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Addition of functional vinylzinc reagents to nitrones: synthesis of (*E*)-*N*-allylhydroxylamines and their rearrangement into (*E*)-*O*-allylhydroxylamines

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The vinylzinc reagents derived from hydrozirconation of alkynes and transmetallation add readily to nitrones to yield pure (*E*)-*N*-allylhydroxylamines; some of these rearrange into *O*-allylhydroxylamines.

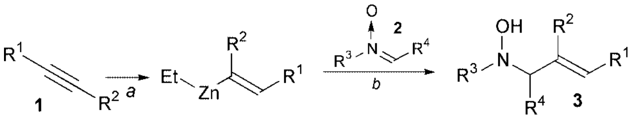
In the course of our studies on nitrones,[1] we became interested in obtaining (*E*)-allylic *N*-hydroxylamines by the addition of organometallic reagents onto nitrones.

In the past, addition of organolithium or organomagnesium reagents onto C=N bonds[2] was studied to a much lesser extent than the corresponding addition onto carbonyl functions, the major reason being that imines are less prone to nucleophilic addition and more prone to deprotonation. In recent years, there has been a renewed interest in the addition of organometallics onto C=N double bonds because of both the availability of more selective organotransition reagents, and the use of more reactive C=N species. Among the latter, nitrones appear to be an interesting choice as precursors. They are reactive, readily available and stable. Indeed, recent work has dealt with the addition of alkyl,[3] allyl[4] and alkynyl[3,5] lithium, magnesium and zinc reagents onto nitrones.

Comparatively fewer examples of the addition of vinylic organometallics to C=N bonds have been described. Imines do, however, react readily with vinylzinc compounds.[6] It has also been shown that vinylmagnesium bromide adds to tosyl imines.[7] Furthermore, it was demonstrated[8] that vinylmagnesium bromide adds rapidly to nitrones. These results were extended to diastereoselective additions onto chiral nitrones[9] but the results were limited to the simplest ethenyl organometallic reagent.

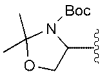
For our study, we needed adducts from γ-functionalized, pure *E*, vinylmetallic species. Thus, we decided to prepare these reagents according to Wipf's procedure:[10] hydrozirconation of alkynes followed by transmetallation to the (*E*)-vinylzinc species. We found that the resultant organometallic reagents add readily onto nitrones, under mild conditions, to give secondary *N*-hydroxylamines in good yields† (Scheme 1, Table 1).

As expected, only the *E* configuration was observed in the double bond of all the products. Also, excellent conversions were obtained for the addition of the vinylzinc species derived from hex-1-yne onto a variety of nitrones **2**. Steric hindrance in the nitrone (entry **g**, 39% conversion) is a limitation. The more hindered vinylzinc reagent derived from hex-3-yne led to incomplete conversion (entry **h**), and the formation of *N*-benzyl-*N*-(1-phenylpropyl)hydroxylamine (10%), resulting from ethylzinc addition, accompanied the allylic product **3h**. Addition onto the chiral nitrone **2d** led to moderate diastereoselectivity at 0 °C. Functionalized alkynes can also be used in this protocol. The pivalate-protected but-3-yn-1-ol led readily to **3i** and **3j**. In other examples however, the ω-cyanoalkyne (entry **k**), the *O*-protected propynol[11] (entries **l**, **m**, **n**, **o**) and the



Scheme 1 *Reagents and conditions*: (*a*) Cp_2ZrHCl, CH_2Cl_2, rt, 1 h; vacuum; Et_2Zn, CH_2Cl_2, −65 to 0 °C; (*b*) CH_2Cl_2, 0 °C, 6 h.

Table 1 Preparation of *N*-allylhydroxylamines

	Alkyne **1**		Nitrone **2**			
Entry	R^1	R^2	R^3	R^4	Conv. of **2** (%)[a]	Isolated yield (%)
a	*n*-Bu	H	$PhCH_2$	Ph	>95	62
b	*n*-Bu	H	*p*-CF_3PhCH_2	Ph	>95	70
c	*n*-Bu	H	*p*-CF_3PhCH_2	Me	>95	58
d	*n*-Bu	H	$PhCH_2$		>95	83 de 72%
e	*n*-Bu	H	Ph	*p*-MeO-Ph	>95	62[c]
f	*n*-Bu	H	*p*-Tolyl	Ph	>95	50[c]
g	*n*-Bu	H	*t*-Bu	Ph	39	29[c]
h	Et	Et	$PhCH_2$	Ph	40	30
i	PivO-$(CH_2)_2$-	H	$PhCH_2$	Ph	>95	58
j	PivO-$(CH_2)_2$-	H	$PhCH_2$	*i*-Pr	>95	60[b]
k	NC-$(CH_2)_3$-	H	$PhCH_2$	Ph	75	5[b]
l	TMSO-CH_2-	H	$PhCH_2$	Ph	90	32[b]
m	TMSO-CH_2-	H	Ph	*p*-MeO-Ph	>95	30[c]
n	MeO-CH_2-	H	$PhCH_2$	Ph	50	35[b]
o	MeO-CH_2-	H	Ph	*p*-MeO-Ph	>95	40[c]
p	$(EtO)_2CH$-	H	$PhCH_2$	Ph	46	16
q	Ph	H	$PhCH_2$	Ph	90	0[d]

[a] Estimated from NMR of the crude product. [b] A significant amount of alkynyl adduct was also isolated, see text. [c] Isolated as the isomeric form **4**, see text. [d] Only alkynyl adduct, 50% yield.

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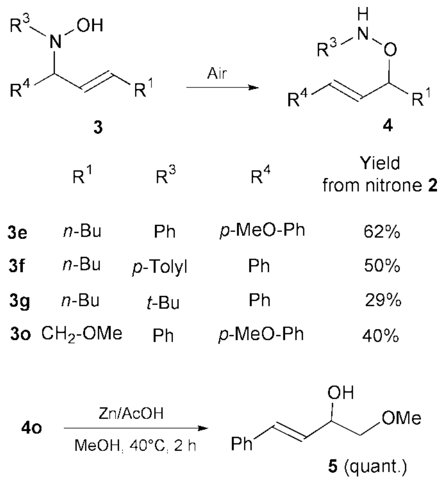

	R^1	R^3	R^4	Yield from nitrone **2**
3e	*n*-Bu	Ph	*p*-MeO-Ph	62%
3f	*n*-Bu	*p*-Tolyl	Ph	50%
3g	*n*-Bu	*t*-Bu	Ph	29%
3o	CH_2-OMe	Ph	*p*-MeO-Ph	40%

Scheme 2 Rearrangement of *N*-allylhydroxylamines **3**.

phenylacetylene (entry **q**) all yielded substoichiometric amounts of vinylzinc reagent, presumably due to a less efficient hydrozirconation step. In these runs, the conversions of nitrones **2** were incomplete, and the expected products **3** were contaminated with *N*-propargylhydroxylamines,‡ derived from the addition of the alkyne **1** onto the nitrone **2**.§

All the vinyl adducts freshly obtained from this procedure were the expected (*E*)-*N*-allylhydroxylamines **3**. Surprisingly however, we observed that on standing (at room temperature), some of the samples (neat or in $CDCl_3$ solutions) isomerized slowly, with allylic transposition, to yield (*E*)-*O*-allylhydroxylamines **4** (Scheme 2). This process occurs particularly readily for *N*-arylhydroxylamines. In these cases, the rearrangement was complete within 24 h at 20 °C and consequently, the rearranged adducts were isolated after completion of this step (entries **e**, **f**, **m**, **o**). This rearrangement also occurred in the case of *N*-*tert*-butylhydroxylamine **3g**. The structure of **4o** was confirmed by its reduction to the (*E*)-allylic alcohol **5** (Zn, AcOH–MeOH 1 : 9, 40 °C, 2 h, quant.).

To our knowledge, this rearrangement has not been previously described, although it can be related with several observations, involving allylic N–O bonds, including the Meisenheimer rearrangement of tertiary amine *N*-oxides.[12]

We observed qualitatively that the rate of this rearrangement depends strongly on the nitrogen atom substitution: Aryl > *t*-Bu >> Bn. Several observations hint at a radical mechanism. First, the reaction seems to be initiated by air: in an early experiment, we observed a 50 : 50 mixture of **3o** and **4o** 2 h after working-up the reaction. We repeated the experiment, using for the hydrolytic work-up freshly distilled solvents and freshly boiled water phases, and handling the crude materials with simple anaerobic precautions: the amount of isomer **4o** was then reduced to less than 3% (NMR) of the crude material. Thereafter, exposure to air induced the rearrangement. EPR of the crude materials during isomerization showed a strong signal, with a fine structure consistent with the aminoxyl radical derived from **3**. Obviously, this radical could be the active species, undergoing a Meisenheimer [2,3] rearrangement. We are currently investigating the mechanism, scope, and limitations of this new reaction.

It is important to note that the above isomerization amounted only to traces if the R^3 substituent on the nitrogen atom was a benzyl group: as seen in Table 1, the *N*-benzyl-*N*-allylhydroxylamines **3** can be isolated in good yields. They can be readily reduced to provide the corresponding (*E*)-*N*-benzyl-*N*-allylamines.

In conclusion, we have shown that the sequence: terminal alkyne hydrozirconation, Zr to Zn exchange and addition to nitrones, is a good method to stereoselectively synthesize (*E*)-*N*-allylhydroxylamines, under mild conditions and in good yields. It is noteworthy that this reaction occurs with no need for an external activating agent such as amino-alcohols.[13] We are currently studying an asymmetric version of this reaction by adding chiral zinc ligands to the reaction mixture.

Notes and references

† Typical experimental procedure: to a suspension of zirconocene hydrochloride (1.2 mmol) in CH_2Cl_2 (2 mL) under an N_2 atmosphere at 20 °C was added hex-1-yne (1.8 mmol) using standard Schlenk procedures. The reaction was stirred at 20 °C until a homogeneous solution was formed. All volatiles were then removed under reduced pressure at 20 °C, to give a yellow vinylchlorozirconocene reagent. To the resultant solid was added CH_2Cl_2 (2 mL) and the mixture was cooled to −65 °C. Diethylzinc (1.2 mmol, as a 1.1 M solution in toluene), was added dropwise (over 10 min) at −65 °C and allowed to stir for 15 min at −65 °C. The vessel was then immersed in an ice bath and a solution of (*N*-benzylidene)benzylamine *N*-oxide (1 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 6 h stirring at 0 °C, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL), and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered through a pad of silica. Removal of the solvents under reduced pressure and purification by chromatography (silica, cyclohexane–ethyl acetate 90 : 10) yielded the pure adduct **3**.

‡ The IUPAC name for propargyl is prop-2-ynyl.

§ We found that a mixture of alkyne **1**, nitrone **2** and diethylzinc in CH_2Cl_2 or toluene at rt leads quantitatively to *N*-propargylhydroxylamine adducts, and we are currently studying this reaction. A similar addition of species generated from the reaction of dialkylzinc with terminal alkynes onto aromatic aldehydes has been described previously.[14]

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