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Allylindium and Allylboronic Acid Pinacolate: Mild Reagents for the Allylation of Resin-Bound Aldehydes. Application to the Solid-Phase Synthesis of Hydroxypropylamines

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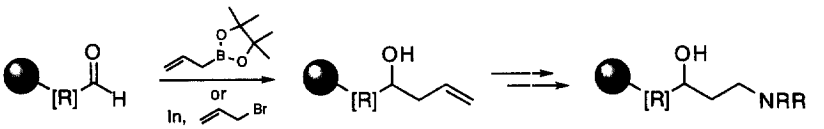
Abstract: Homoallylic alcohols are prepared in high yield and purity by the reaction of the title reagents with resin-bound aldehydes. The mild reaction conditions accommodate the base-sensitive 4-carboxamido-3-nitrobenzyl photolabile linker on standard resins. A practical application of the allylation reaction is demonstrated through the solid-phase synthesis of hydroxypropylamines.

Key words: Indium, allylation, homoallylic alcohol, solid-phase synthesis, hydroxypropylamine

As part of a broad-based drug discovery effort to generate encoded chemical libraries[2] of unique structural composition and diversity, a mild synthetic method was sought to prepare homoallylic alcohols on solid support. Homoallylic alcohols, though not of intrinsic biological interest, were envisaged to serve as common intermediates on solid support from which multiple libraries may be produced. Traditional organometallic reagents (e.g., Grignard reagents) have been successfully used on solid support; however, they suffer from rather narrow functional group compatibility and cannot be used with base-sensitive linkers.[3] In this Letter, allylindium[4a,b] and allylboronic acid pinacolate[5a] are described as reagents for the efficient allylation of resin-bound aldehydes under mild reaction conditions employing a base-sensitive photochemical linker on either TentaGel or polystyrene supports. The potential utility of this carbon-carbon bond forming reaction in library synthesis is demonstrated by the solid-phase conversion of the homoallylic alcohols to hydroxypropylamines.



The arylaldehyde substrate **1** was prepared on TentaGel S-NH_2 (Rapp Polymere) resin via a multi-step sequence (Scheme 1). This involved derivatizing the resin with the photolabile linker, 4-bromobenzyl-3-nitrobenzoic acid, to yield resin **2** (acid, HOBt, and diisopropylcarbodiimide (3 equiv each), DMF, 12 h, 25 °C) followed by displacement of the bromide in **2** with N-butylamine and attachment of 4-carboxybenzaldehyde (**2** → **3** → **1**). Photolysis (365 nm, MeOH, 3 h, 50 °C) of **1** furnished butylamide **4** in 70% isolated yield as a single product. As expected, attempts to add allyl magnesium bromide to **1** to generate **5a** (via **6a**) resulted in the immediate formation of dark resin and poor mass recovery of **4** upon photolysis (Table, entry 1). Allylation of **1** using allyltributyltin and catalysis by Lewis acids was also investigated. Surveying multiple reaction conditions and a variety Lewis acids, afforded only amide **4** after photolytic cleavage (Table, entry 2). It is believed that classical Lewis acid catalysts, such as BF_3, coordinate extensively to the oxygen-rich polyethyleneglycol grafts of TentaGel and hence, may contribute to the failure of these reactions even with excess reagents.

Indium metal has been successfully used to promote the allylation of aldehydes in aqueous media at ambient temperature.[4a,b] This reagent was thought to be ideal for the required application in light of the above allyltributyltin studies. Direct adaptation of the prescribed allylindium reaction conditions[4a] to resin-bound **1** proved troublesome, although homoallylic alcohol **5a** was isolated and characterized after photolytic cleavage of treated resin. After extensive experimentation, sonication was found to greatly facilitate the allylation reaction

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(9 equiv In, 14 equiv allylbromide, 50% aqueous THF, sonication for 4 h, 25 °C), and substrate **1** was reproducibly converted to **5a** in high yield (95%) and purity (**1** → **6a** → **5a**; >98%, HPLC; Table, entry 3).[4c-e,6a,b] Indium-mediated crotylation of substrate **1** to yield **5b** also occurred in high yield (mixture of undefined diasteroemers; Table, entry 4).[4f] Considering that the reaction is carried out in aqueous media and the poor swelling properties of polystyrene resin in water, it is of interest to note that the allylation reaction can be successfully carried on this support as well (Table, entry 6).[7]

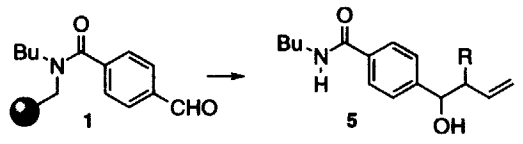
In further studies, the reaction of substrate **1** with allylboronic acid pinacolate was examined. This reagent is reported to react with aldehydes in the absence of Lewis acid catalysis in non-aqueous media.[5a] Homoallylic alcohol **5a** was again obtained in quantitative yield on either TentaGel or polystyrene resin via simple treatment of a methylene chloride suspension of **1** with the allylboronate (6 equiv, 16 h; 25 °C; Lancaster) and photolysis (Table, entries 5 and 7).[5b]

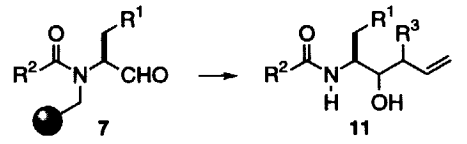
Examination of the allylation protocols against other structurally more sophisticated substrates, including amino acid aldehydes **7a-e**, was carried out. The requisite substrates were prepared as illustrated in the representative synthesis of the phenylalanine-derived substrate **7a** (Scheme 1). The bromide in resin **2** was displaced with the O-(*t*-butyldimethylsilyl)phenylalaninol (10 equiv, DMF, LiI, 2 cycles; **2** → **8**) and the secondary amine subsequently acylated with benzoyl chloride (20 equiv, pyridine, 12 h, 25 °C; **8** → **9**). Acid hydrolysis of the t-butyldimethylsilyl protecting group (**9** → **10**) and oxidation with iodobenzoic acid oxide (IBX; 10 equiv, DMSO, 8 h, 25 °C; **10** → **7a**) furnished optically pure **7a**. The reaction of alkylaldehyde **7a** with either allylindium, crotylindium or the allylboronic acid pinacolate paralleled the arylaldehyde substrate **1** and cleanly provided the corresponding homoallylic alcohols **11a** (1:3 mixture of syn/anti diastereomers; HPLC)[6c] and **11b** (mixture of undefined diastereomers; HPLC) after photolytic cleavage of resins **12a,b** in good yield (Table, entries 8-10). Several other amino acid aldehyde substrates were profiled against the indium-mediated allylation reaction with analogous results (**7b-e** → **11c-f**; Table, entries 11-14).

One envisioned application of the resin-bound homoallylic alcohol intermediates is the synthesis of hydroxypropylamines, putative aspartic acid transition-state isosteres.[2a] Considering the terminal olefin of the homoallylic alcohol as representing a latent aldehyde functionality, it was thought that selective oxidation of the double bond and subsequent reductive amination would provide a facile route to the desired hydroxypropylamine class of agents. It was found that **11a,c,d** undergo smooth osmium tetroxide-mediated dihydroxylation and diol cleavage with sodium periodate on resin to furnish aldehydes **13a,c,d** (Scheme 2). Direct reductive amination of **13a,c,d** with $NaCNBH_3$ in the presence of excess N-acetylpiperidine or morpholine (40 equiv amine, trimethylorthoformate as solvent, 30 min (imine formation); then $NaCNBH_3$, 5% v/v AcOH-MeOH, 12 h) affords clean conversion to the hydroxypropylamines **14a,c,d** after photolysis (*ca.* 50% overall from **7a,c,d**). Alternatively, the hydroxyl group in substrates **11b,e** was protected as its TBS ether (5 equiv TBS-triflate, 8 equiv 2,6-lutidine, CH_2Cl_2) prior to oxidative cleavage of the olefin affording **15b,e**. In this instance, the aldehydes were subjected to reductive amination with isopropylamine followed by acylation with acetyl chloride; cleavage furnished hydroxypropylamines **17b,e**. This later sequence provides an avenue to introduce an additional point of diversity in a library of this structural class.

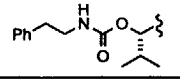
In summary, allylindium and allylboronic acid pinacolate have been described as two complementary reagents for the allylation of aromatic and aliphatic aldehydes on solid-support, providing access to homoallylic alcohols. Of particular merit is the use of the reagents on both TentaGel and polystyrene resins derivatized with a base-sensitive photolabile linker.[7] The allylation reactions are conducted in either aqueous THF or chlorinated solvents and are believed to have broad functional group compatibility. Application of the reaction to a concise synthesis of hydroxypropylamines has been demonstrated with the conversion of substrates **11a-e** to aminoalcohols **14a,c,d** and **17b,e**. Further use of these chemistries in the construction of encoded combinatorial libraries will be reported separately.

Table. Allylation of resin-bound aromatic and aliphatic aldehydes.



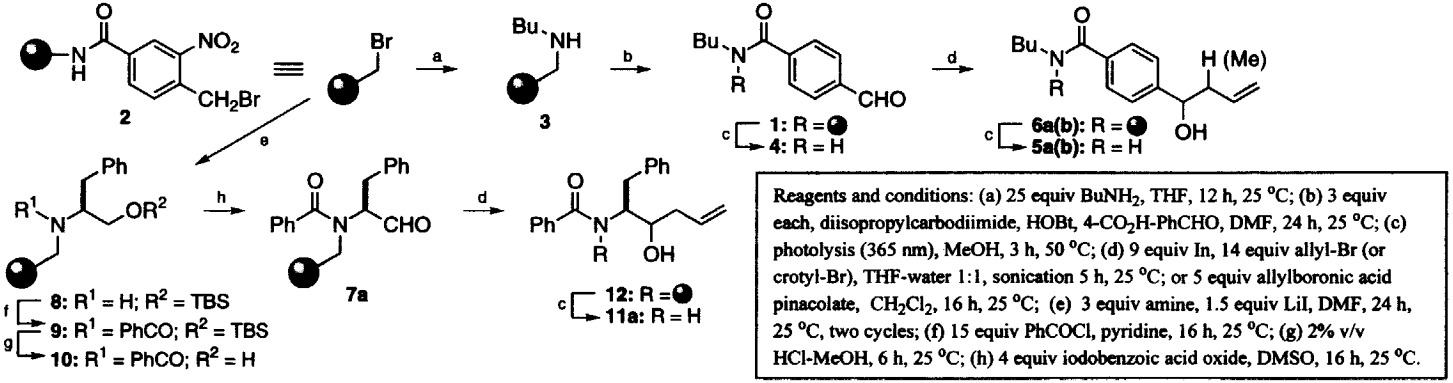


Entry	Resin[a]	Reagent[b]	R	Product[c] (Yield %)
1	TG	allyl-Br, Mg	H	**5a** (0)
2	TG	allyl-$SnBu_3$	H	**5a** (0)
3	TG	allyl-Br, In	H	**5a** (94)
4	TG	crotyl-Br, In	Me	**5b** (93)
5	TG	allyl-$B(OR)_2$	H	**5a** (100)
6	PS	allyl-Br, In	H	**5a** (99)
7	PS	allyl-$B(OR)_2$	H	**5a** (100)

Entry	No.	Resin	Reagent	R_1	R_2	R_3	Product[d] (Yield %)
8	**7a**	TG	allyl-Br, In	Ph	Ph	H	**11a** (75)[e]
9	**7a**	TG	crotyl-Br, In	Ph	Ph	Me	**11b** (65)
10	**7a**	TG	allyl-$B(OR)_2$	Ph	Ph	H	**11a** (70)
11	**7b**	TG	allyl-Br, In	(4-Ph)Ph	1-naphthyl	H	**11c** (75)
12	**7c**	TG	allyl-Br, In	(2,4-OMe_2)Ph	(3,4-Cl_2)Ph	H	**11d** (70)
13	**7d**	TG	allyl-Br, In	C_5H_{11}	(4-Cl)Ph	H	**11e** (75)
14	**7e**	TG	allyl-Br, In	(4-Cl)Ph		H	**11f** (80)

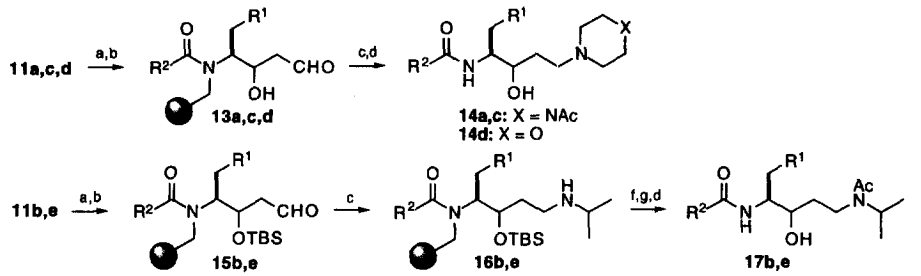
[a]TG = TentaGel S-NH_2 resin; PS = Polystyrene resin; [b]see text; [c]Isolated yield based on **1** (ref 6a); [d]Isolated yield based on alcohol precursor (e.g., **10**; ref 6a). [e]Syn/anti 1:3.

Scheme 1. Solid-phase synthesis of homoallylic alcohols **5a,b** and **11a**.



Reagents and conditions: (a) 25 equiv $BuNH_2$, THF, 12 h, 25 °C; (b) 3 equiv each, diisopropylcarbodiimide, HOBt, 4-CO_2H-PhCHO, DMF, 24 h, 25 °C; (c) photolysis (365 nm), MeOH, 3 h, 50 °C; (d) 9 equiv In, 14 equiv allyl-Br (or crotyl-Br), THF-water 1:1, sonication 5 h, 25 °C; or 5 equiv allylboronic acid pinacolate, CH_2Cl_2, 16 h, 25 °C; (e) 3 equiv amine, 1.5 equiv LiI, DMF, 24 h, 25 °C, two cycles; (f) 15 equiv PhCOCl, pyridine, 16 h, 25 °C; (g) 2% v/v HCl-MeOH, 6 h, 25 °C; (h) 4 equiv iodobenzoic acid oxide, DMSO, 16 h, 25 °C.

Scheme 2. Solid-phase synthesis of hydroxypropylamines.[a,b]



[a]For the R^1 and R^2 designations refer to **11a-e**. [b]Reagents and conditions: (a) 20 mole % OsO_4, 10 equiv morpholine N-oxide (NMO), acetone-water 1:1, 12 h, 25 °C (b) saturated aq $NaIO_4$, 5 min, 25 °C, four cycles; (c) 40 equiv (N-Ac)piperidine, morpholine, or isopropylamine, trimethylorthoformate, 30 min, drain; then 5% v/v AcOH-MeOH, 30 equiv $NaCNBH_3$, 12 h, 25 °C; (d) photolysis (365 nm), MeOH, 3 h, 50 °C; (e) 5 equiv TBS-triflate, 8 equiv 2,6-lutidine, CH_2Cl_2, 1.5 h, 0 → 25 °C; (f) 10 equiv MeCOCl, 15 equiv *i*-Pr_2EtN, cat. DMAP, CH_2Cl_2, 18 h, 25 °C; (g) 2% v/v HCl-MeOH, 6 h, 25 °C.

REFERENCES AND NOTES

[1.] (a) Present address: Coelacanth Corp., New Brunswick, NJ 08901. (b) Pharmacopeia postdoctoral fellow, 1996. Present address: Rhone-Poulenc Rhorer, Collegeville, PA 19426.

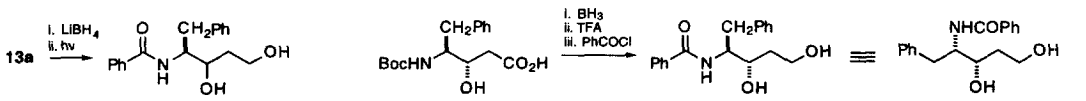
[2.] (a) Carroll, C. D.; Patel, H.; Johnson, T. O.; Guo, T.; Orlowski, M.; He, Z.-M.; Cavallaro, C. L.; Guo, J.; Oksman, A.; Gluzman, I. Y.; Connelly, J.; Chelsky, D.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2315. (b) Baldwin, J. J.; Burbaum, J. J.; Henderson, I.; Ohlmeyer, M. H. J. *J. Am. Chem. Soc.* **1995**, *117*, 5588.

[3.] Wallace, O. B. *Tetrahedron Lett.* **1997**, *38*, 4939.

[4.] (a) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *48*, 7017. (b) Li, C. J.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1992**, 747. (c) General procedure: Resin-bound aldehyde **1** (100 mg, *ca.* 0.05 mmol), In powder (50 mg, 0.44 mmol), THF-water (4 mL), and allyl-Br (60 μL, 0.7 mmol) were combined and sonicated in an ultrasonic cleaning bath. After 5 h, a milky-white precipitate formed (solution pH=3). Sonication was continued for another 1.5 h. The resin was drained, washed with THF and CH_2Cl_2. (Microscopic examination of the resin revealed no bead breakage.) The resin was suspended in MeOH (5 mL) and irradiated (365 nm) for 3 h at 40-50 °C. The product was isolated after filtration, evaporation of solvent, and purification via silica gel column chromatography. (d) The success of the solid-phase reaction suggests that the allylation reaction does not take place on the metal surface. (e) It is of interest to note that the nitro group is known to be unstable to the indium condition (Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919). The survival of this functional group here may be due to the heterogenous nature of the reaction mixture. (f) The regioselectivity and stereoselectivity of the crotylindium reaction is known (Chan, T. H.; Isaac, M. B. *Tetrahedron Lett.* **1995**, *36*, 8957), but was not determined in this study.

[5.] (a) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246. (b) General procedure: Resin-bound aldehyde **1** (400 mg, *ca.* 0.25 mmol) was suspended in CH_2Cl_2 (10 mL) and treated with allylboronic acid pinacolate (210 mg, 1.25 mmol; Lancaster). The resin was shaken for 16 h and then was drained and washed with CH_2Cl_2 and MeOH. Photolytic cleavage and product isolation were carried out as in reference 4c.

[6.] (a) Overall isolated yields based on resin loading were 60-70% for **5a,b** and 30-40% for **11a-f**. (b) All new compounds gave satisfactory physical and spectroscopic properties consistent with their structure. (c) The syn:anti ratio of 1:3 was established by comparison (^{1}H NMR, HPLC) of the diol **18** prepared from **13a** ($LiBH_4$ reduction) and authentic diol **18** prepared from stereochemically defined N-Boc-phenylalanine statine **19** (NovaBiochem) via borane reduction, Boc-deprotection, and selective N-benzoylation. The syn/anti ratio obtained with resin-bound amino acid aldehyde substrates is consistent with the indium-mediated allylation of amino aldehydes in solution (Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293).



[7.] The allylation reactions are also compatible with acid-sensitive linkers. For example allylindination of substrate **20** on RINK resin provided **22** in quantitative yield after cleavage with 95% TFA in CH_2Cl_2.