Solid-Support Synthesis of 1,2-Diols and γ-Lactones Through Addition of α-(Benzoyloxy)crotylindium Reagents to Aldehydes

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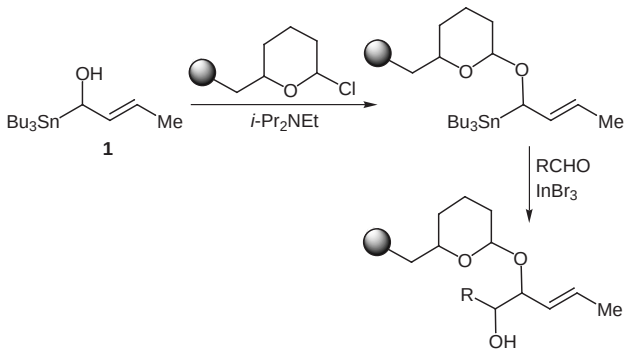
Abstract: A procedure for the solid phase synthesis of 1,2-diols and γ-lactones from α-(hydroxy)crotylstannane has been developed through transmetalation with $InBr_3$. A variety of 1,2-diols and γ-lactones were synthesized in satisfactory yields and, in some cases, with excellent diastereoselectivity. The products are formed free of tin contamination.

Key words: solid-phase synthesis, diols, lactones, α-(benzoyloxy)-crotylindium, α-(benzoyloxy)-crotylstannane

Combinatorial organic synthesis on solid supports has emerged as an important tool in lead structure identification and optimization in drug discovery.[1] Within this field, considerable effort has been made to establish the feasibility of adapting established solution phase reactions to solid supports. Nonetheless, methods for stereoselective construction of carbon-carbon bonds on solid supports remain highly underdeveloped. In that connection, we became interested in extending the applicability of solid support technology to additions of γ-oxygenated allylic indium reagents to afford stereochemically defined 1,2-diols. Specifically, we wished to explore the synthesis and transformations of α-oxygenated allylic stannanes tethered to the support through an ether linkage analogous to known reactions of the corresponding OMOM or OBOM derivatives.[2] The chemistry of interest involved transmetalation of the stannane with $InBr_3$ to form the indium derivative (Scheme 1) and in situ addition of these reagents to aldehydes.[3]

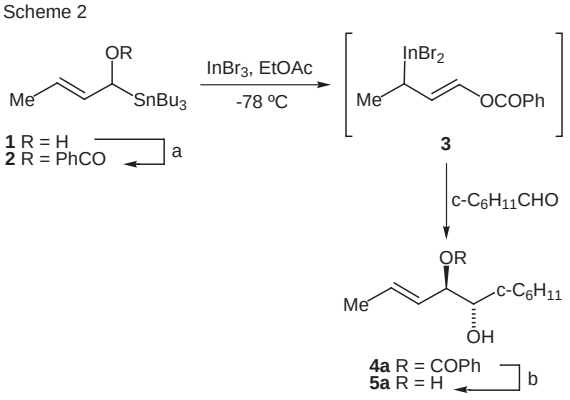
Initial studies were conducted with the racemic Bu_3SnLi adduct[4] of crotonaldehyde **1** and a polystyrene resin with an attached chloropyran group.[5] However, the tetrahydropyranyl ethers of **1** could not be prepared. We therefore elected to esterify the hydroxyl group and explore the transmetalation/addition of the acylated material. As this chemistry was previously unexplored, we first conducted solution phase studies on the benzoate derivative in order to establish experimental conditions and, if possible, determine the probable scope of the additions. Thus, benzoylation of the hydroxy stannane **1**[6] with benzoyl chloride, in the presence of *i*-Pr_2NEt, 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2, afforded benzoate **2**[7] in 90% yield from crotonaldehyde (Scheme 2).

When stannane **2** was treated with $InBr_3$ (3 equiv.) at –78 °C followed by the addition of 3 equivalents of cyclohexanecarboxaldehyde, the expected hydroxy ester **4a** was not formed to an appreciable extent. However, when 20 equivalents of aldehyde and only 1.2 equivalents of $InBr_3$ were employed the addition product, admixed with inseparable tin by-products, was obtained. Treatment with NaOMe in MeOH/THF (1:4) produced the *anti* 1,2-diol **5a** (Scheme 2). Unfortunately, despite efforts to effect purification by chromatography, the diol remained contaminated with stannane by-products and the yield could not be determined. This experiment led us to conclude that the solid-support protocol may be particularly well suited for these additions and no further work was conducted in solution.

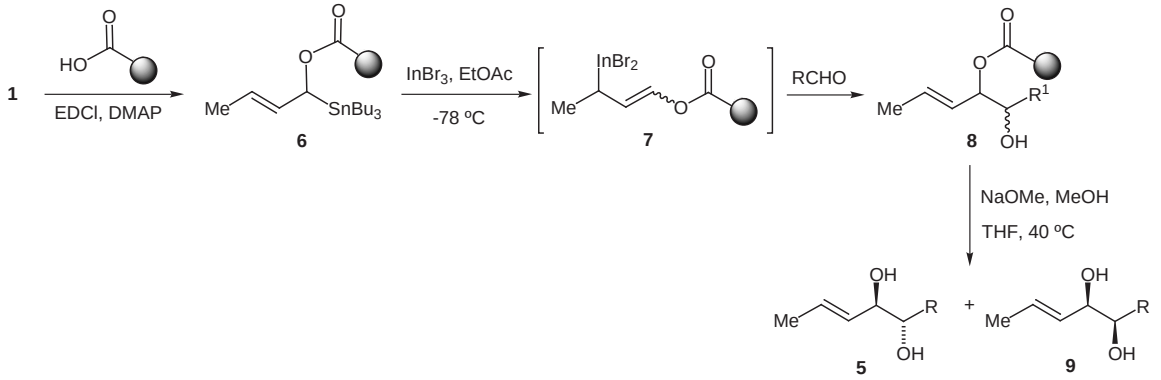


Scheme 1

Scheme 2



Scheme 2 a) PhCOCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2; b) NaOMe, MeOH/THF (1/4)



Scheme 3

The supported α-(benzoyloxy)crotylstannane **6**[8] was readily prepared from a commercially available carboxylic polystyrene resin.[9,10] The resin was swirled with the α-(hydroxy)crotylstannane **1**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride **(**EDCI) and DMAP in CH_2Cl_2[11] at room temperature for 16 h. After consecutive alternate washings with CH_2Cl_2 and ether, the resin was dried in vacuo. A suspension of dried resin in EtOAc was added to a solution of aldehyde (20 equivalents) and $InBr_3$ (1.2 equiv.) in EtOAc at –78 °C and the reaction mixture was allowed to reach room temperature. After 5 h, the resin was washed alternately with CH_2Cl_2 and ether. It was then suspended in MeOH/THF (1/4) and treated with NaOMe[12] after which, simple filtration led to the 1,2-diols **5**[13] (Scheme 3). The results are summarized in Table 1.

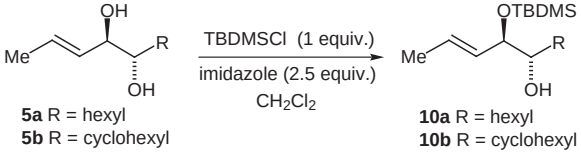
Table 1 Synthesis of 1,2-Diols **5a-e** and **9a-e**.

entry	RCHO	Yield [%][(a)]	5:9
a[14]	*n*-$C_6H_{13}CHO$	57	100:0
b[15]	c-$C_6H_{11}CHO$	58	100:0
c[16]	$CH_3CH{=}CHCHO$	50	57:43
d[17,18]	PhCHO	90	50:50
e[19]	*p*-ClC_6H_4CHO	82	47:53

(a) The yields are reported for the three-step process (from **1**).

The *syn*/*anti* ratio of the 1,2-diols, synthesized from aromatic aldehydes, was determined by ^1H NMR analysis.[18] For the 1,2-diols, synthesized from aliphatic aldehydes, this ratio was determined after selective silylation of the allylic alcohols **5a** and **5b** to **10a**[20,21] and **10b**[21,22] as these are known compounds (Scheme 4).

The formation of the *anti*-1,2 diols **5a** and **5b** from the two aliphatic aldehydes is suggestive of a reaction pathway involving a cyclic transition state of type **A** (Figure 1). Conceivably both (*E*)- and (*Z*)-allylic indium intermediates (*E*)-**7** and (*Z*)-**7** are produced in the transmetalation reaction. It is known that (*E*)-allylic stannanes are more reactive than the (*Z*)-isomers in additions to aldehydes.[23] Thus, if the energy of transition state of type **B** was significantly higher than that of transition state **A**, we could explain the high selectivity and lower yields of adducts **5a** and **5b**. The lower selectivities observed for adducts **5c-e** could be explained by a high reactivity for aryl and conjugated aldehydes with both (*E*)-**7** and (*Z*)-**7**. The reactivity difference was confirmed by a competition experiment. A



Scheme 4

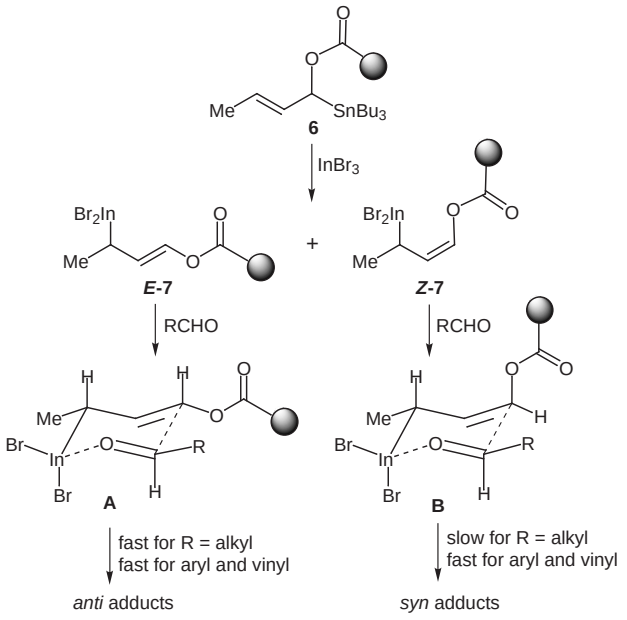


Figure 1 Possible pathways for addition of allylic indium reagents to aldehydes

1:1 mixture of benzaldehyde and cyclohexanecarboxaldehyde gave rise to a 1.0/1.1/1.2 mixture of adducts **5b**, **5d**, and **9d** after exposure to the supported crotyltin reagent **6** to $InBr_3$ and subsequent treatment with NaOMe thus confirming the enhanced reactivity of benzaldehyde *vs.* cyclohexanecarboxaldehyde.

We considered the possibility of a chelated cyclic transition state **C** for additions involving the presumed (*Z*)-**7** indium reagent (Figure 2). However, this possibility was discounted as the expected product would contain a (*Z*) double bond and the diol products were exclusively (*E*).

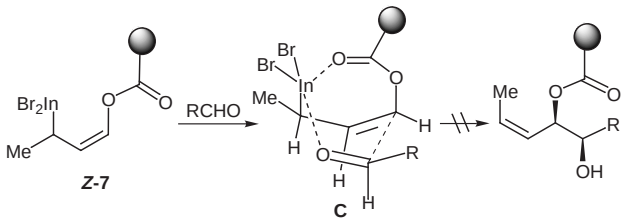
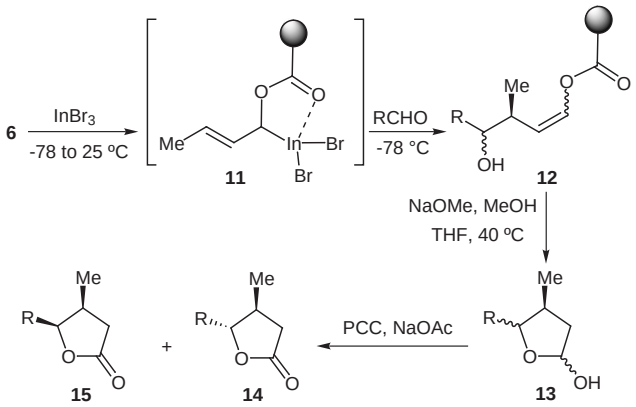


Figure 2 Hypothetical chelation transition state for addition of (*Z*)-**7** to aldehydes.

The foregoing analysis (Fig. 1) assumes that a mixture of (*E*)-**7** and (*Z*)-**7** are formed in the transmetalation reaction. As this reaction is conducted in the presence of aldehyde, we also assume that these intermediates are formed under kinetic control. To further probe this assumption we conducted experiments in which the resin-bound stannane **6** and $InBr_3$ were premixed at −78 °C and allowed to reach room temperature before addition of the aldehyde at −78 °C. It was expected that this protocol would allow the allylic indium intermediates (*E*)-**7** and (*Z*)-**7** to equilibrate before reacting with the aldehyde. When the adducts of these reactions were cleaved from the resin with NaOMe they were found to be the lactols **13** rather than the previously obtained 1,2-diols. To simplify the analysis, these adducts were converted to the lactones **14** and **15** (Scheme 5).[24] Obviously, equilibration of (*E*)-**7** and (*Z*)-**7** gives rise



Scheme 5

to the α-oxygenated indium species **11** which produces adduct **12** and thence the lactols after cleavage. Such adducts are not observed in reactions involving the OMOM analogs of stannane **2** and $InBr_3$.[2] Presumable chelation between the ester carbonyl and the $InBr_2$ moiety, as in **11**, favors this regioisomer.

The diastereoselectivity of these additions was high with the exception of **12d** and **12f**, the adducts of heptanal and dodecanal. The major products of the four-step sequence were the *trans* lactones **14** (Table 2). Unlike the previous additions (Table 1) high *anti*:*syn* ratios were observed both with aromatic aldehydes and cyclohexanecarboxaldehyde. The trend is suggestive of a transition state in which steric factors play a major role (Figure 3). The relatively larger size of aryl and cyclohexyl R groups would favor **D** relative to **E**.

Table 2 Synthesis of Lactones **14a-f** and **15a-f**

entry	RCHO	Yield [%][(a)]	**14**:**15**
a[7,25]	PhCHO	75	88:12
b[7]	*p*-ClC_6H_4CHO	60	89:11
c[7]	*p*-$NO_2C_6H_4CHO$	65	88:12
d[7,26]	*n*-$C_6H_{13}CHO$	40	53:47
e[27]	*c*-$C_6H_{11}CHO$	60	100:0
f[28]	*n*-$C_{11}H_{23}CHO$	50	62:38

(a) The yields are reported for the four-step process (from **1**)

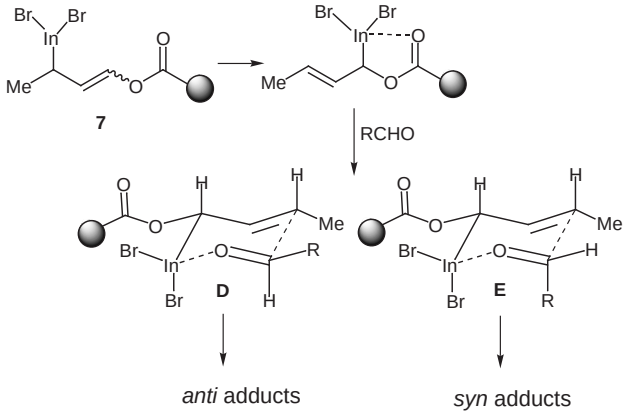


Figure 3 Possible transition states for addition of α-acyl allylic indium reagents

These studies confirm the feasibility of employing solid phase synthesis with resin-bound oxygenated allylic indium reagents to produce either 1,2-diols or γ-lactols through a change in reaction protocol. These adducts can be produced in satisfactory yields and, in some cases, with excellent diastereoselectivity. The products are formed free of contamination by tin and other by-

products. Clearly, it should be possible to improve the yields and reaction stoichiometry through the use of alternative spacer groups and resins. We hope to clarify these issues in future studies.

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(8) Preparation of support-bound α-(benzoyloxy)crotylstannane **6**: To a suspension of carboxypolystyrene (1.0 g, 2 mmol/g, 2 mmol) in CH_2Cl_2 (20 mL) at r.t., were added successively EDCI (1.9 g, 10 mmol, 5 equiv.), DMAP (0.74 g, 6 mmol, 3 equiv.) and **1** (3.6 g, 10 mmol, 5 equiv.). After 16 h, the resin was filtered, alternately thoroughly washed with CH_2Cl_2 and Et_2O and then dried in vacuo to give the crotylstannane supported reagent **6**. IR (KBr): 3022, 2922, 2844, 1728, 1700, 1350 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$) δ : 130.6 (d), 127.8 (m, polystyrene), 119.4 (d), 71.9 (d), 40.3 (m, polystyrene), 28.8 (t), 27.2 (t), 17.7 (q), 13.6 (q), 9.5 (t).

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(13) General conditions for the preparation of 1,2-diols: To a solution of $InBr_3$ (102 mg, 0.29 mmol, 1.2 equiv.) and RCHO (4.80 mmol, 20 equiv.) in EtOAc at −78 °C, was added resin **6** (200 mg, 0.24 mmol, 1 equiv.). The mixture was allowed to reach r.t. After 5 h the resin was filtered, alternately thoroughly washed with CH_2Cl_2 and Et_2O and then dried in vacuo. The resin was then suspended in MeOH/THF (1/4) (5 mL) at r.t. After addition of NaOMe (259 mg, 4.80 mmol, 20 equiv.), the resulting slurry was stirred at 40 °C for 1 h before neutralization by an aqueous solution of HCl (1.2 M). The solution was collected by filtration, dried over $MgSO_4$ and the solvent was removed in vacuo. Purification of the crude material by flash chromatography (EtOAc/petroleum ether: 20/80) afforded 1,2-diols.

(14) **5a**: IR (neat): 3398, 1654, 1577, 1458, 1378, 1071, 968 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ : 5.74 (dq, J = 6.2 and 15.4 Hz, 1H), 5.56 (ddd, J = 1.5, 7.4 and 15.5 Hz, 1H), 4.00 (dd, J = 3.3 and 7.4 Hz, 1H), 3.72-3.60 (m, 1H), 1.72 (dd, J = 1.1 and 6.2 Hz, 3H), 1.50-1.20 (m, 10H), 0.92-0.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 129.5 (d), 128.8 (d), 75.7 (d), 74.1 (d), 32.1 (t), 31.6 (t), 29.2 (t), 25.7 (t), 22.5 (t), 17.8 (q), 14.0 (q). MS (CI, NH_3) m/z: 204 (MH^++NH_3), 202 (4), 187 (2), 186 (18), 175 (5), 174 (48), 172 (5), 169 (7), 141 (3), 123 (100), 109 (12), 107 (2). HRMS (CI) calculated for $C_{11}H_{26}O_2N$ (MH^++NH_3): 204.1964, found: 204.1970.

(15) **(5b**: IR (neat): 3369, 1718, 1449, 1377, 1262, 1084, 968, 800, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ : 5.87-5.73 (m, 1H), 5.62 (ddd, J = 1.5, 7.3 and 15.4 Hz, 1H), 4.17 (m, 1H), 3.41 (dd, J = 3.7 and 8.1 Hz, 1H), 2.10-0.80 (m, 11H), 1.75 (dd, J = 1.1 and 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 129.9 (d), 128.5 (d), 78.0 (d), 73.2 (d), 39.6 (d), 28.7 (t), 28.6 (t), 26.3 (t), 25.8 (t), 25.6 (t), 17.8 (q). MS (EI) m/z: 184 (M^+, 0.07), 113 (7), 112 (6), 96 (8), 95 (100), 93 (5), 83 (8), 81 (6), 79 (3), 73 (4), 72 (70), 71 (16), 70 (4), 69 (10), 67 (16), 57 (16), 55 (16), 53 (6).

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(24) General conditions for the preparation of lactones: To a solution of $InBr_3$ (253 mg, 0.72 mmol, 3 equiv.) in EtOAc at −78 °C, was added resin **6** (200 mg, 0.24 mmol, 1 equiv.). The resulting slurry was allowed to reach r.t. before addition of RCHO (0.72 mmol, 3 equiv.) at −78 °C. After 5 h at r.t., the resin was filtered, alternately thoroughly washed with CH_2Cl_2 and Et_2O and then dried in vacuo. The resin was then suspended in MeOH/THF (1/4) (5 mL) at r.t. After addition of NaOMe (259 mg, 4.80 mmol, 20 equiv.), the resulting slurry was stirred at 40 °C for 1 h, before neutralization by an aqueous solution of HCl (1.2 M). The solution was collected by filtration, dried over $MgSO_4$ and the solvent was removed in vacuo to give lactols **13**. To a solution of lactol (0.24 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at r.t., were added successively molecular sieves (310 mg), NaOAc (9 mg, 0.12 mmol, 0.5 equiv.) and PCC (155 mg, 0.72 mmol, 3 equiv.). The mixture was stirred at r.t. for 6 h before filtration through silica gel (EtOAc/cyclohexane: 70/30). The solvent was then removed in vacuo to give lactones.

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(28) **14f** and **15f**: IR (mixture of two diastereomers, neat): 1781, 1458, 1205, 1160 cm^{-1}. ^1H NMR (300 MHz, mixture of two diastereomers, $CDCl_3$) δ: 4.48-4.35 (m, 0.38H), 4.06-3.97 (m, 0.62H), 2.75-2.62 (m, 1H), 2.64-2.52 (m, 1H), 2.28-2.14 (m, 1H), 1.70-1.25 (m, 20H), 1.14 (d, J = 6.25 Hz, 1.86H), 1.02 (d, J = 7.0 Hz, 1.14H), 0.93-0.84 (m, 3H). ^{13}C NMR (75 MHz, mixture of two diastereomers, $CDCl_3$) δ : 176.8 (s), 176.4 (s), 87.3 (d), 83.6 (d), 37.4 (t), 37.0 (t), 35.9 (d), 33.9 (t), 32.9 (d), 31.8 (t), 29.8 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.3 (t), 29.2 (t), 25.8 (t), 25.6 (t), 22.5 (t), 17.3 (q), 14.0 (q), 13.7 (q). MS for the major diastereomer (EI) m/z: 254 (M^+, 0.5), 236 (5), 195 (10), 194 (61), 142 (12), 110 (11), 99 (100), 98 (9), 97 (17), 96 (17), 83 (17), 82 (11), 71 (25), 70 (13), 69 (23), 68 (11), 57 (13), 55 (23). MS for the minor diastereomer (EI) m/z: 254 (M^+, 0.7), 236 (5), 195 (11), 194 (66), 142 (14), 110 (15), 99 (100), 97 (22), 96 (18), 95 (11), 83 (21), 82 (12), 71 (25), 70 (16), 69 (27), 68 (12), 57 (16), 56 (13), 55 (25).

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