C–H Activation

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Titanium-Catalyzed Hydroaminoalkylation of Alkenes by C–H Bond Activation at sp^3 Centers in the α-Position to a Nitrogen Atom**

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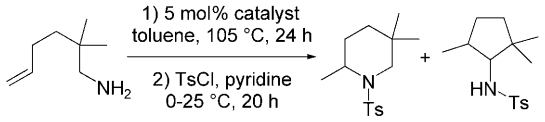
Hydroaminations of alkynes and alkenes[1] have attracted much attention during the past few years. Both transformations allow the synthesis of nitrogen-containing molecules in a single step with 100% atom efficiency. Besides other metal catalysts,[1] titanium complexes have been used extensively for these reactions.[2–4] Recently, we recognized during a study of the Ti-catalyzed intramolecular hydroamination of alkenes that the cyclization of 1-amino-5-hexenes to piperidines (Scheme 1) performed with the catalysts $[Ti(NMe_2)_4]$ or

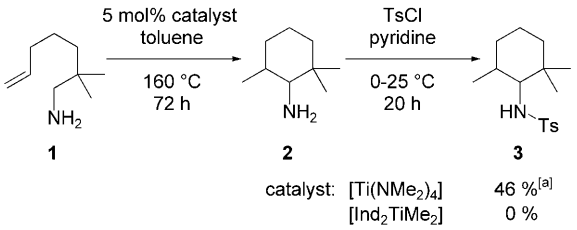


Scheme 1. Formation of an aminocyclopentane side product by C–H bond activation during a Ti-catalyzed hydroamination of a 1-amino-5-hexene. [a] Two diastereomers, *cis*/*trans* = 4:1. Ts = toluene-4-sulfonyl.

$[Ind_2TiMe_2]$ (Ind = indenyl) takes place along with the formation of aminocyclopentane side products.[4d] Interestingly, a corresponding catalytic C–H bond activation[5] at the sp^3 center in the α-position to a primary amino group has never been observed before during a Ti-catalyzed hydroamination.[6] However, this reaction would represent a very useful chemical transformation if it can be achieved selectively, because it offers a direct and highly atom-efficient conversion of simple amines to more complex molecules through C–C bond formation.

A related example of C–H bond activation[5] at sp^3 centers in the α-position to nitrogen atoms[7,8] is the $[Ta(NMe_2)_5]$-catalyzed intermolecular hydroaminoalkylation of alkenes described by Hartwig and Herzon.[9] Although only secondary N-arylated alkyl amines have been used for this reaction and $[Zr(NMe_2)_4]$ was found to be catalytically inactive, the analogy to the formation of aminocyclopentane side products during Ti-catalyzed hydroaminations is obvious. For this reason, we became interested in whether Ti complexes such as $[Ti(NMe_2)_4]$ and $[Ind_2TiMe_2]$ can generally be used as catalysts for selective hydroaminoalkylations of alkenes. To our knowledge and with the exception of the mentioned side reaction,[4d] corresponding Ti-catalyzed reactions have never been reported.[10]

One possibility to suppress the intramolecular hydroamination that competes with the desired C–H activation process is to use a 1-amino-6-heptene as the substrate. In this case, the hydroamination would lead to an unfavorable seven-membered ring, while the C–H bond activation reaction would give a favored six-membered ring. Correspondingly, it can be expected that the desired aminocyclohexane will be formed selectively. Initial studies carried out with 1-amino-2,2-dimethyl-6-heptene (**1**, Scheme 2) and 5 mol%



Scheme 2. Selective formation of an aminocyclohexane from a 1-amino-6-heptene. [a] Two diastereomers, *cis*/*trans* = 2:5.

$[Ti(NMe_2)_4]$ or $[Ind_2TiMe_2]$ revealed that the formation of the desired aminocyclohexane **2** is slow at 105 °C (less than 10% conversion in 24 h, as determined by GC). However, when $[Ti(NMe_2)_4]$ was used as the catalyst, an increase of the reaction temperature (160 °C) and a longer reaction time (72 h) resulted in the formation of the C–H activation product **2**, which could be isolated after conversion to the corresponding *p*-toluenesulfonamide derivative **3** (46% yield). Particularly interesting is the fact that the formation of the hydroamination product, an azepane, has not been observed during the entire study performed with substrate **1**. This result indicates that Ti catalysts are able to convert 1-amino-6-heptenes at elevated temperatures selectively to aminocyclohexanes and that for this purpose no protection of the primary amino group is necessary.

Because secondary amines usually do not undergo Ti-catalyzed hydroamination,[3,4a] an alternative possibility to suppress the hydroamination that competes with the desired C–H activation process is the conversion of the primary amino group to a secondary amino group. For that reason and

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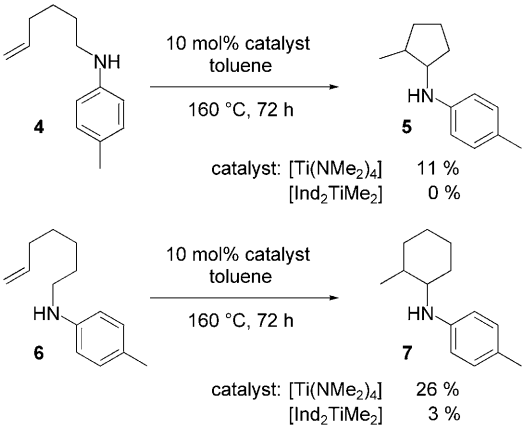
because N-arylated alkyl amines have been found to be particularly good substrates for the hydroaminoalkylations described by Hartwig et al., we tried to convert the N-arylated aminoalkenes **4** and **6** (Scheme 3) to the amino-



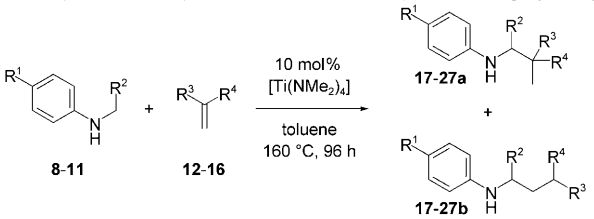
Scheme 3. Formation of aminocyclopentanes and aminocyclohexanes from *N*-aryl aminoalkenes.

cyclopentane and aminocyclohexane derivatives **5** and **7**. Unfortunately, it turned out that reactions performed with 10 mol% $[Ti(NMe_2)_4]$ give the desired products in only poor yields (not more than 26%). Furthermore, an isomerization of the C–C double bond that results in the formation of the corresponding internal alkene takes place almost exclusively when $[Ind_2TiMe_2]$ is used as the catalyst. Additionally, it was found that N-arylated aminoalkenes that are geminally disubstituted in the β-position to the nitrogen atom do not undergo the desired hydroaminoalkylation reaction at all.

To clarify whether N-arylated secondary amines are generally poor substrates for the Ti-catalyzed C–H activation reaction, we investigated the addition of *N*-methylaniline (**8**) to 1-octene (**12**), 3-phenylpropene (**13**), methylenecyclohexane (**14**), styrene (**15**), and norbornene (**16**, Table 1, entries 1–6) in the presence of 10 mol% $[Ti(NMe_2)_4]$. Surprisingly, we found that the desired hydroaminoalkylation products are formed in modest to good yields (up to 94%) in reactions that employ 1-octene (**12**), 3-phenylpropene (**13**), and norbornene (**16**; Table 1, entries 1–3, 6). In case of the terminal alkenes **12** and **13**, two regioisomers were formed, and the branched product (**a**) was always obtained as the major product with high selectivity (90:10). While corresponding reactions performed with methylenecyclohexane (**14**) and styrene (**15**; Table 1, entries 4, 5) did not show any conversion, a significantly improved yield was obtained for the addition of *N*-methylaniline (**8**) to 1-octene (**12**) when the reaction was run in the absence of a solvent and with a larger excess of the alkene (six equivalents, Table 1, entries 1, 2). Subsequently, we investigated the addition of the slightly modified *N*-alkyl anilines **9**–**11** to the representative alkenes 1-octene (**12**) and 3-phenylpropene (**13**, Table 1, entries 7–12). Interestingly, even small alterations of the *N*-alkyl substituent (Table 1, entries 7–10) strongly influence the efficiency of the C–H activation process, while changes at the *N*-aryl substituent (Table 1, entries 1, 3, 7, 8) are less significant. Correspondingly, successful hydroaminoalkylations could only be achieved with *N*-methyl- and *N*-benzyl-substituted aryl amines (**8**, **9**, **11**). On the other hand, reactions of *N*-propylaniline **10** as well as experiments with dialkyl amines (e.g. piperidine) have not been successful yet. Additionally, and in contrast to the intramolecular reaction (Scheme 2), intermolecular hydroaminoalkylations with primary amines could not be achieved so far.

Finally, we investigated the catalytic properties of various other titanium complexes. For this purpose, we chose the hydroaminoalkylation of 1-octene (**12**) with *N*-methylaniline (**8**) as a test reaction (Table 2). Surprisingly, and in contrast to the generally accepted view that Ti complexes do not catalyze corresponding reactions,[10] we found that many neutral Ti complexes are suitable catalysts for intermolecular hydroaminoalkylations of alkenes, which take place by C–H bond activation. Particularly promising for future studies is the fact that not only the yield but also the regioselectivity of the reaction is strongly influenced by the nature of the Ti catalyst. For example, the use of the ansa complex $[\{(\eta^5\text{-}C_5H_4)(Me_2Si)NtBu\}Ti(NMe_2)_2]$ (Table 2, entry 4) results in a sig-

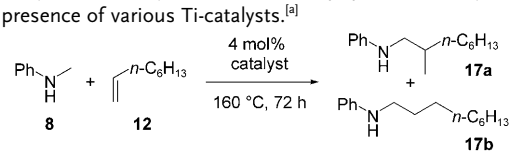
Table 1: Intermolecular hydroaminoalkylation of alkenes in the presence of $[Ti(NMe_2)_4]$.[a]



Entry	Amine	R^1	R^2	Alkene	R^3	R^4	Product	Yield **a**+**b** [%][b]	Selectivity **a**/**b**[c]
1	**8**	H	H	**12**	*n*-C_6H_{13}	H	**17a/b**	32	90:10
2	**8**	H	H	**12**	*n*-C_6H_{13}	H	**17a/b**	62[d]	90:10
3	**8**	H	H	**13**	Bn	H	**18a/b**	94	90:10
4	**8**	H	H	**14**	-$(CH_2)_5$-		**19a/b**	–	–
5	**8**	H	H	**15**	Ph	H	**20a/b**	–	–
6	**8**	H	H	norbornene (**16**)			**21**	78	–
7	**9**	Me	H	**12**	*n*-C_6H_{13}	H	**22a/b**	20	95:5
8	**9**	Me	H	**13**	Bn	H	**23a/b**	80	95:5
9	**10**	Me	Et	**12**	*n*-C_6H_{13}	H	**24a/b**	–	–
10	**10**	Me	Et	**13**	Bn	H	**25a/b**	–	–
11	**11**	H	Ph	**12**	*n*-C_6H_{13}	H	**26a/b**	75	1:1
12	**11**	H	Ph	**13**	Bn	H	**27a/b**	84	1:1

[a] Reaction conditions: amine (2.0 mmol), alkene (3.0 mmol), $[Ti(NMe_2)_4]$ (0.2 mmol, 10 mol%), toluene (1 mL), 160°C, 96 h, Bn = benzyl. [b] Yields refer to the total yield of isolated product (**a**+**b**). [c] GC analysis prior to chromatography. [d] Reaction conditions: amine (1.0 mmol), alkene (6.0 mmol), $[Ti(NMe_2)_4]$ (0.04 mmol, 4 mol%), 160°C, 72 h.

Table 2: Hydroaminoalkylation of 1-octene (**12**) with *N*-methylaniline (**8**) in the presence of various Ti-catalysts.[a]



Entry	Catalyst	Yield **17a**+**17b** [%][b]	Selectivity **17a**/**17b**[c]
1	$[Ti(NMe_2)_4]$	62	90:10
2	$[Cp_2TiMe_2]$	3	n.d.[d]
3	$[Ind_2TiMe_2]$	16	n.d.[d]
4	$[\{(\eta^5\text{-}C_5H_4)(Me_2Si)N\mathit{t}Bu\}Ti(NMe_2)_2]$	77	>99:1
5	$[\{(\eta^5\text{-}C_5H_4)(Me_2Si)N\mathit{t}Bu\}TiMe_2]$	75	>99:1
6	[(ebthi)$TiMe_2$]	–	–

[a] Reaction conditions: amine **8** (1 mmol), alkene **12** (6 mmol), catalyst (0.04 mmol, 4 mol%), 160°C, 72 h. Cp = cyclopentadienyl, ebthi = ethylen-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl). [b] Yields refer to the total yield of isolated product (**17a**+**17b**). [c] GC analysis prior to chromatography. [d] Not determined.

nificantly increased yield (77%) compared to the result obtained with $[Ti(NMe_2)_4]$ (62%). Fortunately, this improvement is accompanied by an increased regioselectivity of greater than 99:1 in favor of the branched product **17a**. Both findings suggest a great potential for further optimization.

Although no mechanistic studies have been carried out to date, we believe that the Ti-catalyzed C–H activation takes place by a process similar to the mechanism proposed by Hartwig,[9] Nugent, et al.[10b] This idea is strongly supported by the fact that enantiomerically pure amines possessing a chiral center adjacent to the nitrogen atom racemize in the presence of neutral Ti catalysts.[11]

In summary, we have shown that various neutral Ti complexes are suitable catalysts for intra- and intermolecular hydroaminoalkylations of alkenes, which take place by C–H bond activation in the α-position to nitrogen atoms. Particularly interesting is the fact that primary and secondary amines can be used as substrates.

Experimental Section

General procedure exemplified by the reaction of **8** with **13** (Table 1, entry 3): Under an atmosphere of nitrogen, a mixture of *N*-methylaniline (**8**, 214 mg, 2.0 mmol), allylbenzene (**13**, 354 mg, 3.0 mmol), $[Ti(NMe_2)_4]$ (44 mg, 0.2 mmol, 10 mol%), and toluene (1 mL) was heated to 160°C for 96 h. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc, 20:1) to give a mixture of the regioisomers **18a** and **18b** (424 mg, 94%, **18a**/**18b** 90:10) as a clear, colorless oil.

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[1] For recent reviews on hydroamination of alkenes and alkynes, see: a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892; b) J.-J. Brunet, N.-C. Chu, M. Rodriguez-Zubiri, *Eur. J. Inorg. Chem.* **2007**, 4711–4722; c) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407–1420; d) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555–4563.

[2] For reviews on Ti-catalyzed hydroamination of alkenes and alkynes, see: a) A. V. Lee, L. L. Schafer, *Eur. J. Inorg. Chem.* **2007**, 2243–2255; b) A. Odom, *Dalton Trans.* **2005**, 225–233; c) S. Doye, *Synlett* **2004**, 1653–1672; d) I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2003**, 935–946.

[3] For selected examples of Ti-catalyzed hydroaminations of alkynes, see: a) E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584–3586; *Angew. Chem. Int. Ed.* **1999**, *38*, 3389–3391; b) I. Bytschkov, S. Doye, *Tetrahedron Lett.* **2002**, *43*, 3715–3718; c) D. Mujahidin, S. Doye, *Eur. J. Org. Chem.* **2005**, 2689–2693; d) K. Marcseková, B. Wegener, S. Doye, *Eur. J. Org. Chem.* **2005**, 4843–4851; e) K. Gräbe, F. Pohlki, S. Doye, *Eur. J. Org. Chem.* **2008**, 4815–4823; f) C. Cao, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 5011–5013; g) D. L. Swartz II, A. L. Odom, *Organometallics* **2006**, *25*, 6125–6133; h) A. Tillack, H. Jiao, I. Garcia Castro, C. G. Hartung, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2409–2420; i) A. Tillack, V. Khedkar, H. Jiao, M. Beller, *Eur. J. Org. Chem.* **2005**, 5001–5012; j) L. Ackermann, R. G. Bergman, R. N. Loy, *J. Am. Chem. Soc.* **2003**, *125*, 11956–11963; k) M. L. Buil, M. A. Esteruelas, A. M. López, A. C. Mateo, E. Oñate, *Organometallics* **2007**, *26*, 554–565; l) C. Li, R. K. Thomson, B. Gillon, B. O. Patrick, L. L. Schafer, *Chem. Commun.* **2003**, 2462–2463; m) Z. Zhang, L. L. Schafer, *Org. Lett.* **2003**, *5*, 4733–4736.

[4] For recent examples of Ti-catalyzed hydroaminations of alkenes, see: a) M. C. Wood, D. C. Leitch, C. S. Yeung, J. A. Kozak, L. L. Schafer, *Angew. Chem.* **2007**, *119*, 358–362; *Angew. Chem. Int. Ed.* **2007**, *46*, 354–358; b) K. Marcseková, S. Doye, *Synlett* **2007**, 2564–2568; c) J. A. Bexrud, C. Li, L. L. Schafer, *Organometallics* **2007**, *26*, 6366–6372; d) C. Müller, W. Saak, S. Doye, *Eur. J. Org. Chem.* **2008**, 2731–2739; e) S. Majumder, A. L. Odom, *Organometallics* **2008**, *27*, 1174–1177; f) A. L. Gott, A. J. Clarke, G. J. Clarkeson, P. Scott, *Chem. Commun.* **2008**, 1422–1424.

[5] For reviews on C–H activation, see: a) F. Kakiuchi, S. Murai, in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, **1999**, pp. 47–79; b) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225–233; c) *Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; d) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463; e) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713–1715; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683–1684; f) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041–4047; g) R. G. Bergman, *Nature* **2007**, *446*, 391–393.

[6] Related side reactions have been observed in base-catalyzed hydroaminations of styrenes with amine substrates possessing acidified α-C–H bonds: P. Horrillo-Martínez, K. C. Hultzsch, A. Gil, V. Branchadell, *Eur. J. Org. Chem.* **2007**, 3311–3325.

[7] For reviews on catalytic C–H activation in the α-position to an N atom, see: a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; b) S. Doye, *Angew. Chem.* **2001**, *113*, 3455–3457; *Angew. Chem. Int. Ed.* **2001**, *40*, 3351–3353.

[8] a) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405–1406; b) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883; c) S.-I. Murahashi, N. Komiya, H. Teraki, *Angew. Chem.* **2005**, *117*, 7091–7093; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931–6933; d) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221; e) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.*

2000, *122*, 12882 – 12883; f) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648 – 5649; g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968 – 6969; h) O. Baslé, C. J. Li, *Org. Lett.* **2008**, *10*, 3661 – 3663; i) S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602 – 2604; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534 – 2536; j) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180 – 12181; k) Z. Li, R. Yu, H. Li, *Angew. Chem.* **2008**, *120*, 7607 – 7610; *Angew. Chem. Int. Ed.* **2008**, *47*, 7497 – 7500.

[9] S. B. Herzon, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 6690 – 6691.

[10] It was reported that $[Ti(NMe_2)_4]$ does not catalyze the hydroaminoalkylation of 1-hexene and 1-pentene with dimethylamine: a) M. G. Clerici, F. Maspero, *Synthesis* **1980**, 305 – 306; b) W. A. Nugent, D. W. Ovenall, S. J. Holmes, *Organometallics* **1983**, *2*, 161 – 162.

[11] F. Pohlki, I. Bytschkov, H. Siebeneicher, A. Heutling, W. A. König, S. Doye, *Eur. J. Org. Chem.* **2004**, 1967 – 1972.

