Regioselective Preparation of 2-Phenylethylamines from 1-Phenyl-2-alkylalkynes by Hydroamination/Reduction Sequences

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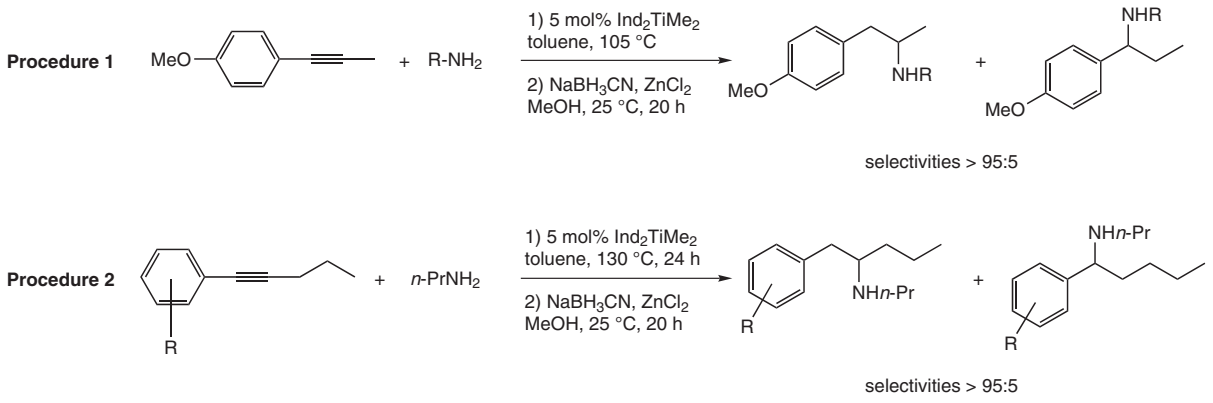
Abstract: Ind_2TiMe_2 is a highly active and general catalyst for the intermolecular hydroamination of alkynes. Particularly impressive is that Ind_2TiMe_2 makes it possible to perform hydroamination reactions of unsymmetrically substituted 1-phenyl-2-alkylalkynes with primary aryl-, *tert*-alkyl-, *sec*-alkyl-, and *n*-alkylamines in a highly regioselective fashion. Since the initially formed imines can easily be reduced with zinc-modified $NaBH_3CN$, 2-phenylethylamines are accessible in reliable one-pot procedures from 1-phenyl-2-alkylalkynes and primary amines on a 10 mmol scale.

Key words: alkynes, aminations, amines, catalysis, titanium



Scheme 1

Introduction

During the last five years, the development of catalytic procedures for the hydroamination of alkynes has attracted much attention.[1] With regard to scope and limitations, the use of titanium complexes as hydroamination catalysts has proven as the most important synthetic method among the various procedures.[2] Combined with a subsequent reduction of the initially formed imines, the Ti-catalyzed hydroamination must be seen as a new and powerful synthetic tool for the conversion of alkynes and primary amines into secondary amines. This interpretation is most impressively illustrated by the fact that corresponding hydroamination/reduction sequences have already been used for highly flexible synthetic approaches towards the synthesis of biologically interesting compounds (e.g. 2-arylethylamines, indolines, indolizidines, pyrrolizidines).[3]

Based on our initial finding that Cp_2TiMe_2 is a suitable catalyst for the inter- and intramolecular hydroamination of alkynes,[4] many other active Ti-catalysts have been identified by us[5] and others.[6–13] However, just recently we presented Ind_2TiMe_2 (Ind = indenyl) as the first general catalyst for the intermolecular addition of primary amines to alkynes that can be used for all possible substrate combinations. With this catalyst, primary aryl-, *tert*-alkyl-, *sec*-alkyl-, and *n*-alkylamines can be reacted with internal and terminal alkynes. Particularly impressive was the finding that Ind_2TiMe_2 makes it possible for the first time to perform hydroaminations of 1-phenylpropyne with sterically less demanding *n*-hexylamine and benzylamine in a highly anti-Markovnikov-selective fashion[14] (Scheme 1).

The catalyst Ind_2TiMe_2 can be synthesized in one-step from Ind_2TiCl_2 and methyllithium (Equation 1).[15] The complex is a stable crystalline yellow compound that can be conveniently handled in air for short periods of time. However, storage of Ind_2TiMe_2 under an atmosphere of argon or nitrogen in the refrigerator is recommended. In contrast, Ind_2TiMe_2 undergoes rapid decomposition in so-

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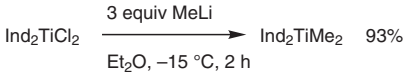
lution (Et_2O, toluene) at room temperature. Therefore, prolonged handling of Ind_2TiMe_2 in solution should be avoided. As a result, the preparation of Ind_2TiMe_2 should be performed at temperatures between –20 °C and –15 °C. Ind_2TiMe_2 is also commercially available from MCAT.[16]



Equation 1

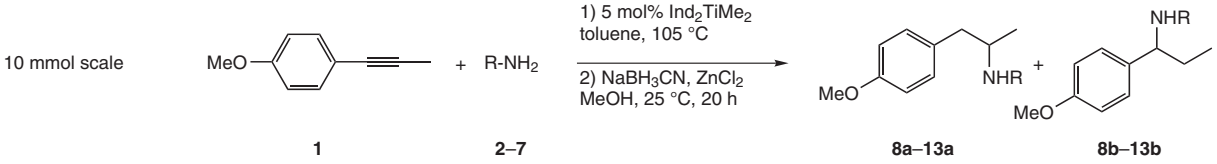
Since it is well established that the biological activity of 2-phenylethylamines is strongly influenced by the presence of a small alkyl substituent at the nitrogen atom and the presence of alkoxy groups at the benzene ring,[17] we additionally developed reliable one-pot procedures for the flexible synthesis of corresponding 2-phenylethylamines from 1-phenyl-2-alkylalkynes. These procedures are characterized by an efficient combination of an anti-Markovnikov-selective Ind_2TiMe_2-catalyzed hydroamination of 1-phenyl-2-alkylalkynes and a subsequent reduction of the initially formed imines.

Scope and Limitations

Equation 2 and Table 1 show some representative examples of one-pot hydroamination/reduction sequences of unsymmetrically substituted 1-(4-methoxyphenyl)propyne (**1**) and primary amines **2**–**7** employing 5 mol% Ind_2TiMe_2 as hydroamination catalyst on a 10 mmol scale. Usually, the initial hydroamination reactions are performed 1) by mixing all components together, and 2) by heating the reaction mixture to 105 °C under TLC-control (usually for 3–24 h). Subsequently, the reductions are performed by addition of a mixture of $NaBH_3CN$ and $ZnCl_2$ in MeOH (**Procedure 1**).[5a,18] It is worth mentioning that these reduction conditions are the result of comprehensive optimization studies. Although, other reduction protocols have been used as well, in our opinion, reductions employing $NaBH_3CN$ and $ZnCl_2$ secure optimal results of the hydroamination/reduction sequences.

As can be seen from Table 1, the yields of the desired 2-phenylethylamines possessing a methoxy group at the benzene ring are usually good to excellent. While hydroamination reactions employing arylamines (entries 1–3) usually need reaction times of approximately 24 hours to reach 100% conversion, alkylamines react significantly faster (3–5 h, entries 4–6). All hydroamination reactions occur with very good to excellent regioselectivities, whereby formation of the desired anti-Markovnikov regioisomer is favored. In this context it is worth to mention that the regioselectivity of hydroamination reactions of 2-alkyl-1-phenylalkynes is generally influenced by the nature of the alkyl substituent of the alkyne and the bulkiness of the primary amine. Increasing regioselectivity is observed with increasing size of the amine and decreasing size of the alkyl substituent of the alkyne.[14] After subsequent reduction, it is possible to separate the major regioisomer from the minor isomer by flash chromatography. To achieve a complete separation of the regioisomers it is usually necessary to perform two subsequent chromatographies. However, even after one chromatography the isolated yield of the major regioisomer is typically acceptable (Table 1).

While **Procedure 1** can be used for high-yielding regioselective hydroamination/reduction sequences of aryl-, *tert*-



Equation 2

Table 1 Reaction of 1-(4-Methoxyphenyl)propyne (**1**) with Amines **2**–**7**

Entry	Amine	R	Time (h)	Yield (**a** + **b**) (%)	Yield (**a**) (%)	Ratio **a**/**b**
1	**2**	Ph	24	97 (**8a/b**)	87[a] (**8a**)	>98:2
2	**3**	4-MeC_6H_4	24	90 (**9a/b**)	71[a] (**9a**)	>98:2
3	**4**	4-ClC_6H_4	24	98 (**10a/b**)	95[a] (**10a**)	98:2
4	**5**	*t*-Bu	5	70 (**11a/b**)	70 (**11a**)	>98:2
5	**6**	cyclopentyl	3	90 (**12a/b**)	68[a] (**12a**)	95:5
6	**7**	*i*-Pr	4	75 (**13a/b**)	66[a] (**13a**)	98:2

[a] Obtained after one chromatography. A complete separation of the regioisomers can be achieved by two subsequent chromatographies.

alkyl-, and *sec*-alkylamines, high boiling sterically less demanding *n*-alkyl- and benzylamines such as *n*-hexylamine and benzylamine need to be added slowly to the reaction mixture. In these cases, the speed of the amine addition needs to be optimized for each reaction.[14] Therefore, this publication does not contain a general procedure for reactions of these substrates. Procedures for transformations of sterically less demanding high-boiling *n*-alkyl- and benzylamines can be found elsewhere.[14]

However, to verify our recent finding that *n*-propylamine (**19**) represents the only sterically less demanding amine that does not need to be added slowly to the reaction mixture during the hydroamination reactions,[14] we developed a general procedure for a regioselective hydroamination/reduction sequence for 1-phenyl-2-alkylalkynes employing **19** on a 10 mmol scale. Equation 3 and Table 2 impressively show that Ind_2TiMe_2-catalyzed additions of *n*-propylamine (**19**) to unsymetrically substituted 1-phenyl-2-alkylalkynes possessing a sterically less demanding alkyl substituent strongly favor the formation of the anti-Markovnikov regioisomers. However, to get the best results on a 10 mmol scale these hydroamination reactions employing *n*-propylamine (**19**) need to be performed at 130 °C (**Procedure 2**). After subsequent reduction with $NaBH_3CN/ZnCl_2$, biologically interesting 2-phenylethylamine derivatives possessing an *n*-propyl substituent at the nitrogen atom are obtainable with good yields and very good regioselectivities. Usually, it is possible to separate the major regioisomer from the minor isomer by flash chromatography (see above). Unfortunately, the same procedure does not give satisfactory results for *ortho*-substituted (MeO, Cl) 1-phenyl-2-alkylalkynes. In these cases, the hydroamination reactions reach only a 30% conversion within 24 hours. However, hydroamination reactions of corresponding substrates under harsher conditions (140 °C, 48 h, 10 mol% Ind_2TiMe_2) combined with reductions gave the corresponding amine products in 55–72% yield.

In summary, 2-phenylethylamines are easily accessible in good to excellent yields from 1-phenyl-2-alkylalkynes and primary amines by hydroamination/reduction sequences employing Ind_2TiMe_2 as highly active and general hydroamination catalyst and zinc-modified $NaBH_3CN$ as reducing agent. Particularly important is the fact that with Ind_2TiMe_2 as the hydroamination catalyst, all possible substrate combinations of alkynes and primary amines can be used. However, the Procedures 1 and 2 given in the experimental part are limited to reactions of aryl-, *tert*-alkyl, and *sec*-alkylamines as well as *n*-propylamine (**19**). Procedures for transformations of sterically less demanding *n*-alkyl- and benzylamines can be found elsewhere.[14]

Table 2 Reaction of Alkynes **14**–**18** with *n*-Propylamine (**19**)

Entry	Alkyne	R	Yield (**a** + **b**) (%)	Yield **a** (%)	Ratio **a/b**
1	**14**	H	80 (**20a/b**)	71[a] (**20a**)	96:4
2	**15**	4-MeO	84 (**21a/b**)	63[a] (**21a**)	96:4
3	**16**	4-Cl	82 (**22a/b**)	63[a] (**22a**)	95:5
4	**17**	3-MeO	83 (**23a/b**)	73[a] (**23a**)	95:5
5	**18**	3-Cl	82 (**24a/b**)	72[a] (**24a**)	96:4

[a] Obtained after one chromatography. A complete separation of the regioisomers can be achieved by two subsequent chromatographies.

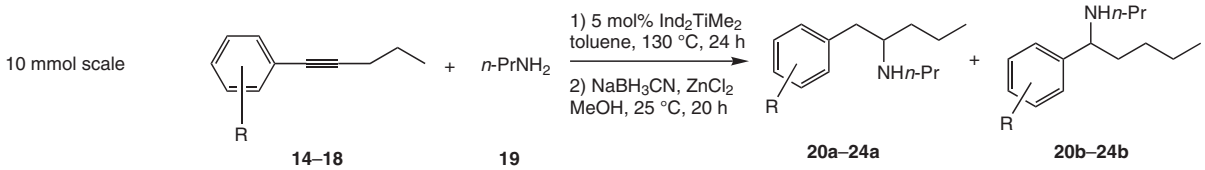
All reactions were performed under argon in flame dried Duran glassware (e.g. Schlenk tubes equipped with Teflon stopcocks). Toluene was distilled from molten sodium under argon. MeOH was dried with molecular sieves (3 Å). Alkynes and amines were distilled and stored over molecular sieves (4 Å). All other reagents were purchased from commercial sources and were used without further purification. All amine products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy. Additional characterization data were obtained by CHN elemental analysis. All ^{1}H NMR spectra are reported in δ units ppm downfield from tetramethylsilane internal standard. The ^{13}C NMR spectra are reported in δ units ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm or the triplet for C_6D_6 at 128.5 ppm. Characterization data are only given for representative examples. PE = light petroleum ether (bp 40–60 °C).

Ind_2TiMe_2[15]

To a mixture of Ind_2TiCl_2 (1.00 g, 2.87 mmol) and Et_2O (30 mL) was added dropwise a 1.6 M solution of MeLi in Et_2O (5.4 mL, 8.61 mmol) over a period of 5 min at –15 °C. After stirring the mixture for 2 h at –15 °C, the resulting orange solution was carefully poured onto a mixture of H_2O and ice (30 mL). The organic layer was separated and dried (Na_2SO_4). After concentration under vacuum, Ind_2TiMe_2 (0.82 g, 93%) was obtained as a yellow crystalline compound. Note: Prolonged handling of Ind_2TiMe_2 in solution should be avoided.

^{1}H NMR (400 MHz, C_6D_6): δ = –0.48 (s, 6 H), 5.38 (t, *J* = 3.3 Hz, 2 H), 5.79 (d, *J* = 3.3 Hz, 4 H), 6.94 (dd, *J* = 6.5, 3.0 Hz, 4 H), 7.20 (dd, *J* = 6.5, 3.0 Hz, 4 H).

^{13}C NMR (100.6 MHz, APT, C_6D_6): δ = 51.4 (CH_3), 105.3 (CH), 117.6 (CH), 125.5 (CH), 125.6 (C), 125.7 (CH).



14–18 **19** **20a–24a** **20b–24b**

Equation 3

Procedure 1

Hydroamination/Reduction Sequence on a 10 mmol Scale Employing 1-(4-Methoxyphenyl)propyne (Table 1)

A 100 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with 1-(4-methoxyphenyl)propyne (**1**; 1.46 g, 10.0 mmol), the appropriate amine (11.0 mmol), Ind_2TiMe_2 (308 mg, 0.5 mmol, 5.0 mol%), and toluene (2.0 mL). The sealed Schlenk tube containing the reaction mixture was heated to 105 °C (TLC control). Then, the mixture was cooled to r.t. and a mixture of $NaBH_3CN$ (1.26 g, 20.0 mmol) and $ZnCl_2$ (1.36 g, 10.0 mmol) in MeOH (20 mL) was added. After this had been stirred at 25 °C for 20 h, CH_2Cl_2 (50 mL) and aq sat. Na_2CO_3 solution (20 mL) were added. The resulting mixture was filtered and the solid residue was washed with CH_2Cl_2 (50 mL). After extraction, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL) and the combined organic layers were dried (Na_2SO_4). After concentration under vacuum, the crude mixture of regioisomers was analyzed by GC (Table 1) and purified by flash chromatography (SiO_2) or Kugelrohr distillation.

Procedure 2

Hydroamination/Reduction Sequence on a 10 mmol Scale Employing *n*-Propylamine (Table 2)

A 100 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with the alkyne (10.0 mmol), *n*-propylamine (**19**; 650 mg, 11.0 mmol), Ind_2TiMe_2 (308 mg, 0.5 mmol, 5.0 mol%), and toluene (2.0 mL). The sealed Schlenk tube containing the reaction mixture was heated to 130 °C for 24 h (due to the small amount of volatile material in the 100 mL Schlenk tube, no special precautions were necessary for the reactions run at 130 °C). Then, the mixture was cooled to r.t. and a mixture of $NaBH_3CN$ (1.26 g, 20.0 mmol) and $ZnCl_2$ (1.36 g, 10.0 mmol) in MeOH (20 mL) was added. After this had been stirred at 25 °C for 20 h, CH_2Cl_2 (50 mL) and aq sat. Na_2CO_3 solution (50 mL) were added. The resulting mixture was filtered and the solid residue was washed with CH_2Cl_2 (20 mL). After extraction, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic layers were dried (Na_2SO_4). After concentration under vacuum, the crude mixture of regioisomers was analyzed by GC (Table 2) and purified by flash chromatography (SiO_2).

Amine 8a

Procedure 1 was used to synthesize amine **8a** from 1-(4-methoxyphenyl)propyne (**1**) and aniline (**2**). The reaction time of the hydroamination step was 24 h. After purification of the crude mixture of regioisomers by flash chromatography (SiO_2, PE–EtOAc, 10:1), amine **8a** (2.11 g, 87%) and a mixture of regioisomers **8a** and **8b** (0.24 g, 10%) were obtained.

IR (neat): 3399, 2962, 2929, 2834, 1601, 1505, 1455, 1318, 1247, 1178, 1153, 1034, 813, 750, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.3 Hz, 3 H), 2.62 (dd, *J* = 13.6, 7.4 Hz, 1 H), 2.83 (dd, *J* = 13.6, 4.8 Hz, 1 H), 3.45 (br s, 1 H), 3.64–3.72 (m, 1 H), 3.74 (s, 3 H), 6.58 (d, *J* = 7.7 Hz, 2 H), 6.67 (t, *J* = 7.4 Hz, 1 H), 6.81 (br d, *J* = 8.5 Hz, 2 H), 7.07 (br d, *J* = 8.5 Hz, 2 H), 7.16 (t, *J* = 7.7 Hz, 2 H).

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 20.0 (CH_3), 41.2 (CH_2), 49.3 (CH), 55.1 (CH_3), 113.3 (CH), 113.7 (CH), 117.0 (CH), 129.3 (CH), 130.3 (CH), 130.4 (C), 147.2 (C), 158.1 (C).

MS (25 °C): *m*/*z* (%) = 241 (6), 121 (13), 120 (100), 91 (2), 77 (6).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.36; H, 8.06; N, 5.85.

Amine 11a

Procedure 1 was used to synthesize amine **11a** from 1-(4-methoxyphenyl)propyne (**1**) and *tert*-butylamine (**5**). The reaction time of the hydroamination step was 5 h. Since only a single regioisomer was detected by gas chromatography, purification of the crude product was performed by Kugelrohr distillation under vacuum. Amine **11a** (1.56 g, 70%) was obtained as a colorless oil.

IR (neat): 2960, 1612, 1512, 1464, 1364, 1300, 1247, 1176, 1139, 1039, 816 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.05 (d, *J* = 6.3 Hz, 3 H), 2.51 (dd, *J* = 13.2, 7.4 Hz, 1 H), 2.60 (dd, *J* = 13.2, 7.0 Hz, 1 H), 2.92 (sext, *J* = 6.6 Hz, 1 H), 3.78 (s, 3 H), 6.82 (br d, *J* = 8.5 Hz, 2 H), 7.09 (br d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 23.8 (CH_3), 29.9 (CH_3), 45.4 (CH_2), 49.2 (CH), 50.8 (C), 55.8 (CH_3), 113.6 (CH), 130.1 (CH), 132.1 (C), 157.9 (C).

MS (25 °C): *m*/*z* (%) = 222 (9), 206 (1), 149 (10), 121 (12), 100 (100), 91 (2).

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.99; H, 10.51; N, 6.22.

Amine 21a

Procedure 2 was used to synthesize amine **21a** from 1-(4-methoxyphenyl)pentyne (**15**) and *n*-propylamine (**19**). After purification of the crude mixture of regioisomers by flash chromatography (SiO_2, PE–EtOAc, 1:1) amine **21a** (1.48 g, 63%) and a mixture of regioisomers **21a** and **21b** (0.49 g, 21%) were obtained.

IR (neat): 2956, 2931, 2872, 1612, 1512, 1465, 1300, 1247, 1177, 1127, 1039, 833, 807 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.4 Hz, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H), 1.21 (br s, 1 H), 1.33–1.48 (m, 6 H), 2.44–2.71 (m, 5 H), 3.79 (s, 3 H), 6.83 (br d, *J* = 8.8 Hz, 2 H), 7.10 (br d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 11.7 (CH_3), 14.3 (CH_3), 19.0 (CH_2), 23.4 (CH_2), 36.2 (CH_2), 39.8 (CH_2), 49.1 (CH_2), 55.1 (CH_3), 59.0 (CH), 113.7 (CH), 130.1 (CH), 131.8 (C), 157.9 (C).

MS (25 °C): *m*/*z* (%) = 236 (5), 192 (2), 121 (8), 114 (100), 72 (6).

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.24; H, 10.80; N, 5.94.

Amine 22a

Procedure 2 was used to synthesize amine **22a** from 1-(4-chlorophenyl)pentyne (**16**) and *n*-propylamine (**19**). After purification of the crude mixture of regioisomers by flash chromatography (SiO_2, PE–EtOAc, 1:1) amine **22a** (1.51 g, 63%) and a mixture of regioisomers **22a** and **22b** (0.46 g, 19%) were obtained.

IR (neat): 2957, 2930, 2872, 1492, 1465, 1407, 1378, 1129, 1092, 1016, 832, 801 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.92 (m, 6 H), 1.03 (br s, 1 H), 1.31–1.48 (m, 6 H), 2.45–2.59 (m, 2 H), 2.61–2.73 (m, 3 H), 7.11 (br d, *J* = 8.5 Hz, 2 H), 7.25 (br d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 11.7 (CH_3), 14.2 (CH_3), 18.9 (CH_2), 23.4 (CH_2), 36.1 (CH_2), 40.1 (CH_2), 49.1 (CH_2), 58.8 (CH), 128.3 (CH), 130.5 (CH), 131.7 (C), 138.3 (C).

MS (25 °C): *m*/*z* (%) = 240 (5), 196 (3), 125 (8), 114 (100), 72 (6).

Anal. Calcd for $C_{14}H_{22}ClN$: C, 70.13; H, 9.25, N, 5.84; Cl, 14.79. Found: C, 70.01; H, 9.34; N, 6.05; Cl, 14.87.

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References

(1) Reviews: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(2) Review: Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935.

(3) (a) Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2002**, 1213. (b) Bytschkov, I.; Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2003**, 2888.

(4) (a) Doye, S.; Haak, E. German Patent DE 19913522, **2000**; *Chem. Abstr.* **2000**, *133*, 266588. (b) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* **1999**, *38*, 3389; *Angew. Chem.* **1999**, *111*, 3584. (c) Bytschkov, I.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715. (d) For early studies on Ti-catalyzed intramolecular hydroaminations of alkynes, see: McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459. (e) See also: McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323. (f) See also: McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485.

(5) (a) Heutling, A.; Doye, S. *J. Org. Chem.* **2002**, *67*, 1961. (b) Pohlki, F.; Heutling, A.; Bytschkov, I.; Hotopp, T.; Doye, S. *Synlett* **2002**, 799.

(6) (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923. (b) Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475. (c) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956.

(7) (a) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967. (b) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011. (c) Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853. (d) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chem. Commun.* **2003**, 586. (e) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880. (f) Li, Y.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 1794.

(8) (a) Tillack, A.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2541; *Angew. Chem.* **2002**, *114*, 2646. (b) Garcia Castro, I.; Tillack, A.; Hartung, C. G.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 3217. (c) Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* **2003**, *5*, 4767. (d) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 3123. (e) Tillack, A.; Jiao, H.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2409.

(9) (a) Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *Organometallics* **2002**, *21*, 2839. (b) Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 8100.

(10) (a) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2462. (b) Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733.

(11) Ackermann, L. *Organometallics* **2003**, *22*, 4367.

(12) Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845.

(13) Ward, B. D.; Maisse-Francois, A.; Mountford, P.; Gade, L. H. *Chem. Commun.* **2004**, 704.

(14) Heutling, A.; Pohlki, F.; Doye, S. *Chem. Eur. J.* **2004**, *10*, 3059.

(15) Balboni, D.; Camurati, I.; Prini, G.; Resconi, L.; Galli, S.; Mercandelli, P.; Sironi, A. *Inorg. Chem.* **2001**, *40*, 6588; and references cited therein.

(16) www.mcat.de.

(17) Lüllmann, H.; Mohr, K.; Ziedler, K. *Taschenatlas der Pharmakologie*, 3rd ed.; Thieme: Stuttgart, **1996**, 80.

(18) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927.