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Allylstannation of *N*-acyliminium intermediates: a possible method for the stereocontrolled synthesis of polyhydroxypiperidines

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Abstract—The stereochemistry of the allylstannation of acyliminium intermediates has been examined for γ-alkoxyallyltins and γ-silyloxyallyltributyltins. In the latter case, the reaction has been shown to afford cleanly the *syn* adduct. Its subsequent ring-closing metathesis and dihydroxylation has allowed the highly stereoselective preparation of a 2-aryl-trihydroxypiperidine.

The allylstannation of aldehydes by α- or γ-oxygenated allyltins has been widely used for the synthesis of 1,2-diol derivatives with efficient diastereocontrol.[1–4] This stereochemical control is directly connected to the nature of the transition state involved: six-membered cyclic transition state, antiperiplanar open transition state or synclinal open transition state. Furthermore, the occurrence of strong stereoconvergent effects has been observed when chiral reagents were involved.[5,6]

In order to use this type of tool for the stereocontrolled building of nitrogen analogues, we can reasonably use the reaction of oxygen-containing allylmetal species on imines or the reaction of nitrogen-containing allyltin reagents on aldehydes. While both approaches have been proved to be possible,[7,8] the first one has shown limitations with γ-oxygenated allyltins[9] and the second one (use of γ-aminoallyltins), while possible in intramolecular reactions,[8] has been proved to be difficult to exploit in intermolecular reactions.[10]

Due to the increasing interest devoted to azasugars and related species such as polyhydroxypiperidines as enzyme inhibitors,[11–13] we were interested in reacting appropriate iminium precursors **1** with γ-oxygenated allyltins, a reaction, which is known to occur smoothly.[14,15] According to this strategy, it was hoped to preserve the advantage of a high tolerance for numerous functionalities, along with the possible variation of the stereochemical outcome using the experimental conditions, the geometry of the double bond and/or the configuration of the α-carbon atom on the allyltin unit.[1–4]

In this preliminary report, the stereochemical course of the allylstannation of *N*-acyliminium intermediates is reported with special attention being devoted to *N*-acyl *N*-allyliminium intermediates whose adducts **3h–j** are able to afford dehydropiperidines through ring-closing metathesis and subsequently provide polyhydroxypiperidines.

The α-ethoxycarbamates **1a–f** (Scheme 1) were obtained according to the literature procedure[16] by reaction of a primary amine with an aldehyde, followed by reaction with diethyl pyrocarbonate.

These α-ethoxycarbamates **1a–f** were subsequently reacted with γ-oxygenated allyltins (CH_2Cl_2, −78 °C) in the presence of boron trifluoride diethyl etherate in order to determine the more appropriate experimental conditions and the influence of the substituents both on

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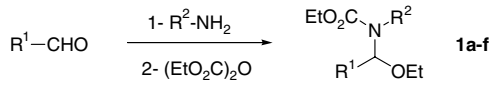
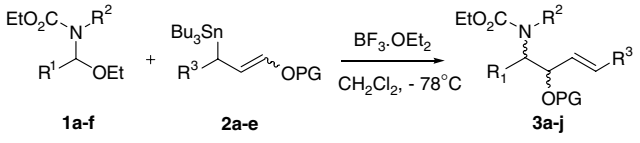


1a (85%; R^1=Ph, R^2=Bn) ; **1b** (68%; R^1=*i*Pr, R^2=Bn);
1c (91%; R^1=*i*Pr, R^2=*n*Bu) ; **1d** (76%; R^1=Ph, R^2=Me);
1e (63%; R^1=Ph, R^2=*n*Bu) ; **1f** (82%; R^1=Ph, R^2=Allyl)

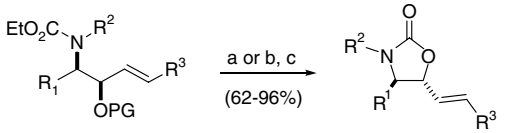
Scheme 1.



Scheme 2.

the iminium salt and on the allyltin on the course of the reaction. For this purpose the readily available **2a-*E*** or **2a-*Z***,[17] **2b-*E***,[6] **2c-*Z***,[17] **2d-*Z***,[6] and **2e-*Z***,[6] have been tested as reagents in order to evaluate their propensity to modify the *syn* or *anti* selectivity of the allylstannation reaction as previously observed with aldehydes (Scheme 2, Table 1).[18–20]

On the basis of entries 1–4, this type of reaction, which has been previously described employing lower amounts of boron trifluoride[23,24] appears to require 3 equiv of Lewis acid to afford the desired adducts in good yields. Starting from γ-silyloxyallyltin **2a-*E***, known to give usually *syn* adducts with aldehydes,[17] the reaction appears to maintain a *syn* preference whatever the nature of the substituents on the iminium salt. Furthermore the reaction appears to be stereochemically unaffected by the use of the *Z* isomer (**2a-*Z***, entry 9) or of a γ-silyloxyallyltin bearing a bulky group α to tin (**2b-*E***, entry 10). The situation is modified when γ-alkoxyallyltins are involved: with unhindered **2c-*Z*** and **2d-*Z***, a similar *syn*/*anti* ratio (78/22) was obtained (entries 11 and 12), while the use of **2e-*Z*** (possessing a bulky α-substituent)

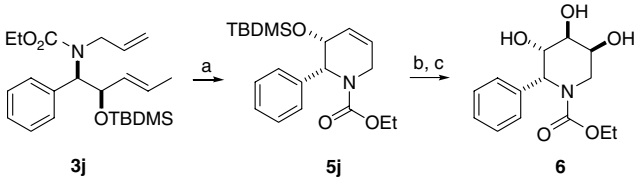


Scheme 3. Reagents and conditions: (a) TBAF, THF, (**3a**–**f**,**j**); (b) HCl, THF; (c) NaOH, MeOH (**3g**).

induces a slight *anti* preference (entry 13). In these last two examples involving *N*-allyl acyliminium intermediates, a good yield was obtained as well as when **1f** was allowed to react with **2a-*E*** (83% yield, 100% **3j-*syn***). In each case no compound with a *Z* carbon–carbon double bond was observed either among the adducts **3a**–**g** and **3j** or the derived oxazolidinones **4a**–**g** and **4j** obtained according to Marshall et al.[15] (Scheme 3).

As we were able to obtain **3j** as a single diastereomer (*syn* compound), and before attempting improvements to the method in order to prepare also the *anti* isomer, we decided to test the potential of this compound for the synthesis of the corresponding dehydropiperidine and trihydroxypiperidine derivatives (Scheme 4).

The first step was planned through a ring-closing metathesis[25] and the second using a catalytic OsO_4 dihydroxylation.[26] The olefin metathesis afforded **5j** in



Scheme 4. Reagents and conditions: (a) $[RuCl_2(PCy_3)_2(CHPh)]$ (5%), CH_2Cl_2, 94%; (b) OsO_4, NMO, 81%; (c) TBAF, THF, 95%.

Table 1. Reaction of γ-oxygenated-allyltributyltins with *N*-acyliminium intermediates

Entry	Iminium precursor[a]	Allyltin-(R^3, PG)[b]	$BF_3{\cdot}Et_2O$ (equiv)[c]	Adducts yield (%) (no: *syn*/*anti*)[d]
1	**1a**	**2a-*E*** (Me, $SiMe_2t$Bu)	1.2	35 (**3a**: 100/0)
2	**1a**	**2a-*E*** (Me, $SiMe_2t$Bu)	2.4	63 (**3a**: 100/0)
3	**1a**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	74 (**3a**: 100/0)
4	**1a**	**2a-*E*** (Me, $SiMe_2t$Bu)	4	71 (**3a**: 100/0)
5	**1b**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	72 (**3b**: 100/0)
6	**1c**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	79 (**3c**: 95/5)
7	**1d**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	79 (**3d**: 89/11)
8	**1e**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	59 (**3e**: 100/0)
9	**1a**	**2a-*Z*** (Me, $SiMe_2t$Bu)	3	71 (**3a**: 100/0)
10	**1a**	**2b-*E*** (tBu, $SiMe_2t$Bu)	3	75 (**3f**: 100/0)
11	**1a**	**2c-*Z*** (Me, MOM)	3	69 (**3g**: 79/21)
12	**1f**	**2d-*Z*** (Me, Bn)	3	81 (**3h**: 78/22)
13	**1f**	**2e-*Z*** (tBu, Bn)	3	88 (**3i**: 42/58)
14	**1f**	**2a-*E*** (Me, $SiMe_2t$Bu)	3	83 (**3j**: 100/0)

[a] Iminium precursors were obtained according to an already described procedure.[16]
[b] Allyltins were used after flash chromatography in order to use pure isomers in the different attempts.
[c] The reactions were performed at −78 °C in CH_2Cl_2 according to the experimental procedure described in footnote.[21]
[d] Yields of adducts are isolated yields. The identification of *syn*/*anti* adducts (**3a**–**g** and **3j**)[22] was achieved unambiguously after deprotection and cyclization of 2-oxazolidinones (**4a**–**g**,**j**) or after ring-closing metathesis of the crude product (**3h**–**i**) to (**5h**,**i**).

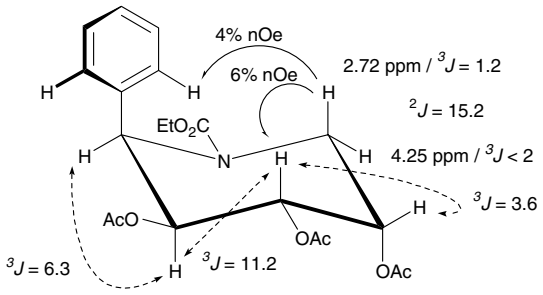


Figure 1. Meaningful NOE and coupling constants for **7**.

high isolated yield using the commercially available Grubbs I catalyst while *cis* dihydroxylation was perfectly directed on the opposite face to the bulky OTBDMS and phenyl substituents to afford **6** after TBAF deprotection. The stereochemistry of **6** was firmly established after its derivatization into the peracetylated analogue **7** whose 400 MHz NMR spectrum allowed an unambiguous characterization (Fig. 1) with no apparent extra signals due to other isomers. Furthermore after crystallization from water, **6** afforded white crystals (mp = 162 °C) whose X-ray structure is shown in Figure 2.[27]

The above result points out the efficiency of this strategy for obtaining the trihydroxypiperidine **6** in a stereocontrolled fashion. Due to the polarity of compounds such as **6**, the removal of organotin residues, which can constitute a problem after formation of compound **3j** appeared to be solved at the end of the sequence. Further developments are planned in order to drive the reaction to *syn* or *anti* adducts as desired or to modify the nature and the position of functional groups in analogues **6**. For the case where α-bulky groups were required, the RCM reaction was achieved on **3i-*syn*** and ***anti*** and proved to be possible using Grubbs II catalyst in toluene (45% unoptimized yield with similar kinetics for both diastereomers). Furthermore the allylstannation reaction has also been shown to proceed cleanly (single isomer observed in NMR) starting from an iminium salt derived from D-glyceraldehyde acetonide.

On the basis of the above results and considering these last remarks, the strategy described should constitute a valuable approach for synthesizing a large variety of polyfunctionalized piperidines because of the high tolerance to functional groups contained both in the substrate and in the reagent.

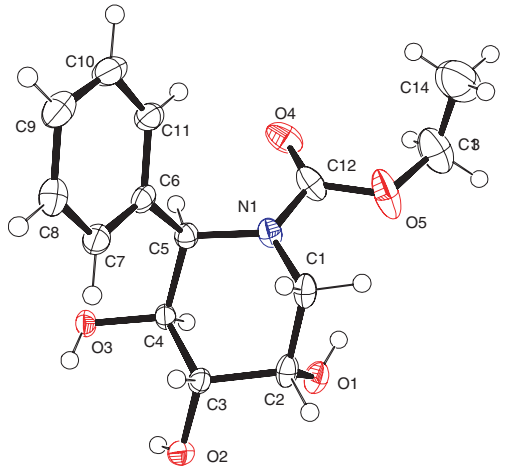


Figure 2. ORTEP drawing of **6** with thermal ellipsoids at 50% probabilities.[27]

Acknowledgements

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21. Preparation of **3a** (typical procedure for allylstannation of iminium intermediates): To a stirred, cooled (−78 °C) solution of **1a** (500 mg, 1.59 mmol) in dry dichloromethane (10 mL) were successively added BF_3–OEt_2 (679 mg, 4.79 mmol) and **2a-*E*** (910 mg, 1.91 mmol). The reaction mixture was stirred for 1 h at −78 °C, quenched with saturated aqueous $NaHCO_3$ and allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/petroleum ether: 5/95) gave **3a** (536 mg, 74%) as a clear oil.

22. *trans*-(*E*)-3-Allyl-4-phenyl-5-(propen-1-yl)oxazolidin-2-one (**4j**). R_f 0.27 (EtOAc/hexanes: 2/8). MS (CI/NH_3) m/z 261 ($M+NH_4^+$), 244 ($M+H^+$). IR (neat) 1757 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.73 (dd, 3H, $^3J = 6.3$ and $^4J = 1.2$ Hz), 3.21 (dd, 1H, $^2J = 15.3$ and $^3J = 8.1$ Hz), 4.19 (ddt, 1H, $^2J = 15.3$, $^3J = 4.8$, $^4J = 1.2$ and $^4J = 1.2$ Hz), 4.38 (d, 1H, $^3J = 7.5$ Hz), 4.61 (dd, 1H, $^3J = 7.3$ and 7.5 Hz), 5.00 (ddd, 1H, $^2J = 2.1$, $^3J = 17.3$ and $^4J = 1.2$ Hz), 5.16 (ddd, 1H, $^2J = 2.1$, $^3J = 9.9$ and $^4J = 1.2$ Hz), 5.58 (ddq, 1H, $^3J = 7.3$ and 15.3, $^4J = 1.2$ Hz), 5.69–5.78 (m, 2H), 7.26–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 17.8, 44.9, 65.6, 82.9, 119.2, 126.6, 127.4 (2C), 129.3 (2C), 129.1, 131.4, 132.5, 136.9, 157.7.
cis-3-(*tert*-Butyldimethylsilyloxy)-1-ethoxycarbonyl-2-phenyl-4,5-dehydropiperidine (**5j**). R_f 0.35 (EtOAc/hexanes: 1/9). MS (CI/NH_3) m/z 362 ($M+H^+$), 230, 184, 127. IR (neat) 698, 776, 838, 1099, 1415, 1700, 2856, 2955, 3032 cm^{-1}. ^1H NMR (C_6D_6, 340 K) δ −0.03 (s, 3H), 0.04 (s, 3H), 0.82 (s, 9H), 1.04 (t, 3H, $^3J = 7.0$ Hz), 3.25 (br d, 1H, $^2J = 18.5$ Hz), 4.10 (q, 2H, $^3J = 7.0$ Hz), 4.20 (br d, 1H, $^2J = 18.5$ Hz), 4.78 (br s, 1H), 5.28 (br d, 1H, $^3J = 10.8$ Hz), 5.80 (br d, 1H, $^3J = 10.8$ Hz), 5.89 (br s, 1H), 7.06–7.67 (m, 5H). ^{13}C NMR (C_6D_6, 340 K) δ −4.7 (2C), 14.7, 18.2, 25.9 (3C), 40.8, 57.2, 61.6, 67.7, 124.0, 127.4–130.0 (5C), 131.0, 138.2, 155.3.
(*rel*-2*R*,3*S*,4*S*,5*S*)-1-Ethoxycarbonyl-3,4,5-trihydroxy-2-phenylpiperidine (**6**). mp 162 °C. R_f 0.14 (EtOAc). MS (CI/NH_3) m/z 299 ($M+NH_4^+$), 282 ($M+H^+$). IR (KBr) 710, 1135, 1310, 1430, 1661, 2957, 3340, 3427 cm^{-1}. ^1H NMR (CD_3OD) δ 1.20 (t, 3H, $^3J = 7.1$ Hz), 2.90 (dd, 1H, $^2J = 14.5$ and $^3J = 1.3$ Hz), 3.80–3.88 (m, 2H), 4.04 (m, 1H), 4.10 (q, 2H, $^3J = 7.1$ Hz), 4.20 (dd, 1H, $^3J = 6.1$ and $^3J = 10.0$ Hz), 5.58 (d, 1H, $^3J = 6.1$ Hz), 7.14–7.53 (m, 5H). ^{13}C NMR (CD_3OD) δ 14.0, 45.3, 58.3, 62.0, 68.9, 69.5, 70.6, 127.1, 128.2 (2C), 128.8 (2C), 138.2, 157.5. Anal. calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.24; H, 6.77; N, 4.93.
(*rel*-2*R*,3*S*,4*S*,5*S*)-3,4,5-Triacetoxy-1-ethoxycarbonyl-2-phenylpiperidine (**7**). R_f 0.18 (EtOAc/hexanes: 3/7). MS (CI/NH_3) m/z 425 ($M+NH_4^+$), 408 ($M+H^+$). IR (neat) 703, 1126, 1228, 1372, 1425, 1699, 1750, 2982 cm^{-1}. ^1H NMR (C_6D_6, 340 K) δ 1.01 (t, 3H, $^3J = 7.1$ Hz), 1.60 (s, 3H), 1.75 (s, 3H), 1.77 (s, 3H), 2.72 (dd, 1H, $^2J = 15.2$ and $^3J = 1.2$ Hz), 4.03 (dq, 1H, $^2J = 10.7$ and $^3J = 7.1$ Hz), 4.08 (dq, 1H, $^2J = 10.7$ and $^3J = 7.1$ Hz), 4.25 (br d, 1H, $^2J = 15.2$ Hz), 5.29 (m, 1H), 5.74 (dd, 1H, $^3J = 3.6$ and $^3J = 11.2$ Hz), 5.88 (dd, 1H, $^3J = 6.3$ and $^3J = 11.2$ Hz), 6.26 (d, 1H, $^3J = 6.3$ Hz), 7.09 (t, 1H, $^3J = 7.2$ Hz), 7.17 (dd, 2H, $^3J = 7.2$ Hz and $^3J = 7.6$ Hz), 7.56 (d, 2H, $^3J = 7.6$ Hz). ^{13}C NMR (C_6D_6, 340 K) δ 14.6, 20.3 (3C), 42.6, 56.4, 62.1, 69.0, 69.1, 69.2, 128.0, 128.8 (2C), 129.0 (2C), 137.0, 156.1, 169.2, 169.5, 169.6.

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27. Crystallographic data for **6**: $C_{14}H_{19}NO_5$, FW = 281.30, monoclinic, $P2_1/a$ space group, $a = 6.7984(1)$, $b = 23.7915(5)$, $c = 8.5079(2)$ Å, $\beta = 103.509(1)°$, $V = 1338.03(5)$ Å^3, $Z = 4$, $D_x = 1.396$ Mg m^{-3}, λ(MoKα) = 0.71073 Å, $\mu = 1.06$ cm^{-1}, $F(000) = 600$, $T = 120$ K. The sample (0.34*0.32*0.26 mm) was studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. Full crystallographic data for the structure, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 221825. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].