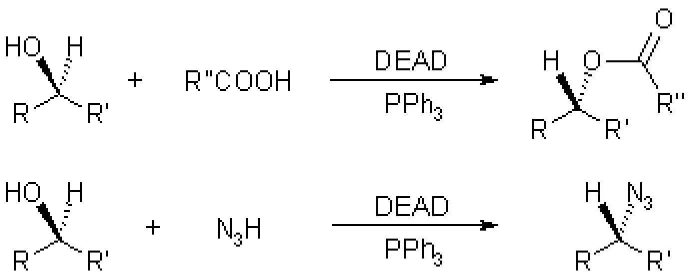
Further Information
Literature

Related Reactions
Appel Reaction
Staudinger Reaction
Synthesis of esters

Mitsunobu Reaction

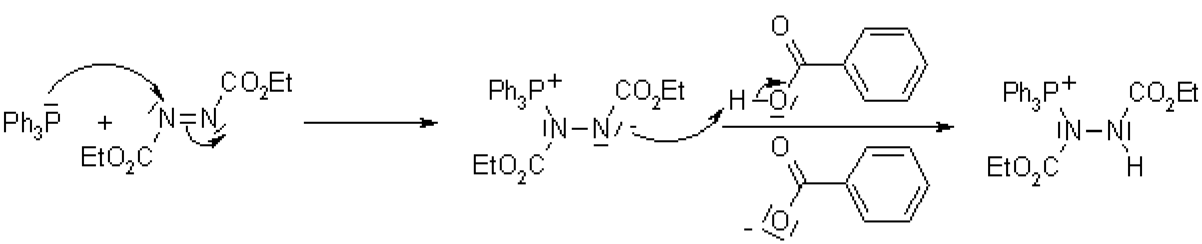


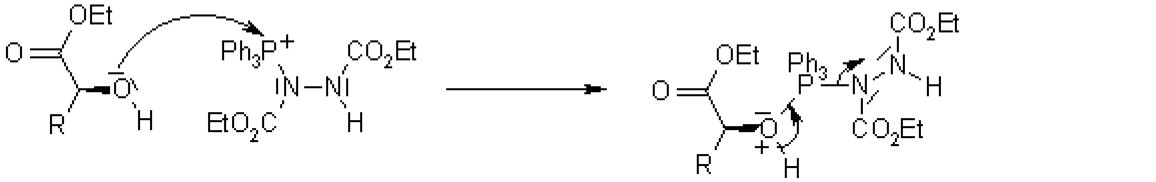
The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds. The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate) must be protonated during the course of the reaction to prevent from side reactions.

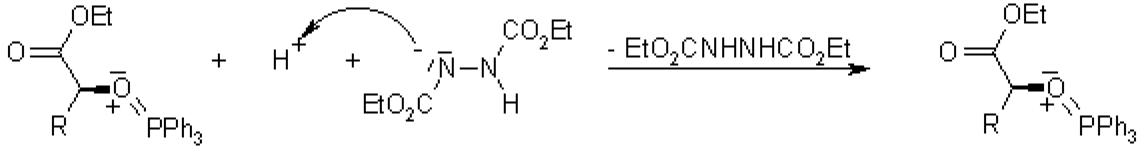
Suitable nitrogen nucleophiles include phthalimide or hydrogen azide; subsequent hydrolysis (in the case of using phthalimide, see Gabriel Synthesis) or selective reduction (in the case of azide formation, see Staudinger Reaction) makes the corresponding amines accessible.

Mechanism of the Mitsunobu Reaction

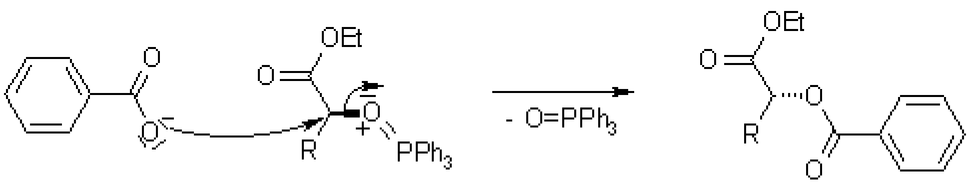
The triphenylphosphine combines with DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Substitution by the carboxylate, mercaptyl, or other nucleophile completes the process.



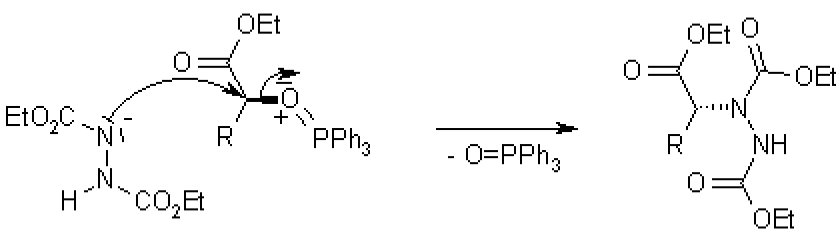




The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a powerful method for the inversion of stereogenic centers in natural product synthesis.

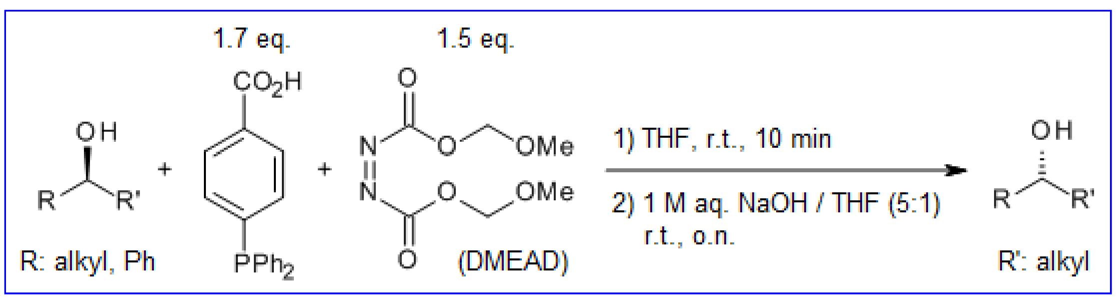


Side Reaction:



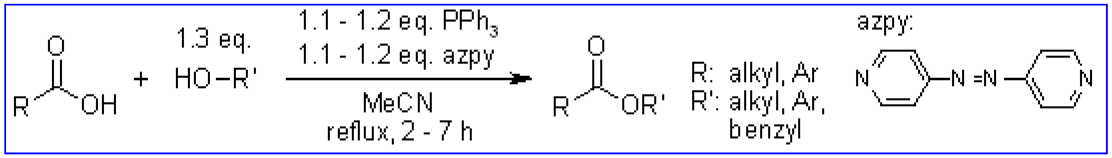
New protocols have been developed which allow better removal of side products and/or the conversion of more basic nucleophiles.

Recent Literature

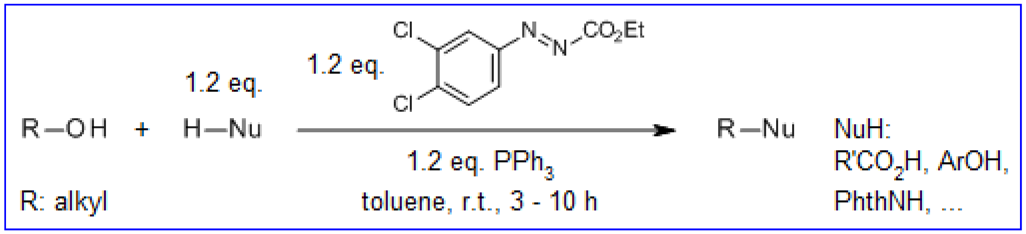


Mitsunobu Reaction with 4-(Diphenylphosphino)benzoic Acid: A Separation-Friendly Bifunctional Reagent that Serves as Both a Reductant and a

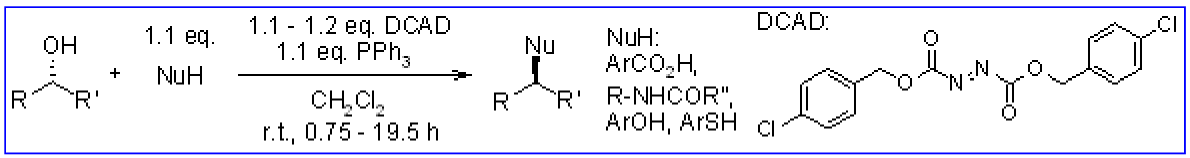
Pronucleophile
N. Muramoto, K. Yoshino, T. Misaki, T. Sugimura, *Synthesis*, **2013**, *45*, 931-935.



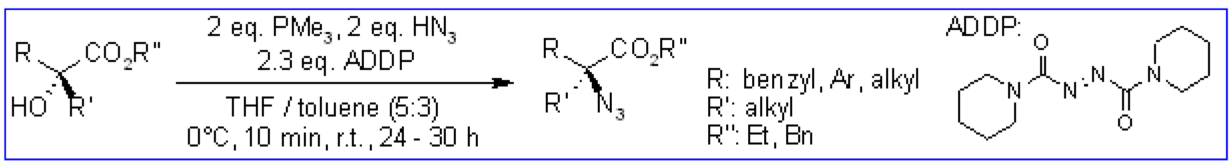
Easily Prepared Azopyridines As Potent and Recyclable Reagents for Facile Esterification Reactions. An Efficient Modified Mitsunobu Reaction
N. Iranpoor, H. Firouzabadi, D. Khalili, S. Motevalli, *J. Org. Chem.*, **2008**, *73*, 4882-4887.



Systematic Evaluation of 2-Arylazocarboxylates and 2-Arylazocarboxamides as Mitsunobu Reagents
D. Hirose, M. Gazvoda, J. Košmrlj, T. Taniguchi, *J. Org. Chem.*, **2018**, *83*, 4714-4729.



Simplification of the Mitsunobu Reaction. Di-*p*-chlorobenzyl Azodicarboxylate: A New Azodicarboxylate
B. H. Lipshutz, D. W. Chung, B. Rich, R. Corral, *Org. Lett.*, **2006**, *8*, 5069-5072.



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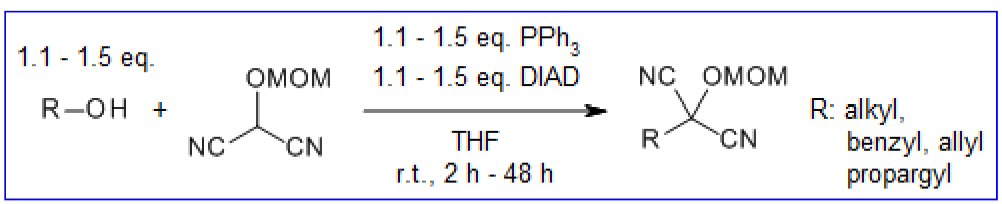
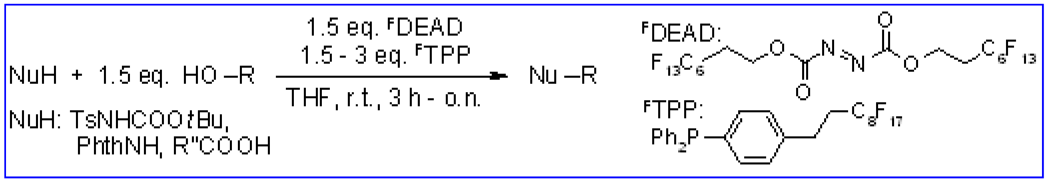
J. E. Green, D. M. Bender, S. Jackson, M. J. O'Donnell, J. R. McCarthy, *Org. Lett.*, **2009**, *11*, 807-810.



One-Carbon Homologation of Primary Alcohols to Carboxylic Acids, Esters, and Amides via Mitsunobu Reactions with MAC Reagents
N. Kagawa, A. E. Nibbs, V. H. Rawal, *Org. Lett.*, **2016**, *18*, 2363-2366.



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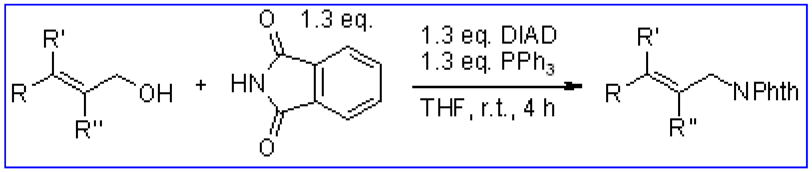
S. Dandapani, D. P. Curran, *Tetrahedron*, **2002**, *58*, 3855-3864.



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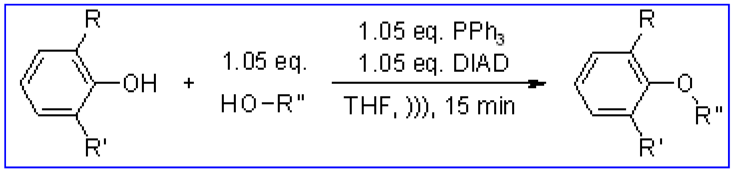
S. E. Sen, S. L. Roach, *Synthesis*, **1995**, 756-758.



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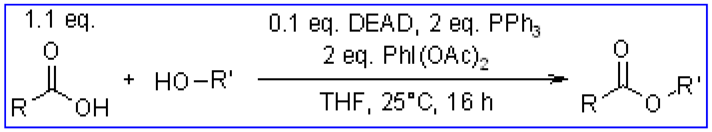
S. D. Lepore, Y. He, *J. Org. Chem.,* **2003**, *68*, 8261-8263.



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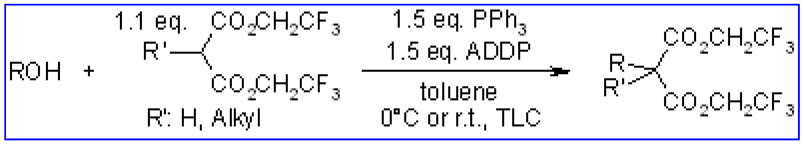
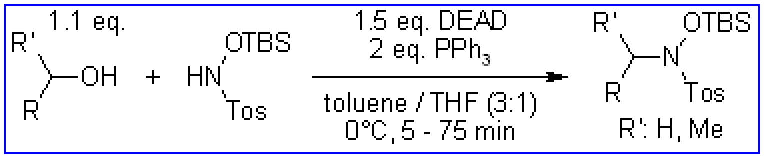
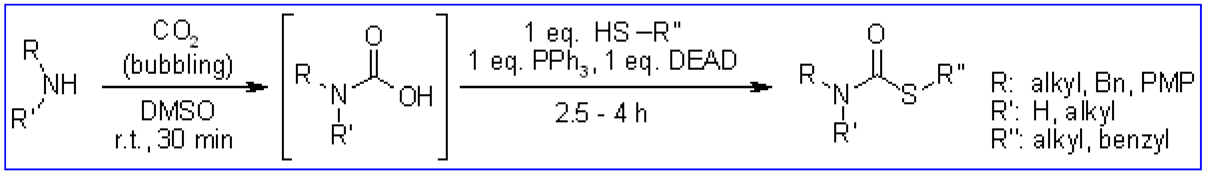


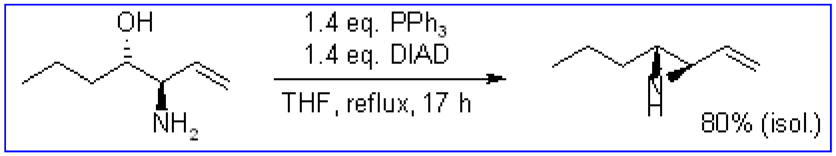
Carbon Nucleophiles in the Mitsunobu Reaction. Mono and Dialkylation of Bis(2,2,2-trifluorethyl) Malonates
J. M. Takacs, Z. Xu, X.-T. Jiang, A. P. Leonov, G. C. Theriot, *Org. Lett.*, **2002**, *4*, 3843-3845.



O-TBS-*N*-tosylhydroxylamine: A Reagent for Facile Conversion of Alcohols to Oximes
K. Kitahara, T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.*, **2008**, *10*, 2259-2261.



An Efficient, One-Pot Synthesis of *S*-Alkyl Thiocarbamates from the Corresponding Thiols Using the Mitsunobu Reagent
D. Chaturvedi, N. Mishra, V. Mishra, *Synthesis*, **2008**, 355-357.



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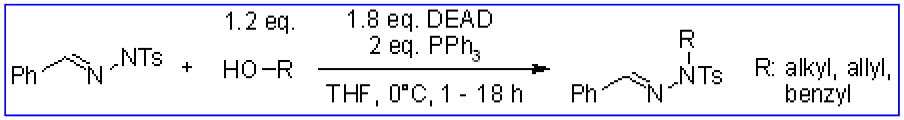
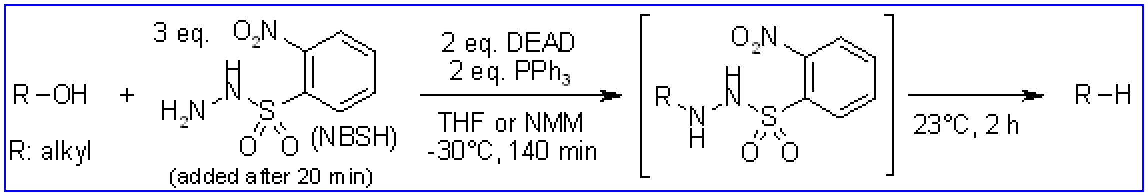
B. Olofsson, R. Wijtmans, P. Somfai, *Tetrahedron*, **2002**, *58*, 5979-5982.



Exploration of the Mitsunobu Reaction with Tosyl- and Boc-Hydrazones as Nucleophilic Agents
J. M. Keith, L. Gomez, *J. Org. Chem.*, **2006**, *71*, 7113-7116.



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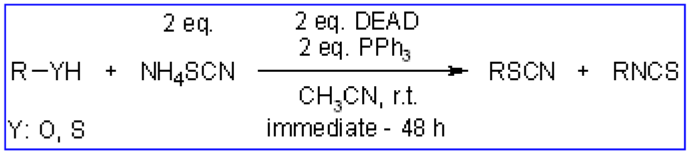
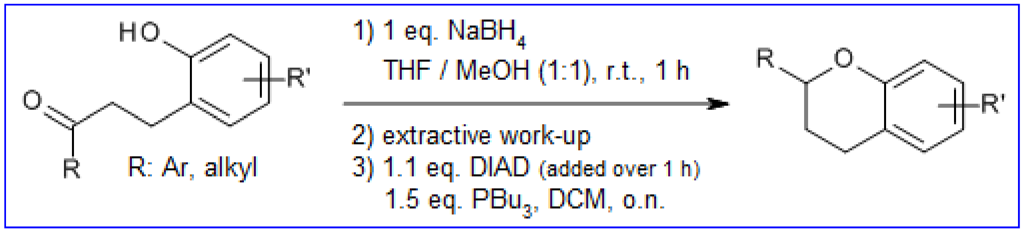
A. G. Myers, M. Movassaghi, B. Zheng, *J. Am. Chem. Soc.*, **1997**, *119*, 8572-8573.



Conversion of Alcohols, Thiols, Carboxylic Acids, Trimethylsilyl Ethers, and Carboxylates to Thiocyanates with Triphenylphosphine/Diethylazodicarboxylate/NH_4SCN
N. Iranpoor, H. Firouzabadi, B. Akhlaghinia, R. Azadi, *Synthesis*, **2004**, 92-96.



A Modular Synthesis of 2-Alkyl- and 2-Arylchromans via a Three-Step Sequence
R. K. Orr, L.-C. Campeau, H. R. Chobanian, H. M. McCabe Dunn, B. Pio, C. W. Plummer, A. Nolting, R. T. Ruck, *Synthesis*, **2017**, *49*, 657-666.