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FACILE ROUTES TO BORON ENOLATES. Et_3B-MEDIATED REFORMATSKY TYPE REACTION AND THREE COMPONENTS COUPLING REACTION OF ALKYL IODIDES, METHYL VINYL KETONE, AND CARBONYL COMPOUNDS

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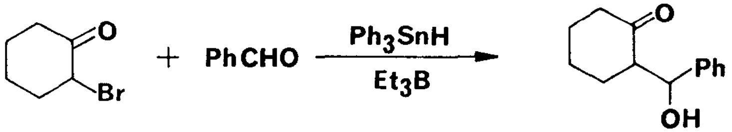
Abstract: Reaction of α-bromoketones with Ph_3SnH in the presence of Et_3B provides boron enolates which react with carbonyl compounds to give β-hydroxyketones in good yields. Et_3B-induced Reformatsky type reaction of α-iodoketones with an aldehyde or ketone proceeds without Ph_3SnH.

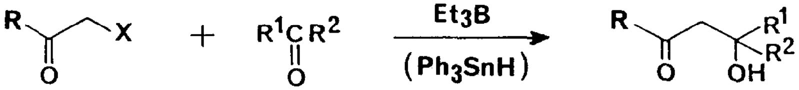
Recently we have shown that Et_3B is an effective initiator for the radical addition of triphenyltin hydride or triphenylgermyl hydride to acetylenes.[1] Here we wish to report a simple and efficient Reformatsky type reaction[2] mediated by Et_3B. A hexane solution of Et_3B (1.0 M, 1.1 mL, 1.1 mmol) was added to a solution of α-bromoketone (1.0 mmol) and aldehyde (1.0 mmol) in benzene (3.0 mL) at 25 °C under an argon atmosphere. To the mixture was added slowly a benzene solution of Ph_3SnH (0.2 M, 5.0 mL, 1.0 mmol) and the resulting mixture was stirred for 5 min at 25 °C. Workup (aq KF,[3] AcOEt) followed by purification by preparative tlc on silica gel gave β-hydroxyketone in good yield. The representative results are summarized in Table 1.[4] Whereas the reaction of 7-bromo-6-dodecanone with benzaldehyde gave a mixture of erythro and threo-β-hydroxy carbonyl compound (entry 13 in Table 1), α-bromocyclopentanone or α-bromocyclohexanone provided threo adducts with high stereoselectivities.[5,6]



Surprisingly, the reaction of α-iodoketones with carbonyl compounds proceeded without Ph_3SnH. For instance, an addition of Et_3B to a solution of α-iodoacetophenone and benzaldehyde in benzene gave 1,3-diphenyl-3-hydroxy-1-propanone in 86% yield after aqueous workup.[7] The results are also shown in Table 1. The erythro/threo ratios of the products were exactly the same as those obtained from the reaction of α-bromoketones. The success of the reaction is ascribed to the characteristics of Et_3B which plays critical two roles: (1) initiation of the radical reaction to generate α-carbonyl radical (or vinyloxy radical) from α-iodocarbonyl compound and (2) trapping this radical as boron enolate.[8]

It was anticipated that the 1,4-addition of alkyl radical generated from alkyl iodide to a double bond of α,β-unsaturated carbonyl compound in

Table 1. Reformatsky type reaction mediated by Et_3B

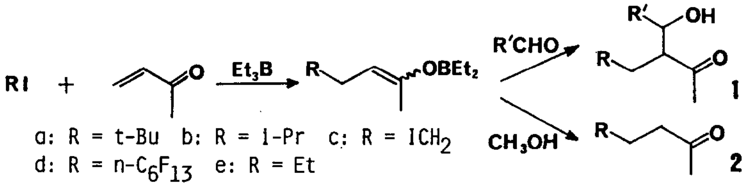


Entry	Bromoketone[a] (Iodoketone)[b]	Carbonyl Compound	Product Yield(%)	Product Erythro/Threo
1	α-Bromoacetophenone	PhCHO	88	——
2		$n\text{-}C_8H_{17}CHO$	77	——
3		$CH_3C(O)(CH_2)_8CHO$	78[c]	——
4		cyclohexanone	81	——
5	2-Bromocyclopentanone	PhCHO	92	15/85
6		$n\text{-}C_6H_{13}CHO$	77	8/92
7		i-PrCHO	73	3/97
8		t-BuCHO	83	0/100
9	2-Bromocyclohexanone	PhCHO	74	22/78
10		$n\text{-}C_6H_{13}CHO$	82	2/98
11		i-PrCHO	76	9/91
12		t-BuCHO	82	0/100
13	7-Bromo-6-dodecanone	PhCHO	80	65/35[c]
14	α-Iodoacetophenone	PhCHO	86	——
15		$n\text{-}C_6H_{13}CHO$	72	——
16		$CH_3C(O)(CH_2)_8CHO$	76[d]	——
17		cyclohexanone	77	——
18	2-Iodocyclopentanone	$n\text{-}C_6H_{13}CHO$	64	6/94
19		i-PrCHO	75	3/97
20		t-BuCHO	70	0/100
21	2-Iodocyclohexanone	PhCHO	83	20/80
22		i-PrCHO	68	6/94
23		t-BuCHO	72	0/100
24		Me_2CO[e]	71	——

a) α-Bromoketone (1.0 mmol), carbonyl compound (1.0 mmol), Et_3B (1.1 mmol), and Ph_3SnH (1.0 mmol) were employed. b) A hexane solution of Et_3B (1.1 mmol) was added slowly to a solution of α-iodoketone (1.0 mmol) and carbonyl compound (1.0 mmol) at 25 °C under an argon atmosphere and the resulting mixture was stirred for 3 min. c) An intermediary boron enolate must be a mixture of stereoisomers (E and Z) whose ratio was not determined. d) Only aldehyde moiety reacted and ketone group remained unchanged. e) Excess acetone (4 equiv) was used.

the presence of Et_3B would provide another route to boron enolate which easily reacts with an aldehyde or ketone to give β-hydroxy carbonyl compound. This was indeed the case as demonstrated by the one-step joining reaction of three components.[9] Typical experimental procedure is as follows. A benzene solution of methyl vinyl ketone (70 mg, 1.0 mmol) was added to a solution of t-butyl iodide (0.55 g, 3.0 mmol), Et_3B (1.0 M hexane solution, 1.0 mL, 1.0 mmol), and heptanal (0.11 g, 1.0 mmol) in benzene (5.0 mL) at 25°C under an argon atmosphere. After stirring for 5 min, the resulting mixture was poured into water. Extractive workup followed by purification by preparative tlc gave 4-hydroxy-3-neopentyl-2-dodecanone (0.15 g) in 63% yield (erythro/threo = 71/29) along with 4-hydroxy-3-propyl-2-dodecanone (5 mg, 2%) derived from the reaction of ethyl radical[10] instead of t-butyl radical. Primary iodide such as MeI did not give satisfactory results because ethyl radical from Et_3B competed with primary alkyl radical derived from alkyl iodide and a mixture of two products were obtained (ethylated hydroxy ketones were main products). Not only sec- or tert-alkyl iodides but also diiodide or perfluoroalkyl iodide such as CH_2I_2, $n\text{-}C_6F_{13}I$ gave the corresponding adducts in good yields (Table 2). Ethylated products were not observed in the reaction of CH_2I_2. The use of methanol instead of aldehydes as the trapping reagents of enolates provided β-alkylated ketones. The presence of 5 mol% of galvinoxyl effectively stopped the reaction of alkyl iodide with methyl vinyl ketone.

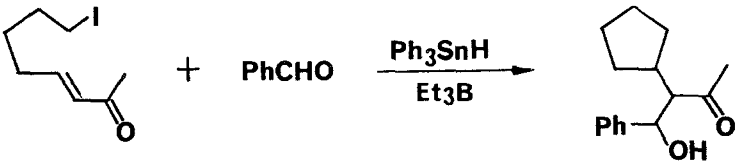
Table 2. Three components coupling reaction of alkyl iodide, methyl vinyl ketone, and carbonyl compound



Entry	RI	R'CHO or CH_3OH^a	Product Yield (%) erythro/threo
1	t-BuI	CH_3OH	**2a** (79) **2e** (5)
2	t-BuI	PhCHO	**1a** (63, 66/34) **1e** (4)
3	i-PrI	CH_3OH	**2b** (79) **2e** (15)
4	i-PrI	PhCHO	**1b** (58, 71/29) **1e** (21)
5	i-PrI	$n\text{-}C_6H_{13}CHO$	**1b** (56, 73/27) **1e** (18)
6	CH_2I_2	CH_3OH	**2c** (69)
7	CH_2I_2	PhCHO	**1c** (74, 61/39)
8	$n\text{-}C_6F_{13}I$	CH_3OH	**2d** (62) **2e** (2)
9	$n\text{-}C_6F_{13}I$	PhCHO	**1d** (31^b) **1e** (2)

a) CH_3OH (2.0 mmol) was employed instead of aldehyde. b) The ratio of erythro/threo or threo/erythro = 23/77).

The Et_3B induced reaction of 8-iodo-3-octen-2-one with PhCHO gave the corresponding cyclopentane derivative in 60% yield.[11,12]



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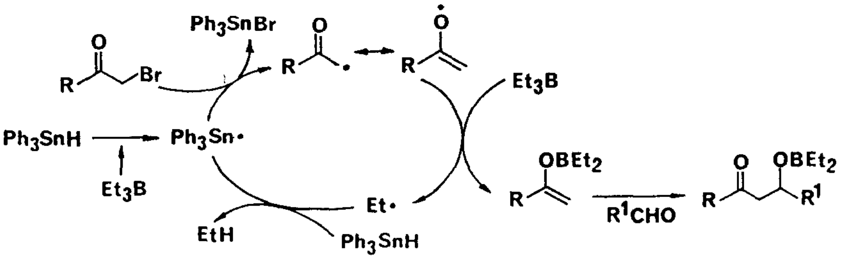
4. The reaction of α-bromoester with Ph_3SnH-Et_3B system resulted in the formation of the reduced ester even in the presence of aldehyde carbonyls. Reformatsky type adduct could not be detected in the reaction mixture.
5. These findings suggested that the reaction proceeded via boron enolates. (E)-Boron enolates have been reported to give threo aldol adducts. Hirama, M.; Masamune, S. Tetrahedron Lett. **1979**, 2225; Horn, D. E. V.; Masamune, S. ibid. **1979**, 2229; Evans, P. A.; Vogel, E.; Nelson, J. V. J. Am. Chem. Soc. **1979**, 101, 6120 and references cited therein.
6. We are tempted to assume following reaction mechanism.



7. Treatment of a solution of α-bromoacetophenone and benzaldehyde in benzene with Et_3B gave the corresponding β-hydroxyketone in only 25% yield after prolonged reaction time (3 h) along with the recovered bromoketone and unidentified complex by-products.
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11. The coexistence of Ph_3SnH was essential for the successful reaction in this case.

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