Efficient 1,3-Asymmetric Inductions during Nucleophilic Additions to Imine and Iminium Ion Derivatives

Claude Agami, Sebastien Comesse, Catherine Kadouri-Puchot*, Marie Lusinchi

Laboratoire de Synthèse Asymétrique associé au CNRS, case courrier 47, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

Fax +33 (1) 44 27 26 20; E-mail: kadouri@ccr.jussieu.fr

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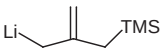
Abstract: Two new β-amino alcohols have been synthesized by a reaction between an organolithium compound **1** involving an allylsilane moiety with either an imine or an oxazolidine derived from *(S)*-phenylglycinol. These reactions occurred in good yields and with high diastereoselectivity. Both amino-alcohols were engaged in cyclization reaction with glyoxal to afford in two steps highly functionalized bicyclic lactones.

Key words: organolithium reagent, asymmetric synthesis, β-amino alcohols

The addition of organometallic reagents to imines derived from phenylglycinol has recently begun to attract interest of chemists.[1] Pioneering works of Takahashi et al.[2] reported the diastereoselective addition of chiral imines and 1,3-oxazolidines with MeMgBr and MeLi. This study prompted many groups to synthesize by this way chiral amines,[3] optically pure β-amino alcohols [4] and various natural and non-natural products.[5] This interesting process is not restricted to such simple organometallic reagents. This Letter relates the reaction of β-amino alcohols-derived substrates with [2-((trimethylsilyl)methyl)prop-2-enyl]lithium **1**, which has been recently synthesized by Livinghouse and Ryter,[6] from an allyl selenide. Kang et al.[7] described the reactivity of an analogous reagent with various aldimines which afford racemic piperidines.



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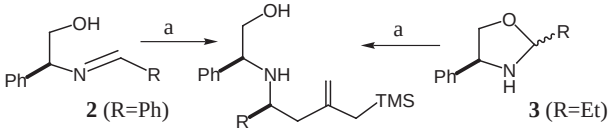
In the course of our studies aimed at extending our methodology that leads to derivatives of pipecolic acid,[8] amino alcohols presenting both a second chiral center and an allylsilane side-chain were required. Chiral imine **2** and oxazolidine **3** were obtained quantitatively by stirring *(S)*-phenylglycinol at room temperature with the corresponding aldehyde in the presence of $MgSO_4$. The structure of the products was established by ^1H NMR. The main product derived from benzaldehyde was the *trans* imine **2** as already described.[2a] The propanal-derived oxazolidine **3** was obtained as a mixture which was epimeric at C-2 (60/40).[9] Subsequent addition of the organolithium reagent **1** on the chiral compounds **2** and **3**[10] afforded β-amino alcohols **4** and **5** respectively in good yields and with high diastereoselectivity (see Scheme 1 and Table 1). As shown in the Table 1, allowing the reaction mixtures to reach room temperature resulted in lower yields; this can be ascribed to the instability of the anionic intermediates prior to the hydrolytic workup.



2 (R=Ph) **3** (R=Et)

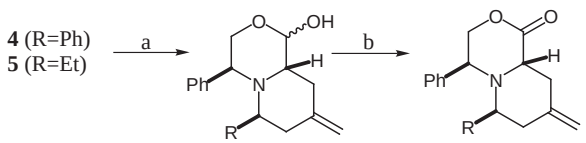
4 (R=Ph)
5 (R=Et)

Scheme 1 a) $TMSCH_2C(=CH_2)CH_2Li$ (**1**), THF, -78 to -20 °C.

Table 1 Reactions of the Lithium Derivative **1** with Compounds **2** and **3**.

R	equiv.	Experimental conditions	Yield (%)	de
Ph	2	-78°C→ rt (8h)	31	87
Ph	3	-78°C→ rt (8h)	69	87
Ph	2.8	-78°C→ -20°C (1h)	78	87
Et	3	-78°C→ rt (8h)	30	90
Et	2.8	-78°C→ -20°C (1h)	80	90

These two new β-amino alcohols **4** and **5** were engaged in cyclization reaction[11] with glyoxal to test, on the one hand, whether our already described methodology could be extended to those new substrates and, on the other hand, to establish the absolute configurations of the stereogenic centers (Scheme 2).



6(R=Ph)
7 (R=Et)

8 (R=Ph)
9 (R=Et)

Scheme 2 a) CHOCHO, THF/H_2O, 93% and 95% from **4** and **5** respectively; b) $COCl_2$, DMSO, NEt_3, 70% for **8** and 93% for **9**.

The reaction of amino alcohols **4** and **5** with glyoxal afforded hemiacetals **6** and **7** respectively in high yields. Swern oxidation produced lactones **8** and **9**, both as a unique diastereomer.[13, 14] A complete stereocontrol was therefore achieved in the formation of the bicyclic lactones. The configuration of compound **9** was established from a NOESY experiment as depicted in Figure 1.

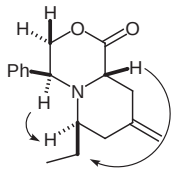


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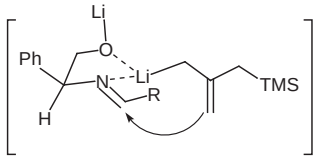
Figure 1

During the whole process, two chiral centers were created owing to two 1,3-asymmetric inductions occurring in different steps. As regards the first stereogenic center, the absolute configuration resulted from attack of the lithium derivative **1** on the oxazolidine **3**. In agreement with previous works,[2b,3a,15] this stereoselectivity can be rationalized by a chelated intermediate **10** in which the less hindered *Si* face of the imine *E*-double bond is attacked by the organometallic moiety.



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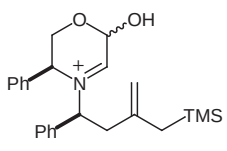
The absolute configuration of the other stereogenic center results from the attack of the allylsilane function on the transient iminium ion **11** according to the same stereochemical outcome that we already described: attack of the allylsilane in an *anti* relationship with respect to the phenyl group.[16] In this case however, the diasteroselectivity was dictated by two stereogenic centers already present in the substrate, both providing 1,3-asymmetric induction.



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This work is in progress to extend the methodology to the preparation of more substituted β-amino alcohols and to use them in the total synthesis of cyclic and functionalized derivatives of amino acids.

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References and Notes

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(9) The composition of the imine-oxazolidine equilibrium was determined in $CDCl_3$. The ratio reported above may not be the same when this reagent was used in THF, but this does not matter since the addition most probably takes place on the imine.
(10) **Typical procedure**: A solution of imine **2** or oxazolidine **3** (4.8 mmol) in THF (10 ml). was added dropwise at –78° to a freshly prepared solution of **1** (13.5 mmol) in THF (150 ml) The mixture was stirred at this temperature for 30 minutes and allowed to –20 °C within 30 minutes. Then, a saturated aqueous solution of NH_4Cl (50 ml) was added. The reaction mixture was extracted with Et_2O (2 x 50 ml) and the organic layer was dried over K_2CO_3. After evaporation under reduced pressure, the residue was chromatographed on silica gel (petroleum ether/ethyl acetate:80/20) to afford the β-amino alcohols.
(11) **Typical procedure**: Glyoxal (2.1 ml) was added to a solution of compound **5** (3.2 mmol) in THF/H_2O (v/v:1/1, 13 ml). The mixture was stirred for 5 h. at rt and water (10 ml) was added. Extraction with CH_2Cl_2 (2 x 10 ml) was followed by drying on $MgSO_4$. After evaporation under reduced pressure, chromatography on silica gel (petroleum ether/ethyl acetate:90/10) gave hemiacetal **7** (0.76 g, 95%). The same procedure was applied when starting from compound **4** (reaction time:36 h.) in order to obtain hemiacetal **6** (93%).[12]
(12) In both cases, the minor diastereomer was eliminated during the chromatography step.

(13) Data for compound **8**:^{1}H NMR (250 MHz, $CDCl_3$):7.42-7.00 (m, 10H), 4.90 (bs, 1H), 4.80 (bs, 1H), 4.51 (dd, J = 12 and 5.9 Hz, 1H), 4.29 (dd, J = 12 and 7.7 Hz, 1H), 3.99 (dd, J = 7.7 and 5.9 Hz, 1H), 3.96 (dd, J = 5.9 and 4.2 Hz, 1H), 3.72 (dd, J = 8 and 4.9 Hz, 1H), 2.90 (dd, J = 13.7 and 4.2 Hz, 1H), 2.44 (dd, J = 13.7 and 5.9 Hz, 1H), 2.36 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$):170.3, 140.9-140.1, 138.1, 128.1, 127.9, 127.2, 127.0, 126.9, 126.5, 110.9, 68.6, 64.4, 56.9, 54.9, 40.4, 32.3. $[\alpha]^{20}_{D}$:-9 (*c* 0.7, $CHCl_3$).

(14) Data for compound **9**:^{1}H NMR (400 MHz, $CDCl_3$):7.38-7.35 (m, 5H), 4.86 (d, J = 1.6 Hz, 1H), 4.70 (d, J = 1.6 Hz,1H), 4.44 (dd, J = 4.5 and 9.7 Hz, 1H), 4.32-4.24 (m, 2H), 4.02 (dd, J = 3.8 and 11.9 Hz, 1H), 2.72 (t, J = 13.9 Hz, 1H), 2.68-2.61 (m, 1H), 2.43 (dd, J = 3.8 and 13.2 Hz, 1H), 2.29 (dd, J = 4.3 and 13.6 Hz, 1H), 1.70 (d, J = 13.6 Hz, 1H), 1.55-1.13 (m, 1H), 1.25-1.13 (m, 1H), 0.82 (t, J = 7.4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$):170.5, 141.3, 136.4, 129.1, 128.8, 128.5, 110.8, 73.8, 56.0, 55.9, 55.7, 33.1, 32.7, 23.4, 10.7. $[\alpha]^{20}_{D}$:+81 (*c* 1, $CHCl_3$).

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