Pergamon

Tetrahedron Letters 43 (2002) 3715–3718

TETRAHEDRON LETTERS

The Cp_2TiMe_2-catalyzed intramolecular hydroamination/cyclization of aminoalkynes

Igor Bytschkov and Sven Doye*

Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

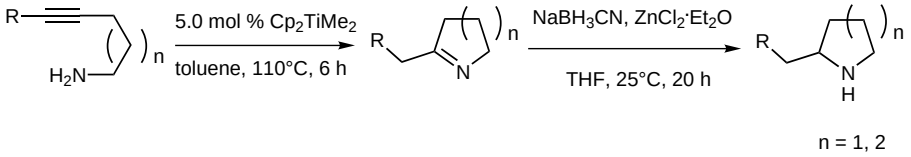
Received 22 February 2002; accepted 22 March 2002

Abstract—Cp_2TiMe_2 has been found to be a competent catalyst for the intramolecular hydroamination/cyclization of aminoalkynes. In the presence of 5.0 mol% Cp_2TiMe_2, the hydroamination reactions proceed smoothly at 100–110°C to give five- and six-membered cyclic imines within 4–6 h. After subsequent reduction performed with zinc-modified $NaBH_3CN$ at room temperature cyclic amines can be isolated in good yields.

The addition of ammonia or primary and secondary amines to alkenes and alkynes offers a very interesting pathway to amines, imines and enamines by converting inexpensive alkenes and alkynes into the desired products in a single reaction without any formation of side products. However, efforts to develop efficient hydroamination protocols have met with only limited success,[1] except by using early transition metal complexes as catalysts for the hydroamination of alkynes.[2] In 1992 Bergman et al. reported that $Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2$ catalyzes the hydroamination of various alkynes with 2,6-dimethylaniline,[2a,2b] and Livinghouse et al. demonstrated that $CpTiCl_3$ and $CpTiMe_2Cl$ can be used as catalysts for the intramolecular hydroamination of aminoalkynes.[2d–g] However, intermolecular hydroaminations using these catalysts were not successful. Since 1999 several reports from our group have dealt with applications of the well known reagent Cp_2TiMe_2[3] as hydroamination catalyst.[2h–m] While this catalyst has been used extensively for intermolecular hydroamination reactions of alkynes, it has not been reported that Cp_2TiMe_2 can also be used for the synthesis of cyclic amines from aminoalkynes by catalytic intramolecular hydroamination and subsequent reduction.[4]

Inspired by a mechanistic investigation of the Cp_2TiMe_2-catalyzed intermolecular hydroamination of alkynes, which suggested that the rate of related hydroamination reactions can be increased by an accelerated [2+2]-cycloaddition between the catalytically active titanium imido complex and the alkyne,[2j] we focused on intramolecular Cp_2TiMe_2-catalyzed hydroamination/cyclization reactions of aminoalkynes (Scheme 1) because in this case the mentioned [2+2]-cycloaddition is supposed to be fast.

As substrates we used the aminoalkynes **1**–**11** (Table 1), which are easily accessible from commercially available starting materials by standard transformations.[5] Initially performed ^1H NMR experiments employing the γ-aminoalkynes **1** and **2** showed that intramolecular hydroamination/cyclization reactions in the presence of 5.0 mol% Cp_2TiMe_2 are in fact fast at 100°C in C_6D_6. After only 4 h, **1** and **2** were completely consumed and transformed into the corresponding cyclic imines in



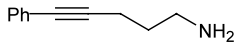
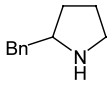
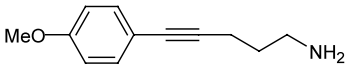
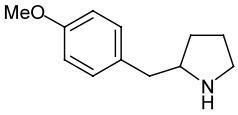
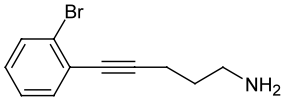
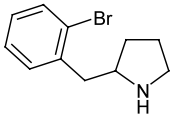
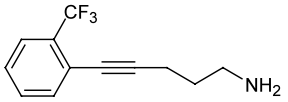
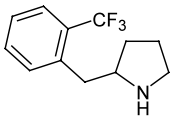
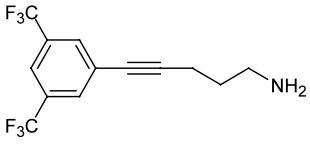
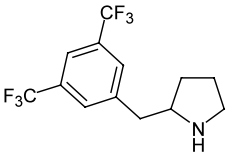
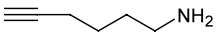
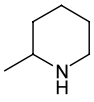
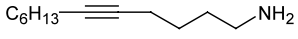
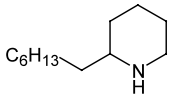
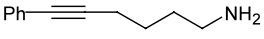
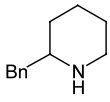
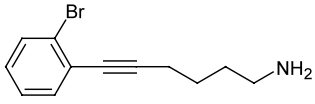
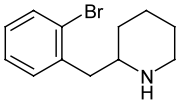
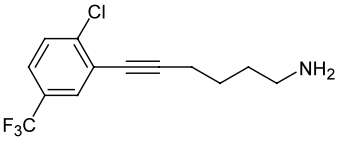
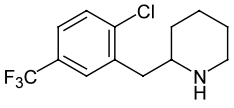
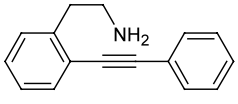
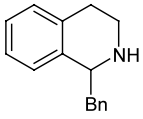
Scheme 1. One-pot synthesis of cyclic amines from aminoalkynes by Cp_2TiMe_2-catalyzed intramolecular hydroamination and subsequent reduction.

Keywords: alkynes; amination; amines; catalysis; titanium.

* Corresponding author. Fax: +49 (0)511 762 3011; e-mail: sven.doye@oci.uni-hannover.de

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00644-5

Table 1. One-pot synthesis of cyclic amines from aminoalkynes by Cp_2TiMe_2-catalyzed intramolecular hydroamination and subsequent reduction

Entry	Aminoalkyne		Product		Yield[a] [%]
1		**1**		**12**	90
2		**2**		**13**	94
3		**3**		**14**	88
4		**4**		**15**	82
5		**5**		**16**	62
6		**6**		**17**	55[b]
7		**7**		**18**	72
8		**8**		**19**	83
9		**9**		**20**	67
10		**10**		**21**	94
11		**11**		**22**	76

[a] Reaction conditions: (1) aminoalkyne (1.0 mmol), Cp_2TiMe_2 (0.05 mmol, 5.0 mol%), toluene (0.5 mL), 110°C, 6 h; (2) $NaBH_3CN$ (2.0 mmol), $ZnCl_2{\cdot}Et_2O$ (1.0 mmol), THF (5.0 mL), 25°C, 20 h. Yields represent isolated yields of pure compounds as determined by ^1H and ^{13}C NMR as well as GC or TLC analysis.

[b] The scale of the reaction was 8.0 mmol. No additional toluene was added to the reaction mixture. The product was isolated by Kugelrohr distillation.

almost quantitative yield (98%, internal standard Cp_2Fe). In both cases no formation of any side products was observed. These results clearly indicate that in contrast to intermolecular reactions reported in the past[2h–k] Cp_2TiMe_2-catalyzed intramolecular hydroamination reactions do not require a sterically demanding amine part of the aminoalkyne to take place efficiently. With these promising results in hand, we focused on a one-pot hydroamination/reduction sequence for the synthesis of cyclic amine derivatives on a preparative scale. For that purpose, we cyclized **1**–**11** in the presence of 5.0 mol% Cp_2TiMe_2 in toluene at 110°C. After a reaction time of 6 h a subsequent reduction performed with zinc-modified $NaBH_3CN$[6,7] in THF at room temperature gave access to the desired cyclic amines **12**–**22** which were isolated in pure form after chromatography on silica gel (Scheme 1, Table 1).[8,9]

The examples shown in Table 1 demonstrate, that under the employed reaction conditions γ- and δ-aminoalkynes can be converted smoothly into five- and six-membered cyclic amine derivatives. Due to the mechanism of the reaction the hydroamination step takes place without any formation of regioisomeric products. An aromatic ring adjacent to the alkyne can be electron neutral (entries 1, 8, 11), electron rich (entry 2) or electron deficient (entries 4, 5, 10) as well as *ortho* substituted (entries 3, 4, 9, 10). However, as can be seen from entries 6 and 7 an aromatic ring adjacent to the alkyne is not required for the hydroamination reaction to proceed. Interestingly, aromatic halide and methoxy substituents, which offer the possibility of further transformations, are tolerated under the reaction conditions. With one exception, the yields are good to excellent for both the synthesis of pyrrolidine and piperidine derivatives. Only in the case of **6** (entry 6), the product **17** was isolated in a modest yield. However, the reason for this might be the low boiling point of **17** and the fact that **17** was isolated by Kugelrohr distillation and not by chromatography. In contrast to the mentioned results, the one-pot synthesis of seven- and eight-membered cyclic amines could not be achieved. Related ^1H NMR experiments performed with corresponding aminoalkynes in C_6D_6 at 100°C proved that the hydroamination/cyclization reactions are very slow in these cases (yields <30% after 3 days). Since intermolecular hydroamination reactions of sterically less demanding *n*-alkylamines are extremely slow in the presence of Cp_2TiMe_2[2h–n] no efforts have been made to expand the Cp_2TiMe_2-catalyzed intramolecular hydroamination to larger rings. Finally, we tried to minimize the amount of the hydroamination catalyst. However, during a cyclization of aminoalkyne **8** performed in the presence of 2.0 mol% Cp_2TiMe_2 at 110°C in C_6D_6 (sealed Schlenk tube) the corresponding imine was only formed in 29% yield after 4 h.

In summary, the results presented clearly indicate that Cp_2TiMe_2 is an active catalyst for the intramolecular hydroamination/cyclization of aminoalkynes. Unfortunately, the employed reaction conditions are relatively harsh compared to most other catalytic procedures for intramolecular hydroaminations.[4] Therefore, Cp_2TiMe_2 does not offer significant advantages over other catalysts. However, since it is well established that this Ti-compound also catalyzes intermolecular hydroamination reactions of alkynes[2h–m] the present study undoubtedly proves that Cp_2TiMe_2 must be recognized as the most general catalyst for the hydroamination of alkynes known today. Furthermore, it is extremely interesting that in contrast to intermolecular reactions, Cp_2TiMe_2-catalyzed intramolecular hydroamination reactions do not require a sterically demanding amine part of the aminoalkyne to take place efficiently. This result strongly supports our interpretations of a mechanistic study of the Cp_2TiMe_2-catalyzed intermolecular hydroamination of alkynes.[2j] However, in combination with an imine reduction, the intramolecular hydroamination reactions can be used for a convenient one-pot synthesis of cyclic amines from aminoalkynes.

Acknowledgements

Generous support by Professor E. Winterfeldt is most gratefully acknowledged. We also thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Bayer AG for financial support of our research.

References

1. For reviews, see: (a) Chekulaeva, I. A.; Kondratjeva, L. V. *Russ. Chem. Rev.* **1965**, *34*, 669–680; (b) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A., Eds.; VCH: Weinheim, 1996; pp. 507–520; (c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703; (d) Müller, T. E.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, pp. 316–330; (e) Haak, E.; Doye, S. *Chem. unserer Zeit* **1999**, *33*, 296–303; (f) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3983–3985.
2. (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719; (b) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753–2763; (c) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923–2924; (d) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459–5469; (e) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323–1324; (f) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489; (g) Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523–1525; (h) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3389–3391; (i) Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* **2000**, *2*, 1935–1937; (j) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2305–2308; (k) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411–4418; (l) Haak, E.; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2002**, 457–463; (m) Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2002**, 1213–1220; (n) Heutling, A.; Doye, S. *J. Org. Chem.* **2002**, *67*, 1961–1964; (o) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967–3969; (p) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011–5013.

3. (a) Petasis, N. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 1, pp. 470–473; (b) Siebeneicher, H.; Doye, S. *J. Prakt. Chem.* **2000**, *342*, 102–106.
4. For catalytic intramolecular hydroaminations of aminoalkynes, see: Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T.-a. *J. Organomet. Chem.* **2001**, *622*, 149–154 and references cited therein.
5. Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275–294.
6. Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927–1932.
7. Other reducing agents (H_2, Pd/C, $LiAlH_4$, DIBAH, etc.) can be used as well. However, best results were obtained with $NaBH_3CN$ in the presence of $ZnCl_2{\cdot}Et_2O$.
8. **General procedure**: Under an inert atmosphere of argon, a flame-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with the aminoalkyne (1.0 mmol), Cp_2TiMe_2 (0.20 mL, $c=0.25$ mol/L in toluene, 0.05 mmol, 5.0 mol%) and toluene (0.3 mL). The resulting mixture was heated to 110°C for 6 h. After the mixture had been cooled to room temperature, the solvent was removed under vacuum and a suspension of $NaBH_3CN$ (126 mg, 2.0 mmol) and $ZnCl_2{\cdot}Et_2O$ (1.0 mL, $c=1.0$ mol/L in Et_2O, 1.0 mmol) in THF (5.0 mL) was added. The resulting mixture was stirred for 20 h at room temperature. After the mixture had been diluted with CH_2Cl_2 (10.0 mL) and aqueous HCl (10.0 mL, $c=2.0$ mol/L), stirring at room temperature was continued for additional 2 h. Then the resulting layers were separated and KOH ($c=2.0$ mol/L) was added to the aqueous layer until pH 7 was reached. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were extracted with water and brine, dried with Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography on silica gel (EtOAc/MeOH, 8:1–1:1) afforded the pure cyclic amine derivative.
9. **Representative characterization data for 13**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.12$ (d, $J=8.7$ Hz, 2H), 6.82 (d, $J=8.6$ Hz, 2H), 3.77 (s, 3H), 3.12–3.22 (m, 1H), 2.98–3.05 (m, 1H), 2.76–2.85 (m, 1H), 2.64–2.74 (m, 2H), 2.23 (br. s, 1H), 1.64–1.87 (m, 3H), 1.31–1.42 (m, 1H) ppm; ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): $\delta=157.9$ (C), 132.1 (C), 129.8 (CH), 113.7 (CH), 60.5 (CH), 55.1 (CH_3), 46.0 (CH_2), 41.2 (CH_2), 31.0 (CH_2), 24.7 (CH_2) ppm; IR: $\nu=3272$, 2956, 2873, 1608, 1539, 1512, 1493, 1453, 1402, 1362, 1311, 1246, 1173, 1152, 1109, 1059, 1034, 957, 906, 811, 767, 740 cm^{-1}; MS (25°C): m/z (%) = 191 (24) [M^+], 190 (11) [M^+-1], 174 (13), 162 (6), 147 (9), 134 (7), 121 (40), 112 (14), 91 (24), 89 (9), 78 (27), 71 (34), 70 (100), 68 (28), 65 (12); purity by GC: 99%. **21**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.90$–10.20 (br. s, 1H), 7.60 (s, 1H), 7.42–7.52 (m, 2H), 3.70 (d, $J=9.2$ Hz, 1H), 3.58 (d, $J=12.9$ Hz, 1H), 3.28–3.38 (m, 2H), 2.95 (t, $J=12.8$ Hz, 1H), 1.96–2.12 (m, 1H), 1.76–1.96 (m, 3H), 1.66 (d, $J=13.7$ Hz, 1H), 1.31–1.42 (m, 1H) ppm; ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): $\delta=138.2$ (C), 134.8 (C), 130.3 (CH), 129.5 (C, q, $J=33$ Hz), 128.7 (CH, q, $J=3.5$ Hz), 125.6 (CH, q, $J=3.8$ Hz), 123.4 (C, q, $J=272$ Hz), 56.3 (CH), 44.8 (CH_2), 36.9 (CH_2), 27.3 (CH_2), 22.2 (CH_2), 21.9 (CH_2) ppm; IR: $\nu=3117$, 3044, 2955, 2929, 2817, 2791, 2762, 2714, 2678, 2559, 2500, 2449, 2360, 2323, 2051, 1983, 1712, 1613, 1587, 1468, 1443, 1415, 1385, 1332, 1275, 1200, 1176, 1122, 1078, 1030, 990, 959, 933, 895, 828, 752, 729, 656, 600, 566, 533, 517 cm^{-1}; MS (60°C): m/z (%) = 277 (1) [M^+], 240 (3), 222 (12), 193 (11), 159 (6), 158 (4), 145 (2), 98 (2), 85 (17), 84 (100), 70 (2), 67 (3); purity by GC: 99%.