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Short asymmetric syntheses of homoallylic, homopropargylic and allenic silylated primary amines

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Abstract—Amino alcohols derived from phenylglycinol and having vinyl-, alkynyl- or allenylsilane moieties were transformed in the corresponding primary amines in two steps: oxidative cleavage of phenylglycinol and transimination with phenylhydrazine. This methodology gave general access to enantiomerically enriched amines without loss of enantioselectivity.

The development of rapid, efficient and practical asymmetric syntheses of functionalized amines[1] is a major objective for organic chemists due to their use as synthetic precursors in the synthesis of nitrogen-containing heterocycles or as ligands. Particularly, access to enantioenriched homoallylic amines has attracted much interest.[2,3] Regarding generation of these chiral amines, the nucleophilic 1,2-addition of organometallic reagents to imines or oxazolidines, derived from β-amino alcohols, is a powerful tool.[1] Such attack leads to enantiomerically enriched primary amines bearing a stereogenic centre at the α-position, which is a characteristic structural feature in bioactive natural products and in pharmaceutically important compounds. On the other hand, in this area, syntheses of amines with an unsaturated silylated function are relatively scarce.[4,5] Such compounds in racemic form and, to a lesser extent, in enantiopure form were used in the synthesis of heterocycles. Owing to the β-silyl carbocation stabilization, these syntheses consist mostly of the use of cationic cyclizations, which occur with high levels of regiocontrol, via iminium or *N*-acyliminium ion intermediates.[6] To the best of our knowledge, only enantiopure tethered vinylsilyl or allylsilyl amines derived from L-alanine or L-phenylalanine[5] have been described up to now, restricting the R-group α to the nitrogen to be methyl or benzyl. In this paper, we report a quick, easy and general access to various silylated unsaturated amines.

Recently, we have described[7] the diastereoselective syntheses of functionalized β-amino alcohols **2**, **3a–c**, **4a–c** and **5** by addition of silylated and unsaturated organometallic derivatives onto 1,3-oxazolidines **1** prepared from phenylglycinol and various aldehydes (Scheme 1).

β-Amino alcohols **2** and **3** were revealed as efficient substrates for the synthesis of pipecolic acid derivatives[8] and disubstituted proline compounds.[9] As part of a research program aimed at the enantioselective synthesis of natural heterocyclic products, we were interested in synthesizing a range of unsaturated primary amines from these amino alcohols in order to check their efficiency in asymmetric intramolecular cyclizations. First, compound **2** was treated with periodic acid in aqueous methanol containing 10 equiv of methylamine.[10] Amine **6** was obtained with 39% yield, but this methodology could not be applied to the amino alcohols **3** or **4**. Therefore, in order to develop general access to these silylated amines, we decided to test another method to obtain the desired amines from the amino alcohols **3**, **4** and **5** (Scheme 2).

Two steps appeared necessary to isolate the primary amines: (i) lead tetraacetate cleavage of phenylglycinol; (ii) hydrolysis of the resulting imines. The first step was already described by Pridgen and Mokhallalati[11] and led to the imines in quantitative yields in all studied cases. These authors also described the transformation into the corresponding amines by acidic hydrolysis. In our hands, however, imines **7** did not react in this medium and imines **9** underwent a desilylating reaction. To obtain the corresponding primary amines,

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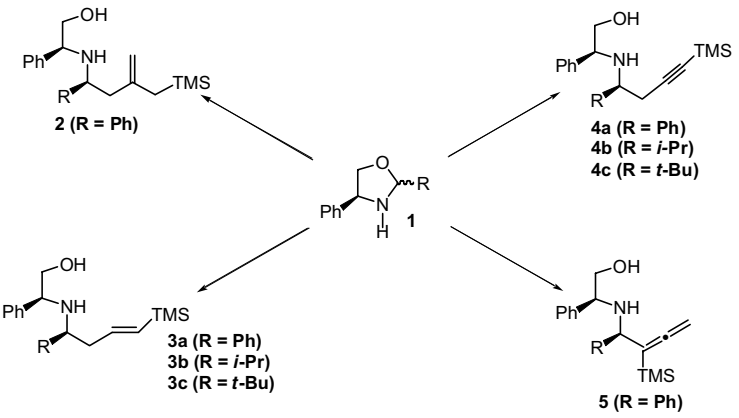
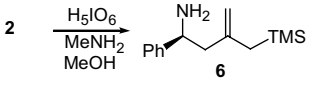


Scheme 1.

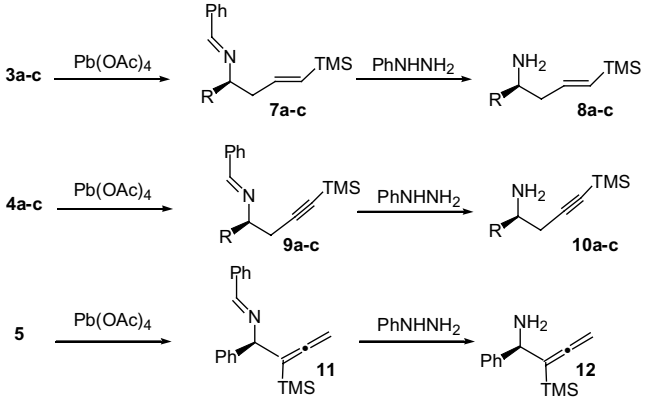


Scheme 2.

phenylhydrazine in hexane was used as a transimination reagent.[12] Thus, the imine of phenylhydrazine precipitated in the medium. This reaction was very efficient since complete disappearance of the starting material and formation of the corresponding amines were observed both on the ^{1}H and ^{13}C NMR spectra in each studied cases. The last purification step required careful micro-evaporator distillation to recover the pure amines, resulting in some low yields (Scheme 3, Table 1).

To show the effectiveness of the two steps in obtaining amine **8c**, amino alcohol **3c** was directly transformed into the N-Boc protected amine **13**, without any purification except after the last step. Now, by avoiding the distillation, compound **13** was obtained in70% yield[13] (Scheme 4).

Chiral HPLC on compounds **8a**, **10a** and **12** showed that epimerization did not occur during these two steps. Diastereoisomeric excesses of the starting β-amino alcohols corresponded to the enantiomeric excesses of the final amines, as described in Table 2.

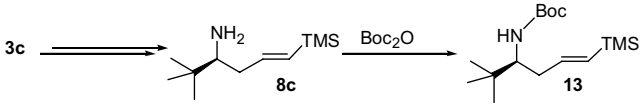


Scheme 3.

Table 1. Preparation of primary amines

Amino alcohol	Product	Yield (%)[a]
3a	**8a**	80
3b	**8b**	84
3c	**8c**	17
4a	**10a**	53
4b	**10b**	91
4c	**10c**	10
5	**12**	33

[a] Isolated yield.



Scheme 4.

Table 2. Diastereoisomeric and enantiomeric ratios of β-amino alcohols and amines

Amino alcohol	Dr[a]	Product	Er[a]
3a	89/11	**8a**	88/12
4a	91/9	**10a**	90/10
5a	95/5	**12**	95/5

[a] Diastereoisomeric and enantiomeric ratios were determined by HPLC analysis (chiralcel OD, 250×4.6 mm); eluent hexane/isopropanol: 95/5, 0.6 mL/min for 15 min) by integration at 220 nm at 25 °C.

In summary, we have developed a general access to functionalized amines; studies to explore their reactivity in cyclization reactions are actively underway in our laboratory.

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13. Procedure for obtaining compound **13**: Lead tetraacetate (1.8 g, 4 mmol) was added to stirred, cooled (0 °C) absolute methanol (41 mL). To this cooled yellow solution was added over 10 min a solution of amino alcohol **3c** (1 g, 3.13 mmol) in CH_2Cl_2 (21 mL). After stirring for another 30 min at 0 °C, the mixture was diluted with dichloromethane (20 mL) and stirred for 2 min. The mixture was then quenched with a 10% aqueous sodium carbonate solution (25 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2×10 mL) and the organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The corresponding imine was treated directly in the next step. Phenylhydrazine (0.3 mL, 3 mmol) was added to a solution of imine (0.818 g, 2.84 mmol) in *n*-hexane (27 mL). The solution was stirred at room temperature under argon during 24 h. The resulting mixture was filtered through a pad of Celite 545®, and washed with *n*-hexane and the filtrate was evaporated very carefully without warming, under reduced pressure. The crude amine **8c** (0.57 g, 2.84 mmol) was directly treated with di-tertio-butyldicarbonate (0.682 g, 3.12 mmol.) in AcOEt (15 mL). The mixture was stirred for 1 h 30 min and the solvent was evaporated. The crude residue was chromatographed to afford compound **13** as a solid (AcOEt/PE: 2/98). Yield: 70%. Mp: 77 °C. $[\alpha]_D^{20} + 42$ (*c* 0.7, $HCCl_3$). ^{1}H NMR: 5.96 (ddd, $J = 5.0$, 7.5 and 18.5 Hz, 1H), 5.90 (d, $J = 18.5$ Hz, 1H), 4.19 (d, $J = 10$ Hz, 1H), 3.49–3.39 (m, 1H), 2.49–2.38 (m, 1H), 1.97–1.85 (m, 1H), 1.38 (s, 9H), 0.86 (s, 9H), 0.05 (s, 9H). ^{13}C NMR: 156.1, 144.4, 132.5, 78.7, 58.3, 38.2, 34.8, 28.6, 26.5, −1.0. Anal. Calcd For $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.10; N, 4.68. Found: C, 64.38; H, 11.18; N, 4.45.