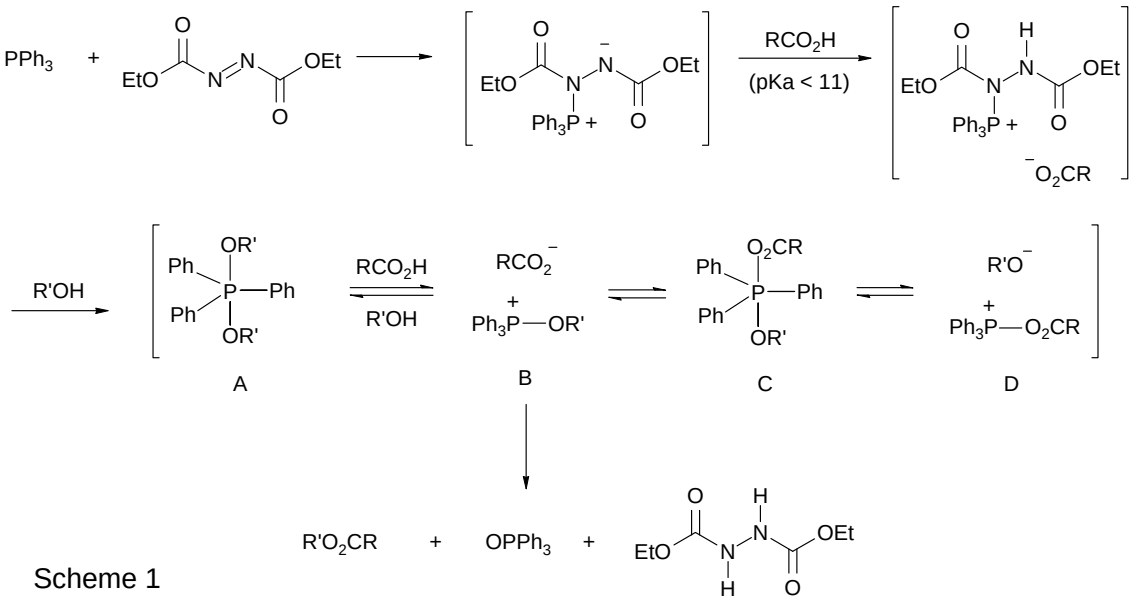
April 12, 2001 Kevin Jantzi

The Mitsunobu Reaction

The Mitsunobu reaction has gained wide acceptance in organic synthesis due to its effectiveness and versatility.[1-3] Discovered in 1967, this mild reaction converts a hydroxyl group into a potent leaving group that is able to be displaced by a wide variety of nucleophiles (Equation 1).[4]

$$\mathrm{ROH} \xrightarrow[\mathrm{DEAD,\ PPh_3}]{\mathrm{NuH}} \mathrm{RNu} \qquad (1)$$

The mechanism has been the subject of some debate centering on the identity of the intermediates and what role(s) they may play.[4-7] Triphenylphosphine and diethyl azodicarboxylate (DEAD) quickly form a betaine intermediate that is able to deprotonate the nucleophile (a carboxylic acid in Scheme 1). The generated carboxylate anion deprotonates the alcohol forming an alkoxide which can then attack the betaine at phosphorus eventually forming phosphorane A and oxyphosphonium ion B in a ratio that is highly dependant on the pKa of the acid and solvent polarity.[6-8] The carboxylate anion participates in a bimolecular nucleophilic displacement of triphenylphosphine oxide which proceeds with inversion. It is generally accepted that the oxyphosphonium ion (B) is the active intermediate which undergoes S_N2 displacement. The other species probably play spectator roles although D may indeed be the active intermediate when the attempted inversion of hindered secondary alcohols yields esters with retained stereochemistry.[9]



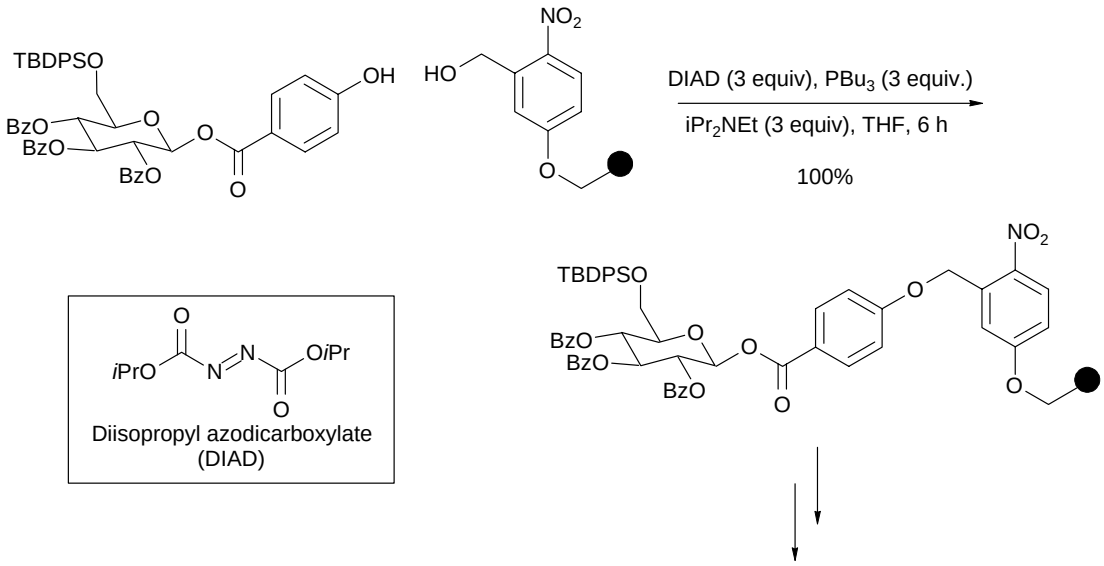
Scheme 1

By far the largest use of the Mitsunobu reaction is the inversion of secondary alcohols, accounting for nearly half of all Mitsunobu publications. This is accomplished by the conversion of a secondary alcohol to an ester (Scheme 1) followed by reduction of the ester. Acetic and benzoic acids have typically been used for this procedure but provide poor results with hindered secondary alcohols. Acids of lower pKa have been shown to give higher yields of inverted products when the alcohol is sterically hindered. *p*-Nitrobenzoic and chloroacetic acid perform quite well in these cases.[10,11] The proposed reason for this increased activity is the evidence that acids of lower pKa tend to favor the oxyphosphonium intermediate (B) over the less reactive phosphane (A).[6,7]

The ability to form carbon-oxygen ester bonds suggested that other types of C-O bonds could be formed. The intermolecular formation of aliphatic ethers is unfortunately hindered by the fact that the betaine intermediate is not basic enough to sufficiently deprotonate the weakly acidic hydroxyl group. However, formation of cyclic ethers via intramolecular condensation proceeds in good yields.[12,13]

Formation of alkyl aryl ethers works well due to the higher acidity of the phenolic proton. This reaction is often used to couple alcohols to resins and has been used by

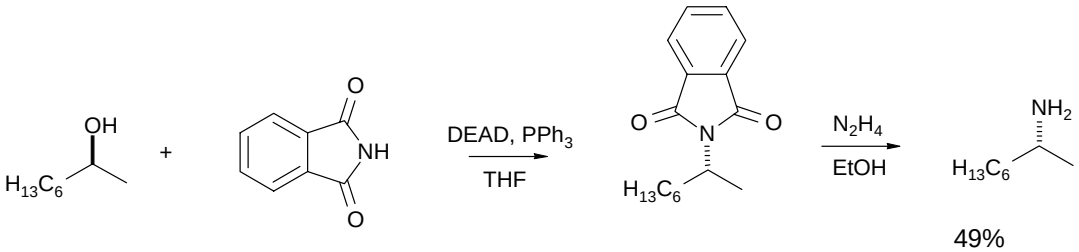
Nicolaou for a solid phase glycosylation in his synthesis of a stereochemically homogeneous dodecasaccharide (Scheme 2).[14]



Scheme 2

stereochemically homogeneous dodecasaccharide

In 1972, Mitsunobu reported the formation of amines from alcohols via phthalimide and subsequent reduction with hydrazine (Scheme 3).[15] Amines are also accessible via Staudinger reductions of azides which are formed in excellent yields using HN_3 under Mitsunobu conditions.[16]



Phthalimide

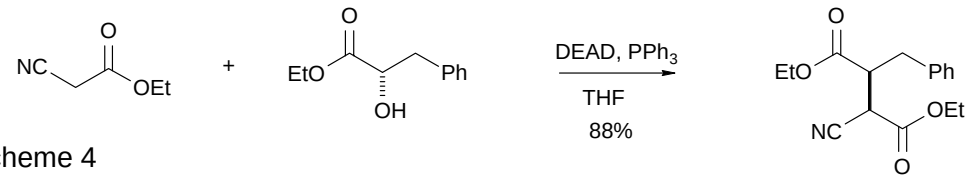
79%

Scheme 3

Formation of β-lactams using the Mitsunobu reaction was originally reported by Miller.[17] This reaction proceeded in good to excellent yields. Use of the Mitsunobu reaction in β-lactam formation was used in the synthesis of a lankicidin C synthon.[18]

The recent FDA approval of the nucleoside reverse transcriptase inhibitor Abacavir as a treatment for HIV is representative of the importance of this class of molecules. Formation of nucleosides and their analogues using the Mitsunobu protocol has become quite popular. A recent example of this is Chu's syntheses of various 4'-fluoro-substituted carbocyclic nucleosides.[19]

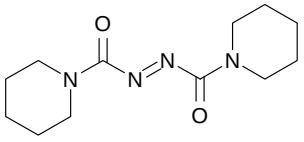
As is typically the case with a new reaction, the question arises as to whether it can be used to form C-C bonds. Indeed this is possible but the low pKa required of the nucleophile restricts the range of carbon nucleophiles to 1,3-substituted methylenes with a pKa of <11 in most cases. The reaction of ethyl cyanoacetate with (S)-(-)-ethyl 2-hydroxy-3-phenylpropionate proceeded in excellent yield with the expected inversion of stereochemistry (Scheme 4).[20] Unfortunately, the same reaction using *n*-propanol resulted in a complex mixture of products including mono- and di-alkylated product and alkylated diethyl hydrazinedicarboxylate. Reaction of 1,3-cyclohexanedione with *n*-propanol resulted in entirely *O*-alkylated products in good yield. Diethyl malonate was unreactive.



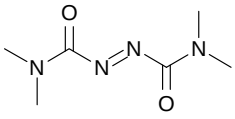
Scheme 4

The displacement of triphenylphosphine oxide with HCN to form nitriles was first reported in 1976.[16] Recently, Wilk has utilized acetone cyanohydrin as a replacement for HCN in these reactions.[21] The yields are comparable to HCN and the reagent is easier to handle and less toxic. A general trend seems to be that yields with primary alcohols tend to be excellent but are drastically decreased when hindered secondary alcohols are used.

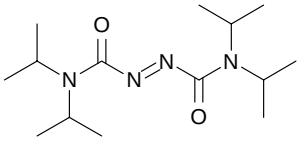
Recently Tsunoda and coworkers have reported some DEAD alternatives of increased basicity that allow carbon nucleophiles having higher pKa's to be used as nucleophiles. The reaction of diethyl malonate with benzyl alcohol using DEAD, PPh_3 in benzene results in a 2% yield after 24h. In stark contrast, the yields using PBu_3 with ADDP (56%), TMAD (66%) and DHTD (75%) are good.[22,23] In general, DHTD gives better yields for the reported *C*-alkylations and works well with secondary alcohols.



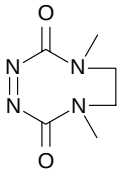
ADDP



TMAD



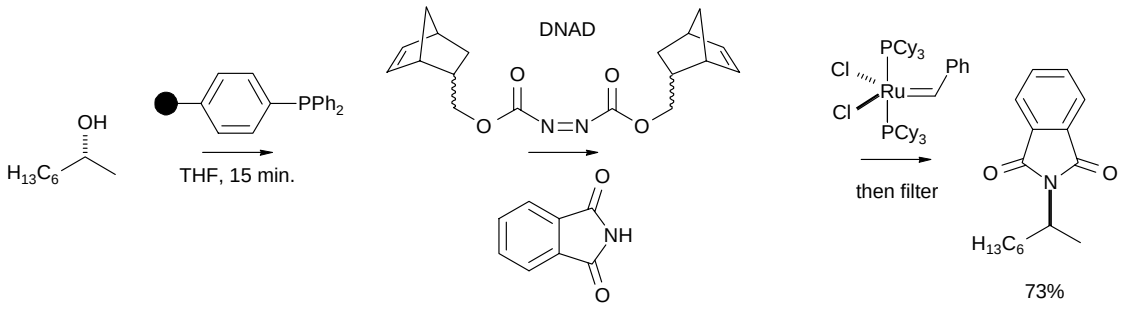
TIPA



DHTD

There has been some excellent work from the labs of Falck on the *C*-alkylation of various 1,3-substituted methylenes. Both the intermolecular and intramolecular reactions of bis-sulfone methylene proceed in good to excellent yields with a wide variety of alcohols.[24] This method nicely incorporates a single carbon and other methods have been developed for two-carbon elongations via (phenylsulfonyl)acetonitrile[25] and methyl phenylsulfonylacetate.[26]

A property that has hampered the Mitsunobu reaction somewhat is the isolation and purification of products from the triphenylphosphine oxide and diethyl hydrazinedicarboxylate byproducts. Various ways of addressing this problem have been developed including triphenylphosphine analogues that can be removed by acid wash.[27,28] A new method reported by Barrett and coworkers aims to remove all impurities via the novel ring opening metathesis (ROM) protocol depicted in Scheme 5.[29] The yields using this procedure were good and the purification proceeded well.



Scheme 5

The Mitsunobu reaction has proven to be a useful, diverse and practical method for C-O, C-N, C-C and C-X bond formation, among other uses. Its mild reaction conditions and excellent stereoselectivity make it an excellent reaction that serves its purpose well. It will no doubt continue to be an important synthetic tool for the practicing organic chemist.

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