Heterocycle Synthesis

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Intramolecular Metalloamination of *N*,*N*-Dimethylhydrazinoalkenes: A Versatile Method to Access Functionalized Piperidines and Pyrrolidines**

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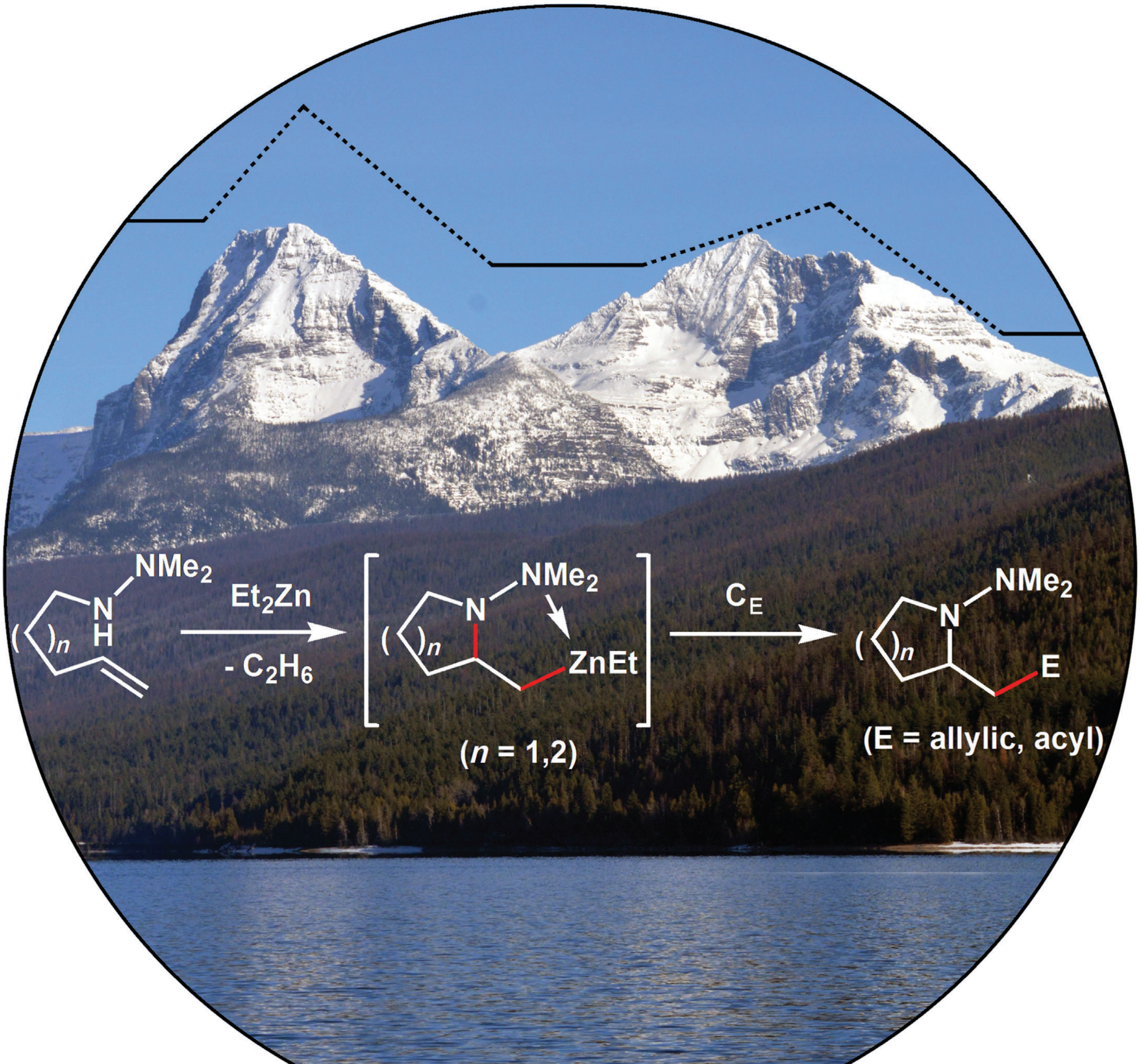
Dedicated to Professor Dr. Reinhard W. Hoffmann on the occasion of his birthday



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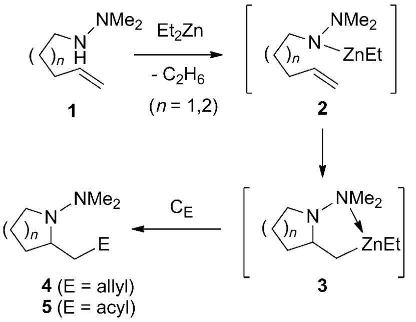
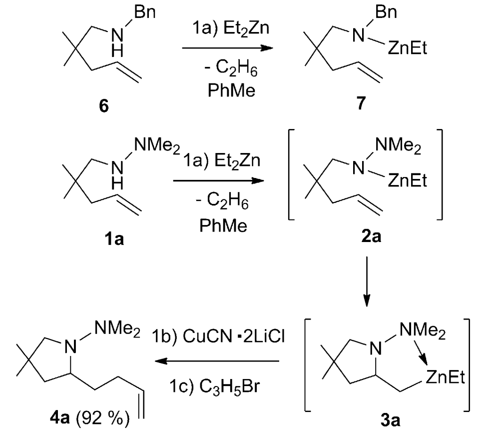
***Abstract:** Highly diastereoselective metalloamination/cyclization reactions of zinc(II) hydrazides obtained through reaction of diethylzinc with N,N-dimethylhydrazinoalkenes are described. The resulting organozinc intermediates undergo facile allylation and acylation, in situ, to provide the corresponding functionalized piperidines and pyrrolidines.*

The catalytic hydroamination/cyclization of aminoalkenes constitutes a synthetic route to nitrogen heterocycles that is endowed with exceptional atom economy.[1] Fairly recently, several cationic Zn^{II} complexes have been shown to have excellent catalytic activity in hydroamination/cyclization reactions.[2] A distinct synthetic disadvantage associated with conventional hydroamination/cyclization rests with the simple delivery of a hydrogen atom to the unsaturated carbon-based addend. Several laboratories have described instances of metalloamination events that lead to consecutive C/N–C–C bond formation. These include transformations that involve either the catalytic utilization of organometallic intermediates derived from Pd^{II},[3a–p] Cu^{II},[3q] Au^{I},[3r] or the stoichiometric use of Ti^{IV} [3s,t] or Zn^{II} intermediates.[3u–w] Due to the fleeting nature of the intermediates in the aforementioned catalytic processes, their overall utility in synthesis suffers from being rather electrophile-limited. In addition, the vast majority of instances involving C–N/C–Ti and carbon–heteroatom/carbon–zinc functionalization rely on a highly exothermic addition to a tethered alkyne.[4] In that sp^3 hybridized C–Zn bonds are subject to functionalization by way of an exceptional number of reliable reactions, the direct metalloamination of alkenes would constitute a valuable addition to organic synthesis. In this Communication, we describe a series of facile alkene metalloamination reactions involving zinc(II) amides generated by the direct metalation of *N,N*-dimethylhydrazinoalkenes with diethylzinc. The resulting organozinc intermediates undergo efficient functionalization with representative carbon-based electrophiles to furnish a variety of piperidines and pyrrolidines (Scheme 1). It is synthetically most relevant that the N–N bond of related hydrazines is subject to facile reductive cleavage under mild conditions using zinc in acetic acid.[5]



Scheme 1. Metalloamination/electrophilic functionalization of hydrazinoalkenes. C$_E$: carbon electrophile.



Scheme 2. Metalloamination/allylation of hydrazinoalkenes.

We initiated this study by examining the prospective metalloamination/cyclization of the Zn^{II} amide obtained from aminoalkene **6** and Et$_2$Zn ([D$_8$]toluene, 110 °C; Scheme 2; only for the initial screening experiments deuterated toluene was used; later it was replaced by toluene). Although the formation of Zn^{II} amide **7** proceeded without incident, further heating led only to decomposition with the deposition of metallic zinc.[6] We next turned to hydrazinoalkene **1a**, based on the premise that the intermediate hydrazide **2a** (or its cyclic dimer) might be more predisposed toward cyclization by virtue of the beneficial formation of an internally coordinated organozinc intermediate of type **3a** (Scheme 2). This indeed proved to be the case as simple heating of **1b** with Et$_2$Zn (1.1 equiv, [D$_8$]toluene, 90 °C) provided **3a** (as evidenced by deuteration, D$_2$O) in $>95\%$ yield (^{1}H NMR). That metalloamination/cyclization was particularly facile was suggested by the absence of any spectroscopic data ascribable to the putative hydrazide intermediate **2a**. The subsequent utilization of organozinc compound **3a** in carbon–carbon bond formation was readily achieved by the direct addition of CuCN·2LiCl[8] (1.5 equiv) followed by allyl bromide (2.5 equiv) to furnish pyrrolidine **4a** (isolated as its trifluoroacetate salt) in 92 % yield overall (Scheme 2).[7] With comparable results, the initial reaction solvent (see below) could be removed under vacuum, followed by the addition of THF, CuCN·2LiCl (1.5 equiv), and an allyl halide (1.2 equiv). Several alternative solvents were examined as media for the metalloamination/cyclization. Of these, (trifluoromethyl)benzene and diisopropyl ether proved satisfactory while the more strongly coordinating ethereal solvent THF suppressed the reaction.

The synthetic scope of this metalloamination/allylation was explored by using a series of *N,N*-dimethylhydrazinoal-

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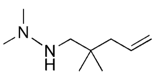
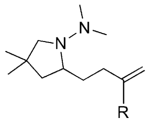
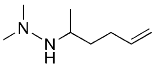
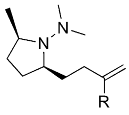
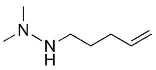
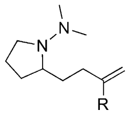
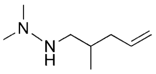
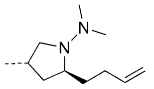
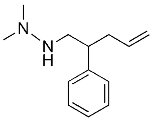
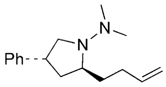
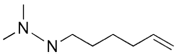
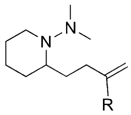
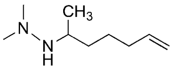
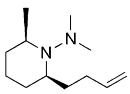
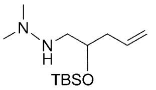
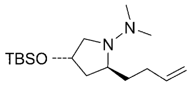
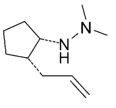
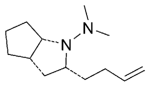
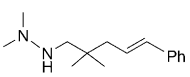
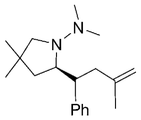
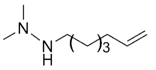
Table 1: Metalloamination/allylation of hydrazinoalkenes.

Hydrazinoalkene		Conversion [%][a]	d.r.	Product		Yield [%][f]
	**1a**	>95 (18 h)[b]	–		**4a**	92 (R=H) 83 (R=Me)
	**1b**	>95 (6 h)[b]	>20:1 (*c*/*t*)		**4b**	81 (R=H) 85 (R=Me)
	**1c**	90 (4 h)[b]	–		**4c**	80 (R=H) 76 (R=Me)
	**1d**	90 (15 h)[c]	1:6 (*c*/*t*)		**4d**	83
	**1e**	90 (24 h)[d]	1:15 (*c*/*t*)		**4e**	83
	**1f**	>95 (3 h)[b]	–		**4f**	93 (R=H) 88 (R=Me)
	**1g**	70 (12 h)[b,e]	9:1 (*c*/*t*)		**4g**	63
	**1h**	90 (8 h)[b]	1:2 (*c*/*t*)		**4h**	83[i]
	**1i**	>95 (16 h)[b]	>20:1 (*c*/*t*)		**4i**	87
	**1j**	90 (24 h)[b]	3:1[g]		**4j**	79[i]
	**1k**	n.r. (3 d)[h]	–	–	–	–

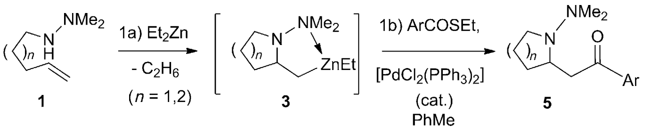
[a] As calculated from ^{1}H NMR spectra utilizing *p*-xylene as an internal standard. [b] Reaction conducted on a 0.1 mmol scale in a 90 °C oil bath with toluene or (trifluoromethyl)benzene as solvent. [c] Reaction conducted at 10 °C. [d] Reaction conducted at 23 °C. [e] Required 2 equiv of $ZnEt_2$. [f] All products were isolated as the TFA salts unless otherwise noted. [g] Stereoselectivity is unoptimized. [h] Cyclization was not observed. [i] Product isolated as the free base.

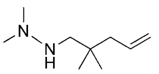
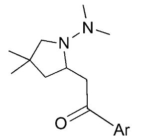
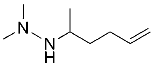
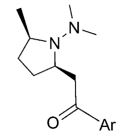
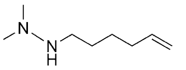
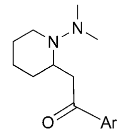
kenes (e.g., **1a**–**1g**) under conditions closely related to those described for the conversion of **1a** to **4a**. The details of this study are summarized in Table 1. The results are noteworthy in several regards, particularly since the yields are excellent in almost all cases. Very significantly, the presence of Thorpe–Ingold conformational acceleration, that is of crucial importance in many hydroamination/cyclization reactions, is not at all a prerequisite for this metalloamination/cyclization being successful. Two striking examples are presented in entries 3 and 6, in which simple 5- and 6-membered rings, respectively, are formed efficiently and faster than observed for **1a** (entry 1). In addition, excellent levels of diastereoselectivity are achievable. Specific cases include the metalloamination/allylation of **1b** to provide pyrrolidines **4b** (*cis*/*trans* >20:1)[9a,11] and **1g** to give piperidine **4g** (*cis*/*trans* = 9:1).[9b,11] An additional noteworthy case is that of **1d**, the metalloamination of which at 90 °C generated the corresponding organozinc compounds **3d** as a 1:1 *cis*/*trans* mixture. In contrast, metalloamination/cyclization of **1d** at 10 °C (15 h) proceeded with good diastereoselectivity (*cis*/*trans* = 1:6) with subsequent allylation preserving this stereochemical preference to furnish pyrrolidine **4d** (entry 4).[10b] Significantly, heating of the 1:6 mixture of the organozinc compound **3d** to 90 °C rapidly led to a 1:1 mixture, suggesting that the metalloamination event is reversible. This behavior is not limited to **1d**. Metalloamination/allylation of **1e** at 90 °C (5 h) provided **4e** as a 1:1 *cis*/*trans* mixture (85 %) whereas cyclization at 23 °C over 24 h generated **3e** (*cis*/*trans* = 1:15) and ultimately gave $\mathbf{4e}_{trans}$ in 83 % yield.[10a] As was the case with **3d**, heating **3e** (*cis*/*trans* = 1:15) at 90 °C led to rapid equilibration to provide a 1:1 mixture of the diastereomers.

It is also of interest that a *tert*-butyltrimethylsilyl (TBS) ether substituent was easily tolerated (entry 8).[12] More significantly, the cyclic hydrazine **1i** readily underwent stereospecific cyclization/allylation to furnish **4i** in 87 % yield.[10c] In addition, the disubstituted alkene **1j** smoothly led to the corresponding organozinc compound **3j**, the subsequent alkylation of which was reasonably efficient, providing **4j** as a 2:1 mixture of diastereomers in 79 % yield (relative configuration not assigned, entry 10). Unfortunately, an attempt to extend our metalloamination/cyclization method to the formation of seven-membered rings has been unsuccessful (entry 11). That our procedure is scalable was demonstrated by the synthesis of unsubstituted **4a**, **4d** (*cis*/*trans* = 1:6), and methylated **4f** in 91, 84, and 93 % yield, respectively, on a 1 mmol scale.

Alternative methods for the electrophilic functionalization of the C–Zn bond in the metalloamination intermediates **3** were also shown to be viable. Accordingly, acylation of **3a**,**b**, and **3f** under the conditions of Fukuyama[13] [4-*t*BuC_6H_4COSEt, $[PdCl_2(PPh_3)_2]$ (5 mol %), toluene] fur-

Table 2: Metalloamination/acylation of hydrazinoalkenes.[c]



Hydrazinoalkene		Conversion [%][a]	d.r.	Product		Yield [%]
	**1a**	> 95 (18 h)[b]	–		**5a**	64
	**1b**	> 95 (6 h)[b]	> 20:1 (*c*/*t*)		**5b**	61
	**1f**	> 95 (3 h)[b]	–		**5f**	61

[a] As calculated from ^1H NMR spectra utilizing *p*-xylene as an internal standard. [b] All reactions conducted at a 0.1 mmol scale with toluene or (trifluoromethyl)benzene as solvent. [c] Ar = 4-*t*BuC_6H_4.

nished the corresponding azacyclic ketones **5** in good yield and with excellent diastereoselectivity. On a preparative scale (1 mmol), **5a** could be isolated in 64% yield after purification (Table 2).

The foregoing applications vividly illustrate the potential of Et_2Zn promoted metalloamination/cyclization for consecutive carbon–nitrogen/carbon–electrophile bond formation, leading to the diastereoselective construction of functionalized nitrogen heterocycles. The novel strategy described herein is expected to enable new and highly efficient pathways to stereochemically diverse molecules of preparative interest.

Experimental Section

General procedure for CuCN mediated allylation of metalloamination intermediates: In an argon-filled glove box, $ZnEt_2$ in *p*-xylene (50 μL, 2.0 M, 0.10 mmol) and toluene or (trifluoromethyl)benzene (0.5 mL) were introduced into a J. Young NMR tube equipped with a teflon screw cap, and hydrazinoalkene (**1a**–**1j**) (0.10 mmol) was subsequently added. The reaction mixture was heated in a 90 °C oil bath until metalloamination was complete (≥ 90% by ^1H NMR, *p*-xylene as internal standard). The volatiles were removed under vacuum and THF (0.5 mL) was introduced to the J. Young tube in an argon-filled dry box, followed by the addition of a solution of $CuCN{\cdot}2LiCl$ in THF (150 μL, 1.0 M, 0.15 mmol). After 5 min, allyl bromide (14.5 mg, 0.12 mmol) [or methallyl chloride (10.9 mg, 0.12 mmol)] was added and the reaction mixture was kept at 23 °C for 2 h (or until the reaction was complete, ≥ 95% ^1H NMR). The teflon screw cap was removed and the reaction mixture transferred to a 10 mL test tube, diluted with diethyl ether (2.0 mL), and an aqueous solution of $NH_4Cl_{(sat)}$ and NH_3/H_2O (1:1 v/v, 2 mL) was subsequently added. The resulting suspension was vigorously stirred for 10 min until the aqueous layer developed a deep blue color. The organic layer was removed and washed with a second portion of NH_4Cl and NH_3/H_2O (1:1 v/v, 2 mL), followed by brine (2 mL), and dried with $MgSO_4$. The ether solution was then transferred to a 10 mL round-bottomed flask equipped with a magnetic stirring bar and a N_2 inlet and cooled to 0 °C. Trifluoroacetic acid (13.7 mg, 0.12 mmol) was added dropwise using a gas-tight syringe, and the reaction mixture was stirred for 1 h. The volatiles were removed under vacuum, and the resultant viscous oil was triturated with pentane (3 × 1 mL) to afford the trifluoroacetate salts **4a**–**4j**.

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Keywords: cyclization · hydrazines · metalloamination · nitrogen heterocycles · organozinc compounds

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