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Diastereoselective alkynylation of chiral non-racemic oxazolidines with mixed organoaluminum compounds.

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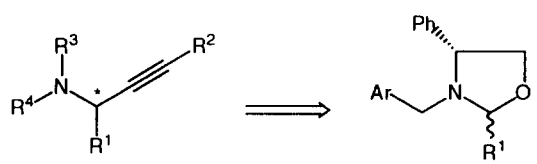
Abstract: : A new efficient and scalable route to chiral non-racemic α-substituted propargylamines is described. The reaction pathway consists of the diastereoselective addition of mixed alkynylaluminum reagents to oxazolidines derived from *R*- (-)-phenylglycinol. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Enantiopure α-substituted propargylamines **1** are useful synthetic intermediates and can also be encountered as part of bioactive compounds[1] or natural products[2] (Figure 1). Among all the asymmetric preparative methods of optically pure α-substituted amines, the diastereoselective addition of organometallic reagents to the C=N bond of chiral imines or their derivatives often proved to be very efficient[3]. However, this strategy gives unsatisfying results for the preparation of propargylamines. Enders and coll. described a general method in 1995 for the asymmetric synthesis of compounds of type **1.** However, the key step involved a 1,2 addition of organocerium reagents to chiral α,β unsaturated aldimines which had to be performed at -100 °C[4]. The nucleophilic addition of alkynyl Grignard reagents on chiral acyliminiums has recently been reported to proceed at more elevated temperature (35 °C) but with moderate d.e. (*ca* 65 %) in most cases[5, 6].



1 **2**

Figure 1

Oxazolidines are known to react in a diastereoselective manner with organometallic compounds, provided that the reaction proceeds via a 2 steps mechanism and that the transient iminium adopts a well defined geometry. The low nucleophilicity of organoaluminum species should favor this mechanistic pathway. It is also well known that mixed alkynylalanes usually react with enones or epoxides by transfering preferentially their alkynyl group[7]. All these results prompted us to study the nucleophilic opening of chiral oxazolidines **2** with mixed alkynylaluminum compounds (Figure 1).

Several oxazolidines were prepared according to reported procedures (Scheme 1)[8] and were used as such.

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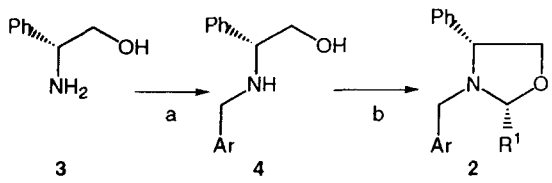
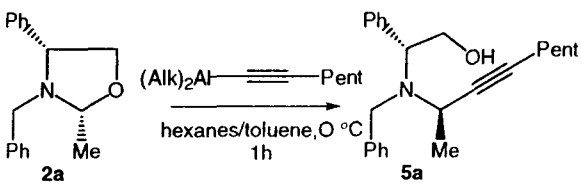


Scheme 1. *Reagents and conditions* : a) ArCHO, $NaBH_4$, MeOH, r.t., 20 h ; b) R^1CHO (3 eq.), THF, $MgSO_4$, Δ, 4h.

compound	Ar	R^1	Yield[a] %	d.e.[b] %
2a	Ph	Me	95	83
2b	3,4-OMe-Ph	Me	92	82
2c	Ph	$(CH_2)_2Ph$	95	87

a) overall yield from **3**. b) Determined by ^1H NMR of the crude reaction mixture

The reaction was at first optimized with compound **2a**. Mixed alanes were prepared by simply stirring trialkylalanes and alkynes in non-polar aprotic solvents for several hours, then **2a** in toluene was added at O °C. The optimal ratio **2a**/alkyne/trialkylalane was found to be 1/2/3. If only one equivalent of mixed alane was used, only 50 % conversion was observed, showing that one equivalent of organoaluminum species is needed for the generation of the iminium intermediate. Interestingly, increasing the size of alkyl groups led to an improvement of diastereoselectivity (Table).

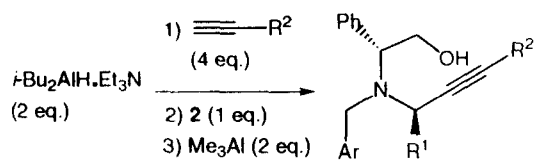


Alkyl	Yield[a] %	d.e.[b] %
Me	93	74
Et	90	83
i-Bu	< 50	94

a) isolated yield . b) Determined by ^1H NMR of the crude reaction mixture

Table

However, when using *i*-Bu3Al, compound **5a** was contaminated with a considerable amount of allylamine (*ca* 50 %) resulting from the hydroalumination of heptyne by *i*-Bu2AlH generated *in situ*. We then tried the Binger's procedure[9] to cleanly generate the alkynylaluminum compounds and avoid this side reaction. However, the resulting *tert*-amine complexes did not react with oxazolidines, probably because the Lewis acidity of the alane was lost. The reactivity of mixed alkynylalanes could be recovered by adding one equivalent of Me3Al to the reaction mixture, after the addition of the oxazolidine. It is possible that this additive shifts the complexation equilibrium towards a Me3Al.Et3N complex and gives back a reactive alkynylalane. Some methylation is observed if Me3Al is added prior to the addition of the oxazolidine . The best results were obtained following the procedure summarized in Scheme 2[10].

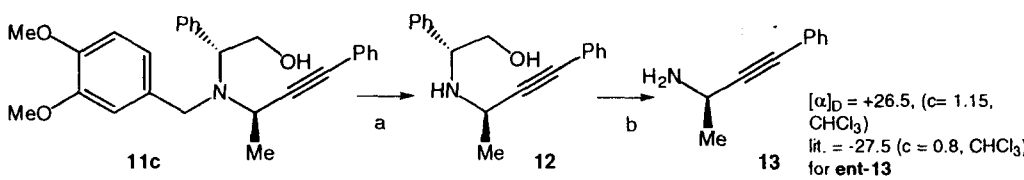


compound	Ar	R^1	R^2	Yield[a] %	d.e.[b] %
5a	Ph	Me	Pent	69	94
6a	Ph	Me	Ph	79	91
7a	Ph	Me	*t*-Bu[c]	69	78
8b	Ph	$(CH_2)_2Ph$	Pent	69	>95
9b	Ph	$(CH_2)_2Ph$	Ph	77	>95
10b	Ph	$(CH_2)_2Ph$	*t*-Bu[c]	72	91
11c	3,4-OMe-Ph	Me	Ph	71	92

a) overall yield from **3**. b) Determined by ^1H NMR of the crude reaction mixture. c) In this case, the alane was prepared by stirring the alkyne and Me_3Al.

Scheme 2.

The absolute configuration of the newly created asymmetric center could not be determined by ^1H NMR. Compound **11c** was therefore deprotected under acidic conditions[11] without any detectable epimerization to give **12** (Scheme 3). As this compound was crystalline, its absolute configuration was determined by crystal structure X-ray analysis (Figure 2)[12].



Scheme 3. *Reagents and conditions* : a) CF_3COOH, anisole, 50 °C, 48 h, 65%; b) H_5IO_6, aq. $MeNH_2$, 68%.

The diastereoselectivity observed is in agreement with the model proposed by Takahashi, Higashiyama and coll. for the opening of oxazolidines with Grignard reagents[13,6].

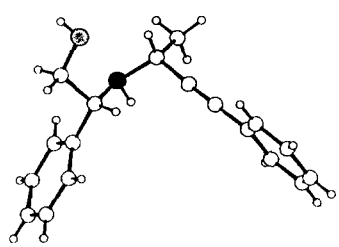
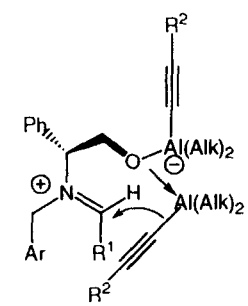


Figure 2. X-ray analysis of compound **12**



Origin of diastereoselectivity

Finally, compound **12** was deprotected by oxydative cleavage using the method developed by Coates and coworkers[14]. The absolute value of the optical rotation of **13** was in good agreement with the previous one reported for **ent-13** by Enders and coll. (Scheme 3)[14a].

In conclusion, a novel and simple route to chiral propargylamines has been reported. Experimental procedure is straightforward, using commercially available reagents and the key step proceeds with good diatereoselectivity and yield at O °C. The extension of this method for the preparation of polysubstituted enantiopure α-alkenyl amines is in progress.

Acknowledgements : One of us (J. B.) thanks the MENRT for a grant.

References and Notes

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[10]. Typical procedure : To a vessel equipped with a reflux condenser under inert atmosphere was added diisobutyl aluminum hydride (10 mL of 1M solution in hexanes) and triethylamine (10 mmol). After 20 min, alkyne (20 mmol) was slowly added. Stirring was maintained under heating (40 °C) for 30 min until hydrogen bubbling stopped. The solution was then cooled (O °C), and oxazolidine **2** (5 mmol) in toluene (15 mL) was added dropwise, followed by Me_3Al (5 mL of 2M solution in hexanes). After 1h at O °C, the mixture was quenched with 25 mL of 6M aqueous NaOH and the organic layer was separated. The aqueous layer was extracted with Et_2O and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude amino-alcohol was purified by flash chromatography on silica gel (EtOAc:Cyclohexane 1:9)

[11]. Phillips GB, Morgan Jr TK, Lumma Jr WC, Gomez RP, Lind JM, Lis R, Argentieri T, Sullivan ME. J. Med. Chem. 1992;35:743-750.

[12]. Compound **12** : Small colourless crystal (0.26 x 0.26 x 0.52 mm) recrystallized from a mixture of cyclohexane/ethyl acetate. C_{18} H_{19} N O, M_W = 265.34, Mp = 78°C. Monoclinic system, space group $P2_1$, Z = 2, a = 11.468 (5), b = 5.849 (5), c = 11.714 (7) Å, β = 107.56 (3)°, V = 749.1 $Å^3$, d_c = 1.176 g cm^{-3}, F(000) = 284, λ (Cu Kα) = 1.5418 Å, μ = 0.56 mm^{-1} ; 2894 data measured (Nonius CAD-4 diffractometer), 2557 unique (Rint = 0.009) of which 2469 considered as observed with I ≥ 2.0 σ(I) ; absorption ignored. The structure was solved by *SHELXS86* and refined by *SHELXL93* . Refinement converged to $R_1(F)$ = 0.0461 for the 2469 observed Fo ≥ 4 σ(Fo) and $wR_2(F^2)$ = 0.1658 for all the 2557 data with goodness-of-fit S = 1.169. In the final difference map, the residual electron density was found between -0.14 and 0.21 $eÅ^{-3}$. Lists of the fractional atomic coordinates, thermal parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file).

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