The Lewis Acid mediated Reaction of Carbamates with γ-Oxygenated Allyltin and its Application to (±)-Statine Synthesis

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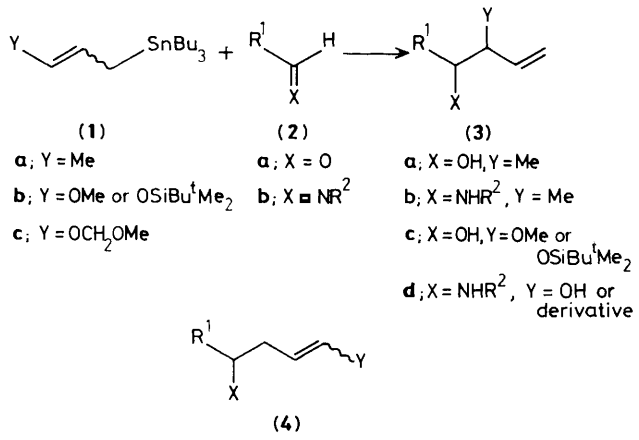
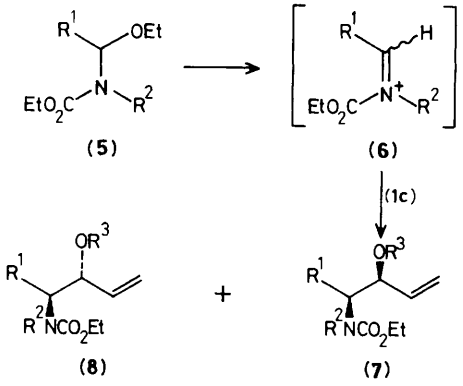
The Lewis acid mediated reaction of acyliminium ions (**6**) with γ-oxygen substituted allyltin (**1c**) gave the amino alcohol derivatives (**7**) and/or (**8**) in good yields; in certain cases very high diastereoselectivity was achieved and the procedure was applied to the synthesis of (±)-statine.

The Lewis acid mediated condensation between crotyltin (**1a**) and aldehydes (**2a**) gives the *erythro* homoallyl alcohols (**3a**) with very high diastereoselectivity (Scheme 1).[1] The reaction of (**1a**) with imines (**2b**) in the presence of Lewis acids produces the homoallylamines (**3b**).[1a,b,2] The diastereoselectivity depends upon the substituents R^1 and R^2. The Lewis acid mediated reaction of the γ-oxygenated allyltin (**1b**) with (**2a**) affords the vicinal diol derivatives (**3c**) with high *erythro* selectivity.[3] The vicinal diol unit is an important functional group. Amino alcohols are equally important since these functionalities are frequently found in a number of natural products. Accordingly, it was expected that the reaction of the γ-oxygenated allyltins (**1b**) and/or (**1c**) with (**2b**) would give the amino alcohol derivatives (**3d**) without formation of the regioisomer (**4**).[4] Indeed, this proved to be the case, and the desired amino alcohol derivatives could be obtained with high diastereoselectivity in certain cases.

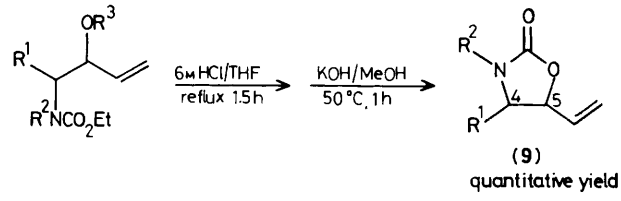
At the outset, the reaction of (**1c**) with *N*-methylbenzyl-



Scheme 1



Scheme 2

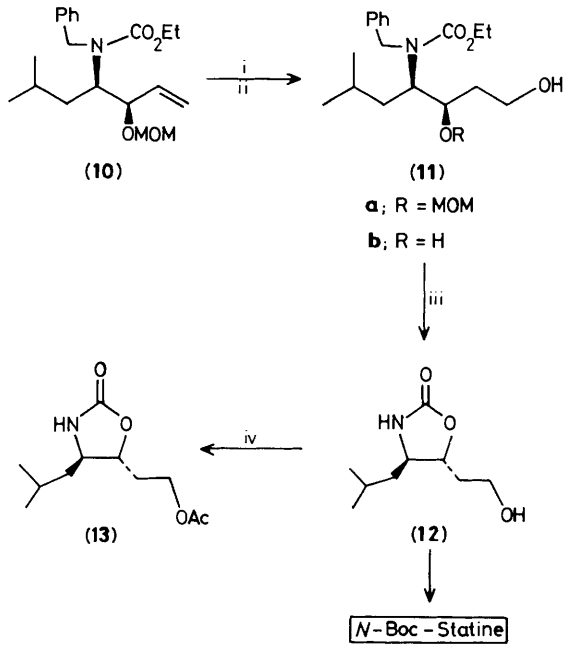


Scheme 3

Table 1. Reaction of (**1c**) with (**5**) in the presence of Lewis acids.[a]

Entry	(5) R^1	(5) R^2	Lewis acid	R^3	Product (7) + (8) isolated yield /%	Ratio (7)/(8)
1	Ph	Me	$TiCl_4$	H	82	0/100
2	Pr^i	$PhCH_2$	$TiCl_4$	MOM	21	68/32
3	Pr^i	$PhCH_2$	$BF_3{\cdot}OEt_2$	MOM	90	72/28
4	Pr^i	$PhCH_2$	$SnCl_4$	—	—	—
5	Pr^i	Me	$BF_3{\cdot}OEt_2$	MOM	16	70/30
6	Ph	$PhCH_2$	$BF_3{\cdot}OEt_2$	MOM	41	100/0
7	Bu^i	$PhCH_2$	$BF_3{\cdot}OEt_2$	MOM	84	100/0

[a] To a CH_2Cl_2 solution of (**5**) (1 mmol) cooled to −78 °C, Lewis acids (1.2 mmol of $TiCl_4$–CH_2Cl_2 or 2 mmol of $BF_3{\cdot}OEt_2$) and then (**1c**) (1.2 mmol) were added. The reaction was quenched at 0 °C with water. The products were isolated by silica gel column chromatography. The isomer ratio was determined by using capillary g.l.c. (SE-30, 25 m) and ^{1}H n.m.r. spectroscopy. MOM = CH_2OMe.



Scheme 4. *Reagents, conditions, and yields*: i, 9-borabicyclo[3.3.1]nonane (9-BBN) (3 equiv.), tetrahydrofuran (THF), room temp., 11 h; NaOH (6 M; 6 equiv.), H_2O_2 (30% 9 equiv.), EtOH, room temp., 1.5 h; (**11a**) was obtained in 46% yield; ii, HCl (6 M; 30 equiv.), THF, 65 °C, 1.5 h; (**11b**) 43% yield; iii, Na/NH_3 (14 equiv.), −70 → 0 °C, 5 h; (**12**) 27% yield; iv, Ac_2O (1.3 equiv.), pyridine, reflux, 2.5 h; (**13**) 33% yield.

ideneamine was examined in the presence of either $BF_3{\cdot}OEt_2$ (3 equiv.) or $TiCl_4$. However, the condensation did not take place and the imine was recovered. α-Ethoxycarbamates (**5**) were used as the precursor for *N*-acyliminium ions (**6**), 'activated imines'.[5] The reaction of (**5**) with (**1c**) in the presence of Lewis acids proceeded smoothly (Scheme 2) and the results are summarized in Table 1.

The chemical yield and isomer ratio are highly dependent upon the Lewis acids and the substituents of (**5**). With R^1 = Ph and R^2 = Me, the *anti*-isomer (**8**) was obtained exclusively (entry 1 of Table 1). For other R^1 and R^2 groups studied, the *syn*-isomer (**7**) was produced either exclusively (entries 6 and 7) or predominantly (entries 2—5). The reason for this variable stereoselectivity is not clear at present, but a similar phenomenon has been observed in the condensation between imines and crotyl organometallic compounds.[2a] $BF_3{\cdot}OEt_2$ or $TiCl_4$ can be used as an activator. $SnCl_4$ is not effective (entry 4), presumably owing to its low ability to generate (**6**) from (**5**).

The stereochemistry of the adducts was determined by conversion to 2-oxazolidone derivatives (**9**) (Scheme 3). It is known that the ^{1}H n.m.r. spectrum of *trans*-(**9**) exhibits J_{4-5} <6.0 Hz and that the *cis*-isomer shows a larger value than the *trans*-isomer.[6] Actually, *trans*-(**9**) with R^1 = Pr^i, R^2 = Me; R^1 = Ph, R^2 = CH_2Ph; and R^1 = Bu^i, R^2 = CH_2Ph gave J_{4-5} 5.5 Hz, and with R^1 = Pr^i, R^2 = CH_2Ph gave J_{4-5} 4.5 Hz. The isomer *cis*-(**9**) with R^1 = Pr^i, R^2 = CH_2Ph and R^1 = Pr^i, R^2 = Me exhibited J_{4-5} 8.0 Hz, and with R^1 = Ph, R^2 = Me showed J_{4-5} 7.5 Hz. The stereochemistry was also confirmed by the synthesis of statine, Scheme 4.

The present methodology was applied to the stereoselective synthesis of (±) statine (Scheme 4), which has received significant attention as an essential component in potential antihypertensive medicinal agents.[6b—d,7]

As shown in entry 7 of Table 1, (**10**) was obtained in 84% yield with 100% diastereoselectivity. Treatment of (**10**) with 9-BBN followed by the usual oxidation gave (**11a**), which was converted to (**11b**) by acid. Oxazolidone (**12**) was obtained by debenzylation and cyclization of (**11b**) with sodium in liquid ammonia. The resulting (**12**) was then converted to (**13**), whose ^{1}H n.m.r. spectrum was in agreement with that of the authentic material. Synthesis of *N*-Boc-statine (Boc = butoxycarbonyl) from (**12**) has been reported already,[7h] and it is clear that the allylic tin–iminium ion condensation reaction provides a short synthesis route for (±)statine.

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