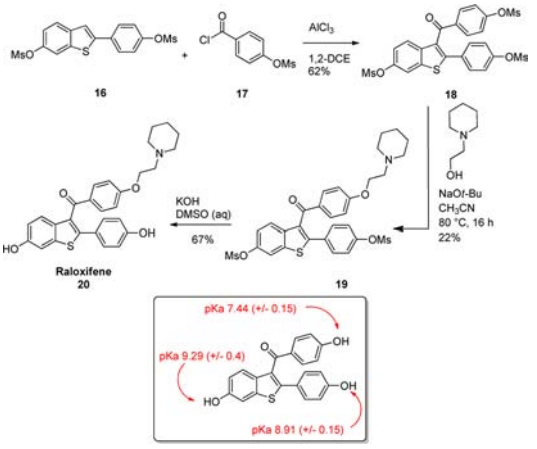
(21) Pregel, M. J.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 307.

the proposed contingent mechanisms in Scheme 2. Pregel and Buncel used an enamine as a sulfene trap in their experiments, and they examined a variety of ArOMs substrates (Ar = *p*-NO_2, *m*-NO_2, *p*-CF_3) using KOEt as the base. They found that in the *p*-NO_2 case, 13% of the sulfene adduct, a 4-membered ring sulfone, was observed. Deuterium exchange studies further suggested that the elimination pathway goes through an E1cb-type mechanism. For their *p*-NO_2 case, they concluded it to react predominantly through an E1Cb-type elimination via a sulfene intermediate with substitution (path a) as a minor concurrent pathway. Based on similar electronic properties of the *p*-NO_2 and *p*-CN substrates, we believe the same E1Cb-type elimination occurs as the predominant pathway with concurrent substitution as a minor pathway in the formation of **7** (Table 2) and possibly **13** (Figure 1). This would help explain mesylate transfer under weakly basic conditions where a fully deprotonated alkoxide is not required. Pregel and Buncel found very little sulfene adduct in the *m*-NO_2, and *p*-CF_3 cases and concluded that substitution (path a) was the dominant pathway for these less stabilized phenolate leaving groups.

As previously mentioned, the excellent stability of the aryl mesylate group to acidic and mildly basic conditions make it a useful phenol protecting group. The current method is therefore applicable to multistep synthesis by using the mesylate, first as a protecting group, and then as an activating group for aryl ether formation. Raloxifene,[22] an important drug used to treat osteoporosis and to decrease the risk of developing invasive breast cancer in women, was selected as an suitable target to highlight this strategy. Based on the calculated phenol pK_a values of the tris-phenol (Scheme 3), we anticipated mesylate transfer on **18** to selectively occur at the most acidic phenol, para to the ketone (pK_a = 7.44).

Friedel–Crafts acylation of bis-mesylate **16**[23] with mesylate protected 4-hydroxybenzoylchloride (**17**) provided **18** in 62% yield. The key step involved reaction of **18** with 2-(piperidin-1-yl)ethanol under the NaO*t*-Bu/acetonitrile conditions at 80 °C leading to **19** in 22% yield.[24] The identity of **19** was confirmed after deprotection using KOH in DMSO to afford **20** (67%). Compound **20** was confirmed to be Raloxifene by comparison to an authentic sample. In this sequence, efforts to improve the yield of **19** were not pursued agressively since the primary purpose of the study was to demonstrate application of the ArOMs group as both protecting and activating group in the synthesis of a credible target. Just as important, the study demonstrated using calculated phenol pK_a values to predict regioselectivity in cases where multiple ArOMs groups are present in a single intermediate.

Scheme 3. Raloxifene Synthesis



In summary, the mesylate transfer reaction represents an alternative to the Mitsunobu reaction for aryl ether formation. Application of this reaction to the recurrent need to rapidly examine a diverse pool of readily available aliphatic alcohols for SAR studies off a phenol template is where this reaction stands out. This is particularly true in cases where the Mitsunobu reaction fails to deliver reasonable yields or purity. The application of microscale screening led to two general reaction conditions: (A) NaO-*t*-Bu in CH_3CN at 80 °C and (B) Cs_2CO_3 in DMF at 100 °C. Other conditions (C) NaH in DMF at 70 °C and (D) LiO-*t*-Bu in DMSO at 150 °C were found through more traditional reaction optimization techniques. Yields comparable to the Mitsunobu reaction were observed for primary alcohols, while secondary alcohols tended to afford lower yields. Finally, the reaction can be employed in multistep synthesis where the mesylate is used as a protecting group and activating group for ether formation. Opportunities for further improvement include telescoping mesylate formation and mesylate transfer to a two-step, one-pot procedure using the same solvent and base for both reactions. If successful, a simplified one-pot procedure could add to the growing arsenal of green chemistry available to the synthetic chemist with improved atom economy relative to the Mitsunobu reaction.[25]

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(24) This is an unoptimized yield with side products identified as regioisomeric monophenol intermediates/hydrolysis byproduct as well as unreacted starting material.

(25) A typical Minsunobu reaction produces 464 g of reagent byproduct for each mole of product formed (assuming 100% yield). The two-step reaction using Et_3N as base in the mesylate formation step and NaO-*t*-Bu in the MsXfer step produces 329 g of reagent byproduct for each mole of product (assuming 100% yield). This represents a 29% improvement in atom economy that can be envisaged by telescoping the reaction to a one-solvent/one-base two-step, one-pot procedure.