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Catalysis

Intermolecular Hydroaminoalkylation of Alkynes

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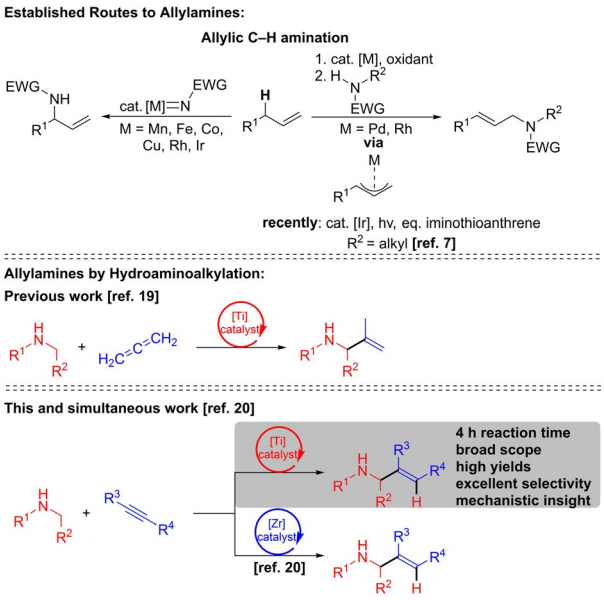
Abstract: Intermolecular hydroaminoalkylation reactions of alkynes with secondary amines, which selectively give access to allylic amines with *E* configuration of the alkene unit, are achieved in the presence of titanium catalysts. Successful reactions of symmetrically substituted diaryl- and dialkylalkynes as well as a terminal alkyne take place with *N*-benzylanilines, *N*-alkylanilines, and *N*-alkylbenzylamines.

Allylamines are synthetically very important molecules given their immense potential as building blocks in organic chemistry and the main structural motif [R_2N–C(R)=CR_2] is part of for example, biological active ingredients.[1] Furthermore, the allylamine fragment itself can be found in many natural products and is easily functionalized at the pendant double bond. Allylamines can be synthesized by several different routes including the Overman rearrangement,[2] the Tsuji–Trost reaction as an exemplarily substitution reaction,[3] alkenylation of imines,[4] or the reductive amination of enones and enals.[5] In the field of direct C–H activation, the allylic C–H amination does not only lead to derivatized allylamines at the N-terminus (e.g., as amides or carbamates)[6] but has very recently been expanded to directly access *N*-alkyl-substituted allylamines by a photocatalyzed variant.[7] The two major strategies utilize either η^3-allyl-metal species followed by nucleophilic attack of the N-compound[8] or C–H insertion of metal nitrenoids (Scheme 1, top).[9] The hydroamination of substrates with two double bonds is another established method.[6] For this reaction dienes, allenes, and alkynes (which are transformed into allenes in situ) are employed together with late transition metals to regioselectively give allylic amines by C–N bond formation. It is worth to mention that the alkyne variant is only possible with alkyl-substituted alkynes.[11] An attractive alternative to synthesize allylamines would be the catalytic intermolecular hydroaminoalkylation of alkynes with amines, which would yield the corresponding allylamines by C–C bond formation at the carbon atom in position α to the amine starting material. The corresponding hydroaminoalkylation of alkenes is well established to date and is possible with late transition metals,[12] following a photocatalytic approach,[13] and even with early transition metals.[14] Especially early transition metals are attractive for this purpose given their overall low cost and abundance compared to late transition metals.[15] Our research is specifically focused on titanium catalysts as titanium is the second most abundant metal in the Earth's crust.[15,16] Since titanaaziridines are considered to be key intermediates in the Ti-catalyzed hydroaminoalkylation of alkenes, stoichiometric reactions between group 4 aziridines and alkynes already foreshadow the potential to realize the corresponding catalytic variant and are well understood.[17,18] In a recent work, our group has reported the synthesis of allylamines by reacting the parent allene propadiene with various secondary amines employing a titanium



Scheme 1. Selected routes for the synthesis of allylamines: allylic C–H amination via either π-allyl intermediates or metal-nitrenoids (top); hydroaminoalkylation of propadiene (middle); hydroaminoalkylation of alkynes (bottom).

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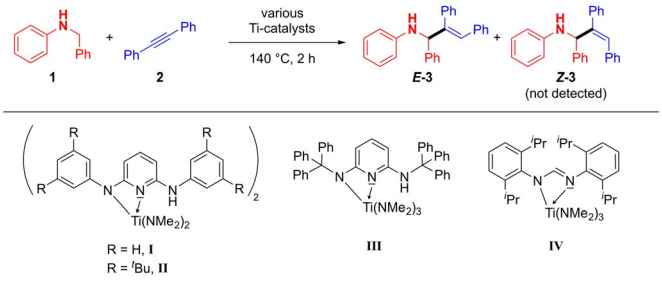
catalyst (Scheme 1, middle).[19] Key finding of our study was that successful hydroaminoalkylation reactions of propadiene can only be achieved with amines possessing an α-methylene group; as a consequence, *N*-methyl anilines, which are known to be among the best substrates for alkene hydroaminoalkylation, do not deliver the desired allylamines. During the preparation of this manuscript Schafer and co-workers reported the targeted goal of the hydroaminoalkylation of internal alkynes with benzylamines to yield α,β,γ-substituted allylic amines with a zirconium catalyst and a bis(ureate) ligand precursor at 145 °C and 48 h reaction time (Scheme 1, bottom).[20] Herein we report on the employment of a highly active titanium catalyst (140 °C, 4 h reaction time) for the hydroaminoalkylation of internal and terminal alkynes with various secondary amines.[21]

Inspired by the good reactivity of *N*-benzyl anilines in hydroaminoalkylation reactions of propadiene,[19] our investigation commenced with an evaluation of a range of titanium complexes as catalysts for the desired hydroaminoalkylation of diphenylacetylene (**2**) with *N*-benzylaniline (**1**, Scheme 2). For



Scheme 2. Investigated intermolecular hydroaminoalkylation of diphenylacetylene (**2**) with *N*-benzylaniline (**1**, top) and part of the investigated catalyst systems **I**–**IV** (bottom).

that purpose, several corresponding catalytic reactions were initially run on a 0.1 mmol-scale in toluene at 140 °C for 2 h with a catalyst loading of 10 mol% in sealed ampoules ($V = 1$ mL).[22] Conversion of the starting materials as well as product formation was detected by GC analysis using *p*-cymene as an internal standard. During these experiments, it was found that both aminopyridinato titanium catalysts **I**[23] and **II**[24] showed conversion of *N*-benzylaniline (**1**) while catalyst **III**[25] and the formamidinato titanium catalyst **IV**[26] as well as additionally investigated homoleptic group 4 or 5 metal catalysts turned out to be inactive (Figures S59–S62).[27] As observed before,[24] among the two aminopyridinato titanium catalysts **I** and **II**, the *meta-tert*-butyl-substituted derivative **II** turned out to be catalytically more active (Figure S60). In this context, it should be mentioned that due to the importance of catalyst **II** for our study, we further improved the synthesis of its aminopyridinato ligand, and we additionally confirmed the molecular structure of **II** by X-ray crystallography (Figure 1).

Subsequent optimization of the reaction conditions (Table S2) showed that the best results are obtained with 10 mol% catalyst loading (**II**), 140 °C, 4 h, and using 1.2 equivalents of diphenylacetylene (**2**). With these optimized conditions in hand, a 1 mmol-scale experiment was performed to isolate

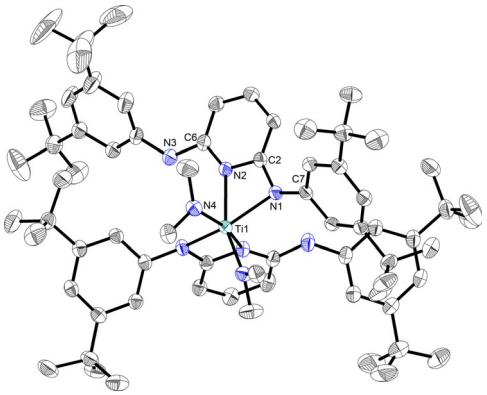


Figure 1. Molecular structure of catalyst **II**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å]: Ti1–N1 2.0958(13), Ti1–N2 2.2229(14), Ti1–N4 2.0958(13), N1–C2 1.368(2), N1–C7 1.411(2), N2–C2 1.363(2), N2–C6 1.338(2), N3–C6 1.376(2).

larger amounts of the desired product for characterization purposes. According to GC analysis, after 4 h the experiment showed full conversion and after subsequent workup and chromatographic purification, the desired pure allylic amine ***E*-3** could be isolated in 82% yield as the single product of the reaction. The corresponding stereoisomeric allylamine ***Z*-3** could neither be isolated nor detected by GC, suggesting that the hydroaminoalkylation reaction takes place with complete stereoselectivity (Figures S64 and S65). To unambiguously assign the structure of ***E*-3**, comprehensive NMR studies [heteronuclear multiple bond correlation (HMBC), heteronuclear multiple quantum correlation (HMQC), nuclear Overhauser effect (NOE), Figures S5–S7][27] were carried out and finally, it was possible to obtain crystals suitable for single-crystal X-ray diffraction. As can be seen from Figure 2, the two phenyl substituents at the C–C double bond of ***E*-3** are oriented *cis* to each other, which overall results in the mentioned *E* configuration.

The exclusive formation of the allylamine product with an *E* configuration at the double bond can easily be explained by the mechanism of the reaction (Scheme 3). Key step of the generally accepted catalytic cycle of hydroaminoalkylation reactions is the insertion of the unsaturated substrate into the Ti–C bond of a catalytically active titanaaziridine (**A**).[16,17a] In

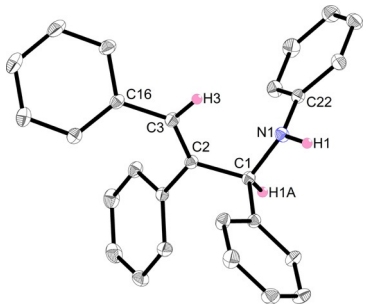
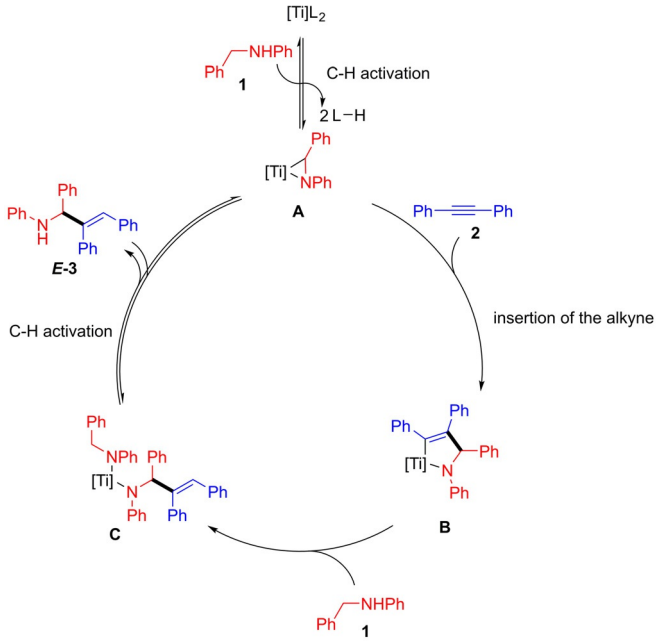


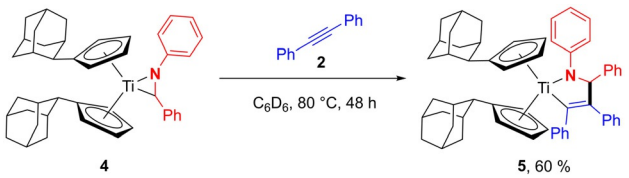
Figure 2. Molecular structure of ***E*-3**. Hydrogen atoms (except H1, H1A, and H3) have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å] and angles [°]: N1–C1 1.4566(9), C1–C2 1.5308(9), C2–C3 1.3438(9), $\Sigma_{(angles)}$(C2) 359.9, $\Sigma_{(angles)}$(C3) 360.0.



Scheme 3. Proposed mechanism of the Ti-catalyzed hydroaminoalkylation of alkynes.

the case of diphenylacetylene (**2**) as the substrate, the corresponding reaction delivers a titanapyrroline (**B**) in which the two phenyl substituents bonded to the C=C double bond must be *cis*-oriented. Subsequent protonation of the Ti–C bond by the amine substrate **1** and regeneration of the catalytically active titanaaziridine **A** then closes the catalytic cycle and liberates the *E*-configurated allylic amine ***E*-3**.

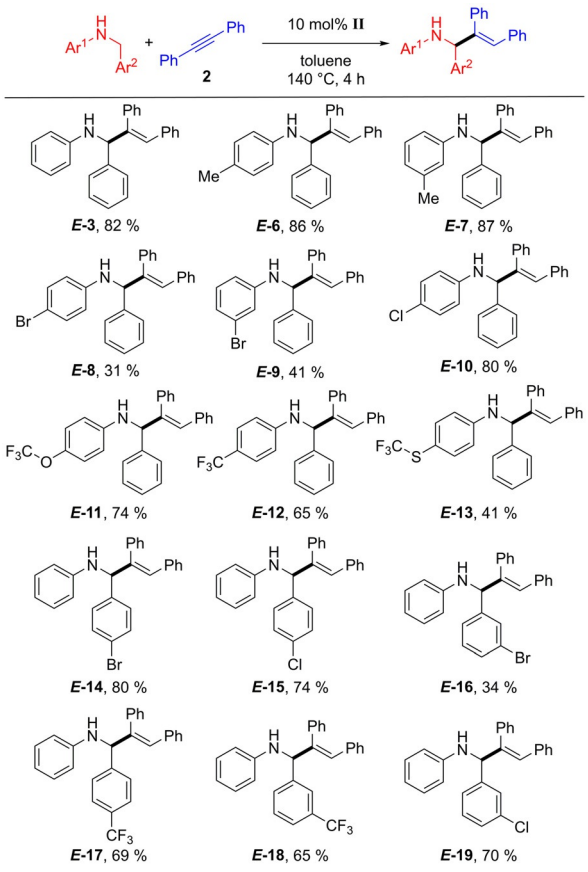
To confirm the possibility of a migratory insertion reaction of the sterically demanding alkyne diphenylacetylene (**2**) into the Ti–C bond of an α-phenyl-substituted titanaaziridine, the reaction of the model titanaaziridine **4**[17b] with **2** was performed (Scheme 4). In this context, it should be mentioned that corresponding insertion reactions of sterically less demanding alkynes such as phenylacetylene, 2-butyne, 1-phenylpropyne, and 1-trimethysilylpropyne have already been described with α-unsubstituted titanaaziridines.[16,17a] It should also be noted that titanaaziridines of type **4** possessing adamantyl-substituted cyclopentadienyl ligands are known to lack any catalytic activity in hydroaminoalkylation reactions and are therefore perfectly suited for the isolation and characterization of stable five-membered intermediates of the expected catalytic cycle. For that reason, it is not surprising that the reaction of **4** with



Scheme 4. Migratory insertion of diphenylacetylene (**2**) into the Ti–C bond of titanaaziridine **4**.

2 took place smoothly at 80 °C to give the expected titanapyrroline **5** in good isolated yield of 60%.

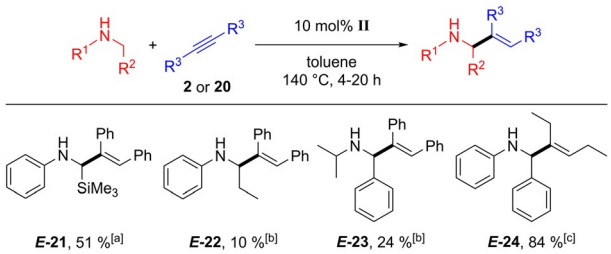
With the optimized conditions in hand, the scope of *N*-benzyl anilines was investigated, and the results are summarized in Scheme 5. While experiments with substrates that contain *para*- and *meta*-substituents on the *N*-phenyl ring or the benzyl group usually delivered the expected *E*-configurated hydroaminoalkylation products within 4 h at 140 °C, it was found that *ortho*-substituted substrates did not show any reactivity, which can be explained by steric hindrance.[23] With regard to functional groups, the reaction tolerates methyl (***E*-6**, ***E*-7**), bromo (***E*-8**, ***E*-9**, ***E*-14**, ***E*-16**), and chloro (***E*-10**, ***E*-15**, ***E*-19**) substitution as well as other pharmacologically promising substituents such as trifluoromethyl (***E*-12**, ***E*-17**, ***E*-18**), trifluoromethoxy (***E*-11**), and trifluoromethylthio groups (***E*-13**). While in most cases, the corresponding *E*-allylamines were formed in good to very good isolated yields (65–87%), the presence of a bromo- or a trifluoromethylthio-group led to reduced yields (31–41%). However, in this context, it should be noted that even in the latter cases, full conversion of the starting materials was observed by GC analysis (Figures S66 and S67). Full conversion was also observed with a series of *para*- and *meta*-methoxy substituted benzylamines but in these cases, we were not able to purify the corresponding allylamine products,



Scheme 5. Ti-catalyzed synthesis of allylamines from diphenylacetylene (**2**) and *N*-benzyl anilines. Reaction conditions: amine (1.0 mmol), diphenylacetylene (**2**, 1.2 mmol), **II** (0.10 mmol, 10 mol%), 140 °C, 4 h, sealed ampoule (V = 5 mL).

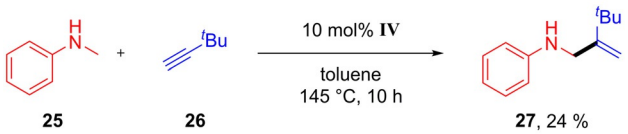
which are undoubtedly formed under the reaction conditions (Figure S68), by distillation or column chromatography. Particularly promising are the good yields in which the chloro-substituted allylamines ***E*-10**, ***E*-15**, and ***E*-19** were formed because the presence of a chloro-substituent offers various possibilities for further functionalization (e.g., Pd-catalyzed cross coupling). An additional single-crystal X-ray diffraction of compound ***E*-15**[27] that confirmed the *E* configuration of the allylamine double bond is in good agreement with the excellent stereoselectivity observed in all hydroaminoalkylation reactions.

Subsequently, we also investigated the behavior of a few alkyl-substituted amines and 3-hexyne (**20**) as the first example of a dialkyl substituted alkyne (Scheme 6). Although **20** turned out to be less reactive than diphenylacetylene (**2**), a simple extension of the reaction time to 20 h led to a successful reaction with *N*-benzylaniline (**1**) that gave access to the corresponding allylic amine ***E*-24** in an excellent yield of 84%. The products ***E*-21**, ***E*-22**, and ***E*-23**, which were obtained from additional reactions of **2** with *N*-alkylanilines or *N*-isopropylbenzylamine, clearly prove that in principle, alkylamines also represent suitable substrates for the hydroaminoalkylation of alkynes, although in these cases, further optimization is required to increase the efficiency of the reaction.



Scheme 6. Ti-catalyzed hydroaminoalkylation reactions of diphenylacetylene (**2**) or 3-hexyne (**20**) with *N*-alkylanilines, a *N*-alkylbenzylamine, or *N*-benzylaniline (**1**). Reaction conditions: amine (1.0 mmol), alkyne (1.2 mmol), **II** (0.10 mmol, 10 mol%), 140 °C, 4, 16, or 20 h, sealed ampoule ($V = 5$ mL). [a] 4 h. [b] 16 h. [c] 20 h.

Finally, we tried to expand the substrate scope of the reaction to unsymmetrically disubstituted alkynes, terminal alkynes, and *N*-methylaniline (**25**, Scheme 7). For that purpose, 1-phenyl-1-butyne, 1-phenyl-1-hexyne, trimethylsilylacetylene, and *tert*-butylacetylene (**26**) were initially reacted with *N*-benzylaniline (**1**) in the presence of catalyst **II** but unfortunately, due to poor regioselectivity (Figures S73 and S74) we were not able to isolate pure products. On the other hand, an additional catalyst screening for the reaction of **26** with **25** revealed that obviously, corresponding reactions of *N*-methyl-substituted



Scheme 7. Ti-catalyzed hydroaminoalkylation reaction of *tert*-butylacetylene (**26**) with *N*-methylaniline (**25**).

amines and terminal alkynes can principally be achieved with the formamidinato titanium catalyst **IV**, which has already shown high catalytic activity in hydroaminoalkylation reactions of alkenes with *N*-methylamines.[26] Although the corresponding product **27** could only be isolated in 24% yield, this result strongly supports the idea that the hydroaminoalkylation of alkynes has a great potential for a wide range of further applications. Because **27** represents the first hydroaminoalkylation product obtained from a terminal alkyne, we were delighted to verify its structure by single-crystal X-ray diffraction of the corresponding hydrochloride **27**·HCl.[27]

In summary, we have developed a simple catalytic protocol for the intermolecular titanium-catalyzed hydroaminoalkylation of alkynes with secondary amines which directly gives access to allylic amines. As a consequence of the C–C bond forming key step of the proposed catalytic cycle, the insertion of the alkyne into the Ti–C bond of a catalytically active titanaaziridine, disubstituted alkynes are exclusively converted into allylic amines with an *E* configuration of the alkene unit. While best results were obtained with various *N*-benzylanilines, reactions of *N*-alkylanilines and *N*-alkylbenzylamines with disubstituted alkynes such as diphenylacetylene or 3-hexyne can also be achieved. Although unsymmetrically disubstituted alkynes react sluggishly, a successful reaction of *N*-methylaniline with a terminal alkyne regioselectively delivered the branched hydroaminoalkylation product. Because the latter result strongly suggests that it should be possible to significantly expand the scope of the catalytic reaction, we think that this work will be the starting point of a synthetically useful and promising new field in hydroaminoalkylation chemistry. Further optimization studies are currently underway in our laboratory and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · amines · C–H activation · hydroaminoalkylation · titanium

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[27] For details, see the Supporting Information. Deposition numbers 2047601, 2047602, 2047603, 2047604 and 2047601 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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