Tetrahedron Letters, Vol.31, No.14, pp 1985-1988, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

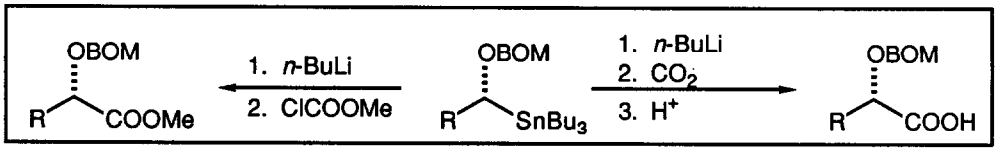
PREPARATION OF ENANTIOMERICALLY ENRICHED α-HYDROXY ACID DERIVATIVES FROM α-ALKOXYORGANOSTANNANES

Philip C.-M. Chan and J. Michael Chong*

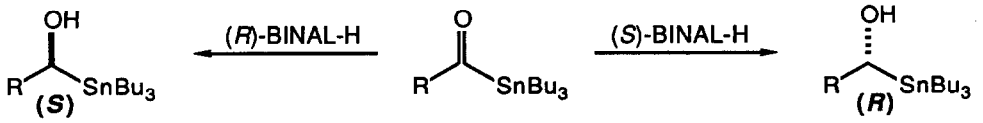
Guelph-Waterloo Centre for Graduate Work in Chemistry
Chemistry Department, University of Waterloo
Waterloo, Ontario, Canada N2L 3G1

Summary: Enantiomerically enriched (95-98%) α-alkoxy acids of defined absolute stereochemistry were prepared in good (83-99%) yields from α-alkoxyorganostannanes.

Optically pure α-hydroxy acids are useful intermediates for the preparation of homochiral natural products,[1] and a number of approaches to these acids have been reported. Recent examples include the alkylation of chiral glycolate enolates,[2] enzymatic reduction of α-keto acids,[3] opening of homochiral 2,3-epoxy alcohols with benzoic acid followed by periodate oxidation,[4] and kinetic resolution of 2-furylcarbinols followed by oxidative cleavage.[5] We now report that α-hydroxy acid derivatives are easily prepared from enantiomerically enriched α-alkoxystannanes *via* transmetalation (*n*-BuLi) and reaction with CO_2 or methyl chloroformate. Furthermore, and very importantly, the reactions proceed with complete retention of configuration to afford compounds with high optical purities and defined absolute configurations.

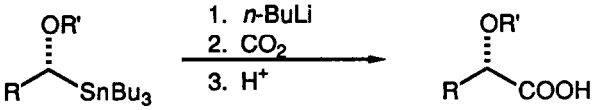


While it has been known for a decade that α-alkoxyorganolithium reagents may be alkylated (Me_2SO_4) with retention of configuration,[6] there have been few reports of the reactions of homochiral α-alkoxyorganolithiums with other electrophiles.[7] The paucity of information in this area is probably related to the difficult chromatographic separation of diastereomers previously required to access homochiral α-alkoxyorganostannanes.[6] Since the latter compounds are now readily available by asymmetric reduction of acylstannanes with BINAL-H,[8] their potential as building blocks for asymmetric synthesis can be explored. In particular, we have shown that reductions of acylstannanes with (*S*)-BINAL-H consistently afford predominantly (94-98% ee) the *R* stannanes while (*R*)-BINAL-H provides the expected antipodes.[9] Thus α-alkoxyorganostannanes of high enantiomeric purity and known absolute stereochemistry are now readily accessible.



The carboxylation of organolithium and Grignard reagents is a well-known process,[10] and it was anticipated that the carboxylation of α-alkoxyorganolithium reagents would be an efficient process. Indeed, when a solution of α-alkoxyorganostannane **1a** was allowed to react with *n*-BuLi (DME, -78 °C, 10 min) followed by CO_2 (-78 °C, 5 min), a single product was isolated in excellent yield after aqueous acidic workup.[11,12] Other organostannanes afforded very similar results (Table I). In all cases, good to excellent yields of the desired α-alkoxy acid were observed. The optical purities of the acids were ascertained by ^1H NMR and HPLC analysis of the derived (DCC, DMAP, HOBT) α-methylbenzylamides. These e.e.'s were compared with the optical purities of the starting stannanes (determined by HPLC analysis of the derived (*R*)-MTPA esters[13]). In all cases, the acids were produced with complete retention of configuration. As the stereochemistry of the acids is predetermined by the absolute stereochemistry of the starting stannane, one should be able to prepare either enantiomer by the appropriate choice of reducing agent.

Table I. Preparation of α-Alkoxy Acids from α-Alkoxyorganostannanes.



Entry	Stannane (1)[a]				Acid (2)			
		R	R'	% e.e.[b]		Yield[c]	$[\alpha]_D$[d]	% e.e.[e]
1	**1a**	Me	BOM	95	**2a**	92	-37°	95
2	**1b**	Et	BOM	95	**2b**	99	-49°	95
3	**1c**	*i*-Pr	BOM	98	**2c**	93	-57°	98
4	**1d**	*n*-C_5H_{11}	BOM	95	**2d**	83	-34°	95
5	**1e**	*n*-C_5H_{11}	MOM	98	**2e**	99	-58°	98
6	**1f**	*i*-Bu	MOM	--	**2f**	88	----	--

[a] Stannanes (except **1f**) were prepared by reduction of the corresesponding acylstannane with (*S*)-BINAL-H according to reference 8. **1f** was racemic.

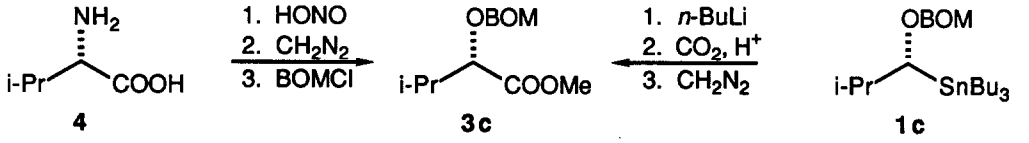
[b] Determined by HPLC (silica, hexanes: *i*-PrOH) analysis of the derived (*R*)-MTPA ester.[13]

[c] Percentage isolated yields of spectroscopically pure materials.

[d] 1% (w/v) solution in $CHCl_3$ at 24 °C.

[e] Determined by HPLC (silica, hexanes: *i*-PrOH) analysis of the amide derived from (*S*)-α-methylbenzylamine.

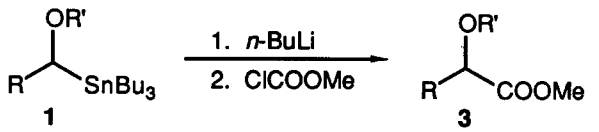
As an additional check on the absolute stereochemistry of the acids produced, acid **2c** was esterified (CH_2N_2) and the rotation of the ester **3c** ($[\alpha]_D$ -54°) was compared with that of material prepared from (*S*)-valine (**4**) ($[\alpha]_D$ -44°).[14] Since the signs of the rotations are identical, the compounds prepared by the two routes have the same (*S*) absolute configuration, and the starting stannane has an (*R*) configuration (as predicted).



4 **3c** **1c**

We also examined the carbalkoxylation of α-alkoxyorganolithium reagents, and have found that reactions with methyl chloroformate afford the desired methyl ester in reasonable yields (Table II). The esters were isolated after column chromatography to remove small amounts of other (unidentified) side-products.

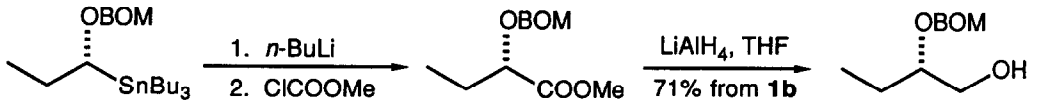
Table II. Preparation of α-Alkoxy Esters from α-Alkoxyorganostannanes.



1 **3**

Stannane	R	R'	Ester	Isolated Yield, %
1b	Et	BOM	**3b**	71
1c	*i*-Pr	BOM	**3c**	76
1d	*n*-C_5H_{11}	BOM	**3d**	69
1e	*n*-C_5H_{11}	MOM	**3e**	73
1g	*i*-Bu	BOM	**3g**	65

Most of the reactions were performed with racemic materials but retention of stereochemistry was observed when enantiomerically enriched **1b** was used. Thus stannane of 95% e.e. provided ester **3b** of 95% e.e. as determined by HPLC analysis of the (*R*)-MTPA ester of the derived (LAH) alcohol **5**. It should be noted that esters **3** may also be prepared quantitatively from acids **2** by treatment with CH_2N_2.



1b 95% e.e. **3b** **5** 95% e.e.

In summary, we have shown that α-alkoxyorganolithium reagents react with CO_2 to form α-alkoxy acids in high yields with total retention of stereochemistry. Thus, these materials may be with defined absolute configurations from homochiral α-alkoxyorganostannanes.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

References and Footnotes

1. (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.
(b) Scott, J. W. in *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, Chapter 1.

2. Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3764.

3. Kim, M.-J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 2959.

4. Martin, V. S.; Nuñez, M. T.; Tonn, C. E. *Tetrahedron Lett.* **1988**, *29*, 2701.

5. Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085.

6. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

7. Retention of stereochemistry has been noted for axial and equatorial cyclohexane derivatives. Electrophiles used were ketones, aldehydes, and halides: Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. Glycosylstannnanes have also been reported: Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930. α-Alkoxyorganolithiums (98-99% ee) have been coupled with α-chloro boronic esters (98-99% ee): Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399.

8. Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584.

9. Both enantiomers of 1,1'-bi-2-naphthol are commercially available or easily produced by an enzymic resolution: Kazlauska, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953.

10. Volpin, M. E.; Kolomnikov, I. S. *Organomet. React.* **1975**, *5*, 313.

11. All new compounds exhibited satisfactory spectroscopic (IR, ^1H NMR, ^{13}C NMR, MS) data and elemental analysis.

12. A typical experimental procedure follows. To a cold (-78 °C) stirred solution of **1** (1.0 mmol) in 10 mL of dry DME was added *n*-BuLi (1.6 M in hexanes, 1.0 mmol). Afer 5 min, CO_2 (g) was bubbled into the resulting yellow solution. The solution decolourized immediately. After a further 10 min, the reaction was quenched with saturated aqueous NH_4Cl, and ether was added. The organic layer was extracted with 2 N NaOH. Acidification of the aqueous layer (2 N HCl) followed by extraction with ether, drying ($MgSO_4$), and concentration *in vacuo* afforded acid **2**.

13. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

14. Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531.

(Received in USA 2 January 1990)