Cyclizations

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Intramolecular Hydroamination of Functionalized Alkenes and Alkynes with a Homogenous Zinc Catalyst**

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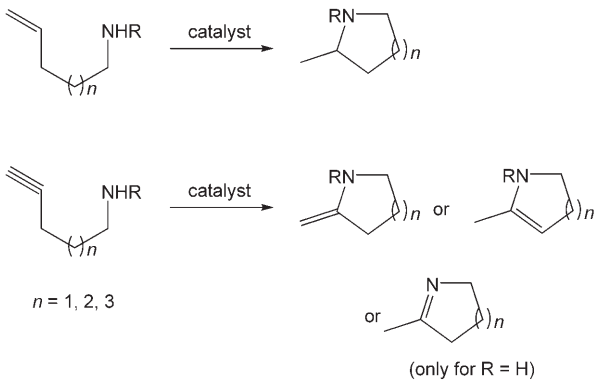
Dedicated to Professor Dr. Herbert W. Roesky on the occasion of his 70th birthday

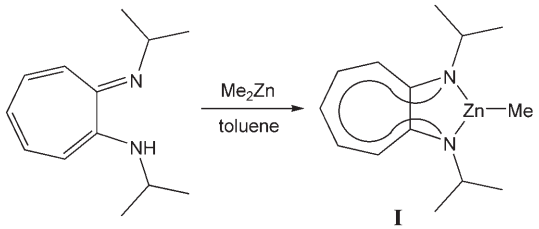


Scheme 1. Intramolecular hydroamination of alkenes and alkynes.

The catalytic addition of an organic amine N–H bond to alkenes or alkynes (hydroamination) to give nitrogen-containing molecules is of great interest to both academic and industrial researchers.[1] At present, most amines are made in multistep syntheses, and as such hydroamination offers an attractive alternative to give nitrogen-containing molecules that are important for fine chemicals, pharmaceuticals, and as useful chiral building blocks. Hydroamination can be catalyzed by d- and f-block transition metals, alkali metals,[2] as well as by calcium compounds, as shown very recently.[3] Early transition metals (Group 4[1d] and especially the lanthanides[1b]) are highly efficient catalysts for the hydroamination reaction of various C–C multiple bonds (Scheme 1), but the high sensitivity of these catalysts towards moisture and air limits their application. Furthermore, they show a very limited tolerance to polar functional groups. On the other hand, late-transition-metal catalysts offer the advantage of greater polar-functional-group compatibility; however, most of these catalysts are based on relatively expensive platinum[4] or on nickel,[5] which has only limited use in the synthesis of pharmaceuticals. Moreover, most of the late-transition-metal catalysts show limited scope, modest selectivity, and sluggish rates in their reactions with non-activated substrates. The scope of catalytic hydroamination was reviewed recently.[1]

Herein we report a new zinc-based catalyst, [*N*-isopropyl-2-(isopropylamino)troponiminato]methylzinc [{(iPr)$_2$ATI}-ZnMe] (**I**), for the hydroamination of non-activated double and triple bonds. Catalyst **I** is compatible with various polar functional groups such as ethers, amides and hydroxylamines. Furthermore, the complex is relatively robust in air and shows excellent catalytic activity. To the best of our knowledge, the only previously investigated molecular zinc compound used in catalytic hydroamination is zinc triflate, which in the presence of amines is only sparingly soluble in toluene.[6,7] Moreover, the intermolecular hydroamination of activated acetylenes by zinc-exchanged montmorillonite clay was reported recently.[8] Compared to other late-transition-metal catalysts, zinc compounds are relatively cheap and nontoxic. Furthermore Zn^{II} is stable against deactivation as it cannot be reduced to the metal under the reaction conditions.[6b]

Compound **I**, which is easily available from {(iPr)$_2$ATI}H and $ZnMe_2$ (Scheme 2), was reported previously by us as an intermediate in the synthesis of aminotroponiminate zinc



Scheme 2. Synthesis of [{(iPr)$_2$ATI}ZnMe] (**I**).

alkoxides.[9] Besides the catalytic properties, we now report the solid-state structure of **I**, which was established by single-crystal X-ray diffraction.[10] Compound **I** is a monomer in the solid state, and therefore the zinc atom has a trigonal-planar coordination sphere (Figure 1). The bond lengths and angles around the zinc center are in the expected range. In contrast to early-transition-metal–alkyl complexes, compound **I** is relatively robust towards moisture and air and thus no special experimental techniques are required for its use. This

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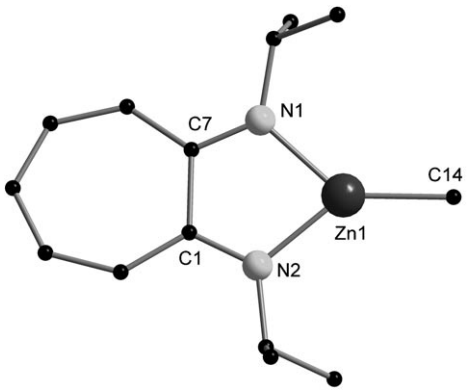


Figure 1. Solid-state structure of **I**. Hydrogen atoms have been omitted. Selected distances [pm] and angles [°]: Zn1–C14 194.1(5), Zn1–N1 198.0(4), Zn1–N2 195.5(4); C14-Zn1-N1 138.5(2), C14-Zn1-N2 139.6(2), N1-Zn1-N2 81.94(14).

behavior is very different to that of the starting material $ZnMe_2$, which is pyrophoric (see Supporting Information). The stability of compounds of the general formula [LZnMe] (L = ligand) has been described before.[11]

The goal of the current study was to explore the scope, selectivity, and functional-group tolerance of the intramolecular hydroamination reaction catalyzed by **I**. For this reason, several substrates bearing different functional groups and leading to different ring sizes were synthesized. The results are given in Table 1 and demonstrate that **I** exhibited good activity in this reaction. The best conditions were found to be when the reaction was carried out in benzene as the solvent at a temperature of 120 °C; under these conditions, total conversion occurred within reasonable reaction times in most cases. In the majority of cases it was possible to lower the catalyst loading from 10 to 1 mol %, and it was also found that the reaction rate could be accelerated by the addition of an equimolar amount (based on **I**) of $[PhNMe_2H][B(C_6F_5)_4]$ as a cocatalyst.

Interestingly, cyclization of propargyl ethers that bear a secondary amine moiety opened a new route to the corresponding 1,4-oxazines, as the double bond migrates to give the thermodynamically more stable vinyl ether. [12] A comparison of the reaction times of the α-branched amino ether **2a** and the corresponding primary amine **3a** demonstrates the greater propensity of secondary amines to react: even though the catalyst loading for substrate **3a** was 20 times higher, the reaction time was nearly double that for substrate **2a**. On the other hand, bulkier substituents, such as an isopropyl group α to the amine moiety, caused a significant decrease in the reaction rate. Nevertheless, valine derivative **4a** could be completely converted into the oxazine **4b** by the addition of 10 mol % of the catalyst/activator system.

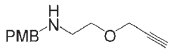
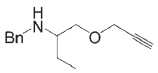
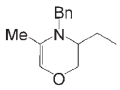
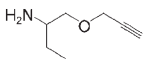
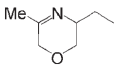
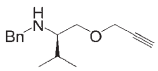
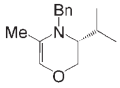
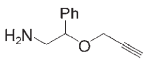
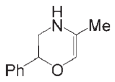
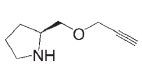
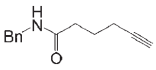
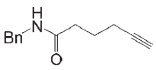
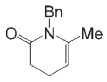
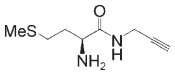
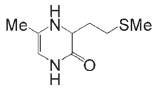
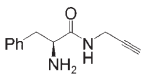
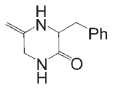
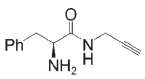
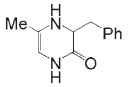
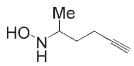
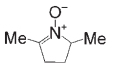
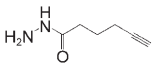
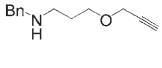
To our surprise, the incorporation of large substituents in the β position had no beneficial effect on the cyclization. Therefore, amino benzyl ether **5a** was cyclized within the same time as substrate **3a**. Cyclic secondary amines, such as proline derivative **6a**, exhibited very high reactivity under these reaction conditions (Table 1, entry 6). Substituted amides underwent cyclization to the corresponding lactams (Table 1, entries 7 and 8). Depending on the reaction conditions, two different products were observed. When the reaction was performed in the absence of the cocatalyst, the cyclized product **7b** with an exocyclic double bond was detected. On the other hand, a 6:1 mixture of the isomerized dihydropyridone **8b** and δ-valerolactam **7b** was observed when an equal amount of the cocatalyst was added.

We were also able to cyclize methionine derivative **9a** to the dihydropyrazinone **9b**. This substrate is of particular interest as it contains both an amide functionality and a thioether group. To the best of our knowledge, this constitutes the first hydroamination of a compound bearing a thioether moiety, which is most likely incompatible with most well-known catalysts for hydroamination. The cyclization of phenylalanine propargylamide (**10a**) revealed an influence of the catalyst concentration on the structure of the product (Table 1, entries 10 and 11): When 10 mol % of the catalyst was used complete conversion into the resulting dihydropyrazinone **11b** was observed. In contrast, when only 5 mol % of the catalyst was added, only the methylene piperazinone **10b** was formed. Moreover we were able to apply our catalytic system to alkynes that bear an hydroxylamine functionality to afford cyclic nitrones (Entry 12).[13] Carbonic acid hydrazide **13a** was also cyclized to the resulting *N*-aminopiperidinone **13b**. Interestingly, the more-electron-poor nitrogen atom added preferentially to the triple bond, thus indicating that ring size has a larger influence than electronic effects on the outcome of the reaction. We were pleased to find that our system catalyzes the formation of seven-membered rings (Table 1, entry 14). It can be concluded that the rate of cyclization for aminoalkynes follows the order five-membered > six-membered ≫ seven-membered ring, consistent with classical, stereoelectronically controlled, cyclization processes.[1b]

With these results in hands, we also investigated the intramolecular hydroamination of non-activated alkenes (Table 2). However, it is well known that the hydroamination of alkenes is significantly slower than that of alkynes.[1g,3,4] Substrates that bear bulky geminal substituents β to the amino group (Thorpe–Ingold effect)[14] could be cyclized with reasonable catalyst/activator loadings of 5 mol % with moderate reaction times (Table 2, entries 1–3). Substrate **16a** was the most reactive and gave the corresponding pyrrolidine within 5 h. Compound **18a**, which is known to be a difficult substrate for this reaction, was converted into 2,5-dimethylpyrrolidine (**18b**) in modest yield.

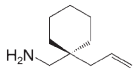
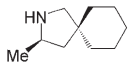
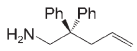
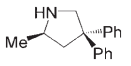
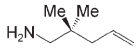
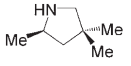
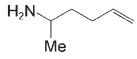
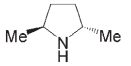
In conclusion, compound **I** has proved to be an efficient catalyst for homogenous intramolecular hydroamination reactions and has a number of practical advantages, such as particularly high functional-group tolerance, good activity in the catalytic conversion of non-activated C–C multiple bonds, and a relatively high stability towards moisture and air. The reaction conditions allowed the manipulation of a multitude of polar functional groups, including ethers, thioethers, and amides. It is also notable that seven-membered heterocycles can be accessed. These advantages lead us to hope that **I**, which is an easily accessible reagent, will find further application as a hydroamination catalyst.

Table 1: Intramolecular hydroamination of functionalized alkynes.[a]

Entry	Substrate		Product		cat. **I** [mol%]	Activ.[b] [mol%]	*t* [h]	Conv. [%][c]
1		**1a**		**1b**	1 1	– 1	144 39	>99[d] >99[d]
2		**2a**		**2b**	1 0.1 1	– 0.1 1	72 8 45	>99 >99, (91)[e] >99[d]
3		**3a**		**3b**	10 2	– 2	144 14	>99 >99, (70)[e]
4		**4a**		**4b**	1 10 1	– 10 1	96 1.5 144	19 >99 94
5		**5a**		**5b**	10 2	– 2	6 14	>99 >99
6		**6a**		**6b**	1 0.1	– 0.1	4 8	95 >99
7		**7a**		**7b**	10	–	60	25
8		**7a**		**8b**	10	10	60	>99[f]
9		**9a**		**9b**	10	–	15	92
10		**10a**		**10b**	5	–	72	51
11		**10a**		**11b**	10	–	15	>99
12		**12a**		**12b**	1 0.5	– 0.5	5 4	98[d] >99[d]
13		**13a**		**13b**	10	–	14	>99
14		**14a**		**14b**	5	–	312	>99

[a] Reaction conditions: amine (430 μmol), catalyst **I**, benzene (0.5 mL), 120°C. [b] Activator: $[PhNMe_2H][B(C_6F_5)_4]$. [c] Determined by ^1H NMR spectroscopy. [d] The reaction was carried out at 60°C. [e] Yield of isolated product; the reaction was performed on a 2-mmol scale. [f] **8b**/**7b** = 6:1.

Table 2: Intramolecular hydroamination of alkenes.[a]

Entry	Substrate		Product		cat. **I** [mol%]	Activ.[b] [mol%]	*t* [h]	Conv. [%][c]
1		**15a**		**15b**	10	–	30	87[d]
					5	–	28	>99
					5	5	8	80
2		**16a**		**16b**	10	–	12	>99
					10	–	24	69[d]
					5	5	5	>99
3		**17a**		**17b**	13.3	–	72	>99
					5	5	52	46
4		**18a**		**18b**	10	10	36	19

[a] Reaction conditions: amine (430 μmol), catalyst **I**, benzene (0.5 mL), 120°C. [b] Activator: $[PhNMe_2H][B(C_6F_5)_4]$. [c] Determined by ^1H NMR spectroscopy. [d] Yield of isolated product; the reaction was carried out at 100°C in toluene.

Experimental Section

I: A solution of $ZnMe_2$ (2.0 M in toluene; 0.64 mL, 1.28 mmol, 1.05 equiv) was diluted in toluene (25 mL) and cooled to −78°C. A solution of {(*i*Pr)$_2$ATI}H (250 mg, 1.22 mmol) in toluene (25 mL) was added. The reaction mixture was slowly warmed up to room temperature, and gas was evolved for about 3 h. The solution was then filtered off, the solvent was evaporated under reduced pressure. The resulting yellow solid was washed with *n*-pentane (3 × 10 mL) and dried under vacuum. Yield: 287 mg (83%). ^1H NMR (C_6D_6, 400 MHz, 25°C): $\delta = 0.00$ (s, 3H; $ZnCH_3$), 1.14 (d, $J = 6.1$ Hz, 12H; $NCH(CH_3)_2$), 3.76 (sept, $J = 6.2$ Hz, 2H; $NCH(CH_3)_2$), 6.35 (d, $J = 9.4$ Hz, 1H; H_{Ar}), 6.57 (d, $J = 10.2$ Hz, 2H; H_{Ar}), 6.95 ppm (dd, $J = 9.4$ Hz, 10.2 Hz, 2H; H_{Ar}); $^{13}C\{^1H\}$ NMR (C_6D_6, 100.4 MHz, 25°C): $\delta = -9.9$ ($ZnCH_3$), 24.5 ($NCH(CH_3)_2$), 48.3 ($NCH(CH_3)_2$), 111.6 (C_{Ar}), 117.7 (C_{Ar}), 134.5 (C_{Ar}), 160.2 ppm (C_{Ar}); MS (EI): *m*/*z* (%): 282 (33) $[M]^+$, 267 (51) $[M-CH_3]^+$, 204 (24) $[M-ZnCH_3]^+$.

NMR-tube-scale intramolecular hydroamination: All NMR-tube-scale reactions were prepared in an N_2-filled glovebox. The aminoalkynes (430 μmol) were dissolved in [D$_6$]benzene (0.5 mL) and then added to the catalyst (e.g. 4.30 μmol for 1 mol%). The mixture was injected into an NMR tube, which was removed from the glovebox and flame-sealed under vacuum. The reaction mixture was then heated to the appropriate temperature for the stated duration of time. All products were analyzed by ^1H, ^{13}C, ^{13}C DEPT, COSY, and HMQC NMR spectroscopy and by IR, MS, and HRMS when possible. The ratio between the reactant and the product was calculated by comparison of the integrations of the corresponding signals in the ^1H NMR spectra. The concentration of the catalyst was controlled by comparing the integration of a well-resolved signal for the heterocyclic product with that for a signal for a catalyst ligand.

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[10] Single-crystal X-ray diffraction data for **1**: $C_{14}H_{22}N_2Zn$ ($M_r = 283.71$): Bruker Smart 1000 CCD, space group $P2_1/c$ (No. 14); $a = 1579(3)$, $b = 906(2)$, $c = 2176(4)$ pm, $\beta = 109.40(4)°$; $T = 173$ K, $Z = 8$, $V = 2935(10) \times 10^6$ pm^3, $\rho = 1.284$ g cm^{-3}, $2\theta_{max} = 55°$, 16208 reflections collected, 6333 unique reflections ($R_{int} = 0.0593$). The structure was solved by Patterson methods (SHELXS-97 and SHELXL-97)[15] and refined by full-matrix least-square techniques with $I > 2\sigma(I)$ to $R1 = 0.0412$ and w$R2 = 0.1097$. CCDC-274802 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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