C–H Activation

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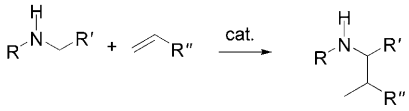
Catalytic Hydroaminoalkylation**

*Peter W. Roesky**

amines · homogeneous catalysis · tantalum · titanium · zirconium

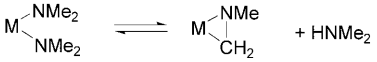
Considering that today most amines are formed in multistep syntheses, atom-efficient routes that lead to amines are of great interest for academic and industrial research. One of the most attractive approaches in this area is the catalytic addition of an amine R_2NH to alkenes or alkynes (hydroamination). This catalytic conversion has attracted the interest of several research groups over the last decade.[1–8] A number of metal catalysts can be employed for this transformation, including complexes based on lanthanoids,[6] Group 4 metals,[4] platinum metals,[7] and also lithium, calcium, and recently gold.[5] Depending on the catalytic system, either an activation of the C–C multiple bond or the N–H function of the substrate takes place.[1] Another route to generate amines is the hydroaminomethylation; that is, a hydroformylation combined with a reductive amination to give amines.[9,10]

The addition of amine α C–H bonds to alkenes to form branched alkylamines (hydroaminoalkylation) has been investigated recently by several research groups (Scheme 1).



Scheme 1. Hydroaminoalkylation.

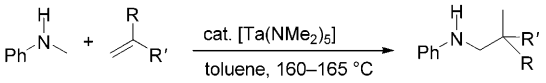
This kind of reaction, which includes C–H bond activation at the α position to an amino group,[11] was first reported at the beginning of the 1980s, but was not further developed until recently.[12,13] The early work of Maspero and Clerici involved the intermolecular α alkylation of dimethylamine with terminal alkenes in the presence of $[Zr(NMe_2)_4]$, $[Nb(NMe_2)_5]$, and $[Ta(NMe_2)_5]$.[12] Moderate yields (38%) were obtained at 200 °C over 150 h. According to mechanistic studies reported later by Nugent et al.,[13] an azametallacyclopropane was suggested as a key intermediate (Scheme 2). In a similar reaction, α-alkylated secondary amines were prepared in the presence of stoichiometric quantities of zirconocene methyl-



Scheme 2. Azametallacyclopropane formation.

amido complexes.[14,15] Azametallacyclopropanes were isolated as intermediates.

Significant progress in the catalytic hydroaminoalkylation of alkenes has been reported in the last few years. In 2007, Hartwig and Herzon investigated the α alkylation of *N*-aryl alkylamines with terminal alkenes catalyzed by homoleptic d^0 dialkylamido complexes, such as $[Ta(NMe_2)_5]$, $[Nb(NMe_2)_5]$, $[Zr(NMe_2)_4]$, and $[(\eta^5\text{-}Cp)_2Zr(NMe_2)_2]$ ($Cp = C_5H_5$).[16] The authors showed that mono- and 2,2-disubstituted terminal alkenes react with *N*-methylaniline in high yields (up to 96%) at 160–165 °C using 4–8 mol% of $[Ta(NMe_2)_5]$ (Scheme 3). In most of the cases that were investigated, high regioselectivities were observed, resulting exclusively in branched monoalkylation products. Moreover, a variety of substituted alkylaniline derivatives, such as *N*-methyl-3,5-dimethylaniline, *N*-methyl-3,5-di-*tert*-butylaniline, *N*-methyl-3,5-difluoroaniline, and *N*-methyl-4-fluoroaniline were added to 1-octene to obtain the corresponding branched alkylamines in high yields (up to 93%) under the conditions described above. The authors suggest that the *N*-aryl substituents of the amine facilitate the generation of an azametallacyclopropane complex by serving as an electron-withdrawing group without deactivating the catalyst by forming a stable chelate.



Scheme 3. Coupling of *N*-methylaniline with terminal alkenes.[16]

The catalytic system was improved by the same research group by using the chloroamido complex $[TaCl_3(NEt_2)_2]$ as precatalyst.[17] The branched addition products formed from the reaction of 1-octene with several types of dialkylamines in high yields and selectivities at 150 °C and 2 mol% $[TaCl_3(NEt_2)_2]$ catalyst loading (Scheme 4). Linear and branched alkyl methylamines were selectively C–H activated at the methyl group. Only *tert*-alkyl methylamines, such as *tert*-butylmethylamine, were unreactive. The authors suggest a mechanism for the hydroaminoalkylation reaction that starts with the elimination of amine from a tantalum bis(amide) complex to form an η^2 imine complex (Scheme 5). This step is

[*] Prof. Dr. P. W. Roesky
Institut für Anorganische Chemie, Universität Karlsruhe (TH)
Engesserstrasse 15, 76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: roesky@chemie.uni-karlsruhe.de

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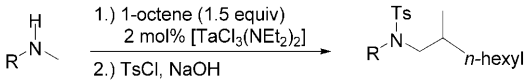
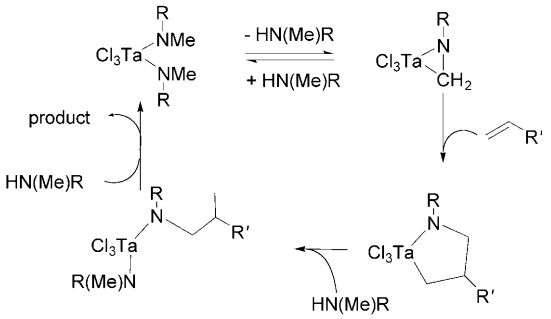
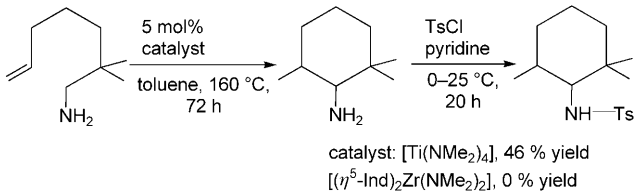


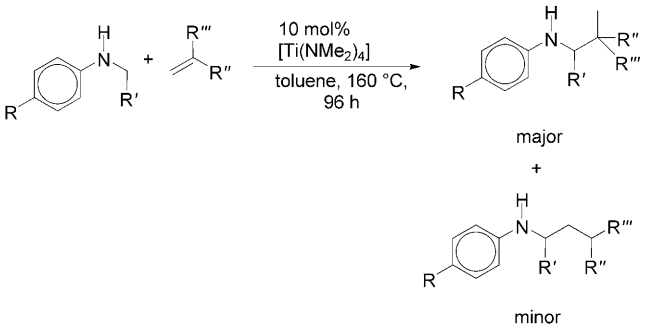
Scheme 4. Alkylation of dialkylamines with 1-octene.[17]



Scheme 5. Proposed mechanism for alkene hydroaminoalkylation using $[TaCl_3(NEt_2)_2]$ as precatalyst. The NEt_2 groups are replaced in the initial step by N(Me)R groups.[17]



Scheme 6. Selective formation of an cyclohexylamine from 1-amino-2,2-dimethyl-6-heptene. Ts = 4-methylphenylsulfonyl.[18]

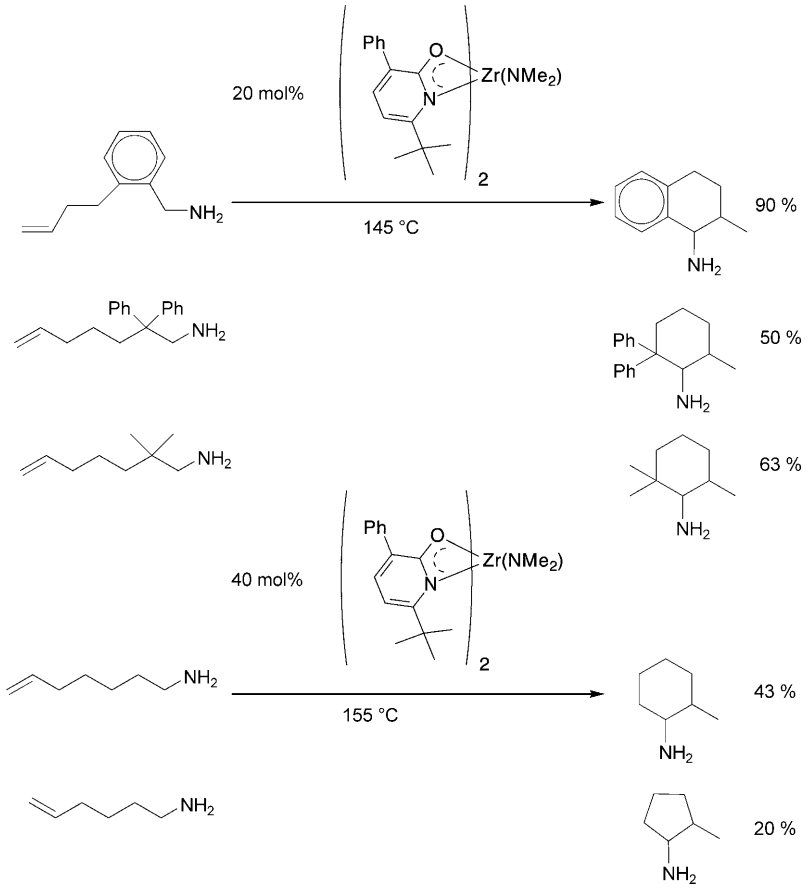


Scheme 7. Intermolecular hydroaminoalkylation of alkenes in the presence of $[Ti(NMe_2)_4]$.[18]

followed by insertion of the alkene into the tantalum–carbon bond of this intermediate. Protonolysis by the amine regenerates the starting bis(amide) and liberates the product.[17] Hydroaminoalkylations of α alkenes with *N*-alkyl arylamines were also reported[17] by using the closely related chlorotantalum anilide $[(TaCl_3\{N(Me)Ph\}_2)_2]$ as catalyst.

Early this year, Doye et al. presented a hydroaminoalkylation reaction using titanium catalysts $[Ti(NMe_2)_4]$ and $[(\eta^5\text{-Ind})_2Zr(NMe_2)_2]$ (Ind = indenyl).[18] As these complexes also catalyze the hydroamination reaction, the authors tried to suppress that reaction pathway by using substrates that are unfavorable for the hydroamination reaction. Initial studies on an intramolecular reaction carried out at 160 °C over 72 h with 1-amino-2,2-dimethyl-6-heptene and 5 mol% $[Ti(NMe_2)_4]$ resulted in the formation of the desired aminocyclohexane (Scheme 6) in moderate yields (46%). A related conversion was observed as a side reaction in the base-catalyzed hydroamination of styrenes with benzhydrylamine.[19]

Moderate to high yields (up to 94%) were obtained in the intermolecular reaction of *N*-arylated secondary amines, such as *N*-methylaniline, with 1-octene, 3-phenylpropene, methylenecyclohexane, styrene, and norbornene in the presence of 10 mol% of $[Ti(NMe_2)_4]$ (Scheme 7).[18] By using *N*-methylaniline and the terminal alkenes 1-octene or 3-phenylpropene as substrates, the branched regioisomer was always obtained as the major product with high selectivity (90:10). The authors could also show that other titanium reagents, such as $[\{(\eta^5\text{-}C_5H_4)(Me_2Si)NtBu\}Ti(NMe_2)_2]$ and $[\{(\eta^5\text{-}C_5H_4)(Me_2Si)NtBu\}TiMe_2]$ can catalyze the hydroaminoalkylation of 1-octene with



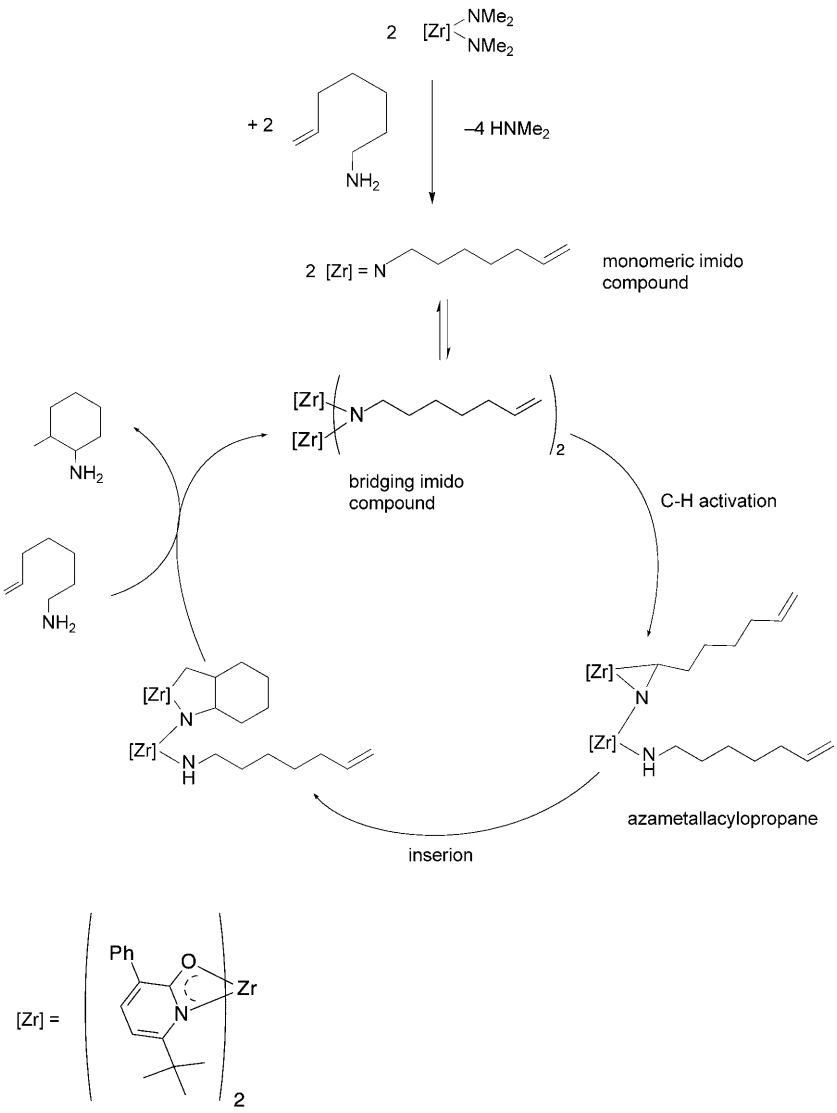
Scheme 8. Examples of hydroaminoalkylation catalyzed by the di-2-pyridonate zirconium bis(amide) catalyst.[20]

N-methylaniline in high yields (77% and 75%) and high regioselectivity (99% branched isomer).[18]

A titanium-catalyzed intramolecular hydroaminoalkylation of primary amines was reported by Schafer et al.[20] The catalyst, a di-2-pyridonate zirconium bis(amide), was obtained by the reaction of two equivalents of 6-*tert*-butyl-3-phenyl-2-pyridone with $[Zr(NMe_2)_4]$. Reaction of 20 mol% of this precatalyst with various aminoalkenes at 145°C led to the corresponding intramolecular hydroaminoalkylation products (Scheme 8). Neither a hydroamination nor a hydroaminoalkylation was observed when this reaction was attempted at 110°C with 20 mol% $[Ti(NMe_2)_4]$ as precatalyst. In contrast to the tantalum-catalyzed reactions, no conversions were observed when secondary *N*-methyl or *N*-phenyl aminoalkene substrates were treated with the di-2-pyridonate zirconium bis(amide) catalyst, even at elevated temperatures.

The authors propose dimeric imido complexes, which were thought to be catalytically inactive for the hydroamination reaction, as precursors to reactive bridging azametallacyclopropanes, which are required for catalytic α alkylation (Scheme 9).[20]

The recent developments have shown that substrates that do not readily undergo catalytic hydroamination can favor the formation of hydroaminoalkylation products. The reaction procedures reported to date require high reaction temperatures and long reaction times. Thus, improvements in catalyst design that promote the hydroaminoalkylation are anticipated to expand the scope and selectivity of this very useful transformation.



Scheme 9. Proposed simplified mechanism for α C–H alkylation of primary aminoalkenes.[20]

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