Notes

$Cp^*_2TiMe_2$: An Improved Catalyst for the Intermolecular Addition of *n*-Alkyl- and Benzylamines to Alkynes

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Abstract: $Cp^*_2TiMe_2$ has been found to be a competent catalyst for the intermolecular addition of sterically less demanding *n*-alkyl- and benzylamines to internal alkynes. In the presence of 2.0−6.0 mol % of the catalyst, hydroamination reactions between *n*-propyl-, *n*-hexyl-, benzyl-, *p*-methoxybenzyl- or 2-phenylethylamine and diphenylacetylene, 3-hexyne or 4-octyne go to completion within 24 h or less at 114 °C (oil bath temperature). After subsequent reduction of the initially formed imines with zinc-modified sodium cyanoborohydride in MeOH at 25 °C, the corresponding secondary amines can be isolated in excellent yields (>78%). Hydroamination/reduction sequences employing the unsymmetrically substituted alkyne 1-phenylpropyne give access to mixtures of regioisomeric secondary amines. The observed regioselectivity is low.

The addition of ammonia or primary and secondary amines to nonactivated alkenes and alkynes is potentially the most efficient approach toward the synthesis of higher substituted nitrogen-containing products. It represents the most atom economic process for the formation of amines, imines and enamines, which are important bulk and fine chemicals or building blocks in organic chemistry. Therefore, the hydroamination of alkenes and alkynes is of fundamental interest for organic chemistry. However, at the moment only a few efficient hydroamination methods are known.[1−5]

Recently, we found that titanium complexes can be used as catalysts for the intermolecular hydroamination of alkynes. Among the investigated titanium compounds, Cp_2TiMe_2[6] was found to be the most efficient catalyst.[7] With this catalyst, primary aryl- and alkylamines can be coupled to symmetrically and unsymmetrically substituted alkynes. In the case of arylalkylalkynes, the reaction occurs with high regioselectivity, forming the anti-Markovnikov products exclusively. In contrast, reactions employing terminal alkynes lead to regioisomeric mixtures.[8] While aniline derivatives and sterically hindered *sec*- and *tert*-alkylamines react smoothly under the reaction conditions (100−110 °C, toluene) a significant

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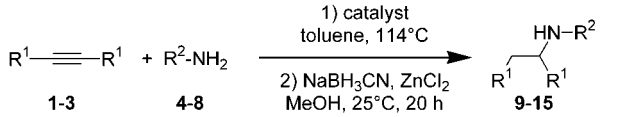
decrease in reactivity was observed for sterically less hindered *n*-alkyl- and benzylamines. For example, the obtained yields for addition reactions of *n*-hexylamine or benzylamine to diphenylacetylene were below 20% when Cp_2TiMe_2 was used as catalyst.[7b] However, a mechanistic investigation showed that unfavorable equilibria between titanium imido complexes, imido complex dimers, and bisamides which are involved in the catalytic cycle are responsible for the decreased reactivity of sterically less demanding amines.[9] The mentioned investigation further suggested that the use of bigger ligands at the titanium center should result in accelerated reactions of sterically less demanding amines.

Since the pentamethylcyclopentadienyl ligand (Cp*) is much more space demanding than the cyclopentadienyl ligand (Cp), we decided to investigate the catalytic properties of $Cp^*_2TiMe_2$.[10,11] In an initial experiment, diphenylacetylene **1** (1.0 equiv) was reacted with *n*-propylamine **4** (1.1 equiv) in the presence of 6.0 mol % $Cp^*_2TiMe_2$ at 114 °C (oil bath temperature) in toluene. TLC-control showed that the reaction reached 100% conversion after 4 h. After subsequent reduction performed with zinc-modified $NaBH_3CN$[12] in methanol at 25 °C the amine **9** was isolated in 86% yield (Table 1, entry 1). In comparison, an identical hydroamination reaction performed with 6.0 mol % Cp_2TiMe_2 did not even reach 100% conversion after 48 h. In this case, the subsequent reduction gave access to only 10% of the desired amine **9**. Furthermore, 65% of diphenylacetylene **1** could be recovered (Table 1, entry 4). While the hydroamination reaction was very clean in the presence of $Cp^*_2TiMe_2$, several side products were observed in the case of Cp_2TiMe_2. A similar behavior was observed for the addition of *p*-methoxybenzylamine **5** (PMB−NH_2) to diphenylacetylene **1** followed by reduction. With $Cp^*_2TiMe_2$ as the catalyst, the hydroamination reaction went to completion within 6 h. After reduction, the corresponding amine **10** was obtained in 97% yield (Table 1, entry 5). In the case of Cp_2TiMe_2, the same hydroamination did not reach 100% conversion after 48 h. After reduction, a sluggish reaction mixture was obtained. Purification by chromatography afforded 65% of recovered diphenylacetylene **1**. However, isolation of the desired amine **10** was not possible in pure form (Table 1, entry 6). In an additional hydroamination/reduction sequence employing **1** and *n*-hexylamine **6**, the secondary amine **11** was formed in 89% yield (Table 1, entry 7). In this case, the hydroamination reaction was complete after 5 h (TLC control). Inspired by the mentioned results, we tried to minimize the amount of the hydroamination catalyst for the representative reaction sequence between **1** and **4**

Table 1. Synthesis of Secondary Amines via Hydroamination/Reduction Sequences Employing Alkynes and *n*-Alkyl or Benzylamines as Starting Materials



entry	alkyne	amine	catalyst	time[a] [h]	product	yield[b] [%]
1	Ph—≡—Ph **1**	*n*-Pr-NH_2 **4**	$Cp^*_2TiMe_2$ 6.0 mol %	4	HN−*n*-Pr, Ph, Ph **9**	86
2	**1**	**4**	$Cp^*_2TiMe_2$ 3.0 mol %	8	**9**	82
3	**1**	**4**	$Cp^*_2TiMe_2$ 2.0 mol %	12	**9**	89
4	**1**	**4**	Cp_2TiMe_2 6.0 mol %	48	**9**	10[c]
5	**1**	PMB-NH_2 **5**	$Cp^*_2TiMe_2$ 6.0 mol %	6	HN−PMB, Ph, Ph **10**	97
6	**1**	**5**	Cp_2TiMe_2 6.0 mol %	48	**10**	--[c,d]
7	**1**	*n*-Hex-NH_2 **6**	$Cp^*_2TiMe_2$ 6.0 mol %	5	HN−*n*-Hex, Ph, Ph **11**	89
8	Et—≡—Et **2**	**5**	$Cp^*_2TiMe_2$ 6.0 mol %	24[e]	HN−PMB, Et, Et **12**	91
9	**2**	Bn-NH_2 **7**	$Cp^*_2TiMe_2$ 6.0 mol %	24[e]	HN−Bn, Et, Et **13**	87
10	**2**	Bn, NH_2 **8**	$Cp^*_2TiMe_2$ 6.0 mol %	24[e]	Bn, HN, Et, Et **14**	78
11	Pr—≡—Pr **3**	**8**	$Cp^*_2TiMe_2$ 6.0 mol %	24[e]	Bn, HN, Pr, Pr **15**	82

[a] Reaction time of the hydroamination step. [b] Reaction conditions: (a) alkyne (2.40 mmol), amine (2.64 mmol), catalyst (2.0−6.0 mol %), toluene (1.0 mL), 114 °C; (b) $NaBH_3CN$ (4.80 mmol), $ZnCl_2$ (2.40 mmol), MeOH (10.0 mL), 25 °C, 20 h. [c] 65% diphenylacetylene **1** could be recovered. [d] The product could not be isolated in pure form. [e] The reaction time has not been minimized.

(Table 1, entries 2 and 3). During this study, we found that a catalyst loading of 2.0 mol % $Cp^*_2TiMe_2$ is sufficient to obtain **9** in excellent yield (89%, 12 h reaction time of the hydroamination step at 114 °C). However, in several experiments, no complete conversion was observed with catalyst loadings below 2.0 mol %. The reason for this is probably hydrolysis of the catalyst caused by trace amounts of water present on the glassware or in the starting materials.

With the mentioned results in mind, we tried to react the dialkylalkynes 3-hexyne **2** and 4-octyne **3** with various benzyl- and *n*-alkylamines. In all investigated reaction sequences (Table 1, entries 8−11), the desired amines (**12**−**15**) were obtained in high yields (78−91%). Due to the low boiling points of 3-hexyne **2** and 4-octyne

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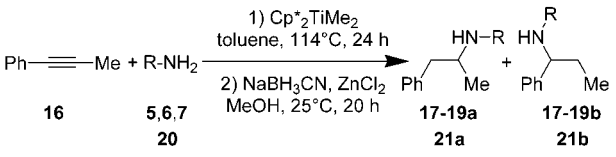
Table 2. Observed Regioselectivity for Hydroamination/ Reduction Sequences Employing 1-Phenylpropyne 16



entry	amine	$Cp^*_2TiMe_2$ [mol %]	product	yield[a] [%]	product	yield[a] [%]
1	PMB-NH_2 **5**	3.0	**17a**	46	**17b**	36
2	*n*-Hex-NH_2 **6**	6.0	**18a**	52	**18b**	41
3	Bn-NH_2 **7**	6.0	**19a**	70	**19b**	24
4	*p*-Tol-NH_2 **20**	6.0	**21a**	92	**21b**	3

[a] Reaction conditions: (a) alkyne (2.40 mmol), amine (2.64 mmol), $Cp^*_2TiMe_2$ (3.0 or 6.0 mol %), toluene (1.0 mL), 114 °C, 24 h (not minimized); (b) $NaBH_3CN$ (4.80 mmol), $ZnCl_2$ (2.40 mmol), MeOH (10.0 mL), 25 °C, 20 h.

3, hydroamination reactions employing these alkynes have not been followed by TLC control. Therefore, the reaction times have not been minimized. All of these reactions were stopped after 24 h. Subsequently, the obtained reaction mixtures were reduced under standard conditions to give the desired products.

On the basis of these results, we focused on reactions of the unsymmetrically substituted alkylarylalkyne 1-phenylpropyne **16**. Hydroamination/reduction sequences using $Cp^*_2TiMe_2$ as hydroamination catalyst were performed with *p*-methoxybenzyl- **5**, *n*-hexyl- **6**, and benzylamine **7** in toluene. All hydroamination reactions were performed at 114 °C (oil bath temperature). The reaction time was always 24 h (not minimized). The catalyst loading was 3.0 or 6.0 mol %. As can be seen from Table 2, mixtures of regioisomers were isolated from all mentioned reaction sequences (Table 2, entries 1−3). While the observed regioselectivities are low, the obtained yields of both regioisomers are high (82−94%) and the anti-Markovnikov products (**17a**, **18a**, **19a**) represent the major product in all three investigated examples.

In addition, a control experiment employing the sterically more demanding amine 4-methylaniline **20** (*p*-Tol-NH_2) was carried out in the presence of $Cp^*_2TiMe_2$ (Table 2, entry 4). Interestingly, in this case the anti-Markovnikov product **21a** was isolated in 92% yield and only trace amounts of the regioisomeric product **21b** (3%) were obtained (yield (**21a** + **21b**) 95%, selectivity ~ 97:3). An additional experiment employing amine **20** gave access to a comparable mixture of regioisomers (yield (**21a** + **21b**) 95%, selectivity ~98:2) when Cp_2TiMe_2 was used as the catalyst under identical conditions. These results indicate that obviously the properties of the employed amines (and not the Cp*-ligands) are responsible for the low regioselectivity of $Cp^*_2TiMe_2$-catalyzed hydroamination reactions performed with sterically less demanding *n*-alkyl- and benzylamines.

Finally, we focused on reactions of terminal alkynes. For that purpose, we performed hydroamination reactions with phenylacetylene, *p*-methoxyphenylacetylene and 1-hexyne in the presence of 6.0 mol % $Cp^*_2TiMe_2$ at 114 °C employing the amines **5** and **6** (reaction times 1−24 h). However, after reduction we were not able to isolate any hydroamination products from the obtained complex reaction mixtures. In all investigated reactions, several new products without an amine function were formed (probably by alkyne oligo- or polymerization).

In summary, the presented results clearly indicate that $Cp^*_2TiMe_2$ represents an excellent catalyst for the intermolecular addition of various sterically less hindered *n*-alkyl- and benzylamines to internal alkynes. Therefore, the developed procedure strongly expands the scope of the titanocene-catalyzed intermolecular hydroamination of alkynes. The imines, initially obtained from the hydroamination reactions, can be reduced with $NaBH_3CN$ in the presence of $ZnCl_2$ to give secondary amines in high yields. If the unsymmetrically disubstituted alkyne 1-phenylpropyne is used, mixtures of regioisomers are obtained. Further investigations dealing with the addition of ammonia to alkynes are currently underway in our laboratories.

Experimental Section

All reactions were performed under an inert atmosphere of argon in flame dried Duran glassware (e.g., Schlenk tubes equipped with Teflon stopcocks). Toluene was distilled from molten sodium under argon. Methanol was distilled and stored over molecular sieves (4 Å). $Cp^*_2TiMe_2$ was synthesized according to a literature procedure.[10] Diphenylacetylene **1** was dissolved in CH_2Cl_2, dried over Na_2SO_4, and recovered by evaporation of the solvent. The alkynes **2** and **3** as well as the amines **4**−**8** were distilled and stored over molecular sieves (4 Å). All other reagents were purchased from commercial sources and were used without further purification. PE: light petroleum, bp 40−60 °C.

General Procedure. A Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with the alkyne (2.40 mmol), the amine (2.64 mmol), $Cp^*_2TiMe_2$ (50 mg, 0.144 mmol, 6.0 mol %), and toluene (1.0 mL). The resulting mixture was heated to 114 °C (oil bath temperature; reaction times are given in the following paragraphs, Tables 1 and 2, and the Supporting Information). Then the mixture was cooled to room temperature, and a suspension of $NaBH_3CN$ (302 mg, 4.80 mmol) and $ZnCl_2$ (326 mg, 2.40 mmol) in methanol (10 mL) was added. After being stirred for 20 h at room temperature, the mixture was filtered. The solid residue was washed with CH_2Cl_2 (50 mL), and saturated Na_2CO_3 solution (20 mL) was added to the filtrate. After extraction, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (6× 50 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under vacuum and flash chromatography on silica gel afforded the pure amine derivative.

Amine 9. The general procedure was used to convert **1** and **4** into the title compound. The reaction time of the hydroamination step was 4 h. Purification by flash chromatography (PE/EtOAc, 3:1) afforded amine **9** (494 mg, 2.06 mmol, 86%) as colorless oil: IR (neat) ν 1602, 1494, 1453, 756, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10−7.35 (m, 10H), 3.83 (dd, J = 5.9, 8.0 Hz, 1H), 2.93 (dd, J = 5.9, 13.4 Hz, 1H), 2.88 (dd, J = 8.2, 13.4 Hz, 1H), 2.28−2.41 (m, 2H), 1.51 (br. s, 1H), 1.37 (sex, J = 7.3 Hz, 2H), 0.76 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$) δ 144.1 (C), 139.0 (C), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 126.9 (CH), 126.3 (CH), 64.8 (CH), 49.6 (CH_2), 45.3 (CH_2), 23.1 (CH_2), 11.6 (CH_3); MS (25 °C) *m*/*z* 239 (2) [M^+], 148 (100) [$M^+ - C_7H_7$]. Anal. Calcd. for $C_{17}H_{21}N$: C, 85.31; H, 8.84; N, 5.85. Found: C, 84.91; H, 8.82; N, 5.88.

Amine 13. The general procedure was used to convert **2** and **7** into the title compound. The reaction time of the hydroami-

nation step was 24 h. Purification by flash chromatography (PE/EtOAc, 5:1) afforded amine **13** (399 mg, 2.09 mmol, 87%) as colorless oil: IR (neat) ν 1603, 1494, 1454, 731, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17−7.35 (m, 5H), 3.77 (d, J = 13.1 Hz, 1H), 3.74 (d, J = 13.1 Hz, 1H), 2.50 (quin, J = 5.8 Hz, 1H), 1.26−1.52 (m, 7H), 0.90 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$) δ 141.1 (C), 128.3 (CH), 128.1 (CH), 126.7 (CH), 57.8 (CH), 51.2 (CH_2), 35.9 (CH_2), 26.2 (CH_2), 18.9 (CH_2), 14.4 (CH_3), 9.8 (CH_3); MS (25 °C) m/z 191 (4) [M^+], 162 (72) [$M^+ - C_2H_5$], 148 (72) [$M^+ - C_3H_7$], 91 (100) [$C_7H_7^+$]. Anal. Calcd. for $C_{13}H_{21}N$: C, 81.62; H, 11.06; N, 7.32. Found: C, 81.31; H, 11.36; N, 7.72.

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Supporting Information Available: Experimental details and characterization data for compounds **10**, **11**, **12**, **14**, **15**, **17a**, **17b**, **18a**, **18b**, **19a**, **19b**, **21a** and **21b** (6 pages). This material is available free of charge via the Internet at http://pubs.acs.org. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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