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Efficient and stereocontrolled synthesis of polysubstituted tetrahydropyrans by an allylstannylation/Bi(III)-promoted cyclisation strategy

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Abstract—A novel sequence, involving the condensation between a highly functionalised allylstannane and various aldehydes, followed by a bismuth triflate-promoted intramolecular Sakurai cyclisation (IMSC) of the resulting homoallylic alcohols, allows a rapid and stereocontrolled access to a range of polysubstituted tetrahydropyrans. © 2001 Elsevier Science Ltd. All rights reserved.

Due to their widespread occurrence in many complex natural products possessing important biological activities, tetrahydropyran units are important synthetic targets in organic and medicinal chemistry. Several elegant strategies have thus been developed for the construction of such heterocycles.[1] Recently, we have reported a concise synthetic sequence leading, in a stereocontrolled fashion, to functionalised tetrahydropyrans **3** (Fig. 1).[2]

Titanation of allylcarbamate **1**, followed by metallo-ene condensation with various aldehydes, generated (*E*)-homoallylic alcohols **2** as single geometric isomers. Subsequent intramolecular Sakurai cyclisation (IMSC) of **2** with a second aldehyde afforded, with excellent yields, tetrahydropyrans **3** bearing the carbamate substituent exclusively in the axial position.[3]

Though this methodology appeared to be quite general, some functionalised aldehydes (particularly α-alkoxyaldehydes) proved to be reluctant to undergo IMSC condensation.[4] Therefore, an alternative strategy, allowing the introduction of such unreactive aldehydes before the cyclisation, was explored. We envisioned that tetrahydropyran **3** could arise from the reaction between an aldehyde and homoallylic alcohol **4**. This alcohol would be obtained by the addition of functionalised allylstannane **5** onto another carbonyl

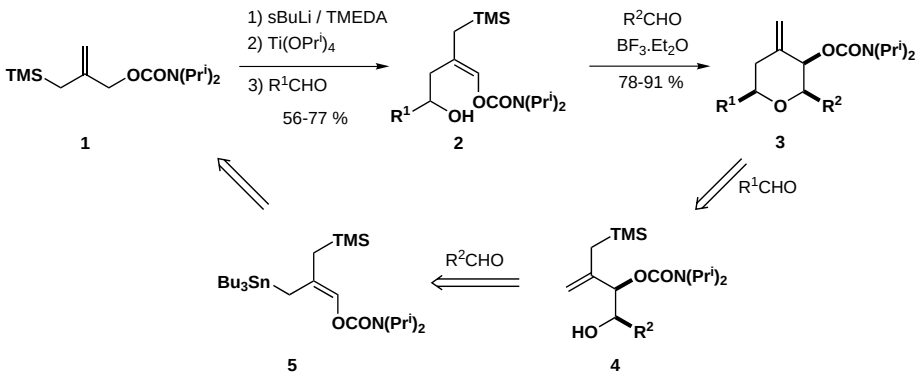

Figure 1.

Keywords: allylation; tin; cyclisation; Sakurai reactions; carbamate; bismuth.

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derivative (Fig. 1). In this communication, we wish to report some preliminary results on the successful implementation of this alternative strategy.

Allylcarbamate **1** was successfully condensed with tributyltin chloride using a protocol inspired by the pioneering work of Hoppe[5] (Fig. 2). Remarkably, only the (*Z*) isomer of allylstannane **5** is obtained. It is interesting to note that compound **5**, which combines in one small reagent allylstannane, allylsilane and enol ether functionalities, is a versatile building block.[6]

Taking advantage of the greater nucleophilic propensity of the allylstannane function over the allylsilane one, **5** was treated with various aldehydes in the presence of several Lewis acids. We were pleased to find that boron trifluoride etherate efficiently promoted the condensation of **5** with a range of aldehydes. Representative examples are collected in Table 1. Primary and secondary aldehydes react smoothly (entries 1–3), as do unsaturated ones (entry 4). Provided that tin tetrachloride was used as the Lewis acid, α-alkoxyaldehydes proved to be suitable substrates (entry 5). Even more gratifying was the complete *syn* stereocontrol observed in all these transformations. Moreover, no loss of the silicon moiety, nor double addition or cyclisation reactions were observed.

With a ready access to the desired homoallylic alcohols **6** in hand, we next turned our attention to the IMSC cyclisation step. Using boron trifluoride etherate, the crucial formation of tetrahydropyran **8** from homoallylic alcohol **7** proved to be effective, although a significant amount of desilylated product **9** was also produced. This side reaction became predominant in the condensation of alcohol **10** and dihydrocinnamaldehyde (Fig. 3).

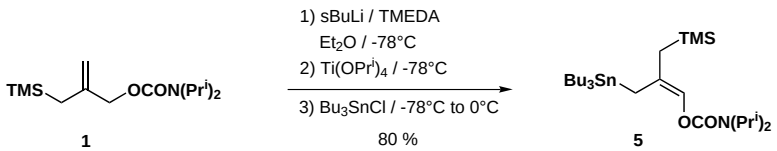
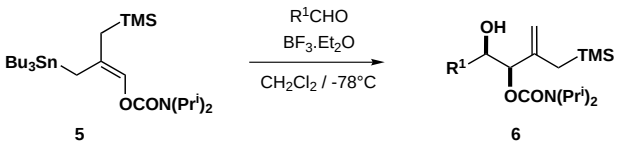
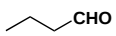
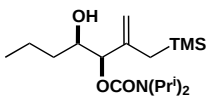
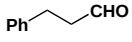
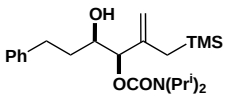
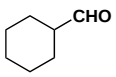
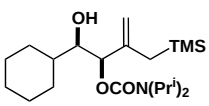
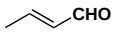
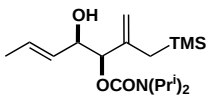
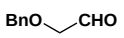
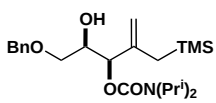


Figure 2.

Table 1. Allylstannylation of aldehydes



Entry	R^1CHO	Product	Yield[a]
1			94 %
2			92 %
3			94 %
4			98 %
5			70 %[b]

[a] All yields refer to pure, isolated products. All new compounds were fully characterised by spectroscopic and elemental analysis.
[b] $SnCl_4$ (2 equiv.) was used as Lewis acid.

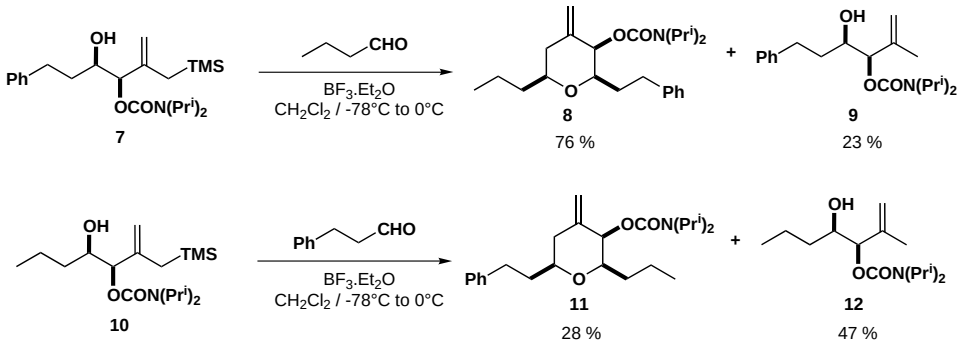
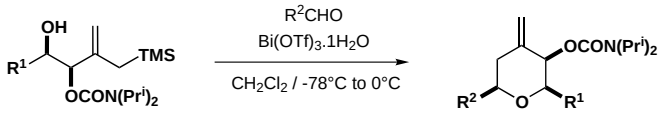


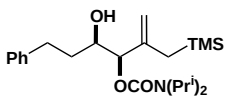
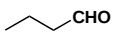
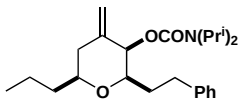
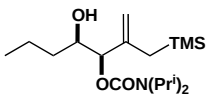
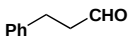
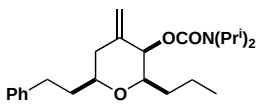
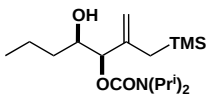
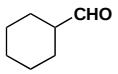
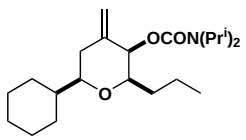
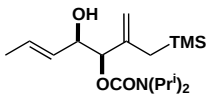
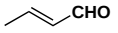
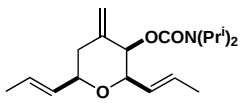
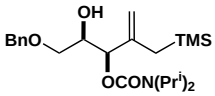
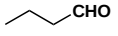
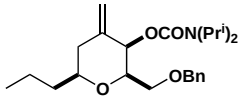
Figure 3.

In order to circumvent this problem and to find a reliable cyclisation procedure, we screened a variety of Lewis acids. Much to our delight, we found monohydrated bismuth(III) triflate[7] to be an efficient catalyst for the condensation between various homoallylic alcohols **6** and aldehydes (Table 2). In all cases, the yields were excellent and none of the desilylated byproducts were observed. Furthermore, the axial configuration of the carbamate group provides a reliable confirmation of the *syn* configuration of the starting homoallylic alcohols.[8] To the best of our knowledge, these are the first examples of Sakurai type reactions promoted by Bi(III) triflate.

In summary, we have developed an efficient and stereoselective synthesis of polysubstituted tetrahydropyrans.[9] This novel strategy nicely complements our initial procedure in that the two aldehydes required for the construction of the side chains of the ring can now be introduced in the opposite order. Moreover, protected α-alkoxyaldehydes, unsuitable for IMSC condensation, can now be introduced into the allylstannyl-

Table 2. Intramolecular Sakurai cyclisation of homoallylic alcohols



Entry	Alcohol	R^{2}CHO	Product	Yield[a]
1				91 %
2				95 %
3				91 %
4				84 %
5				98 %

[a] All yields refer to pure, isolated products. All new compounds were fully characterised by spectroscopic and elemental analysis.

ation step. Subsequent cyclisation offers a route to previously inaccessible tetrahydropyrans.

Acknowledgements

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References

1. For excellent reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309; (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291 and references cited therein.
2. Markó, I. E.; Leroy, B. *Tetrahedron Lett.* **2000**, *41*, 7225.
3. For other applications of IMSC reactions, see: (a) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595; (b) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141; (c) Markó, I. E.; Bayston, D. J. *Synthesis* **1996**, 297; (d) Feneau-Dupont, J.; Declercq, J.-P.; Bayston, D. J.; Markó, I. E. *Bull. Chem. Soc. Belg.* **1997**, *106*, 173; (e) Markó, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259.
4. Markó, I. E.; Leroy, B., unpublished results.
5. (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932; (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283.
6. For other examples of tin–silicon bis-allylic compounds, see: (a) Tsuji, Y.; Obora, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9368; (b) Obora, Y.; Tsuji, Y.; Kobayashi, M.; Kawamura, T. *J. Org. Chem.* **1995**, *60*, 4647; (c) Clive, D. L. J.; Chua Paul, C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028; (d) Kang, K.-T.; Kim, E. H.; Kim, W. J.; Song, N. S.; Shin, J. K.; Cho, B. Y. *Synlett* **1998**, 921.
7. Bismuth triflate was recently shown to catalyse various reactions such as acylation of hindered alcohols, Friedel–Craft acylation and sulfonylation, Diels–Alder and Mukaiyama aldol condensations. For some leading references, see: (a) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2877; (b) Repichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743; (c) Repichet, S.; Le Roux, C.; Hernandez, P.; Dubac, J.; Desmurs, J. R. *J. Org. Chem.* **1999**, *64*, 6479; (d) Laurent-Robert, H.; Garrigues, B.; Dubac, J. *Synlett* **2000**, 1160; (e) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249. For the preparation of bismuth triflate, see: Labrouillère, M., Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J.; Desmurs, J. R. *Synlett* **1999**, *40*, 285.
8. Axial configuration of the carbamate group was unambiguously assigned by analysis of the coupling constant in ^{1}H NMR (see Ref. 2).
9. Typical experimental procedure. Preparation of **7**: To a solution of allylstannane **5** (100 mg, 0.181 mmol) and dihydrocinnamaldehyde (25 mg, 0.181 mmol) in dry dichloromethane (2 ml) at −78°C was added $BF_3{\cdot}Et_2O$ (23 μl, 0.181 mmol) and the mixture was stirred at −78°C for 45 min. The solution was quenched at −78°C with saturated $NaHCO_3$ (5 ml). After warming up to rt, the mixture was diluted with dichloromethane (20 ml) and water (20 ml). The aqueous layer was separated and extracted with dichloromethane (2×20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 10:1) to give homoallylic alcohol **7** as a colourless oil (67 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.25 (5H, m), 4.99 (1H, d, $J=3.9$ Hz), 4.90 (1H, bs), 4.77 (1H, s), 3.89 (2H, hept, $J=6.8$ Hz), 3.68 (1H, m), 2.81 (1H, ddd, $J=13.7$; 9.1; 6.2 Hz), 2.66 (1H, ddd, $J=13.7$; 9.1; 7.1 Hz), 2.22 (1H, d, $J=4.1$ Hz), 1.73–1.82 (2H, m), 1.52 (1H, d, $J=14.3$ Hz), 1.33 (1H, d, $J=14.1$ Hz), 1.18 (12H, d, $J=6.9$ Hz), 0.01 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.44, 144.66, 142.63, 129.14, 129.00, 126.44, 110.92, 80.08, 71.32, 47.05–46.32, 35.75, 32.72, 24.61, 21.09–22.52, −0.61. IR (film) 3438, 2967, 1684, 1636, 1438, 1303. MS (EI) m/z: 405.3 ($M^{\bullet+}$, 12), 128.1 ((iPr)$_2$NCO$^+$, 100). Anal. calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.69; N, 3.45; found: C, 68.05; H, 9.84; N, 3.32%. Preparation of **8**: To a solution of homoallylic alcohol **7** (34 mg, 0.084 mmol) and butyraldehyde (7 mg, 0.092 mmol) in dichloromethane (2.5 ml) at −78°C was added $Bi(OTf)_3{\cdot}1H_2O$ (62 mg, 0.092 mmol) in one portion. The temperature was allowed to warm to 0°C over 1.5 h and the solution was stirred at 0°C for 30 min. The reaction mixture was poured onto saturated $NaHCO_3$ (20 ml) and the aqueous layer was extracted with dichloromethane (3×20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 15:1) to give tetrahydropyran **8** as a colourless oil (29 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.29 (5H, m), 5.11 (1H, s), 5.07 (1H, s), 4.88 (1H, s), 3.98–4.24 (1H, m), 3.60–3.82 (1H, m), 3.25–3.32 (2H, m), 2.66–2.84 (2H, m), 2.20 (1H, t, $J=13.4$ Hz), 2.13 (1H, dd, $J=13.5$; 2.7 Hz), 1.98 (1H, dtd, $J=13.9$; 8.5; 5.5 Hz), 1.77 (1H, dtd, $J=12.9$; 8.3; 4.4 Hz), 1.38–1.68 (4H, m), 1.19–1.25 (12H, bs), 0.95 (3H, t, $J=6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.87, 143.64, 142.65, 129.23, 128.81, 126.34, 114.04, 79.40, 78.96, 74.81, 45.35–47.08, 39.16, 38.23, 33.86, 32.24, 21.26–22.29, 19.48, 14.80. IR (film) 2960, 2934, 1689, 1657, 1435, 1286, 1133, 1049. MS (EI) m/z: 387.3 ($M^{\bullet+}$, 12), 128.1 ((iPr)$_2$NCO$^+$, 100). Anal. calcd for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62; N, 3.61; found: C, 74.38; H, 9.75; N, 3.52%.