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Asymmetric synthesis of α-substituted propynyl amines. Application to the preparation of a polysubstituted dihydroisoindoline framework

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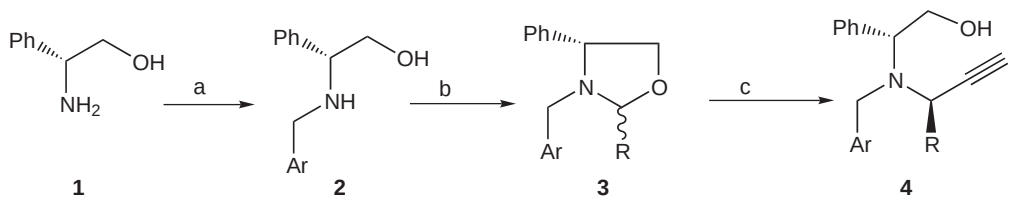
Abstract—A new route towards the asymmetric preparation of α-substituted propynylamines has been developed. The key step involved a diastereoselective addition of diethylalkynylaluminum to oxazolidines derived from *R*-(−)-phenylglycinol. The use of this reaction for the rapid preparation of a polysubstituted isoindoline framework is described.

Enantiopure α-substituted propargylamines are useful synthetic intermediates.[1] Among them, propynyl amines are particularly interesting since they can be further functionalized with the help of the unique acetylide reactivity.[2] Asymmetric synthesis of such derivatives has recently been investigated by Tabor's group, and involved the nucleophilic ring-opening of chiral non-racemic tetrahydro-oxazines with protected acetylenic Grignard reagents under Lewis acidic conditions.[3] This strategy led to the corresponding propargylic amines in moderate to good enantioselectivities, but required the use of 4 equiv. of the expensive trimethylsilylacetylene.

We recently described a new route towards the asymmetric synthesis of α-substituted propargylic amines, based on the diastereoselective opening of chiral non-racemic oxazolidines by mixed organoaluminum compounds. The use of dialkylalkynyl alanes proved to be essential to get high diastereoselectivities and chemical yields without requiring low temperature conditions.[4]

We report in this paper our work on the preparation of α-substituted propynyl amines using mixed organoaluminum compounds as nucleophiles, and their transformation into polysubstituted dihydroisoindolines.

Oxazolidines **3** were prepared as previously described and used without any purification for the alkynylation step (Scheme 1). Unprotected diethylethynylaluminum was prepared by a simple transmetallation from the inexpensive, commercially available sodium acetylide with diethylaluminum chloride.[5] Compounds **4a–g** were obtained in good overall yield, with moderate to good diastereoselectivity[6] (Table 1).



Scheme 1. *Reagents and conditions*: (a) ArCHO, $NaBH_4$, MeOH, 12 h; (b) RCHO, $MgSO_4$, CH_2Cl_2, Δ, 1 h; (c) $HC{\equiv}CAlEt_2$ (3 equiv.), toluene, −10°C.

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Table 1.

Compound	Ar	R	Yield (%)[a]	d.e. (%)[b]
4a	Ph	Me	92[c]	66
4b	Ph	CH_2CH_2Ph	84	79
4c	Ferrocenyl	Me	80[c]	66
4d	Ferrocenyl	CH_2CH_2Ph	64	82
4e	2-Furyl	Me	81[c]	72
4f	2-Furyl	*i*Pr	87	>97
4g	2-Furyl	Ph	66	>97

[a] Overall yield of diastereomerically pure compound from **1**.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Yield of diastereomeric mixture.

The absolute configuration of the newly created asymmetric center was established according to our previous results with mixed organoaluminum compounds as nucleophiles.[4]

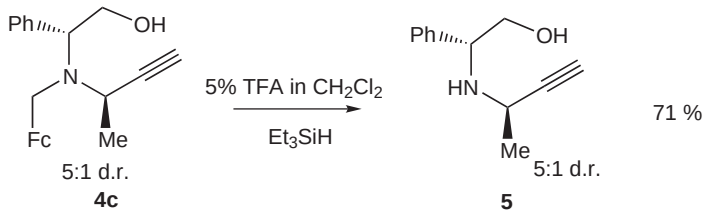
As previously observed, the methylene ferrocenyl protective group can be easily removed without any racemization (Scheme 2).

Moreover, propynyl amines **4** can be further functionalized using the terminal acetylenic reactivity. As an example, compounds **4e**,**f** could be selectively *O*-protected and *C*-carboxymethylated without any epimerization (Scheme 3). Compounds **6e**,**f** were not purified at this step, since they rapidly underwent an intramolecular furyl Diels–Alder (IMDAF) cycloaddition.[7] Completion of this reaction could be obtained after 76 h in toluene at 50°C. Under these conditions, compound **4f** led to cycloadduct **7f** as a single diastereomer and the diastereomeric mixture of compounds **4e** led to diastereomerically pure adduct **7e** after chromatographic purification.

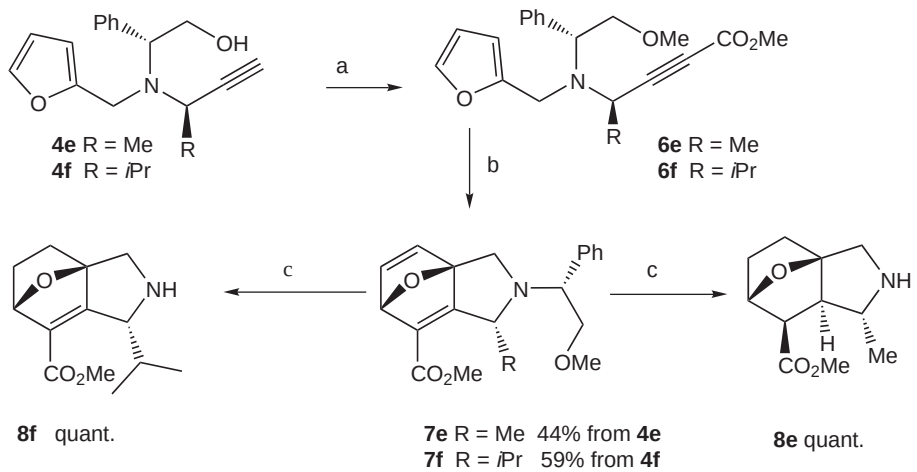
Cycloadducts could be hydrogenated and *N*-deprotected in the same step in a quantitative yield, leading to perhydroisoindoline **8e** from **7e**. Reduction of the most hindered double bound of isopropyl-substituted derivative **7f** did not occur under the same conditions.

Relative configuration of compound **8e** could be established by NOE experiments, showing that hydrogenation occurred from the less hindered face of the *trans* bicyclic cycloadduct. The excellent diastereoselectivity of the IMDAF reaction can be explained by the reversibility of this reaction, leading to the most stable *trans* compound under thermodynamic conditions.[8]

In conclusion, unprotected diethylethynylaluminum reacts in an efficient and diastereoselective manner with chiral non-racemic oxazolidines, leading to α-substituted propynyl amines. These synthetic intermediates can be used for the preparation of more elaborate molecules. As an example, polysubstituted isoindolines derivatives could be obtained in enantiomerically pure form via a highly stereoselective intramolecular Diels–Alder reaction. These isoindolines can act as chiral building blocks for the elaboration of biologically active compounds.



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) (i) NaH, MeI, THF, 3 h, (ii) MeLi, ClCOOMe, 30 min; (b) toluene, 50°C, 72 h; (c) H_2, Pd/C, MeOH, 8 h.

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6. General procedure (the preparation of **7f** is representative): To a cold (−10°C) solution of diethylaluminum chloride (20 mL, 1 M in hexane, 20 mmol) was slowly added sodium acetylide (7.4 mL, 18% wt. slurry in xylene, 4 equiv.) under argon. The resulting mixture was stirred for 2 h at rt, cooled at −10°C and oxazolidine **3f** (1.82 g, 6.73 mmol) in toluene (10 mL) was dropwise added. After stirring for 1 h, the solution was transferred to a 1 M Rochelle salts water solution (50 mL). The aqueous layer was extracted twice with diethylether (50 mL) and the combined organic layers were washed with a saturated NaCl aqueous solution, dried over magnesium sulfate and evaporated. The crude reaction mixture was purified by column chromatography (silica gel, 9/1 cyclohexane/ethyl acetate) to furnish 1.83 g of **4f** (91%, 87% from phenylglycinol **1**). Compound **7f** (colorless oil): $[\alpha]_D = +55$ (*c* 0.8, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 7.28 (m, 6H), 6.29 (dd, $J = 3.3$, 1.9 Hz, 1H), 6.14 (d, $J = 3.3$ Hz, 1H), 4.02 (m, 3H), 3.89 (d, $J = 15.4$ Hz, 1H), 3.79 (d, $J = 15.4$ Hz, 1H), 3.13 (dd, $J = 10.1$, 2.2 Hz, 1H), 2.55 (br s, 1H), 2.29 (d, $J = 2.2$ Hz, 1H), 1.68 (m, 1H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 153.7, 141.6, 138.8, 128.8, 127.9, 127.3, 110.2, 107.9, 83.1, 73.9, 66.9, 61.9, 61.9, 59.8, 43.5, 32.0, 20.3, 19.6. MS (NH_3): 298 (MH^+).
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