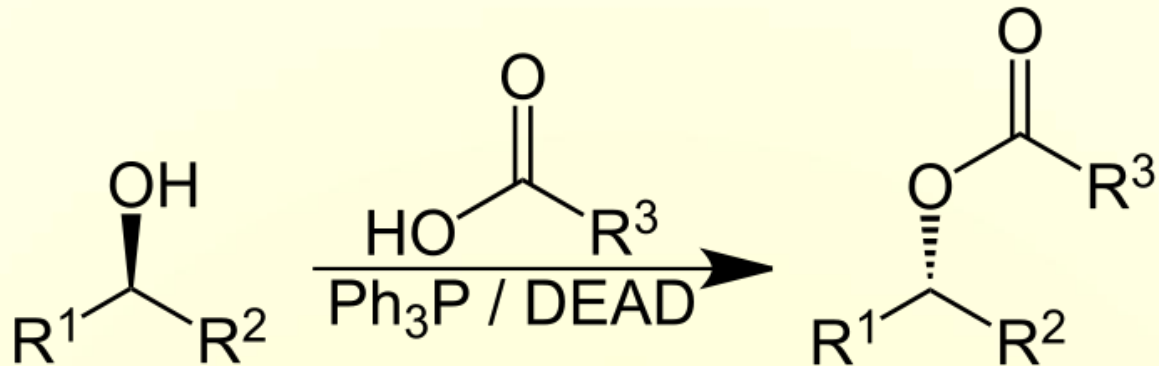


Mitsunobu Reaction

2016-06-21

WZQ

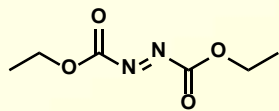
Mitsunobu Reaction



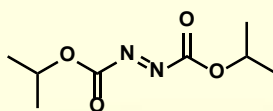
- The Mitsunobu reaction is an organic reaction that converts an alcohol into a variety of functional groups, such as an ester, using triphenylphosphine and an azodicarboxylate such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).
- The alcohol undergoes an inversion of stereochemistry.
- It was discovered by Oyo Mitsunobu (1934–2003)

Mitsunobu Reaction

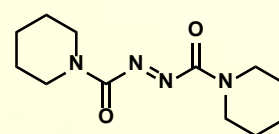
Azodicarboxylate reagents



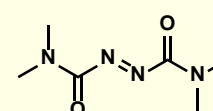
DEAD



DIAD

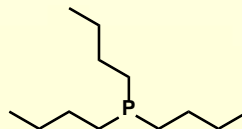
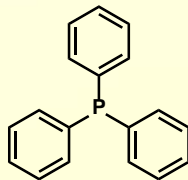


ADDP



TMAD

Phosphines



Alcohols

1/2 alkyl, aryl, heteroaryl, alkenyl and some 3

H-Nuc

O-, S-, N- and C-nucleophiles: $pK_a < 13$

solvent

THF, dioxane, DCM, $CHCl_3$, DMF, toluene, benzene, HMPA

temperature

0-25°

Mitsunobu Reaction

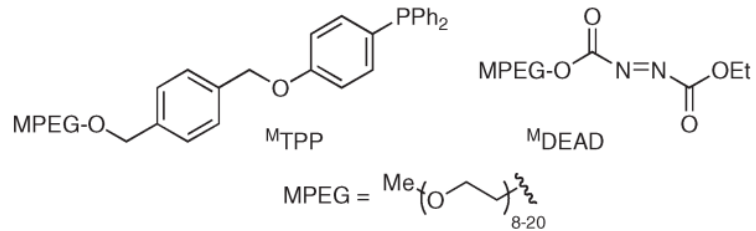
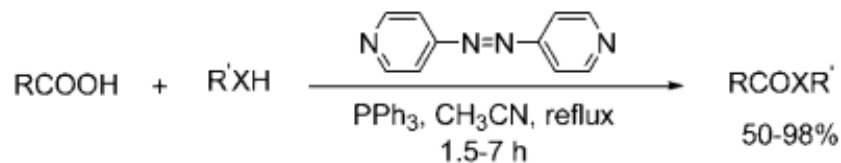


Figure 3. MPEG-tagged reagents for the Mitsunobu reaction.



R = Alkyl, Aryl
 R' = Alkyl, Aryl
 X = O, S

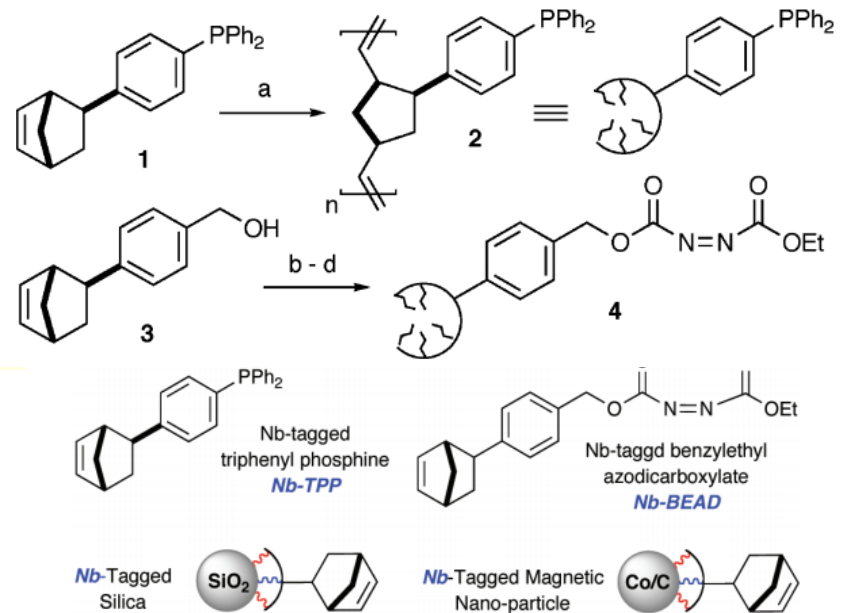
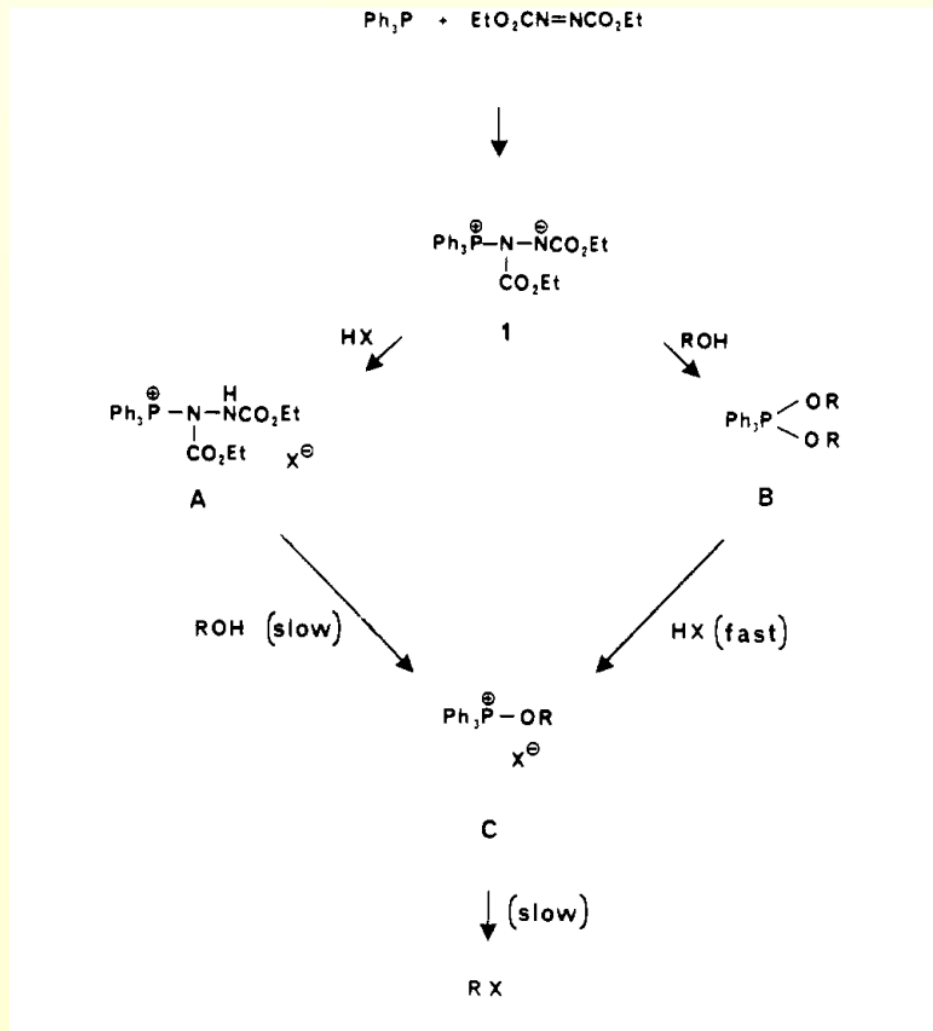


Figure 1. Norbornenyl-tagged reagents and Co/C Np's for MoM Mitsunobu Reactions.

Mitsunobu Reaction

Reaction mechanism

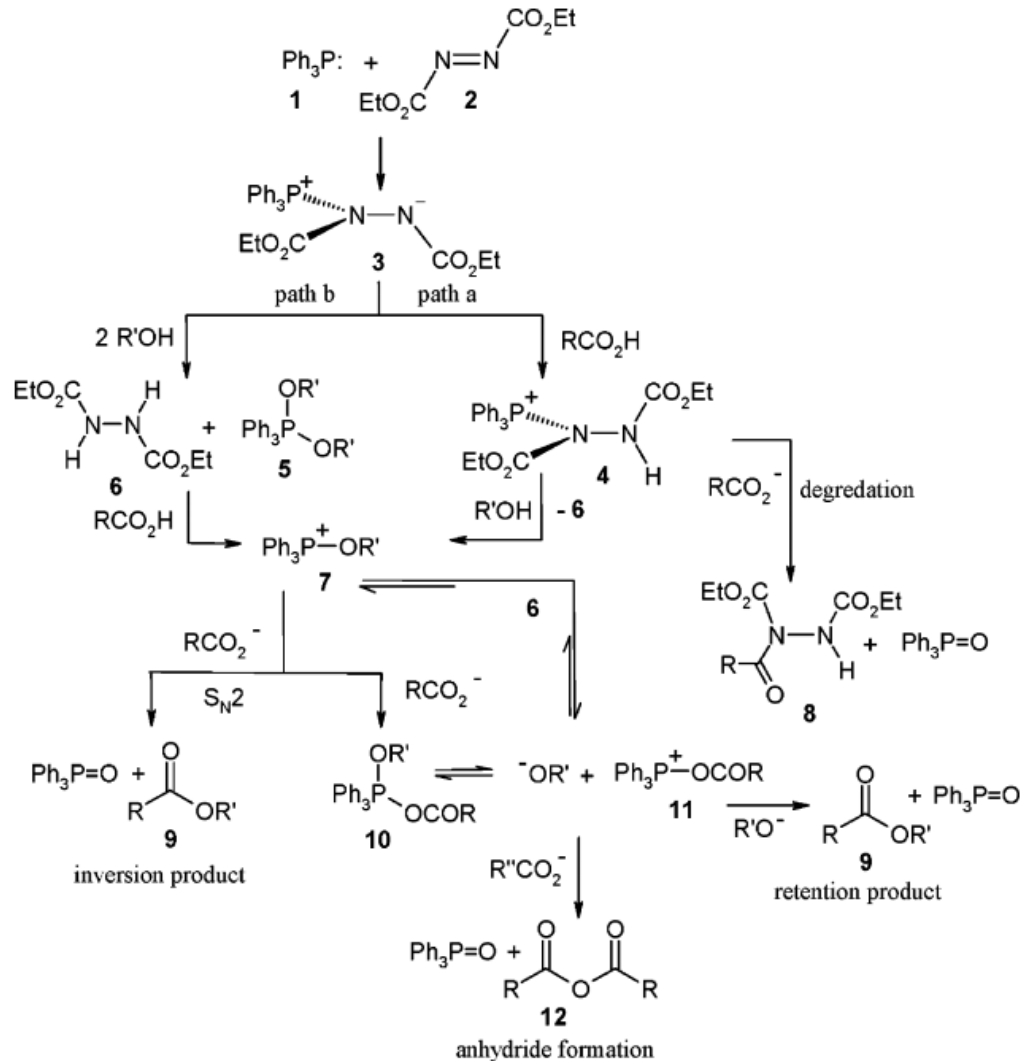


J. Org. Chem. 1987,
52, 4235-4238

Mitsunobu Reaction

Reaction mechanism

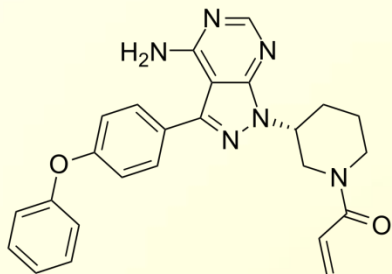
Scheme 1. Postulated Mechanisms of the Mitsunobu Reaction



J. AM. CHEM. SOC.
2005, 127, 12566-12576

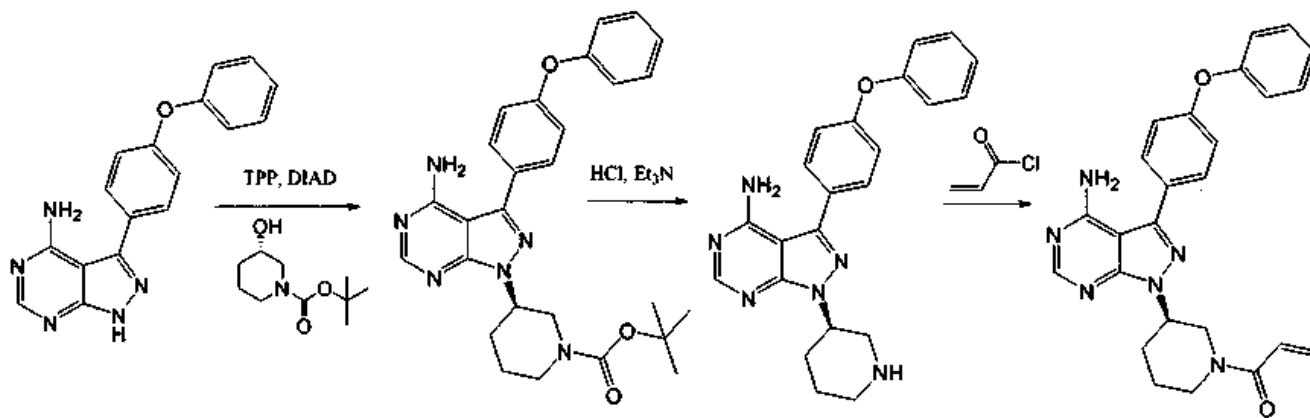
Mitsunobu Reaction

Applications

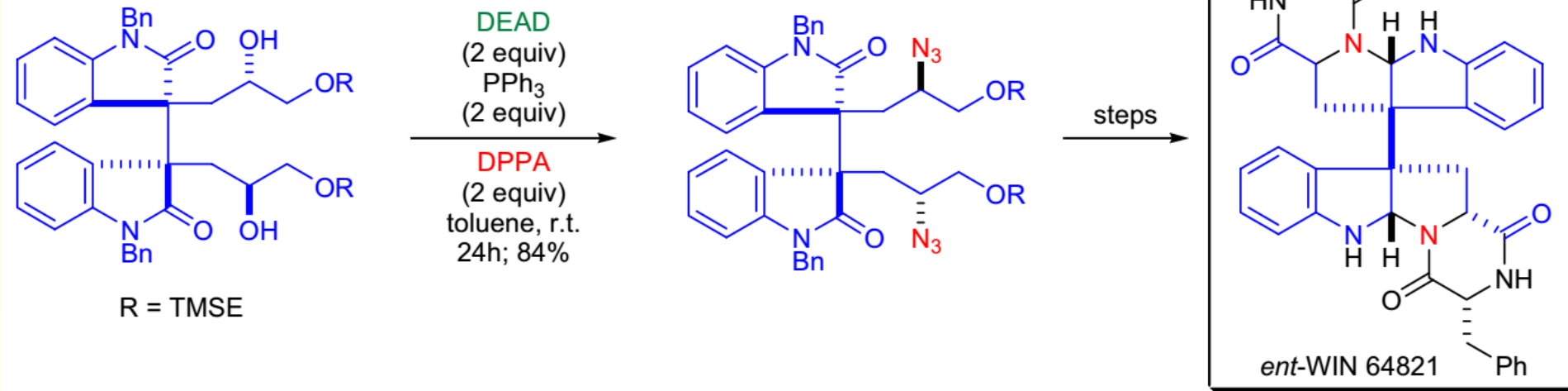
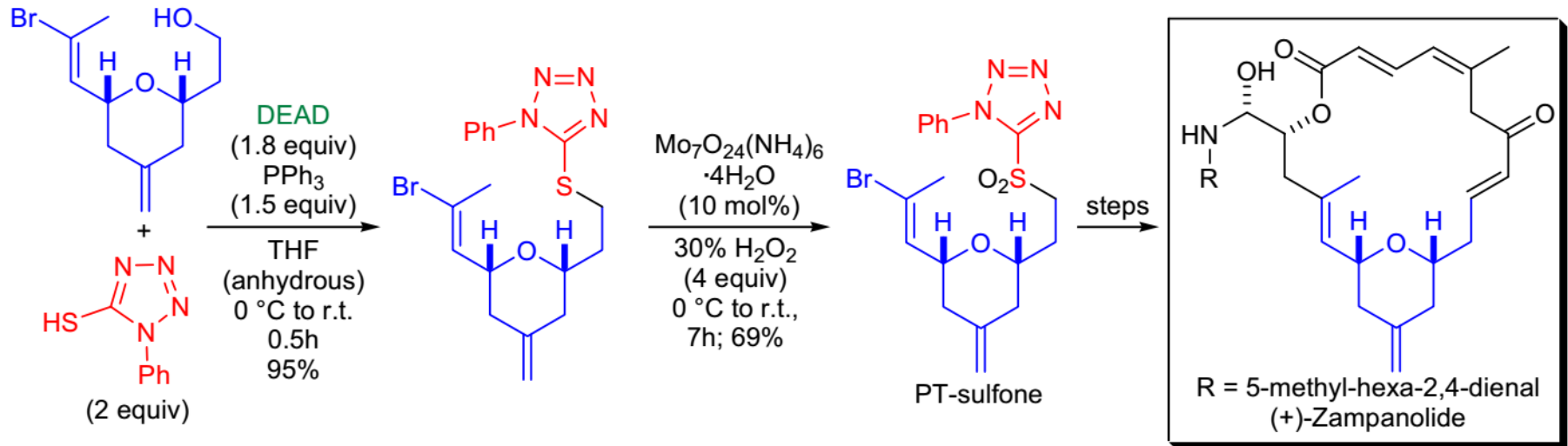


Ibrutinib

[0005]

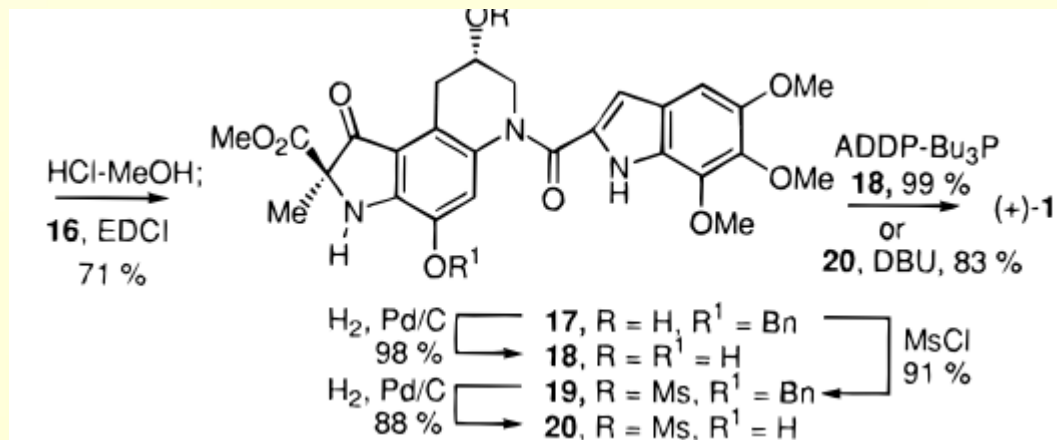
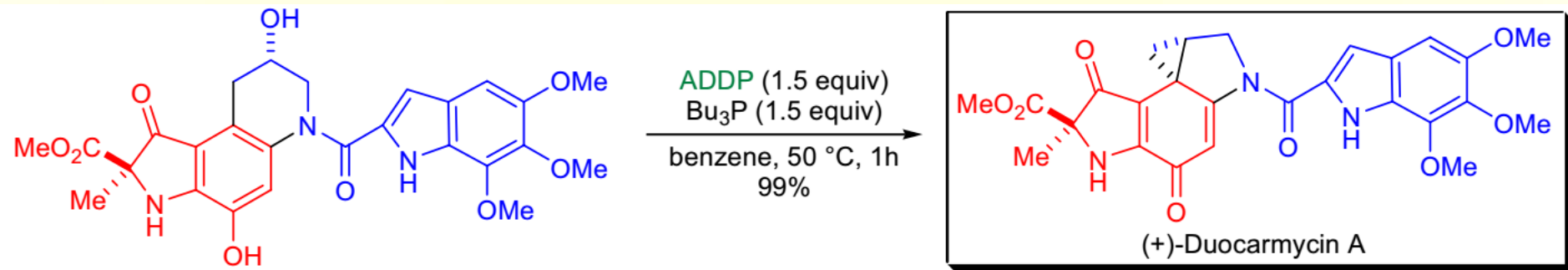


Mitsunobu Reaction



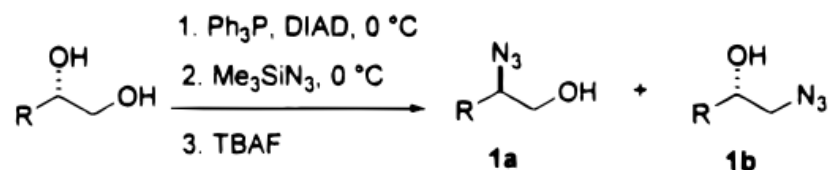
Mitsunobu Reaction

Applications



Mitsunobu Reaction

Table 2. Solvent Effects on the Regioselectivity of Azidation under Mitsunobu Conditions^a



R	Solvent	Product Ratio (1a/1b)	Combined Yield of 1a and 1b (%)
<i>p</i> -MeOC ₆ H ₄ OCH ₂ -	THF	2:1	82
	CH ₂ Cl ₂	3:1	81
	PhCH ₃	4:1	84
<i>n</i> -C ₁₄ H ₂₉ -	THF	20:1	82
	CH ₂ Cl ₂	32:1	80
	PhCH ₃	47:1	89
<i>n</i> -C ₁₃ H ₂₇ -≡CH ₂ -	THF	7:1	77
	CH ₂ Cl ₂	10:1	80
	PhCH ₃	12:1	74

J. Org. Chem., Vol. 64, No. 16, 1999