Hydroaminations of unactivated alkenes with basic alkylamines: group 4 metal halide catalysts and Brønsted-acid organocatalysts†

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Two distinct economical catalysts for intramolecular hydroaminations of electronically unactivated alkenes with basic amines are described, which are based on (a) group 4 metal halides under basic reaction conditions or (b) Brønsted-acid organocatalysts.

Introduction

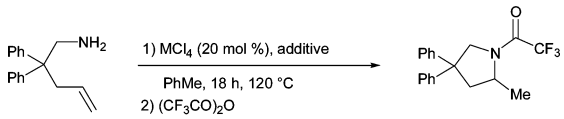
Saturated N-heterocycles are ubiquitous in natural products as well as biologically active compounds.[1] Their synthesis through direct intramolecular additions of basic amines to alkenes are attractive, because of their atom-economical nature.[2] Recently, significant progress has been achieved through the use of group 4 metal complexes, previously developed for elegant hydroaminations of alkynes and allenes.[3] Thus, cyclizations of both secondary[4,5] and primary[6] aminoalkenes were reported, and for the latter transformations strong evidence was provided for a mechanism involving group 4 metal imido complexes.[7] We proposed comparable imido species as intermediates for the use of the inexpensive Lewis-acid $TiCl_4$ (99.9%, Acros 2006, 0.01 EUR $mmol^{-1}$)[8] (and $HfCl_4$) in hydroamination reactions.[9] Given the importance of economical heterocycle syntheses, we became interested in probing preparatively useful group 4 metal halide-based catalysts for intramolecular addition reactions of basic alkylamines to unactivated olefins. Additionally, as Brønsted-acids have thus far only been employed as catalysts for addition reactions of significantly less basic amides[10,11] or anilines,[12] we explored their use in organocatalytic additions of basic alkylamines to unactivated alkenes.

Results and discussion

Group 4 metal halide catalysts

At the outset of our studies, we probed various additives for $TiCl_4$-catalyzed intramolecular hydroamination reactions using aminoalkene **1a** (Table 1). Previously employed *t*-$BuNH_2$[8,9] provided unsatisfactory results (entry 1). In contrast, excess of a basic pyridine or amine gave rise to more efficient conversion of amine **1a** (entries 2 and 3, respectively). A significantly increased reactivity was achieved with catalysts comprising a group 4 metal halide and LDA as additive, particularly when using $HfCl_4$[9d] or $ZrCl_4$ (entries 5 and 6, respectively). Importantly, these transformations proceeded in the presence of an excess of either a sterically hindered pyridine (entry 2)[13] or a basic amide (entries 4–6), rendering Brønsted-acid catalysis less likely. Based on a control experiment a base-catalyzed[14] hydroamination is also unlikely (entry 7).

Table 1 MCl_4-catalyzed hydroamination of an unactivated alkene

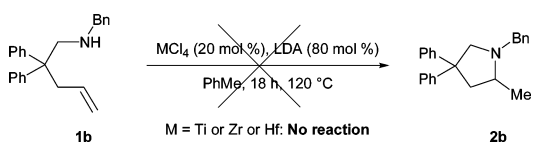


1a **2a**

Entry[a]	MCl_4	Additive (equiv.)[b]	Yield (%)
1	$TiCl_4$	*t*-$BuNH_2$ (1.2)	11[c]
2	$TiCl_4$	*t*-$BuNH_2$ (1.2), 2,6-(*t*-Bu)$_2C_5H_3N$	29
3	$TiCl_4$	TMP (1.2)	26
4	$TiCl_4$	LDA (0.8)	37[c]
5	$HfCl_4$	LDA (0.8)	59
6	$ZrCl_4$	LDA (0.8)	87
7	—	LDA (0.8)	6

[a] *Reagents and conditions*: **1a** (1.0 mmol), MCl_4 (20 mol%), PhMe (2.0 mL), 18 h, 120 °C; $(CF_3CO)_2O$ (2.0 mmol), 20 °C, 15 min. [b] TMP: 2,2,6,6-tetramethylpiperidine; LDA: lithium diisopropylamide. [c] GC conversion.

Further, the catalysts were probed using secondary amine **1b**. Interestingly, formation of heterocycle **2b** was not observed using catalytic amounts of either $TiCl_4$, $HfCl_4$ or $ZrCl_4$ in combination with LDA (Scheme 1). This lack of reactivity suggests that alkene hydroamination is catalyzed by *in situ*-generated group 4 metal imido complexes, which subsequently undergo an intramolecular [2 + 2] cycloaddition reaction with the alkene.



1b **2b**

Scheme 1 Test reaction using secondary amine **1b**.

This Bergman mechanism is well established for alkyne hydroaminations[3] and has been postulated for alkene hydroaminations.[6,7]

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Brønsted-acids as organocatalysts

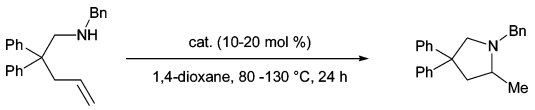
Intramolecular hydroamination reactions of unactivated alkenes with basic alkylamines are often employed to evaluate the performance of metal-based catalysts. As studies on the use of Brønsted-acids as catalysts in these important transformations have not previously been reported, we probed the efficacy of such reagents in the challenging conversion of basic primary and secondary aminoalkenes.[15] We observed unprecedented Brønsted-acid-catalyzed hydroamination reactions with basic alkylamines (Table 2). Particularly, salts of weakly coordinating anions[16] enabled efficient catalysis. While $PhMe_2NH^+ {}^-B(C_6F_5)_4$ (98%, Strem, 120.16 EUR mmol^{-1}) proved highly active (entries 13 and 14), the use of $NH_4^+ {}^-O_2CCF_3$ (98%, Aldrich, 0.12 EUR mmol^{-1})[17] constitutes an economically attractive, preparatively simple, yet efficient alternative (entries 15 and 16).

With two highly promising catalysts in hand, we studied the scope of the methodology (Table 3). The mild reaction conditions allowed for the use of substrates bearing a variety of valuable functional groups, such as a chloro- (entry 2), an ester- (entry 3), a nitro- (entry 4) or a cyano-substituent (entry 5). Further, a hydroxy-substituted substrate was chemoselectively converted to pyrrolidine **2h** in high yield (entry 6). Importantly, *gem*-disubstitution[18] is not a stringent requirement for the success of the protocol, and more challenging substrates were converted with high efficacy (entries 9 and 10). Finally, it is noteworthy that this methodology is not limited to secondary aminoalkenes, but also proved applicable to primary alkylamines (entry 11).

Conclusions

In summary, we have presented herein two distinct economical catalysts for intramolecular addition reactions of basic amines to unactivated olefins. Under basic reaction conditions, group 4 metal halides were employed for efficient hydroamination reactions of primary aminoalkenes, which likely proceed through *in situ* generation of group 4 metal imido complexes. Further, we have described the unprecedented use of Brønsted-acids for generally applicable and efficient catalytic hydroamination reactions of unactivated alkenes with basic alkyl-substituted amines. Generally, these findings are of fundamental significance for the evaluation of metal-based hydroamination catalysts. Form a preparative viewpoint, $NH_4^+ {}^-O_2CCF_3$ represents an economically attractive catalyst with a broad functional group tolerance.

Table 2 Brønsted-acid-catalyzed hydroamination with a basic amine

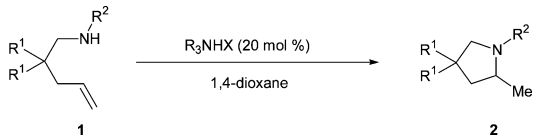


1b **2b**

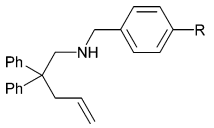
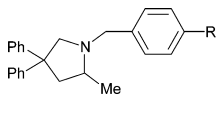
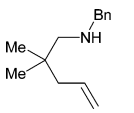
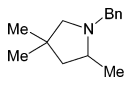
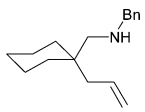
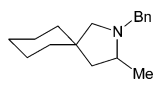
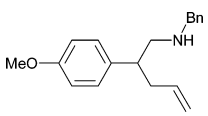
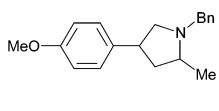
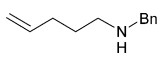
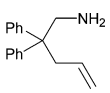
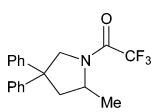
Entry[a]	Catalyst	T/°C	Yield (%)
1	—	130	—
2	$(NH_4)_2SO_4$	120	—
3	$NH_4^+ {}^-O_2CCH_3$	120	7[b]
4	NH_4F	120	<5[b]
5	NH_4Cl	120	5[b]
6	NH_4Br	120	5[b]
7	NH_4I	120	10[b]
8	$NH_4^+ {}^-O_3SCF_3$	130	20[b]
9	$(NH_4)BF_4$	120	25[b]
10	BINOLP(O)OH	130	33
11	NH_4PF_6	120	39
12		130	44
13[c]	$PhMe_2NH^+ {}^-B(C_6F_5)_4$	120	83
14		80	76
15	$NH_4^+ {}^-O_2CCF_3$	120	56
16		130	74

[a] *Reagents and conditions* (unless otherwise indicated): **1b** (1.0 mmol), catalyst (20 mol%), 1,4-dioxane (2.0 mL), 24 h. [b] GC conversion. [c] *Reagents and conditions*: **1b** (0.5 mmol), catalyst (10 mol%), 1,4-dioxane (1.0 mL).

Table 3 Hydroamination of unactivated alkenes with basic amines



1 **2**

Entry	Substrate	Product	Yield (%)
			
1[a]	R = OMe		**2c** 63
2[a]	R = Cl		**2d** 84
3[a]	R = CO_2Me		**2e** 93
4[a]	R = NO_2		**2f** 80
5[a]	R = CN		**2g** 82
6[b]	R = OH		**2h** 84
7[b]			**2i** 75
8[b]			**2j** 84
9[b]			**2k** 82 (2.6 : 1)[c]
10[b,d]			**2l** 74
11[e]			**2a** 83

[a] *Reagents and conditions*: **1** (1.0 mmol), $NH_4^+ {}^-O_2CCF_3$ (20 mol%), 1,4-dioxane (2.0 mL), 24 h, 130 °C. [b] *Reagents and conditions*: **1** (0.5 mmol), $PhMe_2NH^+ {}^-B(C_6F_5)_4$ (10 mol%), 24 h, 120 °C. [c] Diastereomeric ratio. [d] Reaction conducted at 130 °C. [e] *Reagents and conditions*: **1** (0.5 mmol), $PhMe_2NH^+ {}^-B(C_6F_5)_4$ (20 mol%), 18 h, 120 °C; $(CF_3CO)_2O$ (2.0 mmol), 20 °C, 15 min.

Experimental†

Representative procedure for MCl_4-catalyzed intramolecular hydroaminations of unactivated olefins

1-Trifluoroacetyl-2-methyl-4,4-diphenylpyrrolidine (2a, Table 1, entry 6). An oven-dried sealed tube was charged under a positive pressure of nitrogen with $ZrCl_4$ (47 mg, 0.20 mmol, 20 mol%), toluene (2 mL) and LDA (2.0 M in THF–*n*-heptane–ethylbenzene, 0.40 mL, 0.80 mmol). The resulting solution was stirred for 30 min at ambient temperature, followed by the addition of **1a** (237 mg, 1.00 mmol). The reaction mixture was stirred at 120 °C for 18 h. The cold solution was subsequently treated with trifluoroacetic anhydride (420 mg, 2.00 mmol). After stirring for 15 min at ambient temperature, Et_2O (50 mL) and saturated aqueous $(NH_4)_2CO_3$ (30 mL) were added. The separated aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-pentane–Et_2O = 60 : 1 → 30 : 1) to yield **2a** (290 mg, 0.87 mmol, 87%) as a light yellow solid (mp 78.8–79.6 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34–7.37 (m, 10H), 4.61 (dt, J = 11.5, 1.8 Hz, 1H), 4.12–4.02 (m, 1H), 3.98 (d, J = 11.5 Hz, 1H), 3.06–2.97 (m, 1H), 2.32–2.25 (m, 1H), 1.40 (d, J = 6.2 Hz, 3H). ^{13}C-NMR (75 MHz, DEPT, $CDCl_3$): δ = 155.3 (q, J = 36.1 Hz, CO), 144.7 (C_q), 143.6 (C_q), 128.8 (CH), 128.7 (CH), 126.9 (CH), 126.8 (CH), 126.5 (CH), 126.3 (CH), 116.1 (q, J = 288.0 Hz, CF_3), 56.2 (q, J = 2.6 Hz, CH_2), 54.6 (CH), 53.3 (C_q), 44.4 (CH_2), 18.9 (CH_3). ^{19}F-NMR (275 MHz, $CDCl_3$): δ = −72.37 (s). IR (ATR): 3060, 2932, 1685, 1496, 1446, 1253, 1205, 1180, 1136, 1033, 753, 696 cm^{-1}. MS (EI), *m*/*z* (relative intensity) 334 (18) [M + H$^+$], 333 (90) [M$^+$], 220 (19), 207 (46), 193 (66), 179 (100), 115 (40), 91 (31), 69 (35). HR-MS (EI) *m*/*z* calcd for $C_{19}H_{18}F_3NO$ 333.1340, found 333.1322.

Representative procedure for $NH_4O_2CCF_3$-catalyzed hydroamination reactions

1-Benzyl-2-methyl-4,4-diphenylpyrrolidine (2b, Table 2, entry 16). A solution of **1b** (328 mg, 1.00 mmol) and NH_4^+ $^-O_2CCF_3$ (26.2 mg, 0.20 mmol, 20 mol%) in dry 1,4-dioxane (2.0 mL) was stirred in a sealed tube under N_2 for 24 h at 130 °C. After cooling to ambient temperature, saturated aqueous $NaHCO_3$ (80 mL) and Et_2O (80 mL) were added. The separated aqueous phase was extracted with Et_2O (2 × 80 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-pentane–Et_2O = 30 : 1) to yield **2b** (243 mg, 74%) as a yellow solid (mp 70.6–72.2 °C). The spectral data were in accordance with those reported in the literature.[15a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 15H), 4.12 (d, J = 13.3 Hz, 1H), 3.70 (d, J = 10.0 Hz, 1H), 3.30 (d, J = 13.3 Hz, 1H), 2.99–2.83 (m, 3H), 2.25 (dd, J = 12.2, 7.2 Hz, 1H), 1.21 (d, J = 6.1 Hz, 3H). ^{13}C-NMR (75 MHz, DEPT, $CDCl_3$): δ = 150.5 (C_q), 148.6 (C_q), 139.9 (C_q), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 125.8 (CH), 125.4 (CH), 66.4 (CH_2), 59.7 (CH), 58.0 (CH_2), 52.5 (C_q), 47.9 (CH_2), 19.5 (CH_3). IR (ATR): 3061, 3029, 2960, 2924, 2788, 1491, 1445, 1373, 730, 695 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 327 (18) [M$^+$], 312 (75), 147 (100), 91 (64), 56 (98). HR-MS (EI) *m*/*z* calcd for $C_{24}H_{25}N$ 327.1987, found 327.2002.

Acknowledgements

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