Tetrahedron Letters, Vol. 34, No. 1, pp. 47-50, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

An Efficient Enantiomeric Three Step Synthesis of β-Amino Acids (Esters)

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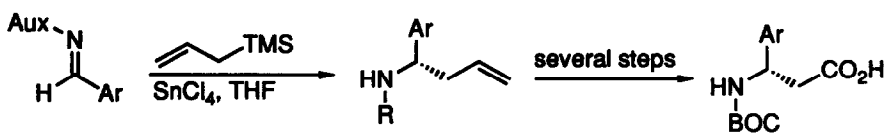
Key Words: Enantioselective Synthesis of β-Amino Acids (Esters); Ethyl Tributylstannylacetate Addition; (*R*)-2-Aryl or Alkyl-4-phenyl-1,3-oxazolidines

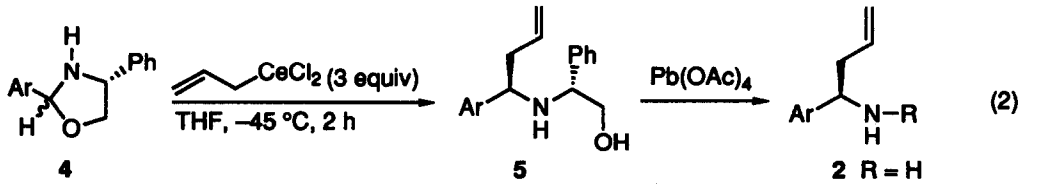
Abstract: *Ethyl tributylstannylacetate was reacted with (R)-2-aryl or alkyl-1,3-oxazolidines* ***6*** *under very specific ($ZnCl_2/Et_2O{\cdot}BF_3$, 0.5 equiv each) Lewis Acid catalyzed conditions to yield (1R, 1'R)-N-2'-hydroxy-1'-phenylethyl-1-aryl or alkyl-2-carboethoxyethylamine* ***8*** *in 91–99% de. The amino alcohol products* ***8*** *were converted to aromatic and aliphatic β-amino esters* ***9****, useful precursors to β-lactams.*

Chiral β-amino acids are highly important intermediates in certain very attractive syntheses of β-lactam derivatives.[1] As a consequence, several varied approaches have been reported for their synthesis.[2–4] One of these approaches, employed principally by Kunz,[4] is based on a diastereoselective addition of allylsilane to carbohydrate derived Schiff bases followed by oxidative cleavage of the *protected* amino olefin (eq 1).

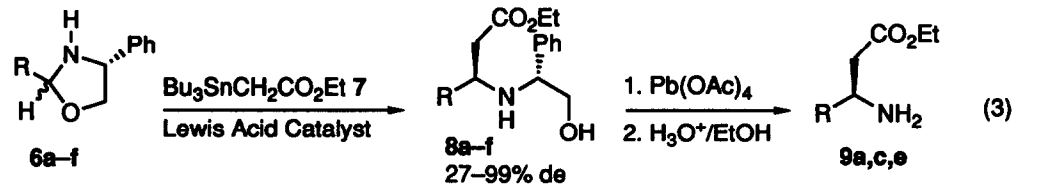


1 **2** R = Aux **3** (1)

Our entry into this area relied on the more efficiently prepared chiral 2-aryl-1,3-oxazolidine **4** as a substrate in an allyl organocerium stereoselective addition reaction (~88% de). The resulting amino alcohol product **5** was subsequently oxidized upon treatment with lead tetraacetate to yield homoallyamine **2** (R = H, eq 2).[5b]



Since that initial report, we have investigated means to further increase the efficiency of this approach, *without using protecting groups*. We now report that the highly stable ethyl tributylstannylacetate (7)[6] adds directly to oxazolidine **6**[7] under Lewis acid catalyzed conditions with remarkable stereocontrol, despite the prolonged reaction conditions (Table I and eq 3).



a, R = Ph **d**, R = 1-naphthyl
b, R = *p*-$CH_3C_6H_4$ **e**, R = cyclohexyl
c, R = *p*-BrC_6H_4 **f**, R = *i*-propyl

Table I presents the results of the addition of ethyl tributylstannylacetate (**7**) to oxazolidines **6a–f** yielding amino alcohols **8a–f**. Reaction of **6a** with **7** in the presence of $ZnCl_2$ in refluxing THF resulted in only a 39% crude yield of **8a** after a 100 h reflux, but at the same time providing a 98:2 ratio of diastereomeric amino alcohols. Using boron trifluoride etherate as a catalyst on the same substrate accelerated the rate of addition, albeit at the expense of stereoselectivity (entry 2). We also employed a variety of other Lewis acid catalysts (Table I) but none were as effective as either $ZnCl_2$ or $Et_2O{\cdot}BF_3$. Further reasoning that $ZnCl_2$ was acting primarily as a chelator that would restrict flexibility in a transition state similar to (A) *and* $Et_2O{\cdot}BF_3$ was most probably activating **7** by complexation with the ester carbonyl,[9] we used combinations of these two catalysts. The 0.5 equiv of each of the Lewis acids, $ZnCl_2$ and $Et_2O{\cdot}BF_3$, represents our best found combination to obtain both good chemical yields and high diastereofacial selectivity (entries 8–13).[10]

Equation 4 with its transition state (A) appears to best depict our experimental observations which are similar to our earlier reports.[5,11] Namely, the nucleophilic acetate adds across the *re* face of the imino/oxazolidine moiety, opposite the (*R*)-phenyl of the auxiliary. This highly selective and efficient synthesis of β-amino esters is applicable for synthesizing both antipodal isomers of *aliphatic and aromatic* derivatives.[12] *A method was developed to oxidatively cleave the auxiliary in consistently high yields that uses an improved version of the $Pb(OAc)_4$ conditions reported earlier.*[5] *This method is applicable to both aliphatic and aromatic compounds* (Table I). Experimental details for the oxidative cleavage will be reported elsewhere.[14]

A Possible Transition State

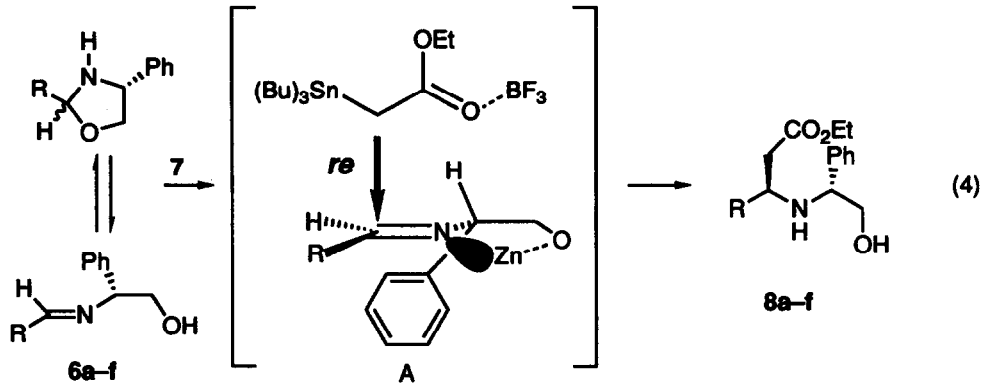


Table I. Lewis Acid Catalyzed Addition of Ethyl Tributylstannylacetate (7) to 2-Substituted-4-phenyl-1,3-oxazolidines **6a–f** and Conversion of **8a,c,e** to **9a,c,e.**

Entry	Substrate	Lewis Acid[a]	Rxn Time (h)[b]	Yield[c] 8 (%)	de, %	Yield[c] 9 (%)	ee, %
1	**6a**	$ZnCl_2$	100	39[d]	96		
2	**6a**	$Et_2O{\cdot}BF_3$	6	82[d]	28		
3	**6a**	$Ti(^iOPr)_3Cl$	48[e]	43[d,f]	–		
4	**6a**	$TiCl_4$	15[g]	43	40		
5	**6a**	$Sn(OTf)_2$	72[h]	53	70		
6	**6c**	$ZnCl_2$	72	21[d]	96		
7	**6c**	$Et_2O{\cdot}BF_3$	72	68[d]	27		
8	**6a**[10]	$ZnCl_2/Et_2O{\cdot}BF_3$	66	71	92	86	91
9	**6b**	$ZnCl_2/Et_2O{\cdot}BF_3$	192	58	92		
10	**6c**	$ZnCl_2/Et_2O{\cdot}BF_3$	96	67	91	87	95
11	**6d**	$ZnCl_2/Et_2O{\cdot}BF_3$	144	60	99		
12	**6e**	$ZnCl_2/Et_2O{\cdot}BF_3$	72	33	94	73	94
13	**6f**	$ZnCl_2/Et_2O{\cdot}BF_3$	264	43	96		

[a] Entries 1–7 (1 equiv), 8–13 (0.5 equiv of each). [b] Refluxing THF except where noted. [c] Isolated yield after flash chromatography except when indicated. [d] Crude yield. [e] Reflux in CH_2Cl_2. [f] Mixture of *i*-propyl and ethyl esters. [g] In CH_2Cl_2 (–78 °C → rt). [h] In THF at rt.

Acknowledgements: The authors are indebted to the SmithKline Beecham post-doctoral program for financial support for this work and Dr. M. McGuire for the initial supplies of 7.

References and Notes

1. Salzman, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Boufford, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

2. (a) d'Angleo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (b) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. (c) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717.

3. Estermann, V. H.; Seebach, D. *Helv. Chim. Acta*, **1988**, *71*, 1824 and references therein.

4. Laschat, S. ; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883 and references therein.

5. (a) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (b) Wu, M.-J.; Pridgen, L. N. *Synlett*, **1990**, 635.

6. Zapata, A.; Acuña A.; C. *Synth. Comm.* **1984**, *14*, 27. The methyl acetate analog reacts similarly.

7. For the preparation of **6** (R = aryl), see ref. 5a. Alkyl derivatives of **6** were prepared according to Takahashi's[8] procedure and the crude products were used without further purification. All compounds reported herein have satisfactory combustion and/or spectroscopic data.

8. Takahashi, H.; Chida, Y.; Yoshii, T.; Susuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071.

9. Activation of **7** through the use of a fluoride source (*e.g.* KF + 18-Crown-6) was ineffective.

10. **Typical procedure:** Boron trifluoride etherate (0.43 g, 3 mmol) was added to a stirred solution of oxazolidine **6a** (1.35 g, 6 mmol), ethyl tributylstannylacetate (**7**) (4.53 g, 12 mmol), and $ZnCl_2$ (3 mL of 1 M solution in ether, 3 mmol) in 10 mL of dry THF and the mixture was refluxed for 66 h. After cooling to room temperature, the reaction mixture was poured into 40 mL of 10% aqueous NH_4OH and stirred for 1 h. The mixture was extracted with ether (3 x 30 mL) and the combined ether extracts were washed with brine (10 mL), then extracted with 3 x 30 mL of 10% aqueous HCl. The total acidic extract was basified with solid K_2CO_3, then extracted with ether (3 x 30 mL). The ether extracts were combined, dried ($MgSO_4$), and rotoevaporated to leave 1.56 g of **8a** as a light tan oil. Purification by flash chromatography (40% EtOAc/hexane) afforded 1.34 g of a colorless thick oil (71% yield, 92% de); $[\alpha]_D^{25}$ +1.19° (*c* 1, $CHCl_3$, oxalate salt).

11. The X–ray structure of the hydrochloride salt of **8c** is interesting in that it shows the unit cell as a dimeric entity exhibiting hydrogen bonding with chlorine atoms. For examples of similar X-ray results of amino alcohols see: Barr, D.; Berrisford, D. J.; Jones, R. V. H.; Slawin, A. M. Z.; Snaith, R.; Stoddard, J. F.; Williams, D. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1044.

12. A recent report by Pedrosa[13] describes the addition of the moisture sensitive Reformatsky reagent to a benzylated analog of **6** . This approach is limited to aliphatic amino esters because of the use of Pd/C to remove the auxiliary. In addition, their lower observed diastereoselectivity of addition serves to reinforce our earlier observation[5] that the secondary amino function is necessary for greater selectivity.

13. Andrés, C.; González, A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895.

14. Amino alcohol **8** in CH_2Cl_2 was added to a suspension of $Pb(OAc)_4$ (1.3 equiv) in MeOH at 0 °C. Acidic hydrolysis of the resulting imine intermediate in EtOH afforded the β-amino ester **9** in 73–87% yield.

(Received in USA 1 September 1992; accepted 5 October 1992)