Homogeneous Catalysis

Hydroamination/Hydrosilylation Sequence Catalyzed by Titanium Complexes**

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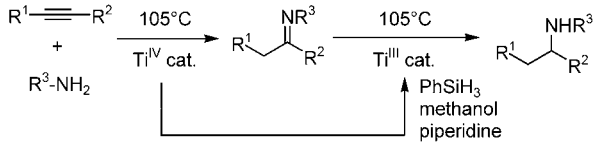
Over the past few years, strategies for the one-pot synthesis of interesting target molecules that require more than one chemical transformation have gained increasing attention. In this context, the use of a single catalyst for a combination of different catalytic reactions (multifunctional catalysis) is one of the most promising approaches.[1] One way to realize a corresponding strategy is the combination of different transitions-metal-catalyzed reactions into a sequence. In this case, a single catalyst that mediates several consecutive reactions is used for the one-pot process. Each individual reaction is initiated by a change of the reaction conditions or the addition of a new reagent.[2]

During the last few years, we have been intensively involved in the development of the Ti-catalyzed hydroamination of alkynes, which converts alkynes and primary amines into imines in the presence of Ti^{IV} catalysts.[3] The corresponding imine products were usually reduced with stoichiometric amounts of $NaBH_3CN$ to give secondary amines. Herein, for the first time, we describe a sequential combination of the Ti-catalyzed hydroamination of alkynes with the Ti-catalyzed reduction of imines.[4] By this new reaction sequence, alkynes and primary amines can be converted into secondary amines in a fully catalytic one-pot protocol employing a single Ti-precatalyst (Scheme 1).[5]



Scheme 1. Ti-catalyzed hydroamination/hydrosilylation sequence.

The catalytically active species involved in the Ti-catalyzed reduction (hydrogenation, hydrosilylation) of imines is presumed to be a Ti^{III} hydride.[4b] This species is generated in situ immediately prior to the reaction from a Ti^{IV} precursor

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and a reducing agent. Since a Ti^{IV} species remains in the reaction mixture obtained after a successful hydroamination of an alkyne, we assumed that this Ti^{IV} compound can also be converted into a Ti^{III}-species, which then catalyzes the reduction of the generated imine. To verify this assumption, a mixture of 1-phenylpropyne (**1**) and aniline (**2**) in toluene was heated to 105 °C for 24 h in the presence of 10 mol % $[Cp_2TiMe_2]$.[6] Subsequently, phenylsilane (3 equiv), piperidine (40 mol %), and MeOH (40 mol %)[4d] were added, and the resulting mixture was heated to 105 °C for additional 24 h.[6] After aqueous workup (decomposition of NSi compounds), the corresponding secondary amine **12a** was isolated in 85 % yield [Eq. (1), Table 1, entry 1].

With this promising result in hand, we performed a number of hydroamination/hydrosilylation sequences under identical reaction conditions employing 1-phenylpropyne (**1**) and various amines [Eq. (1), Table 1]. We found that aromatic amines (entries 1–8) gave comparable good results as long as they do not possess an *ortho* substituent. While the hydrosilylation reaction still proceeded slowly in the case of 2-methylaniline (**7**; 57 % yield after a hydrosilylation reaction time of 48 h), no successful reduction was observed when the sterically very demanding 2,6-dimethylaniline (**8**) was used. However, worse results were obtained with alkyl amines (entries 9–12). In these cases, under the employed reaction conditions, the desired secondary amines could be isolated in only modest to poor yields, even when the reaction time for the hydrosilylation was extended to 48 h.[7] Since the regioselectivity of the reaction sequence is generally determined during the hydroamination step, the ratios of the regioisomeric secondary amines are very good to excellent, as expected.[3] Additionally, two reaction sequences were performed with the *ansa* complex **22**[8] as the precatalyst (entries 5, 11). Both reactions also led to the formation of the desired secondary amines.

We also investigated the performance of various alkynes in Ti-catalyzed hydroamination/hydrosilylation sequences. For that purpose, we compared several reaction sequences employing 4-methylaniline (**5**) and the alkynes **1** and **23**–**29** [Eq. (2), Table 2]. We found that 1-phenylpropyne derivatives (**1**, **23**, **24**) and terminal alkynes (**25**–**27**) were very good substrates, while sterically more demanding alkynes such as diphenylacetylene (**28**) and 3-hexyne (**29**) gave worse results. In the case of highly reactive terminal alkynes, very good results were obtained in the presence of only 5 mol % of the catalyst. Furthermore, only short reaction times (3 h) were necessary for the hydroamination step. The observed regioselectivities were again in the expected ranges for the various substrates.[3]

Finally, we focused on intramolecular reaction sequences of aminoalkynes **37** and **38** [Eq. (3), Table 3]. In addition to $[Cp_2TiMe_2]$ and **22** we also employed the chiral catalysts [(*S*,*S*)-(ebthi)$TiMe_2$] (**41**)[4] and (*R*,*R*)-**42**[9] (ebthi = ethylene-1,2-bis(η^2-4,5,6,7-tetrahydro-1-indenyl). The expected cyclic secondary amines **39** and **40** were obtained in modest to good yields in all cases, and the products were generated in enantiomerically enriched form (up to 66 % *ee*) when [(*S*,*S*)-(ebthi)$TiMe_2$] (**41**) and (*R*,*R*)-**42** were used as precatalysts.[10,11]

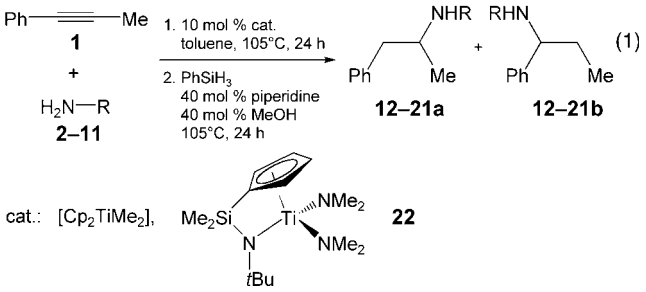
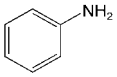
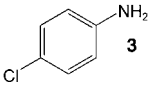
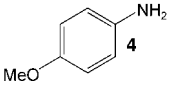
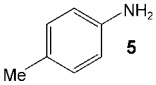
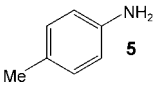
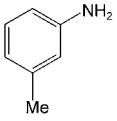
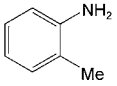
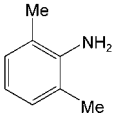
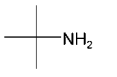
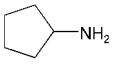
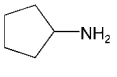
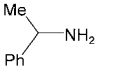
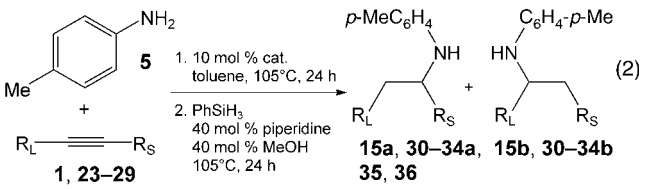


Table 1: Intermolecular Ti-catalyzed hydroamination/hydrosilylation sequence employing various amines [Eq. (1)].

Entry	Amine	Cat.	Yield [%][a]	Sel. **a**/**b**[b]
1	 **2**	$[Cp_2TiMe_2]$	85 (**12a**)	99:1
2	 **3**	$[Cp_2TiMe_2]$	83 (**13a**)	99:1
3	 **4**	$[Cp_2TiMe_2]$	86 (**14a**)	99:1
4	 **5**	$[Cp_2TiMe_2]$	85 (**15a**)	99:1
5	 **5**	**22**	99[c] (**15a**)	99:1
6	 **6**	$[Cp_2TiMe_2]$	71 (**16a**)	99:1
7	 **7**	$[Cp_2TiMe_2]$	35 (**17a**), 57[d] (**17a**)	99:1
8	 **8**	$[Cp_2TiMe_2]$	–[d] (**18a**)	
9	 **9**	$[Cp_2TiMe_2]$	6[d] (**19a**)	99:1
10	 **10**	$[Cp_2TiMe_2]$	39[d] (**20a**/**b**)	95:5
11	 **10**	**22**	44[c,d] (**20a**/**b**)	95:5
12	 **11**	$[Cp_2TiMe_2]$	11[d] (**21a**/**b**)	92:8

[a] Reaction conditions: 1) alkyne **1** (2.40 mmol), amine (2.64 mmol), $[Cp_2TiMe_2]$ (0.33 mol L^{-1} in toluene, 0.24 mmol, 10 mol %), toluene (0.28 mL), 105 °C, 24 h; 2) $PhSiH_3$ (7.20 mmol), piperidine (0.96 mmol, 40 mol %), MeOH (0.96 mmol, 40 mol %), 105 °C, 24 h. Yields refer to isolated compounds. Reaction times have not been minimized. All hydroamination reactions reached 100 % conversion. [b] GC–MS analysis prior to chromatography. [c] **22** (0.24 mmol, 10 mol %), toluene (1.0 mL). [d] The reaction time of the hydrosilylation step was 48 h.

We have shown that a sequential combination of the Ti-catalyzed hydroamination of alkynes with the Ti-catalyzed hydrosilylation of imines, which employs simple precatalysts, is an efficient and fully catalytic one-pot process for the conversion of alkynes and primary amines into secondary amines. The application of related Ti precatalysts is presently under investigation in our laboratories.



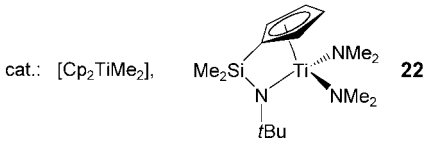


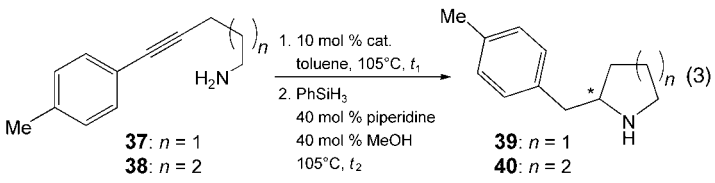
Table 2: Intermolecular Ti-catalyzed hydroamination/hydrosilylation sequence employing various alkynes [Eq. (2)].

Entry	Alkyne	Cat.	Yield [%][a]	Sel. **a**/**b**[b]
1	Ph—≡—Me **1**	$[Cp_2TiMe_2]$	85 (**15a**)	99:1
2	4-MeOC$_6$H$_4$—≡—Me **23**	$[Cp_2TiMe_2]$	83 (**30a**)	98:2
3	4-ClC$_6$H$_4$—≡—Me **24**	$[Cp_2TiMe_2]$	86 (**31a**)	98:2
4	*n*C$_6$H$_{13}$—≡—H **25**	$[Cp_2TiMe_2]$	88[c,d,e] (**32a**/**b**)	31:69
5	Ph—≡—H **26**	$[Cp_2TiMe_2]$	65[c,d] (**33a**/**b**)	57:43
6	Ph—≡—H **26**	**22**	50[c,f] (**33a**/**b**)	76:24[g]
7	Ph—≡—H **27**	$[Cp_2TiMe_2]$	76[c,d,e] (**34a**/**b**)	39:61
8	Ph—≡—Ph **28**	$[Cp_2TiMe_2]$	31 (**35**)	
9	Et—≡—Et **29**	$[Cp_2TiMe_2]$	33 (**36**)	

[a] Reaction conditions: 1) alkyne (2.40 mmol), amine **5** (2.64 mmol), $[Cp_2TiMe_2]$ (0.33 mol L^{-1} in toluene, 0.24 mmol, 10 mol%), toluene (0.28 mL), 105 °C, 24 h; 2) $PhSiH_3$ (7.20 mmol), piperidine (0.96 mmol, 40 mol%), MeOH (0.96 mmol, 40 mol%), 105 °C, 24 h. Yields refer to isolated compounds. Reaction times have not been minimized. All hydroamination reactions reached 100% conversion. [b] GC—MS analysis prior to chromatography. [c] The reaction time of the hydroamination step was 3 h. [d] Prior to the addition of alkyne, $[Cp_2TiMe_2]$, amine **5**, and toluene were heated to 105 °C for 90 min. [e] Reaction conducted with 5 mol% $[Cp_2TiMe_2]$, 20 mol% piperidine, and 20 mol% MeOH. [f] Reaction conducted with **22** (0.24 mmol, 10 mol%) and toluene (1.0 mL). [g] Small amounts of the imine that corresponds to amine **33b** were observed, **a**/**b** (including imine) 69:31.

Experimental Section

A Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with 1-phenylpropyne (**1**, 279 mg, 2.40 mmol), 4-methylaniline (**5**, 283 mg, 2.64 mmol), $[Cp_2TiMe_2]$ (0.72 mL, 0.33 M in toluene, 0.24 mmol, 10.0 mol%), and toluene (0.28 mL). The resulting mixture was heated to 105 °C for 24 h. The brown mixture was then cooled to room temperature, and phenylsilane (0.89 mL, 7.20 mmol), piperidine (95 μL, 96 mmol), and methanol (39 μL, 0.96 mmol) were added. The mixture was heated to 105 °C for further 24 h, cooled to room temperature, diluted with Et_2O (25 mL), and poured into 1 N aqueous NaOH (25 mL). After this mixture had been stirred at 25 °C for 20 h, the organic layer was separated. The aqueous layer was extracted with Et_2O (4 × 30 mL), and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum, the residue was purified by flash chromatography (SiO_2).



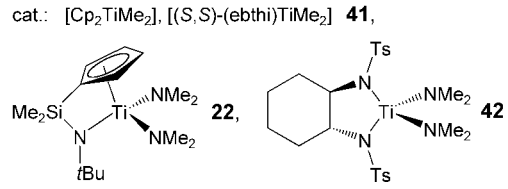


Table 3: Intramolecular Ti-catalyzed hydroamination/hydrosilylation sequence employing various aminoalkynes [Eq. (3)].

Entry	*n*	Cat.	t_1 [h]	t_2 [h]	Yield [%][a]	*ee* [%][b]
1	1	$[Cp_2TiMe_2]$	6	22	62 (**39**)	–
2	1	**22**	6	22	82 (**39**)	–
3	1	**41**	15	36	46 (**39**)	66
4	1	**42**	6	36	68 (**39**)	25
5	2	**22**	6	22	68 (**40**)	–
6	2	**41**	15	36	50 (**40**)	60
7	2	**42**	6	36	68 (**40**)	55

[a] Reaction conditions: 1) aminoalkyne (1.0 mmol), cat. (0.1 mmol, 10 mol%), toluene (0.42 mL), 105 °C; 2) $PhSiH_3$ (3.0 mmol), piperidine (0.4 mmol, 40 mol%), MeOH (0.4 mmol, 40 mol%), 105 °C. Yields refer to isolated compounds. Reaction times have not been minimized. All hydroamination reactions reached >95% conversion (TLC). [b] GC–MS analysis of the corresponding (*S*)-(−)-*N*-(trifluoroacetyl)-prolyl amides.

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[6] In order to compare the various experiments, reaction times were kept constant and were not minimized.

[7] For comparison: The $[Cp_2TiMe_2]$-catalyzed hydroamination between **1** and **10** followed by reduction with $NaBH_3CN/ZnCl_2$ gave **20a/b** in 89% yield.

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[10] Chiral catalysts (*S*,*S*)-**41** and (*R*,*R*)-**42** both favor formation of the same enantiomers of **39** and **40**. We are currently investigating which enantiomer is the main product.

[11] For recent examples of enantioselective hydroaminations of alkenes, see: a) P. W. Roesky, T. E. Müller, *Angew. Chem.* **2003**, *115*, 2812 – 2814; *Angew. Chem. Int. Ed.* **2003**, *42*, 2708 – 2710; b) P. D. Knight, I. Munslow, P. N. O'Shaughnessy, P. Scott, *Chem. Commun.* **2004**, 894 – 895.

