DOMINO-HYDROFORMYLATION-ALLYLBORATION-HYDROFORMYLATION FOR THE SYNTHESIS OF *TRANS*-2-ALKYLPIPERIDIN-3-OLS

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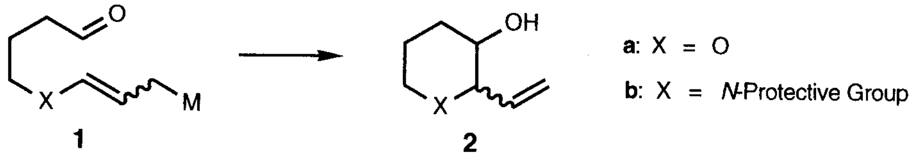
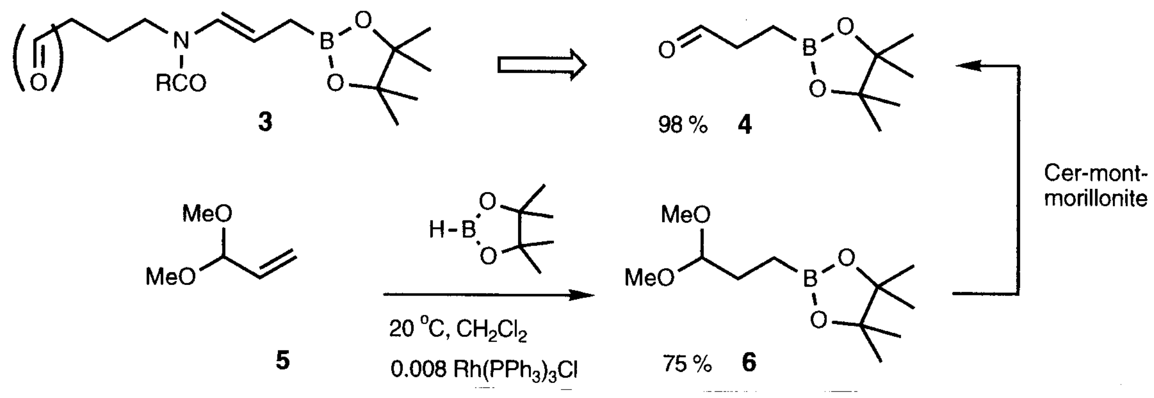
Abstract - Hydroformylation of an *N*-allyl-γ-amidoallylboronate (**7d**) generates a formyl function which allows intramolecular allylboration to proceed to give a vinylpiperidinol (**11**). The latter is again hydroformylated under the reaction conditions to furnish an oxa-aza-decalin ring system (**12**).

Intramolecular allylmetallation of ω-oxo-allylmetallic species (**1a**) has been successfully applied to the synthesis of oxygen heterocycles (**2a**).[1]

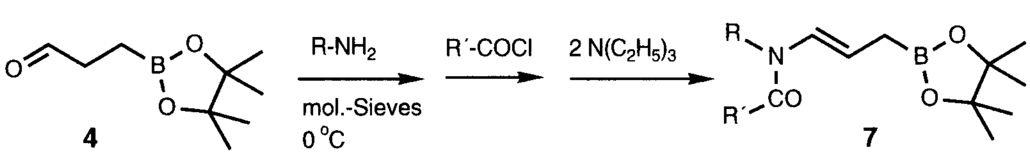


Recent studies from the Yamamoto group[2] showed that *cis*-2-vinylpiperidine-3-ols (**2b**) can be selectively accessed by thermal cyclisation of **1** (X = NBoc, M = $SnBu_3$). Lewis-acid mediated cyclization furnished mixture of the *trans*- and *cis*-isomers. We therefore wanted to explore the scope of the corresponding allylboration reaction. Aiming at **3** with an *E*-configurated double bond as the starting point for the heterocyclization, we faced the synthesis of the hitherto unknown γ-amidoallylboronates and the standard problem of generating a formyl function in the presence of an allylboronate moiety. We present here novel solutions to both tasks.

Enamide functions are usually generated from an amine an acylating agent and an aldehyde.[3] This points to the aldehyde (**4**) as a key precursor.



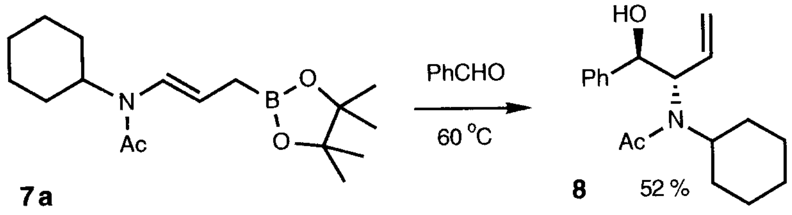
We developed a convenient access to the aldehyde (**4**) by Rh-catalysed hydroboration[4,5] of 3,3-dimethoxypropene (**5**) (75%) followed by mild acetal hydrolysis using cerium montmorillonite[6] in moist dichloromethane (98%). The aldehyde (**4**) could be converted into a series of γ-aminoallylboronates (**7**) in a one pot sequence involving imine formation (R-NH_2 + molecular sieves), acylation with RCOCl, and treatment with 2 equivalents of triethylamine. The products (**7**) have a uniform *E*-geometry of the double bond, as seen from the $^3J_{H,H}$-coupling constants of the olefinic protons (**7a**: J = 13.7 Hz).



4 **7**

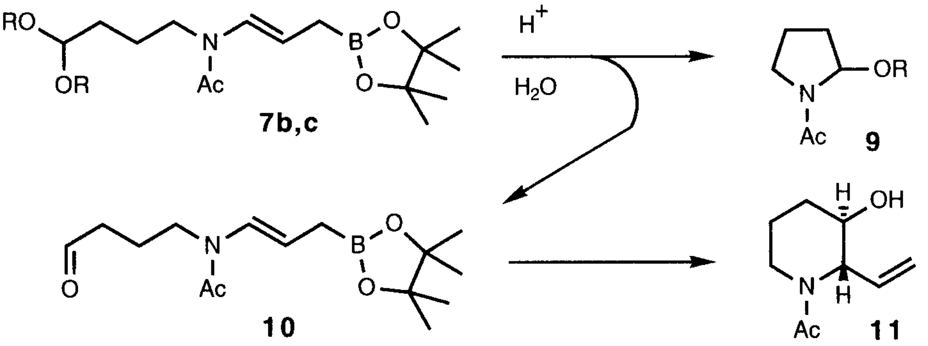
	R	R′	Yield (%)
7a	c-C_6H_{11}-	CH_3-	59
7b	$(C_2H_5O)_2CH$-$(CH_2)_3$-	CH_3-	92
7c	$(CH_3O)_2CH$-$(CH_2)_3$-	CH_3-	95
7d	CH_2=CH-CH_2-	CH_3-	92
7e	CH_2=CH-CH_2-	$PhCH_2O$-	90

The compound (**7a**) entered into a clean allylboration reaction with benzaldehyde (5 h, neat at 60°C) to give 52% of the homoallyl alcohol (**8**) as colorless crystals of mp 105°C. The relative configuration of **8** (= anti) was secured by crystal structure analysis.



7a **8**

Intramolecular allylboration of the aldehyde (**10**) to give the piperidinol (**11**) required the selective generation of a formyl function. Hydrolyses of the acetal moieties in **7b** or **7c** could be effected with the Lipshutz system[7] ($LiBF_4$ in wet CH_3CN) or with $Yb(OTf)_3$[8] in wet CH_2Cl_2, but was accompanied by significant hydrolysis of the acid-labile enamide moiety leading to *N*-acetyl-2-methoxypyrrolidine (**9**) as the major product. Nevertheless, the desired piperidine derivative (**11**) could be obtained in up to 45% yield.

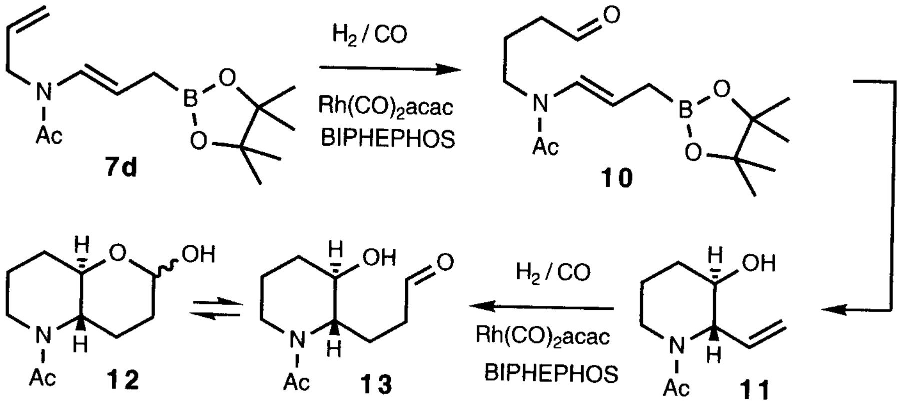


7b,c **9** **10** **11**

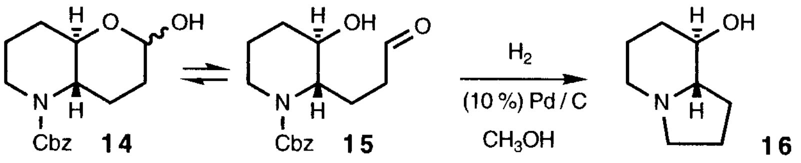
43 % **7b**, $LiBF_4$, CH_3CN, H_2O

45 % **7c**, $Yb(OTf)_3$, CH_2Cl_2, H_2O

The weak point is obviously the generation of the aldehyde in the presence of the acid-labile enamide moiety. We noted that aldehydes may be generated under essentially pH-neutral and anhydrous conditions by the hydroformylation reaction of terminal alkenes. While the selectivity towards the formation of unbranched aldehydes needs attention,[9,10] this reaction is attractive in the present context, because it allows a rapid elaboration of a heterocyclic system in a domino process:[11] Given the allylamide (**7d**), hydroformylation would generate the aldehyde (**10**), which could undergo *in situ* allylboration to give the vinylpiperidinol (**11**). The reaction would, however, not stop at this stage, since **11** has a newly generated terminal C-C double bond. **11** should therefore undergo the second hydroformylation to expand the carbon skeleton further to give **13**.[10] At this point, the reaction should be terminated by formation of the lactol (**12**).



Hydroformylation of **7d** with 25 bar of H_2/CO with 0.01 equivalents of $Rh(CO)_2$ acac and 0.2 equivalents of BIPHEPHOS[9] furnished an equilibrium mixture of **12** and **13**. In the ^{1}H-NMR spectrum signals of methyl groups - resulting from undesired hydroformylation to branched aldehydes - were absent. Otherwise the ^{1}H-NMR spectrum of this mixture was too complex due to amide rotamers being present to prove the expected *trans*-arrangement of the substituents at the piperidine ring. To this end the carbobenzoxy derivative (**7e**) was subjected to hydroformylation conditions to generate 66% of a mixture of **14** and **15**. Hydrogenation of this mixture with palladium on charcoal then led in another domino process directly to the known[12] indolizidine (**16**) (60%). Here, the ^{1}H-NMR spectrum allowed a clear identification of the relative configuration of the product as indicated.



We have shown in this study, that intramolecular allylboration of *E*-configurated δ-oxoalkylaminoallylboronates (**3**) leads in a stereochemically defined manner to a *trans*-2-vinylpiperidin-3-ol (**11**). This transformation was part of a domino-hydroformylation-allylboration-hydroformylation sequence converting the readily accessible allylenamides (**7d**, **7e**) into the piperidine derivatives (**12**).

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Molecular sieves A4 (1 g) and allylamine (225 µL, 3 mmol) were added to a solution of the aldehyde(**4**) (486 mg, 2.64 mmol) in THF (6 mL) at 0°C. The solution was transferred after 3 h into a solution of benzylchloroformate (460 µL, 3.15 mmol) in THF (3 mL) at 0°C. Triethylamine (836 µL, 8 mmol) was added after 15 min. After stirring for 3 h pentane (9 mL) was added. The mixture was filtered over Kieselgur and concentrated to give the allylboronate(**7e**)(1.07 g) as a slightly yellowish oil. The latter was taken up in THF (10 mL), the solution was added into a solution of Rh(CO)$_2$acac (7.7 mg, 0.03 mmol) and BIPHEPHOS (47.2 mg, 0.06 mmol) in THF (5 mL). The mixture was stirred for 5 d at 65°C under 5 bar of CO/H$_2$ (1:1) in an autoclave. Aqueous NaHCO$_3$ solution (15 mL) was added. The phases were separated and the aqueous phase was extracted with t-butyl methyl ether. The extracts were dried (MgSO$_4$) and concentrated. Flash chromatography of the residue with pentane/acetone = 4:1 furnished 506 mg (66 % based on **4**) of a mixture of **14** and **15**. Characteristic NMR signals: ^{1}H NMR **14**: 4.81 (m, 5.22 (m); **15**: 9.68 (s). ^{13}C NMR **14**: 91.2, 95.5; **15**: 74.5, 201.2. This mixture was dissolved in methanol (4.4 mL), 10% Pd on carbon (50 mg) was added and the suspension was stirred under 1 bar of H$_2$ for 24 h. The mixture was filtered and the filtrate was concentrated to give 148 mg (60%) of the amine(**16**) as a yellowish oil. - ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.37 (ddd, J = 10.8, 8.8, 4.5 Hz, 1 H), 3.06 (td, J = 8.7, 2.1 Hz, 1 H), 2.99 (m, 1 H), 2.15 (pseudo-q, J = 9.0 Hz, 1 H), 2.06 (m, 1 H), 1.99 (m, 1 H), 1.92 (td, J = 11.5, 3.2 Hz, 1 H), 1.78 (m, 1 H), 1.61 - 1.72 (m, 4 H), 1.53 (m, 1 H), 1.18 (m, 1 H). ^{13}C-NMR-data identical to those reported in ref.[12]

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