DEAD Methodology

Lively Chemistry!

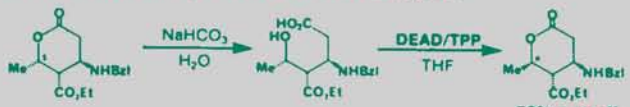
The salt formed by the interaction of **diethyl azodicarboxylate (DEAD)** and **triphenylphosphine (TPP)** very effectively activates alcohols toward nucleophilic displacement *via* an alcohol-salt complex. In the 14 years since the original report,[1] the scope of the reaction has been expanded tremendously to include a wide variety of nucleophiles in both inter- and intramolecular applications.[2]

DEAD/TPP activation easily effects closure of both large and small rings:

40%[3]

90%[4]

An elegant application exploited the S_N2 nature of the alcohol displacement to effect a critical stereochemical inversion of a lactone precursor to thienamycin:[5]



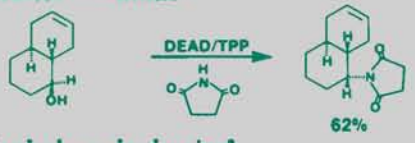
53% overall

DEAD/TPP also enables the closure of *trans*-diols to form epoxides:

77%[6]

The enormous synthetic utility of the intermolecular reaction becomes apparent when one considers the following recent and diverse functional-group transformations:

Alcohol → imide[7]



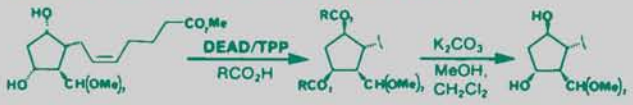
62%

(+)-gephyrotoxin precursor

Alcohol → hydrazine[8]

78%

Alcohol → ester (→ inverted alcohol)[9]



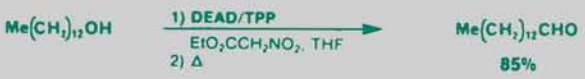
R = 4-biphenyl

40% overall

α-Hydroxystannane → α-chlorostannane[10]

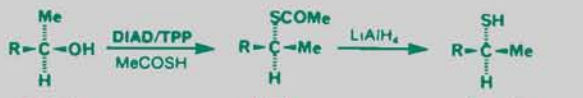
65%

Dr. Mitsunobu, the pioneer of **DEAD/TPP** chemistry, recently reported a neutral, mild alcohol oxidation whereby **ethyl nitroacetate** displaces the alcohol.[11] The resulting *aci*-nitro ester thermally decomposes to afford the carbonyl compound in high yield:



85%

Recently, **diisopropyl azodicarboxylate (DIAD)** emerged as a welcome addition to azodicarboxylate chemistry.[12] When complexed with **DIAD/TPP**, alcohols are smoothly displaced by **thiolacetic acid** to form thiol esters which are easily reduced to thiols. As seen below, the reaction is virtually stereospecific:



(*R*)-(-)
80.8% optical purity

98%
(R = *n*-hexyl)

(*S*)-(+)
80.4% optical purity

We are pleased to add **DIAD** to our inventory.

References:

1) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
2) For a comprehensive review, see Mitsunobu, O. *Synthesis* **1981**, 1.
3) Bass, R.J.; Banks, B.J.; Leeming, M.R.G.; Snarey, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 124.
4) Miller, M.J.; Mattingly, P.G.; Morrison, M.A.; Kerwin, Jr., J.F. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
5) Melillo, D.G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913.
6) McGowan, D.A.; Berchtold, G.A. *J. Org. Chem.* **1981**, *46*, 2381.
7) Hart, D.J. *ibid.* **1981**, *46*, 3576.
8) Dow, R.L.; Kelly, R.C.; Schletter, I.; Wierenga, W. *Synth. Commun.* **1981**, *11*, 43.
9) Swain, M.L.; Turner, R.W. *Chem. Commun.* **1981**, 840.
10) Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1981**, *22*, 2397.
11) Mitsunobu, O.; Yoshida, N. *ibid.* **1981**, *22*, 2295.
12) Volante, R.P. *ibid.* **1981**, *22*, 3119.

D9,000-8	**Diethyl azodicarboxylate**, 95%*	**25g $19.80** **100g $70.00**
T8,440-9	**Triphenylphosphine**, 99%*	**100g $8.75** **1kg $79.65**
19,233-3	**Ethyl nitroacetate**	**5g $12.05; 25g $42.95**
T3,080-5	**Thiolacetic acid**, tech.	**100g $13.75; 500g $50.60**
22,554-1	**Diisopropyl azodicarboxylate**, 97%	**100g $18.00**

*Available in bulk quantities.

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