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First Synthesis of Optically Pure Propargylic *N*-Hydroxylamines by Direct, Highly Diastereoselective Addition of Terminal Alkynes to Nitrones**

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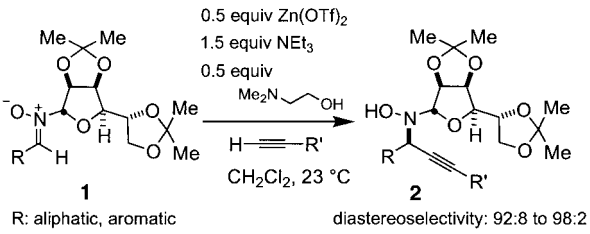
Dedicated to Professor Andrea Vasella

Optically active propargylic alcohols serve as versatile building blocks for asymmetric synthesis.[1] The corresponding propargylic amines or *N*-hydroxylamines could also serve in a similar capacity were it not for the fact that general, useful methods that provide access to such compounds are not available.[2] The latter are not only synthetic equivalents of the former, but also are amenable to further elaborations, such as cyclization to afford isoxazolines.[3] Herein, we document the first general method for the preparation of optically active propargylic *N*-hydroxylamines [Eq. (1), Tf = trifluoromethanesulfonyl]. The method prescribes the use of nitrones which are conveniently prepared through condensation of the corresponding aldehydes and a mannose-derived glycosidic *N*-hydroxylamine.[4] Reaction of the nitrones with a broad range of terminal acetylenes in the presence of Zn^{II} ions, 2-dimethylaminoethanol, and NEt_3 gives adducts in high diastereoselectivity and yield. Following its addition, the auxiliary is easily removed by treatment of the products with *N*-hydroxylamine hydrochloride; a process which allows for re-isolation and reuse of the auxiliary. The method we document should find use in medicinal chemistry to provide access to a new class of useful building blocks for the asymmetric synthesis of pharmacologically important compounds.



(1)

There are scant, scattered reports that document diastereoselective additions to chiral nitrones. These typically involve additions of Grignard or organolithium compounds

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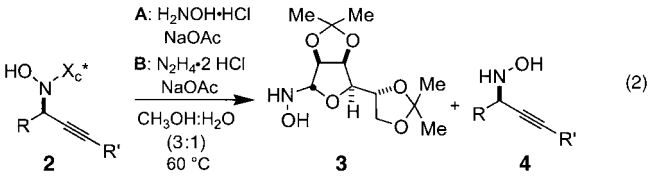
to chiral starting materials, and are limited in scope.[4b,5–8] Moreover, because they are generally single-substrate studies, the generality of these additions as a means to provide broad access to chiral *N*-hydroxylamines is unclear.

We recently reported a method for the catalytic in situ generation of Zn^{II}–alkynilides and their addition to achiral nitrones.[9] Accordingly, we were interested in extending the methodology to include an asymmetric version. Preliminary screening of auxiliaries for use in diastereoselective nitrone additions led us to single out carbohydrate-based structures, such as **3**, derived from mannose, acetone, and *N*-hydroxylamine.

The use of *N*-glycoside-derived nitrones and in particular those prepared from mannose were deemed attractive on account of: 1) the preparation of the glycosidic *N*-hydroxylamines from inexpensive starting materials has been shown to be straightforward (two steps, 85%); 2) addition reactions of phosphinates to such nitrones have been shown to furnish a limited number of aminophosphinic acids in high diastereoselectivity;[5a,b] and 3) after the addition reaction, the auxiliary **3** is easily removed and recycled [Eq. (2), X_C^* = chiral auxillary].[5c]



(2)

The requisite nitrones for study (**1**) were conveniently prepared by treating a solution of glycosyl *N*-hydroxylamine **3** and aldehyde in CH_2Cl_2 with a desiccant such as Na_2SO_4 or $MgSO_4$. As shown in Table 1, the additions can be carried out on a wide variety of branched, unbranched, aromatic, and C-substituted nitrones as well as with an equally broad range of terminal alkynes. Thus, treatment of a solution of a terminal alkyne and a nitrone **1** with 0.5 equivalents of $Zn(OTf)_2$, 0.5 equivalents of 2-dimethylaminoethanol, and 1.5 equivalents of NEt_3 in CH_2Cl_2 (0.33 M) at 23 °C affords adducts **2** in up to 99% yield and excellent diastereomeric ratios ranging from 92:8 to 98:2.[10,11] In the course of optimization studies, we observed that the use of 2-dimethylaminoethanol was beneficial, because not only did its use lead to enhanced reaction rates (fivefold), it also furnished homogenous solutions throughout the course of the reaction.

A convenient aspect of the process is the fact that removal of the auxiliary is effected upon heating a MeOH:H_2O (3:1) solution of adducts **2** with 1.6 equivalents of $H_2NOH{\cdot}HCl$ and 1.5 equivalents of NaOAc at 50–60 °C (Table 2, method A).[5c] In certain cases (entries 1 and 6) more forcing conditions were necessary to effect removal of the auxiliary, wherein $N_2H_4{\cdot}2\,HCl$ was substituted for $H_2NOH{\cdot}HCl$ (Table 2, method B). Optically active propargylic *N*-hydroxylamines **4** can be isolated in useful yields by using either method.

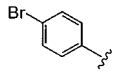
In summary, we report a novel, general, practical method for the highly stereoselective synthesis of optically active secondary propargylic *N*-hydroxylamines. A key salient feature of this process is the fact that a wide range of terminal acetylenes and nitrones participate in additions under conditions where the nucleophilic alkynilides are generated in situ by utilizing substoichiometric amounts of $Zn(OTf)_2$; as such, the terminal alkynes were used directly without

Table 1. Diastereoselective additions of in situ generated Zn^{II}–alkynilides to nitrones **1**.[a]

Entry	R	R′	Yield [%]	*dr*[b]
1	Me	Ph	88	95:5
2		$Ph(CH_2)_2$	45	96:4[c]
3			99	95:5[d]
4		Me_3Si	75	92:8
5		n-C_4H_9	80	97:3[e]
6	*i*Pr	Ph	89	92:8
7		$Ph(CH_2)_2$	87	97:3
8			98	96:4[d]
9			94	96:4
10	c-C_6H_{11}	Ph	91	94:6
11		$Ph(CH_2)_2$	91	95:5
12			94	93:7[d]
13		n-C_4H_9	82	98:2
14	c-C_3H_5	Ph	92	94:6
15		$Ph(CH_2)_2$	73	96:4
16			54	96:4
17	*t*Bu	Ph	91	97:3
18	Ph	Ph	82	95:5[f,g]
19		Me_3Si	88	95:5[g]
20			83	95:5[d,g]
21		Ph	79	95:5

[a] Addition reactions were conducted as described in the text. For additional details, see the Supporting Information. [b] The diastereomeric ratio of the adducts was assayed by ^1H NMR spectroscopy. [c] The corresponding isoxazoline, generated by cyclization of the adduct, was isolated as the main product in 48% yield. [d] 2-Methyl-3-butyne-2-ol was utilized as the solvent, and gave much higher yields than the standard reaction protocols (entry 16). [e] Besides the product (80%), 12% of the corresponding isoxazoline was isolated. [f] In the course of the reaction, the adduct entirely cyclized to the corresponding isoxazoline which was then isolated. [g] The reaction was conducted using $Zn(OTf)_2$ (1.1 equiv), NEt_3 (1.5 equiv), and 2-dimethylaminoethanol (1.1 equiv).

Table 2. Cleavage of the auxiliary and generation of **4**.[a]

Entry	R	R′	*t* [h]	Method	Yield [%]
1	Me	Ph	4.5	**B**	99
2		Me_3Si	3	**A**	86
3	*i*Pr	Ph	1.5	**A**	96
4			4.5	**A**	95
5	Ph	Me_3Si	2	**A**	85
6	Ph		3.5	**B**	73[b]
7	Me		1	**A**	54[b]

[a] For reaction conditions, see text. [b] The moderate yield in entries 6 and 7 is caused by the high polarity and low stability of the product. The work-up and isolation procedures are currently being optimized.

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requiring a separate deprotonation or activation step. Given the fact that acetylenes are readily and conveniently converted into numerous other functional groups, the method provides access to a large range of *N*-hydroxylamines in optically active form for the first time. Such compounds are of increasing importance in medicinal chemistry, where the corresponding hydroxamic acids, for example, have been shown to possess potent broad-spectrum activities against matrix metalloproteases and tumor necrosis factor α (TNF-α) converting enzymes.[12]

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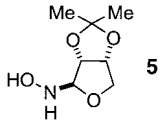
[10] Nitrones bearing the erythronolactone-derived auxiliary **5** furnished the addition products with opposite absolute configurations in comparable yield and stereoselectivity.



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[11] The absolute configuration of the products was determined by conversion of the propargylic *N*-hydroxylamine adducts (entries 1, 6, and 19, Table 1) into the corresponding *N*-(2-naphthoyl)alanine, -valine, and -phenylglycine derivatives, which were compared against authentic standards.

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A Stoichiometric Aromatic C–H Borylation Catalyzed by Iridium(I)/2,2′-Bipyridine Complexes at Room Temperature

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Increasing attention has been devoted to the direct functionalization of unreactive hydrocarbons by metal-catalyzed reactions because of their wide availability and low cost.[1] A recently developed protocol for hydrocarbon functionalization provides a convenient and direct method for the synthesis of arylboron compounds by the C–H borylation of arenes by bis(pinacolato)diboron (pin_2B_2, $pin = Me_4C_2O_2$) or pinacolborane (pinBH) catalyzed by $[Cp^*Ir(PMe_3)(H)(Bpin)]$ ($Cp^* = \eta^5$-C_5Me_5),[2] $[Cp^*Re(CO)_3]$,[3] $[Cp^*Rh(\eta^4$-$C_6Me_6)]$,[4] $[RhCl(PiPr_3)_2(N_2)]$,[5] $[(Cp^*RhCl_2)_2]$,[5] $[(\eta^5$-$C_9H_7)Ir(cod)]$/dppe or dmpe (cod = 1,5-cyclooctadiene; dppe = 1,2-bis(diphenylphosphanyl)ethane; dmpe = 1,2-bis(dimethylphosphanyl)ethane),[6] and 1/2$[IrCl(cod)]_2$/2,2′-bipyridine.[7] Among them, iridium(I) complexes generated from $[\{IrCl(cod)\}_2]$ and 2,2′-bipyridine (bpy) exhibited exceptionally high catalyst activity and turnover numbers in neat arene substrate at 80 °C.[7] Moreover, the combination of $[IrCl(coe)_2]_2$ (coe = cyclooctene) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) catalyzed the same reaction at room temperature.[7] We report here the development of catalysts that allow for the first time the direct borylation of arenes or heteroarenes at room temperature in an inert solvent with a stoichiometric ratio of pin_2B_2[8] (**1**) to arene (**2**) to produce the corresponding arylboronates (**3**) in high yields (Scheme 1).

During subsequent studies of the aromatic C–H borylation, we found that the effect of varying the anionic ligands (X) on iridium(I) precursors could provide a greater effect on catalyst

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