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$ZnCl_2$-Mediated Stereoselective Addition of Terminal Alkynes to D-(+)-Mannofuranosyl Nitrones

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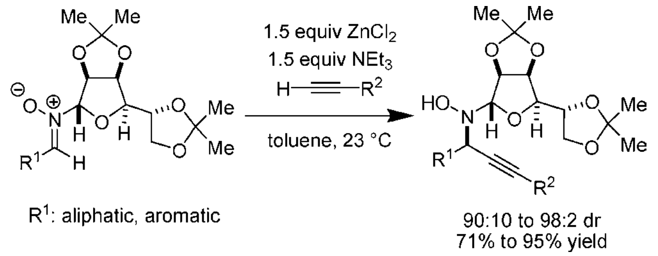
ABSTRACT



An optimized process for the addition of terminal alkynes to chiral nitrones using $ZnCl_2$ and NEt_3 in toluene is reported. The new reaction protocol is facile to perform and cost-effective. The resulting optically active propargyl *N*-hydroxylamines are isolated in good to excellent yield and high diastereoselectivity.

Optically active propargyl *N*-hydroxylamines can serve as versatile building blocks for asymmetric synthesis.[1] They are readily converted to amines and are amenable to further synthetic elaborations, such as cyclization to furnish 2,3-dihydroisoxazoles.[2] Recently, we reported the first general process for the preparation of optically active propargyl *N*-hydroxylamines.[3] The method prescribes the use of chiral nitrones[4] with a broad range of terminal acetylenes in the presence of $Zn(OTf)_2$, NEt_3, and *N*,*N*-dimethylethanolamine. After addition, the chiral controlling group is easily removed by treating the products with *N*-hydroxylamine hydrochloride, a process allowing reisolation and reuse of the auxiliary.[5]

Our continuing interest in the chemistry of metal alkynylides[3,6] prepared in situ from terminal alkynes led us to search for alternative sources of Zn(II). A preliminary screening revealed that rigorously dried $ZnCl_2$ is capable of inducing the addition of terminal alkynes to *N*-benzylnitrones. However, unexpectedly, most of the product propargyl

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[1] For a review, see: (a) Aschwanden, P.; Carreira, E. M. Addition of Terminal Acetylides to C═O and C═N Electrophiles. In *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley: Weinheim, 2005.

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[4] (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273. (b) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103. (c) For a detailed review on the use of monosaccharides as chiral auxiliaries for asymmetric synthesis, see: Hale, K. J. Monosaccharides: Use in Synthesis as Chiral Templates. In *Second Supplements to the 2nd Editon of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1993; Vol. IE/F/G, Chapter 23b, p 273.

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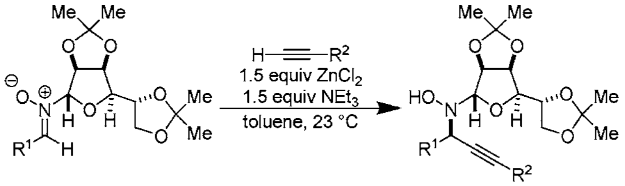
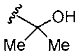
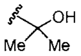
Table 1. $ZnCl_2$-Induced Diastereoselective Addition of Alkynes to *N*-Mannofuranosylnitrones[a]



entry	R^1	R^2	time	yield	dr[b]
1	Me	$SiMe_3$	15 h	95%	90:10
2	*i*Pr	$SiMe_3$	15 h	92%	94:6
3	*t*Bu	$SiMe_3$	15 h	88%	98:2
4	*c*-propyl	$SiMe_3$	15 h	92%	96:4
5	*c*-hexyl	$SiMe_3$	15 h	94%	98:2
6[c]	Ph	$SiMe_3$	15 h	71%	98:2
7[d]	Me		15 h	94%	94:6
8[d]	*c*-hexyl		15 h	93%	98:2
9	*c*-hexyl	Ph	15 h	91%	98:2

[a] A 10-mL Schlenk tube charged with $ZnCl_2$ (102 mg, 0.750 mmol, 1.50 equiv) was put under vacuo and heated to 100−200 °C (heat gun) for 3 min. After the tube was cooled to 23 °C, nitrone (0.500 mmol, 1.00 equiv) and solvent (1.0 mL) were added. The resulting mixture was stirred until a homogeneous solution was obtained. TMS-acetylene (74 mg, 0.75 mmol, 1.5 equiv) and NEt_3 (76 mg, 0.75 mmol, 1.5 equiv) were added via syringe, and the resulting solution was stirred at 23 °C for 15 h. Upon completion, the reaction was quenched with aq NH_4Cl (3.0 mL). Workup and purification by chromatography on silica gel afforded the pure propargyl *N*-hydroxylamines. [b] Diastereomeric ratios (dr) were determined by ^1H NMR analysis. [c] Toluene/CH_2Cl_2 = 2:1 used as solvent. [d] Alkyne used as solvent.

N-benzylhydroxylamines were prone to cyclization in the presence of $ZnCl_2$, affording the corresponding 2,3-dihydroisoxazoles.[2] Interestingly, the use of TMS-acetylene under these novel reaction conditions led to the desired propargyl *N*-benzylhydroxylamines as the sole product. It is likely that this results from the bulk of the silyl group, which prevents cyclization.

The addition of TMS-acetylene to the chiral *N*-mannofuranosylnitrone derived from cyclohexanecarboxaldehyde was employed as a test substrate in the examination and optimization of the reaction conditions. Due to the low boiling point of TMS-acetylene (52 °C), a slight excess (1.5 equiv) was used to provide optimal yields. The results with this substrate revealed that $ZnCl_2$ conveniently affords optically active propargyl *N*-hydroxylamines in 94% yield and 98:2 diastereoselectivity. In contrast to the procedure employing $Zn(OTf)_2$, homogeneous reaction solutions were now observed, rendering unnecessary the need for an additional ligand, such as *N*,*N*-dimethylethanolamine, which we had previously prescribed. The best diastereoselectivity was observed using toluene as solvent, which additionally provides the benefit of being an environmentally more friendly system than the initially published process which employed dichloromethane.

The optimized reaction conditions were applied to a wide range of nitrones affording the desired propargyl *N*-hydroxylamines in good to excellent yield and high diastereoselectivity (Table 1). In a typical reaction, powdered and dried $ZnCl_2$ (98% ACS reagent), D-(+)-mannofuranosyl nitrone, TMS-acetylene, and NEt_3 were stirred in toluene at 23 °C for 15 h. Acidic workup (NH_4Cl) and purification by flash chromatography on silica gel afforded the desired optically active propargyl *N*-hydroxylamines. The chiral nitrone derived from benzaldehyde (Table 1, entry 6) proved to be insoluble in toluene. Therefore, a mixture of toluene/CH_2Cl_2 = 2:1 was used as solvent, affording the desired propargyl *N*-hydroxylamine in acceptable yield and excellent diastereoselectivity. In reactions involving the inexpensive 2-methyl-3-butyne-2-ol, the alkyne could be utilized as the solvent, affording higher yields than the standard protocol (Table 1, entries 7 and 8).

In summary, we have developed an optimized process for the diastereoselective addition of terminal alkynes to chiral nitrones using $ZnCl_2$ and NEt_3 in toluene. The new reaction protocol has considerable advantages over that initially described as it is facile to perform, cost-effective, and environmentally friendly. The resulting optically active propargyl *N*-hydroxylamines are isolated in good to excellent yield and high diastereoselectivity and are potentially highly versatile building blocks for organic synthesis, following removal of the labile auxiliary.[3] In a broader context, the observations underscore the ability of simple Zn(II) salts to participate in alkyne activation and nucleophilic additions. This sets the stage for further investigations, the results of which will be reported as they become available.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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