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Stereospecific synthesis of chiral tertiary alkyl-aryl ethers via Mitsunobu reaction with complete inversion of configuration

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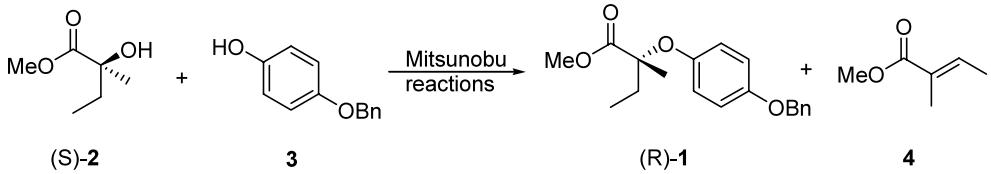
Abstract—Mitsunobu reaction of chiral tertiary alcohol (*S*)-**2** with phenol **3** provides the desired ether (*R*)-**1** in moderate yields at elevated temperatures (80–100°C). The S_N2 displacement pathway is evident by complete inversion of the (*S*)-alcohol to (*R*)-ether.

The Mitsunobu reaction has become a useful tool in organic synthesis since its discovery in 1967.[1] In this series, the coupling of primary or secondary alcohols with a phenol in the presence of diethyl azodicarboxylate (DEAD)/triphenyl phosphine (TPP) is widely used for the synthesis of alkyl-aryl ethers.[2] Specifically, when a chiral secondary alcohol is employed, the reaction usually undergoes an S_N2 displacement with inversion of configuration.[3] Mitsunobu reactions of tertiary alcohols with a phenol, however, have rarely been reported.[4] Furthermore, there is no precedence of Mitsunobu reactions of chiral tertiary alcohols with phenols relating to the inversion of configuration on the chiral tertiary center.[5]

In conjunction with our recent process development, chiral ether (*R*)-**1** is the key intermediate in the synthesis of an investigational drug candidate. Although the target (*R*)-**1** could be obtained by chiral HPLC separation of the racemic ether [(±)-**1**],[6] an efficient synthesis of the target (*R*)-**1** is highly desired. After initial attempts using classical resolution of its corresponding acid by various chiral amines proved fruitless, we explored asymmetric routes.[7] One selected approach is the Mitsunobu reaction of chiral tertiary alcohol (*S*)-**2**[8] with phenol **3** as shown in Scheme 1.

Initially, when the Mitsunobu reaction was carried out under the usual conditions by mixing diisopropyl azodicarboxylate (DIAD), alcohol (*S*)-**2**, phenol **3**, and TPP in THF at 0°C and then aged at either 0°C or ambient temperature, desired **1** was not detected. However, when the mixture was heated at 50°C for 16 h, a trace amount of the product **1** was observed by HPLC. In order to further raise the reaction temperature,[9] the reaction solvent was switched to toluene. When the reaction mixture was heated at 100°C for 14 h, the alcohol (*S*)-**2** totally disappeared and the desired **1** was obtained in 47% yield along with the dehydrated side product methyl tiglate (**4**). At this reaction temperature, using NMP instead of toluene, the yield dropped to 18%. However, an improved yield (54%) was realized by slow addition of neat or a toluene solution of DIAD to a toluene solution of the reaction mixture at 100°C.[10] To verify the expected S_N2 displacement pathway, chiral HPLC assays were carried out by sampling the reaction mixture during and after the reaction. The



(S)-**2** **3** (R)-**1** **4**

Scheme 1.

Keywords: Mitsunobu reaction; tertiary alcohols; alkyl aryl ether; S_N2 displacement; inversion.
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results showed the formation of the desired (*R*)-**1** with >99% ee with respect to starting material (*S*)-**2** (>99% ee) throughout the reaction. Thus, complete inversion at hydroxy carbon occurred, revealing that the Mitsunobu reaction underwent the typical S_N2 displacement pathway (Scheme 1).[2b,c,3]

Additional evaluation of the reaction was conducted using the alcohol (*S*)-**5** at various temperatures and in a different order of addition of reagents as depicted in Scheme 2. At various temperatures (60, 80, 100, and 130°C),[9] the reactions were conducted by slow addition of a solution made from alcohol (*S*)-**5** and DIAD in toluene (or chlorobenzene for 130°C).[11] The reaction at 60°C was slow and incomplete. The results obtained from 80 and 100°C were comparable and superior to one obtained at 130°C in terms of the reaction profile. In addition, benzyl tiglate (**7**) was obtained as the major side product for all reactions. The S_N2 displacement pathway was confirmed again by chiral HPLC assays showing a complete conversion of alcohol (*S*)-**5** to ether (*R*)-**6**.

The reaction was further probed using phenols with various electronic and steric effects and is shown in Scheme 3. The results are summarized in Table 1.

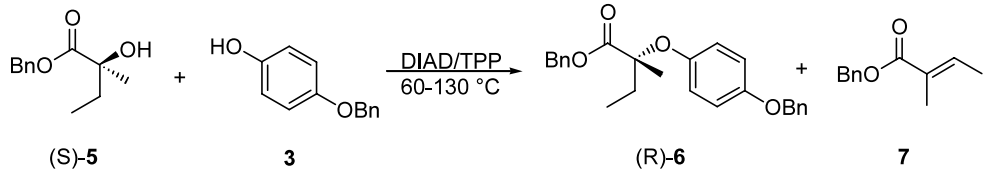
In Table 1 the data from entries 1–5 reflects the electronic effects of a substituent group at 4-position of phenols towards the reaction. There is little difference among donating groups (-OBn, -OMe and -Me) and withdrawing groups (-NO_2 and -CN), although slightly lower yields are observed from the latter groups (entries 4 and 5 versus entries 1 and 3). In addition, steric effects via introduction of an *ortho* group to the phenol were examined. The results (entries 6 and 7) indicate that there is minimal steric effect. This was further confirmed when 2,6-dimethoxyphenol was used in the reaction affording the desired ether in 53% yield.

Steric effects on the alcohol component were observed when the diethyl analogy **20** was used, where reaction with phenol **3** was very sluggish, yielding the dehydrated product as the major product. In comparison, the reaction of dimethyl analogy **22** with phenol **3** afforded the desired **23** in 59% yield, which is comparable to the yield obtained using alcohol (*S*)-**5** (Scheme 4).

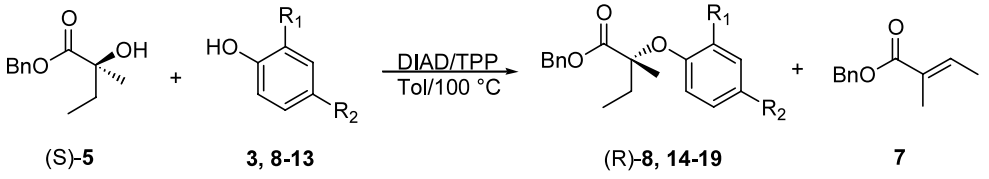
In conclusion, we have demonstrated an unprecedented Mitsunobu reaction of a chiral tertiary alcohol with phenols undergoing clean S_N2 displacement to provide the desired tertiary alkyl-aryl ethers in moderate yields. The reaction is sensitive to the steric bulk of the chiral alcohol, whereas the phenolic component is insensitive to both steric and electronic effects.

Table 1. Mitsunobu reaction with various phenols

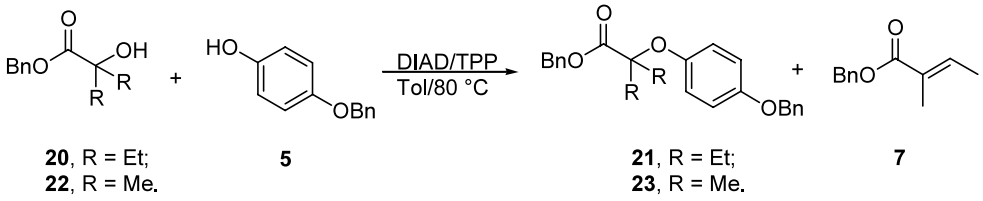
Entry	Phenols	R_1	R_2	(*R*)-ethers	Yield[12]
1	**3**	H	OBn	**6**	56
2	**8**	H	H	**14**	51
3	**9**	H	CH_3	**15**	58
4	**10**	H	NO_2	**16**	51
5	**11**	H	CN	**17**	52
6	**12**	CH_3	H	**18**	55
7	**13**	OCH_3	H	**19**	54



Scheme 2.



Scheme 3.



Scheme 4.

Acknowledgements

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References

1. Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
2. Reviews of the Mitsunobu reaction: (a) Mitsunobu, O. *Synthesis* **1981**, 1; (b) Hughes, D. L. *Org. Reactions* **1992**, *42*, 335; (c) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.
3. Dirlam, N. L.; Moore, B. S.; Urban, F. J. *J. Org. Chem.* **1987**, *52*, 3587.
4. For intermolecular reactions: (a) Bittner, S.; Assaf, Y. *Chem. Ind.* (*London*) **1975**, 281; (b) Subramanian, R. S.; Balasubramanian, K. K. *Synth. Commun.* **1989**, *19*, 1255; (c) Subramanian, R. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1989**, *30*, 2297; (d) Brunner, H.; Hankofer, P.; Treittinger, B. *Chem. Ber.* **1990**, 1029. For intramolecular reactions: (d) Reisch, J.; Voerste, A. A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3251.
5. The S_N2 displacement of tertiary hydroxy centers with different nucleophiles: (a) $SOCl_2$/pyridine, Müller, P.; Rossier, J.-C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2232 and references cited therein; (b) DAST, Wachtmeister, J.; Mühlman, A.; Classon, B.; Samuelsson, B. *Tetrahedron* **1999**, *55*, 10761 and references cited therein.
6. Racemic ether (±)-**1** was made from alkylation of 4-(benzyloxy)phenol with methyl 2-bromobutyrate followed by α-methylation with methyl iodide and subsequent chiral HPLC separation afforded enantiomerically pure (*R*)-**1** and (*S*)-**1** (communication with Dr. R. Desai in our laboratories).
7. Attempts to synthesis chiral ether (*S*)-**1** using the Pd-catalyzed cross-coupling of chiral alcohol (*S*)-**2** and 4-(benzyloxy)phenyl bromide were unsuccessful. However, the copper-promoted cross-coupling of (*S*)-**2** with 4-(benzyloxy)phenylboronic acid has afforded a low yield of (*S*)-**1** with compete retention of configuration that was confirmed by chiral HPLC assay (unpublished results of Conlon, D. A.; Drahus, A. L. and Shi, Y.-J. in our laboratories). For the copper-promoted arylation of phenols with arylboronic acid, see: Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
8. (a) The chiral alcohol (*S*)-**2** is activated by the α-ester moiety, see: Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *5*, 4645 and references cited therein; (b) For synthesis of chiral alcohol (*S*)-**2**, see: Tan, L.; Chen, C.-y.; Frey, L.; King, A. O.; Tillyer, R. D.; Xu, F.; Zhao, D.; Grabowski, E. J. J.; Reider, P. J.; O'Shea, P.; Dagneau, P.; Wang, X. *Tetrahedron* **2002**, *58*, 7403.
9. For temperature effects on the Mitsunobu reaction, see Ref. 2b.
10. The order of addition of reagents was critical, see Ref. 2b.
11. **A typical procedure**: A solution of chiral alcohol (*S*)-**2** (0.76 g, 5.76 mmol) and DIAD (1.40 ml, 7.12 mmol) was made in toluene (4.0 ml) and then slowly added to a mixture of phenol **3** (1.30 g, 6.49 mmol) and TPP (1.87 g, 7.12 mmol) in toluene (8.0 ml) at 100°C over 4 h via a syringe pump. It was kept at 100°C until the disappearance of (*S*)-**2** (2-5 h) was observed and then cooled to room temperature. Solvents were removed in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:14) to afford 1.04 g of the ether (*R*)-**1** as a colorless oil in 57% yield. (*R*)-**1** was obtained in >99% ee as determined by chiral assay [ChiralCell OJ-RH, 150×4.6 mm, eluent (A): H_2O (0.1% H_3PO_4), eluent (B): MeCN, gradient (25°C): A/B from 40/60 to 20/80 over 20 min, 1.0 ml/min, 210 nm, retention time: 9.84 min for (*R*)-**1** and 13.38 min for (*S*)-**1**].
12. The typical procedure was used (Ref. 11) and the isolated products were identified by NMR (^1H and ^{13}C) and LCMS.