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COMMUNICATION

Dimethylamine as Substrate in Hydroaminoalkylation Reactions

Jens Bielefeld and Sven Doye*

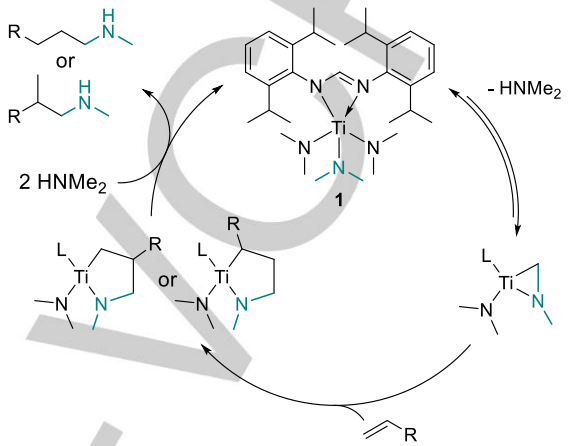
Abstract: *Transition metal catalyzed hydroaminoalkylations of alkenes have made great progress over the last decade and are heading to become a viable alternative to the industrial synthesis of amines through hydroformylation of alkenes and subsequent reductive amination. In the past, one major obstacle of this progress has been the inability to apply these reactions to the most important amines, methylamine and dimethylamine. Herein, we report the first successful use of dimethylamine in catalytic hydroaminoalkylations of alkenes with good yields. We also report the applicability for a variety of alkenes to show the tolerance of the reaction towards different functional groups. Additionally, we present the dihydroaminoalkylation reaction using dimethylamine, which has never been reported before.*

It is established that the widespread industrial synthesis of amines through hydroformylation of alkenes and subsequent reductive amination can, in principle, be replaced by a direct hydroaminoalkylation of alkenes with amines. This concept not only allows to skip one reaction step, it also offers the possibility to make the overall synthesis more energy efficient and to replace cobalt or rhodium containing hydroformylation catalysts[1] with inexpensive catalysts that are based on less toxic metals such as titanium.[2]

Hydroaminoalkylations were first reported in 1980 by Clerici and Maspero, who were able to react dimethylamine with alkenes using Group 4 and Group 5 metal catalysts.[3] However, the reaction was only shown with unfunctionalized alkenes and afforded mostly poor yields; only traces of product were observed with Ti-, V- and Mo-catalysts. Due to the low activity, relatively expensive catalysts (Zr, Nb, Ta) and harsh reaction conditions (up to 200 °C),[3,4] the scientific interest in this reaction type remained minimal until Herzon and Hartwig reported in 2007 that *N*-arylalkylamines possess a much higher reactivity in hydroaminoalkylations.[5] The overall research then began to focus mostly on *N*-alkylanilines and up to now, no relevant improvements on gaseous amines were made.[6,7]

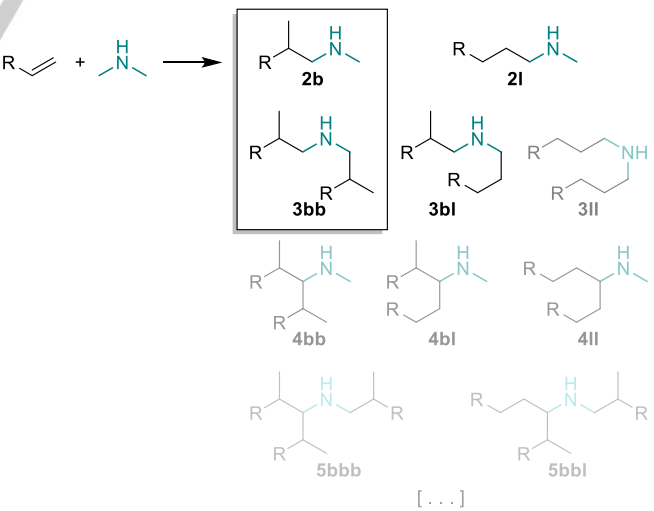
Because dimethylamine is (alongside methylamine) by far the most important substrate for this reaction,[8] we considered it essential for the overall importance and the industrial applicability of hydroaminoalkylation reactions to develop a reliable and inexpensive method to facilitate its addition to alkenes in good yields. We recently found the titanium complex **1**, that had first been reported by Eisen et al. as a catalyst for the polymerization of propylene,[9] to be active in the α-C−H-activation of dimethylamine. In 2015, this catalyst has been shown by us to be highly active in hydroaminoalkylations with *N*-methylaniline, even capable of converting notoriously difficult subtrates like styrenes and internal alkenes.[10]

To underline how inexpensive and available this titanium catalyst is, we synthesized a 48 g batch (88 mmol) of **1** from $TiCl_4$ and determined our production cost, including all chemicals and solvents, to be 59 € (synthesis and calculation are given in the supporting information).



Scheme 1. Mechanism of the Ti-catalyzed hydroaminoalkylation of alkenes.[11]

The mechanism of alkene hydroaminoalkylation employing catalyst **1** can be assumed based on kinetic studies we published in 2011.[11] As the equilibrium in Scheme 1 suggests, dimethylamine is activated through deprotonation of the methyl group, leading to a titanaazaridine and free dimethylamine. We would like to emphasize that this also means that a high concentration of free dimethylamine will inhibit the reaction. Since the reaction can, in theory, take place at any α-C−H-bond of amines, a broad variety of products could be expected (Scheme 2).



Scheme 2. Hypothetical products of alkene hydroaminoalkylations with dimethylamine (b = branched, l = linear).

Fortunately, the α-C−H-activation strongly prefers methyl groups over methylene groups and the according *iso*-alkylamines (**4** and **5**) were never observed as side products under the reaction conditions depicted in this work. The catalyst **1** is also known to generally possess a very good regioselectivity (S_{regio}) towards

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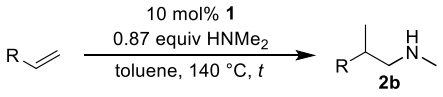
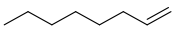
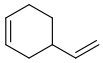
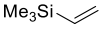
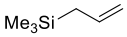
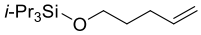
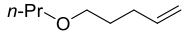
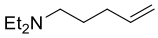
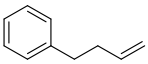
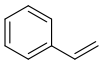
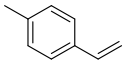
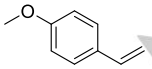
branched products; the linear side product **2l** and the branched-linear side product **3bl** were therefore usually only observed in trace amounts. The hypothetical linear-linear product **3ll** was not observed in any instance.

To furthermore ensure a good product selectivity (S_{prod}) towards the monohydroaminoalkylation products (**2b** and **2l**), finding the optimal load of dimethylamine turned out to be the key factor. A load too low shifts the selectivity towards the dihydroaminoalkylation products (**3bb** and **3bl**). We would like to emphasize that, because dimethylamine evaporates easily from solutions at elevated reaction temperatures, several other factors (i.e. solvent, amount of solvent, size of reaction vessel, pressure) have a similar, indirect effect on the yield and selectivity of this reaction. On the other hand, a dimethylamine load too high can easily inhibit the reaction entirely due to destabilization of the titanaaziridine intermediate (see equilibrium in Scheme 1). We found a slight excess of dimethylamine (including the three dimethylamide ligands of the catalyst) over alkene to provide the best compromise between yield and selectivity.

Table 1. Monohydroaminoalkylation.[a]



Alkene	*t* [d]	Yield [%][b]	S_{regio} [**2b**/**2l**][c]	S_{prod} [**2**/**3**][c]
	2	66	> 99/1	95/5
	6	31[d,e]	99/1	97/3
	6	54[d]	97/3	83/17
	6	45[d]	99/1	86/14
	6	55	96/4	83/17
	6	43	98/2	91/9
	6	57	98/2	81/19
	3	43	97/3	92/8
	2	28[d]	53/47	95/5
	2	22[d]	56/44	96/4
	4	24	68/32	99/1

[a] Reaction conditions: alkene (1.5 mmol), **1** (82 mg, 0.15 mmol, 10 mol%), $HNMe_2$ (0.95 M in toluene, 1.37 mL, 1.3 mmol) in an 5 mL-ampoule, 140 °C, 2-6 d. [b] Isolated yield of **2b**. For styrenes, the isolated yield of **2b** + **2l** is given. [c] Selectivities were determined by GC-analysis prior to chromatography. [d] Due to its volatility, the product was tosylated prior to chromatography. [e] The reaction occurs at the terminal alkene exclusively.

The reactions had to be carried out in ampoules small enough to ensure that no significant outgassing of dimethylamine takes place (sealed 5 mL-ampoules were used for approximately 2 mL of reaction mixture). The conversion of alkene can easily be enhanced by increasing the reaction time, but at the cost of severely impairing the product selectivity (i.e. the hydroaminoalkylation of 4-phenylbutene over 6 d gives isolated yields of 58 % of **2b** and 27 % of **3bb**). As shown in Table 1, the obtained yields are typically decent to good while selectivities are very good to excellent. To our knowledge, these are the first examples of dimethylamine being converted in catalytic hydroaminoalkylations of alkenes with satisfactory yields. A wide variety of functional groups are tolerated without problems, such as tertiary amines, ethers, silanes, less reactive alkenes and protected alcohols, although the tendency to undergo a second addition of alkene from **2** to **3** is slightly influenced by the functionalization. Styrenes are converted to pharmaceutically interesting phenethylamines; unfortunately, the yields and regioselectivities are low (an average yield of 14 % of phenethylamine is isolated). This is not surprising, as styrenes are known to be demanding substrates and catalyst **1** has already been reported by us to possess rather mediocre regioselectivity when applied to styrene.[10] Nevertheless, this is the first example of dimethylamine being converted in a catalytic hydroaminoalkylation of styrenes at all.

We did not observe any product formation with internal alkenes (attempted with 2-octene and 3-octene), cycloalkenes (attempted with cyclopentene and cyclohexene), dienes [attempted with (*E*)-1-phenyl-1,3-butadiene and (*E*)-1,3-decadiene], and acetal-protected ketones [attempted with 2-(but-3-en-1-yl)-2-methyl-1,3-dioxolane]. The conversion of most of these substrates has already been reported with more reactive amines (mostly *N*-methylaniline),[10] so it is reasonable to believe that more active catalysts in the future might be able to achieve a reaction between them and dimethylamine.

We then wanted to modify the reaction conditions to instead selectively give the dihydroaminoalkylation product **3bb** in a one-pot synthesis. The methylalkylamines, like **2b**, which appear as intermediates in this reaction, are already known to be challenging substrates in hydroaminoalkylations, thereby making product selectivity the main concern. We employed a very effective method to completely turn around the product selectivity by simply increasing the volume of the reaction vessel (sealed 100 mL-Schlenk tubes were used for approximately 2 mL of reaction mixture). Under the reaction conditions (140 °C), dimethylamine is then almost entirely gaseous and thus the dimethylamine concentration in solution is very low. The intermediate **2b** remains liquid under the reaction conditions and is therefore the preferred target for further C−H-bond activation, leading selectively to the dihydroaminoalkylation product **3bb**. Due to steric hindrance and low activity of **1** in the activation of methylene groups, **3bb** is roughly inert over the investigated timespan and doesn't undergo further addition to alkene (see **5** in Scheme 2). Additionally, because this type of catalyst generally experiences substrate inhibition (see equilibrium in Scheme 1) to some extent, the lower amine concentration in solution also leads to substantially shorter reaction times.

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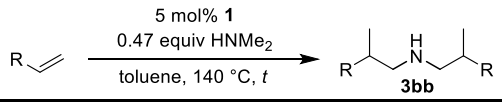
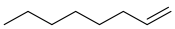
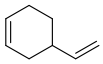
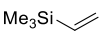
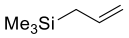
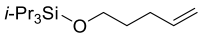
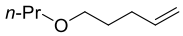
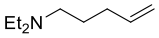
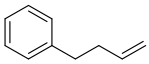
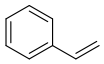
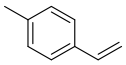
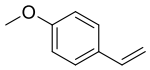
Table 2. Dihydroaminoalkylation.[a]



Alkene	*t* [d]	Yield [%][b]	S_{regio} [**3bb**/**3bl**][c]	S_{prod} [**2**/**3**][c]
	2	61	95/5	7/93
	4	31[d]	88/12	8/92
	6	48	80/20	6/94
	2	65	96/4	15/85
	4	55	95/5	8/92
	2	45	95/5	6/94
	2	70	95/5	7/93
	3	73	95/5	7/93
	6	6	39/61	29/71
	4	4	43/57	30/70
	2	3	88/12	50/50

[a] Reaction conditions: alkene (3.0 mmol), **1** (76 mg, 0.14 mmol, 5 mol%), $HNMe_2$ (1.49 M in toluene, 0.94 mL, 1.4 mmol) in a 100 mL-Schlenk tube, 140 °C, 2-6 d. [b] Isolated yield of **3bb**. [c] Selectivities were determined by GC-analysis prior to chromatography. [d] The reaction occurs at the terminal alkene exclusively.

The yields of the dihydroaminoalkylation (as shown in Table 2) are generally good and selectivities are very good to excellent. Again, styrenes are the exception, giving very poor yields and selectivities. Interestingly, even with styrenes the selectivity towards dihydroaminoalkylation is fair, considering how slow the reaction takes place compared to the monohydroaminoalkylation of styrenes shown in Table 1. While this is clearly not a satisfying procedure to produce **3bb** from styenes, it still shows how very effective the larger reaction vessel is in regulating the product selectivity.

Although two diastereoisomers are expected for the product **3bb**, no significant diastereoisomeric preference towards the chiral or the *meso*-product has been observed.[12]

In summary, we successfully demonstrated that dimethylamine can be used in catalytic hydroaminoalkylations of alkenes, and that good yields can be achieved with various substrates. We presented methods to either obtain the monohydroaminoalkylation product or the dihydroaminoalkylation product, both of which can be synthesized with very good selectivity. The catalyst needed for this reaction is inexpensive and easily obtainable. We hope that this work can increase the public and industrial interest in this rapidly growing field of chemistry.

Experimental Section

General information: Hydroaminoalkylation mixtures were prepared in a glovebox under N_2 atmosphere. All substances were dried and degassed before use.

General procedure for the monohydroaminoalkylation: A 5 mL-ampoule was charged with catalyst **1** (82 mg, 0.15 mmol, 10 mol%), alkene (1.5 mmol) and dimethylamine solution (0.95 M in toluene, 1.37 mL, 1.3 mmol). The ampoule was sealed and heated to 140 °C for 2-6 d. The product **2b** was either isolated by chromatography or (in case of volatile products) tosylated. For tosylation, the crude reaction mixture was diluted with CH_2Cl_2 (20 mL), then TosCl (679 mg, 3.56 mmol) and NaOH solution (2 M, 5.3 mL, 11 mmol) were added. The mixture was stirred over night and then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried with $MgSO_4$, concentrated and purified by chromatography.

General procedure for the dihydroaminoalkylation: A 100 mL-Schlenk tube with magnetic stir bar and Teflon stopcock was charged with catalyst **1** (76 mg, 0.14 mmol, 5 mol%), alkene (3.0 mmol) and dimethylamine solution (1.49 M in toluene, 0.94 mL, 1.4 mmol). The tube was sealed and heated to 140 °C for 2-6 d. The product **3bb** was isolated by chromatography.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft for financial support of this project. We thank Jessica Reimer for support of the experimental work.

Conflict of interest

The authors declare no conflict of interest.

Keywords: hydroaminoalkylation • titanium • dimethylamine • alkenes • alkylation

[1] For a review on hydroformylation reactions, see: R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675-5732.

[2] Titanium metal as well as TiO_2 that precipitates during workup from the reaction mixtures depicted in this work possess no acute toxicity. For further information, see: *Patty's Toxicology*, 6th ed., *Vol. 1* (Eds.: E. Bingham, B. Cohrssen), Wiley, Hoboken, **2012**, 428-438.

[3] M. G. Clerici, F. Maspero, *Synthesis* **1980**, *4*, 305-306.

[4] W. A. Nugent, D. W. Ovenall, S. J. Holmes, *Organometallics* **1983**, *2*, 161-162.

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

[6] For a review on hydroaminoalkylation reactions, see: E. Chong, P. Garcia, L. L. Schafer, *Synthesis* **2014**, *46*, 2884-2896.

[7] Despite low achieved yields, the following article might be of interest for some readers; it serves as a proof of concept for the reaction of dimethylamine in the presence of a heterogenous (silica-bound) catalyst: B. Hamzaoui, J. D. A. Pelletier, M. E. Eter, Y. Chen, E. Abou-Hamad, J. M. Basset, *Adv. Synth. Catal.* **2015**, *357*, 3148-3154.

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[8] K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, 4th ed., Wiley-VCH, Weinheim, **2003**, 51-52.
[9] T. Elkin, N. V. Kulkarni, B. Tumanskii, M. Botoshansky, L. J. W. Shimon, M. S. Eisen, *Organometallics* **2013**, *32*, 6337-6352.
[10] J. Dörfler, T. Preuß, C. Brahms, D. Scheuer, S. Doye, *Dalton Trans.* **2015**, *44*, 12149-12168.
[11] I. Prochnow, P. Zark, T. Müller, S. Doye, *Angew Chem* **2011**, *28*, 6525-6529; *Angew. Chem. Int. Ed.* **2011**, *50*, 6401-6405.
[12] The ^{13}C NMR data suggests that both diastereoisomers are formed in approximately equal amounts. Further details are given in the supporting information.

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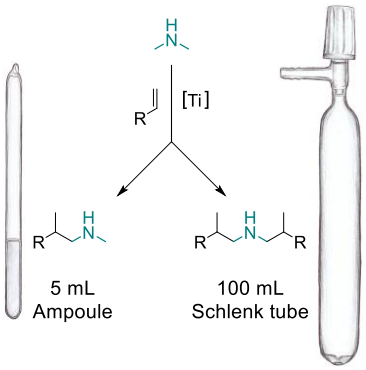
COMMUNICATION

Size matters: For the first time since catalytic hydroaminoalkylation chemistry started 37 years ago, dimethylamine can efficiently be added to alkenes using an inexpensive and easily obtainable Ti-catalyst. The size of the flask determines what product this reaction yields - monohydroaminoalkylation or dihydroaminoalkylation.



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