

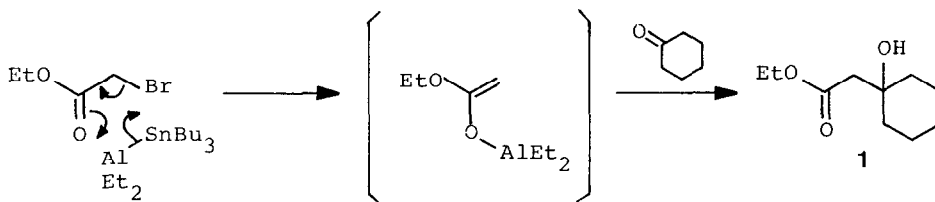
REFORMATSKY TYPE REACTION BY MEANS OF $\text{Bu}_3\text{SnAlEt}_2$ or $\text{Bu}_3\text{PbAlEt}_2$

Noriyuki Tsuboniwa, Seihiro Matsubara, Yoshitomi Morizawa, Koichiro Oshima*,
and Hitosi Nozaki

Department of Industrial Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Kyoto 606, Japan

Abstract: Treatment of α -halo carbonyl compounds with title Sn-Al or Pb-Al reagents provides enolates which react with aldehydes or ketones to give β -hydroxy carbonyl compounds effectively.

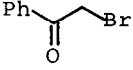
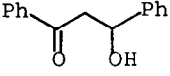
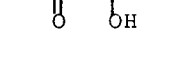

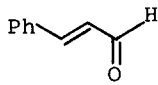
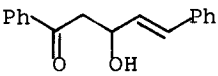
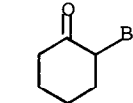
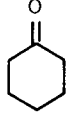
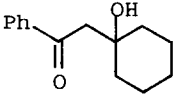

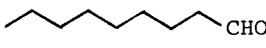
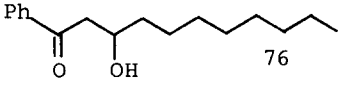
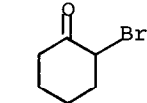
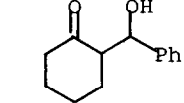
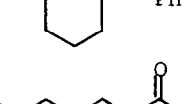
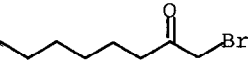
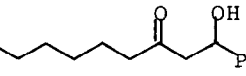

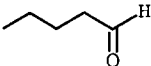
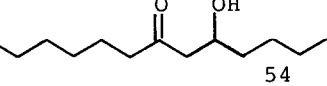
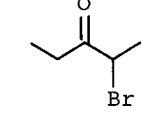
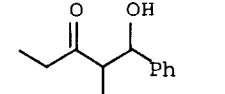
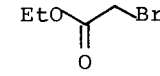
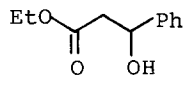
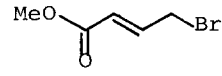
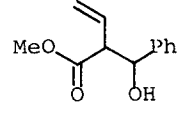

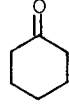
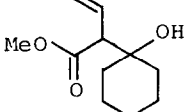
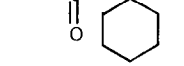
The reaction of terminal acetylenes with the organometallic compounds prepared from Bu_3SnLi and MeMgI or Et_2AlCl affords vinylstannanes under good control of the regio- and stereoselectivity in the presence of various transition-metal catalysts.¹ Here we wish to report another application of the $\text{Bu}_3\text{SnAlEt}_2$ reagent to the regiospecific aldol synthesis of α -bromo carbonyl derivatives and aldehydes or ketones.^{2,3} This new method is successfully extended to the Reformatsky reaction giving β -hydroxy esters under mild conditions.^{4,5}



A hexane solution of diethylaluminium chloride (1.0 M, 2.0 ml, 2.0 mmol) was added to a solution of Bu_3SnLi ⁶ prepared from butyllithium (1.6 M, 3.8 ml, 6.0 mmol) and SnCl_2 (0.38 g, 2.0 mmol) in THF (3 ml) at 0°C. After 10 min, a mixture of ethyl bromoacetate (0.17 g, 1.0 mmol) and cyclohexanone (0.10 g, 1.0 mmol) in THF (3 ml) was added and the whole was stirred for 30 min. Aqueous workup (1N-HCl) and purification by column chromatography gave β -hydroxy ester (**1**)⁷ (0.16 g) in 87% yield.

The reaction of methyl γ -bromocrotonate and benzaldehyde with $\text{Bu}_3\text{SnAlEt}_2$ afforded only the α -adduct (entry 10, Table 1). The same regioselectivity was observed in the reaction by means of $\text{Zn/Et}_2\text{AlCl}$ system^{3a} and diethylaluminium 2,2,6,6-tetramethylpiperidide.^{3h} The strong

Table 1. Synthesis of β -hydroxy carbonyl compounds in the presence of $\text{Bu}_3\text{SnAlEt}_2^{\text{a}}$

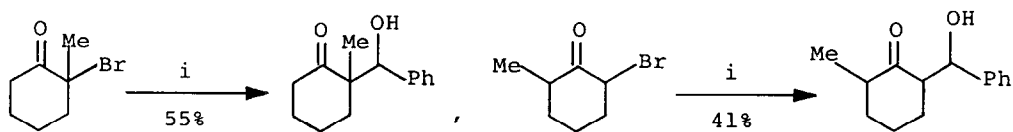
entry	α -Bromo Carbonyl Compound	Carbonyl Compound	Reagent ^b	Aldol Product	Yield(%) (erythro:threo)
1		PhCHO	A		92
			B		86
			C		78
2		PhCHO	A		70 ^c
3			A		76
4			A		76
5		PhCHO	A		69 (25:75)
			B		77 (28:72)
6		PhCHO	A		81
7			A		54
8		PhCHO	A		61 (50:50)
9		PhCHO	A		75 ^c
10		PhCHO	A		74 (54:46)
11			A		90
			C		74 ^c

Foot note of Table 1

- Two mmol of reagent, one mmol of α -halo carbonyl compound, and one mmol of carbonyl compound were employed.
- Reagent A: $\text{Bu}_3\text{SnAlEt}_2$, Reagent B: $\text{Bu}_3\text{PbAlEt}_2$;
Reagent C: $\text{Ph}_3\text{PbAlEt}_2$.
- A catalytic amount (5 mol%) of $\text{Pd}(\text{PPh}_3)_4$ was added.

affinity of tin to bromine is well documented and used for the oxidation of alcohols.⁸

The regioselectivity of the reaction was demonstrated by the treatment of 2-bromo-2-methylcyclohexanone⁹ or 2-bromo-6-methylcyclohexanone¹⁰ with $\text{Bu}_3\text{SnAlEt}_2$ in the presence of PhCHO to give the corresponding β -hydroxy ketone without any contamination of the regioisomer.



i: PhCHO , $\text{Bu}_3\text{SnAlEt}_2$, 0°C , 30 min.

Notably, the aldol reaction proceeds much more easily and efficiently in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$. For example, the reaction of α -bromoacetophenone with cinnamaldehyde gave β -hydroxy ketone in 70% yield as compared to 54% yield in the absence of $\text{Pd}(\text{PPh}_3)_4$.

The reaction of α -bromoacetophenone and benzaldehyde with $\text{Me}_2\text{PhSiAlEt}_2$ or $\text{Ph}_3\text{GeAlEt}_2$ instead of $\text{Bu}_3\text{SnAlEt}_2$ gave no desired β -hydroxy carbonyl compound. On the other hand, $\text{R}_3\text{PbAlEt}_2$ ($\text{R} = \text{Bu}, \text{Ph}$) proved to be as effective as $\text{Bu}_3\text{SnAlEt}_2$. A typical experimental procedure is as follows. Diethylaluminum chloride (1.0 M, 2.0 ml, 2.0 mmol) was added to a solution of Ph_3PbLi ¹¹ prepared from phenyllithium (6.0 mmol) and PbCl_2 (0.56 g, 2.0 mmol) in THF at 0°C . $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) was added and the resulting mixture was cooled to -20°C . A solution of α -bromoacetophenone (0.32 g, 1.6 mmol) and cinnamaldehyde (0.16 g, 1.2 mmol) in THF (3 ml) was added slowly over 15 min at -20°C . The reaction mixture was poured into 1N-HCl. Usual workup and purification by silica gel column chromatography gave 1,5-diphenyl-3-hydroxy-4-penten-1-one⁷ (0.25 g) in 84% yield. Additional examples are also summarized in Table 1.¹²

references and Notes

- J. Hibino, S. Matsubara, Y. Morizawa, K. Oshima, and H. Nozaki,

- Tetrahedron Lett., in press. Other example using $R_3SnCu-Me_2S$, see E. Piers and J. H. Chong, J. Chem. Soc. Chem. Comm., **1983**, 934.
- For a general discussion, see H. O. House, "Modern Synthetic Reactions", 2nd ed. W. A. Benjamin, New York, N. Y., 1972, pp 629-732.
 - For recent synthetic methods of regiospecific aldol synthesis, see (a) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **99**, 7705 (1977); (b) *idem*, Bull. Chem. Soc. Jpn., **53**, 3301 (1980); (c) T. Harada and T. Mukaiyama, Chem. Lett., **1982**, 467; (d) T. Mukaiyama, T. Haga, and N. Iwasawa, *ibid.*, **1982**, 1601; (e) J. Kato and T. Mukaiyama, *ibid.*, **1983**, 1727; (f) Y. Yamamoto and K. Maruyama, J. Am. Chem. Soc., **104**, 2323 (1982); (g) A. Itoh, S. Ozawa, K. Oshima, and H. Nozaki, Bull. Chem. Soc. Jpn., **54**, 274 (1981); (h) H. Nozaki, K. Oshima, K. Takai, and S. Ozawa, Chem. Lett., **1979**, 379; (i) K. Kobayashi, M. Kawanisi, T. Hitomi, and S. Kozima, *ibid.*, **1983**, 851; (j) E. Nakamura and I. Kuwajima, Tetrahedron Lett., **24**, 3347 (1983); (k) H. Urabe and I. Kuwajima, *ibid.*, **24**, 5001 (1983).
 - The classical Reformatsky reaction, see, R. L. Shriner, Org. React., **1**, 1 (1942); M. W. Rathke, *ibid.*, **22**, 423 (1975).
 - (a) T. Harada and T. Mukaiyama, Chem. Lett., **1982**, 161; (b) J. G. A. Luiten, Chem. and Ind. (London), **1972**, 103; (c) M. W. Rathke and A. Lindert, J. Org. Chem., **35**, 3966 (1970); (d) J. F. Ruppert and J. D. White, *ibid.*, **39**, 269 (1974); (e) R. D. Rieke and S. J. Uhm, Synthesis, **1975**, 452.
 - C. Tamborski, F. E. Ford, and E. J. Soloski, J. Org. Chem., **28**, 237 (1963); W. C. Still, J. Am. Chem. Soc., **99**, 4836 (1977) and **100**, 1481 (1978); W. Kitching, H. A. Olszowg, and K. Harvey, J. Org. Chem., **47**, 1893 (1982).
 - The spectra supported in all respects the formulas given.
 - K. Saigo, A. Morikawa, and T. Mukaiyama, Bull. Chem. Soc. Jpn., **49**, 1656 (1976); Y. Ueno and M. Okawara, Tetrahedron Lett., **1976**, 4597; T. Ogawa and M. Matsui, J. Am. Chem. Soc., **98**, 1629 (1976).
 - The compound was prepared regioselectively by the addition of Br_2 to 2-methylcyclohexanone according to the following literature. E. W. Garbisch, Jr., J. Org. Chem., **30**, 2109 (1965).
 - The treatment of trimethylsilyl enol ether derived from 2-methylcyclohexanone and LDA/ Me_3SiCl with NBS gave 2-bromo-6-methylcyclohexanone exclusively.
 - H. Gilman, L. Summers, and R. W. Leeper, J. Org. Chem., **17**, 630 (1952).
 - Financial support by the Ministry of Education, Science and Culture, Japanese Government (Grant-in-Aid for Special Project Research 58110005) is acknowledged. We also thank Toyo Stauffer Chemical Company for a gift of Et_2AlCl .

(Received in Japan 10 March 1984)