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Diastereoselective addition of terminal alkynes to chiral nitrones: asymmetric synthesis of propargylic *N*-hydroxylamines

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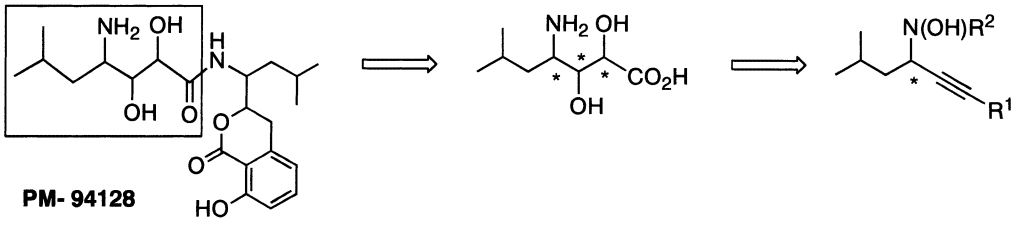
Abstract—1,3-Asymmetric induction in the Et_2Zn-catalyzed addition of terminal alkynes was studied with nitrones bearing a chiral auxiliary on their nitrogen atom. The obtained propargylic *N*-hydroxylamines were generally isolated in good yields and with satisfactory to excellent diastereoselectivities.

During the course of a program aimed at the development of a general method for the asymmetric synthesis of γ-amino-α,β-functionalized acid derivatives, we considered the direct addition of 3-carbons, highly functionalisable synthons, such as propiolic acid esters or other functionalized terminal alkynes, to the C=N bond of nitrones.[1,2] The obtained functionalized propargylic *N*-hydroxylamines represent versatile intermediates for the synthesis of natural and/or biologically active products.[3] In particular, we are interested in the asymmetric synthesis of PM-94128, a cytotoxic isocoumarin antibiotic extracted from the culture broth of *Bacillus* sp. PhM-PHD-090 isolated from a marine sediment,[4] which showed activity against several tumor cell lines. However, its relative and absolute configurations are still unknown, which calls for the development of an appropriate methodology for its synthesis.

Our group has recently developed a new method for the synthesis of propargylic *N*-hydroxylamines, involving the Et_2Zn-induced addition of various alkynes to nitrones.[5] This reaction proved highly efficient with a variety of alkynes and nitrones, and proceeds under very mild conditions, at room temperature. In the present letter, we describe our work on an asymmetric version of this reaction, for which we have selected as chiral auxiliaries (R* in Scheme 1) β-amino ethers[6] derived from 2-(*S*)-α-phenylglycinol and 2-(*S*)-valinol, and a 2,3:5,6-di-*O*-isopropylidene-protected (D)-mannose derivative developed by Vasella and co-workers.[7] The recent publication by Carreira et al.[8] of results obtained using Vasella's auxiliary prompted us to disclose our own findings.

The (*Z*)-aldonitrones **4**–**5** bearing a chiral auxiliary on their nitrogen atom were prepared in good yields (69–93%) by condensation of isovaleraldehyde with the corresponding *N*-hydroxylamines in the presence of $MgSO_4$ (Scheme 2).[9] For nitrones **4a**–**c**, the required chiral *N*-hydroxylamines were prepared through oxidation of the corresponding amines, in a three-steps procedure[10–12] which proved more efficient (47–73% overall yield) than the previously described direct oxidation with dibenzoyl peroxide.[6,13] Nitrone **5** was obtained from the 2,3:5,6-di-*O*-isopropylidene-protected (D)-mannose oxime[7] and isovaleraldehyde.

With these enantiopure nitrones in hand, we studied their reactivity in the Et_2Zn-induced addition of alkynes, using the conditions developed in our laboratories[5] (Scheme 1, Table 1). As anticipated, the addition of a



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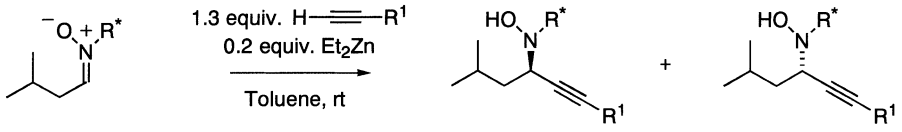
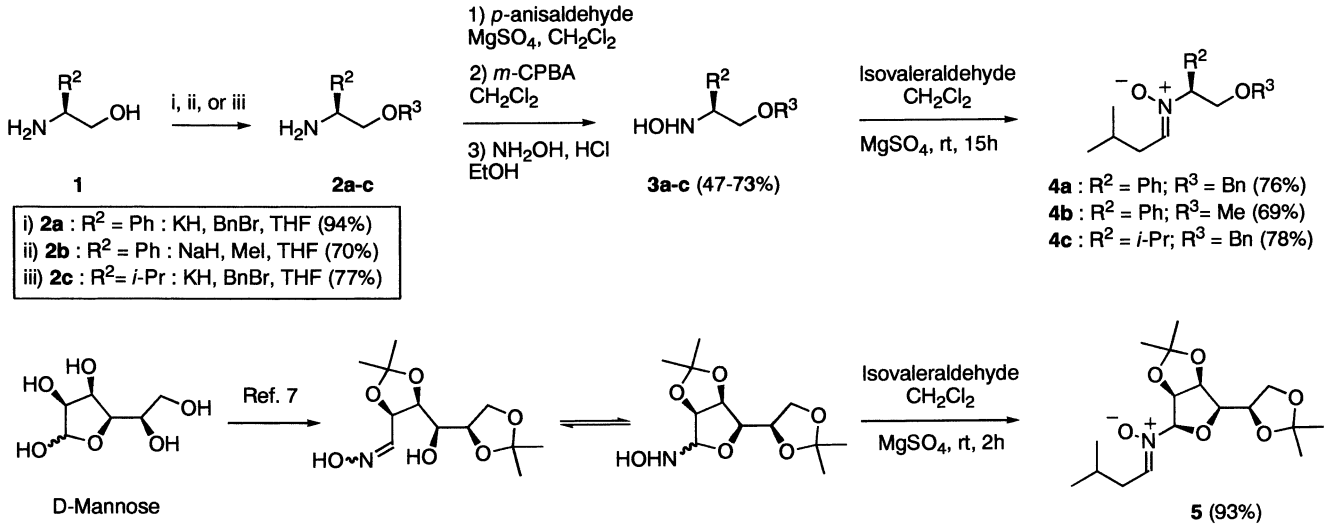


Scheme 1. Diastereoselective Et_2Zn-induced addition of terminal alkynes to chiral nitrones.



Scheme 2. Preparation of chiral nitrones **4**–**5**.

simple alkyne (1-hexyne) to the nitrone **4a** (entry 1) proceeded smoothly to afford the corresponding propargylic *N*-hydroxylamines in excellent yields and with a 88:12 diastereomeric ratio. Then we turned our attention to functional alkynes such as propargylic ethers and alkyl propiolates, and we found that their reaction with nitrone **4a** was equally efficient (entries 2–4). The addition of *t*-butyl propiolate to nitrones (entry 4) is noteworthy as it is *the first example of successful addition of propiolic acid derivatives in non-basic conditions*. This result is remarkable when considering that the corresponding lithium or magnesium organometallic species are known to be unstable above −60°C, and to add sluggishly to electrophiles.

More than the nature of the alkyne, the nature of the chiral auxiliary in the nitrone was found to have a significant effect on the reaction outcome. In particular, steric hindrance on the nitrogen atom seems to limit the efficiency of the reaction. When the (*S*)-valinol-derived nitrone **4c** was used as the substrate (entry 6), the addition of *t*-butyl propiolate (as well as 1-hexyne or 3-methoxy-propyne, not shown in Table 1) was very sluggish, and only traces of the desired adducts were detected after 72 h, along with unreacted nitrone.

The use of *N*-glycosylnitrones was next considered, and nitrone **5** was prepared according to Vasella's procedure. To our delight, it was found that 1-hexyne, propynal diethylacetal, and *t*-butyl propiolate added smoothly to this nitrone (entries 7–9), in short reaction times, and with excellent diastereoselectivities.

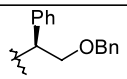
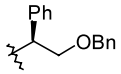
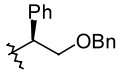
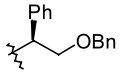
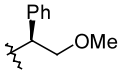
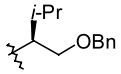
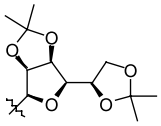
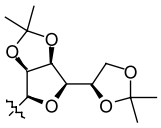
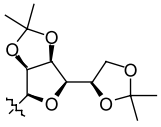
The major diastereomer of the obtained propargylic *N*-hydroxylamines exhibits *R* absolute configuration at the new stereocenter, in all cases. This assignment was ascertained by X-ray analysis of the minor diastereoisomer in one case (entry 4),[†] and was established on the basis of NMR studies in the other cases where β-aminoether auxiliaries were involved (additions to nitrones **4a**–**c**). The chemical shifts of the propargylic proton at the new stereocenter was characteristic, in that it appeared at lower field ($\Delta\delta$ ppm 0.5–0.9) in the major *R* diastereomer when compared to the minor *S* diastereomer. When nitrone **5** was used as the substrate, the absolute configuration of the single *N*-hydroxylamine produced was assumed to be *R*, in comparison with Carreira's report.[8‡]

The formation of a chelated transition state[6] involving the coordination of Zn to an heteroatom of the chiral auxiliary may explain the observed diastereoselectivities in this reaction, preferential attack occuring at the *Si* face of the nitrones.

[†] Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 195172.

[‡] In this paper, the absolute configuration of the products was ascertained by chemical correlation.

Table 1. Et_2Zn-induced addition of terminal alkynes to nitrones **4a–c** and **5**[a]

Entry	R*	R[1]	Time	Diastereoselectivity (d.r.)[b]	Yield[c]
1		C_4H_9	7 h	88:12	96%
2		CH_2OMe	9 h	82:18	91%
3		CH_2O*t*-Bu	8 h	82:18	92%
4		CO_2*t*-Bu	72 h	85:15	80%
5		CO_2*t*-Bu	24 h	55:45	65%
6		CO_2*t*-Bu	72 h	-	Traces
7		C_4H_9	12 h	> 95:5[d]	80%
8		$CH(OEt)_2$	2 h	90:10	80%
9		CO_2*t*-Bu	1 h	-	57% [e]

a) **General procedure:** To a solution of the nitrone (0.5 mmol) and 1-alkyne (0.65 mmol) in dry toluene (2 mL) was added a solution of diethylzinc in hexanes (1M, 100 μL, 0.1 mmol). The mixture was stirred at room temperature during the indicated time. The mixture was then hydrolyzed by addition of a saturated aqueous solution of sodium hydrogenocarbonate (4 mL) and extracted with diethyl ether (2x10 mL). The organic layers were washed with brine (3x15 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by chromatography on silica gel using 20% ethyl acetate in pentane as eluent afforded the pure propargylic *N*-hydroxylamines.
b) The diastereomeric ratio (d.r.) was determined by NMR analysis of the crude material.
c) Combined yield of isolated diastereomers after chromatography.
d) Only one diastereoisomer could be detected on the ^1H NMR spectrum of the crude product.
e) Yield in isolated major diastereomer (18% nitrone recovered), after chromatography. The minor diastereomer could not be detected and in this case, d.r. could not be measured on the ^1H NMR spectrum of the crude product.

In conclusion, we report an efficient asymmetric synthesis of functional propargylic *N*-hydroxylamines and γ-*N*-hydroxy-amino-α,β-acetylenic esters, under mild conditions. The chiral auxiliaries can be readily cleaved.[6,8] We are currently working on further elaboration of these enantiopure propargylic *N*-hydroxylamines, for the synthesis of γ-amino-α,β-acetylenic, γ-amino-α,β-ethylenic, and γ-amino-α,β-dihydroxy acids.

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