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Stereoselective Synthesis of Tertiary Allylic Amines by Titanium-Catalyzed Hydroaminoalkylation of Alkynes with Tertiary Amines

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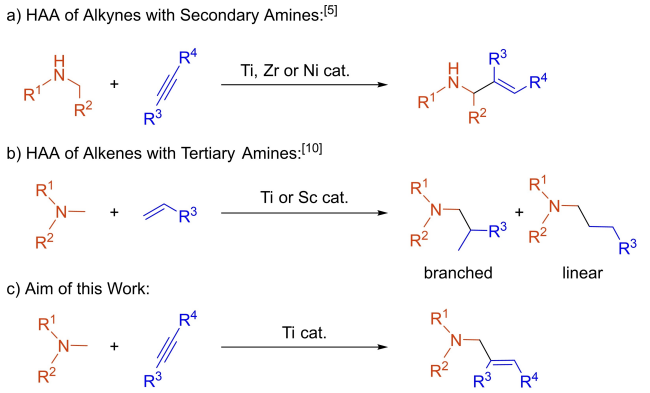
In memory of Klaus Hafner

Abstract: Intermolecular hydroaminoalkylation reactions of symmetrical and unsymmetrical alkynes with tertiary amines take place in the presence of catalytic amounts of $TiBn_4$, $Ph_3C[B(C_6F_5)_4]$, and a sterically demanding aminopyridinato ligand precursor. The resulting products, synthetically and pharmaceutically useful tertiary β,γ-disubstituted allylic amines, are formed in convincing yields and with excellent stereoselectivity. Particularly promising for future applications is the fact that even the industrial side product trimethylamine can be used as a substrate.

Introduction

In the chemical industry, nitrogen-containing compounds are widely found in many influential areas such as pharmaceuticals, as nitrogen-containing compounds often show high biological activity and therefore are of great interest for the development of new drugs.[1] One major pattern are tertiary allylic amines because they are synthetic precursors for amino acids,[2] alkaloids,[3] or carbohydrate derivatives.[4] With regard to organic synthesis, very recently, the hydroaminoalkylation (HAA) of alkynes with secondary amines has been used to produce allylic amines (Scheme 1a).[5] Since the hydroaminoalkylation reaction[6,7] is a 100% atom-economical addition of the α-C–H bond of a simple amine to the C–C multiple bond of an unsaturated substrate, it can generally be regarded as a very attractive route for the preparation of pharmaceutically interesting amines. Ye and Shi demonstrated the Ni-catalyzed hydroaminoalkylation of alkynes with *N*-sulfonylamines to produce a series of *N*-protected allylamines.[5a,b] For that purpose, Ye used "double ligands" of a N-heterocyclic carbene (IPr) and tricyclohexylphosphine,[5b] while Shi used a chiral phosphorus ligand which even allowed an enantioselective reaction.[5a] On the other hand, Schafer's group[5c] and ours[5d] have shown that alkyne hydroaminoalkylation also works with unprotected secondary amines in the presence of early transition metal catalysts based on Zr or Ti to obtain secondary allylic amines. Secondary amines as well as tertiary amines can also be used for hydroaminoalkylation reactions of alkenes and in the case of tertiary amines, a lot of progress has been achieved with late transition metal catalysts or using photocatalytic approaches.[8,9] Unfortunately, typical substrates require either a metal-binding directing group or an activated alkene moiety. In recent years, Hou's group and ours have also achieved the hydroaminoalkylation of non-activated alkenes with simple tertiary amines (Scheme 1b).[10] While the Hou group used cationic scandium catalysts,[10a–c] we achieved the first successful results with a cationic titanium catalyst system generated in situ from $TiBn_4$ and $Ph_3C[B(C_6F_5)_4]$.[10f] In this context, it is worth mentioning that titanium is *i)* significantly less expensive than scandium,[11] *ii)* the second most abundant transition metal in the earth's crust, and *iii)* a non-toxic metal.[12] The fact that both, the hydro-



Scheme 1. Selected protocols for the hydroaminoalkylation (HAA) of alkynes or alkenes with secondary or tertiary amines.

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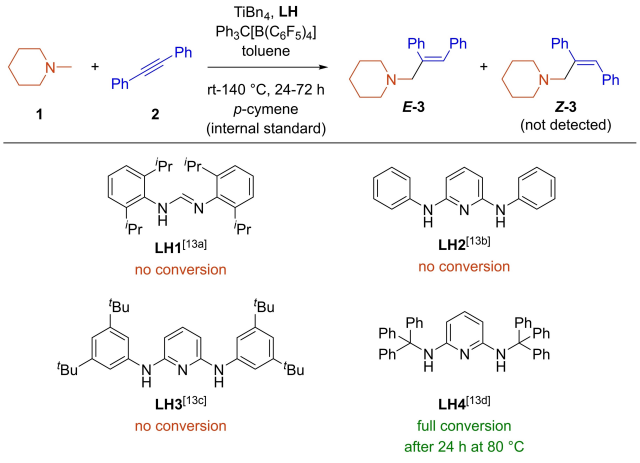
aminoalkylation of alkynes with secondary amines as well as the hydroaminoalkylation of alkenes with tertiary amines, work quite well with titanium catalysts, inspired us to identity a suitable titanium catalyst for the hydroaminoalkylation of alkynes with tertiary amines to directly obtain tertiary allylamine building blocks (Scheme 1c). The corresponding results are reported herein.

Results and Discussion

Our investigation began with an evaluation of the hydroaminoalkylation of diphenylacetylene (**2**) with *N*-methylpiperidine (**1**) performed in the presence of catalytic amounts of $TiBn_4$,[10f] $Ph_3C[B(C_6F_5)_4]$, and a range of ligand precursors (**LH1**-**LH4**)[13] that have already been used successfully in hydroaminoalkylation chemistry (Scheme 2). For that purpose, several corresponding catalytic reactions were initially run on a 0.2 mmol-scale in toluene at various temperatures (rt-140 °C) for 72 h with a catalyst loading of 10 mol% $TiBn_4$, 10 mol% of one of the ligand precursors, and 8 mol% of $Ph_3C[B(C_6F_5)_4]$ in sealed ampoules ($V = 1$ mL).[14] *p*-Cymene was used as an internal standard to analyze the conversion of the starting materials as well as product formation by gas chromatography. While all experiments performed in the presence of **LH1**-**LH3** or in the absence of a ligand precursor did not lead to any conversion of the starting materials, we were delighted to see that the hydroaminoalkylation of diphenylacetylene (**2**) with *N*-methylpiperidine (**1**) proceeds smoothly at 80 °C in the presence of N^2,N^6-ditritylpyridine-2,6-diamine (**LH4**)[13d] as the ligand precursor (Table S1, Figures S48–S51). Subsequent optimization of the reaction conditions showed that the best result is obtained at 80 °C after a reaction time of 24 h (Table S2). Control experiments performed in the absence of $TiBn_4$ or $Ph_3C[B(C_6F_5)_4]$ additionally revealed that both compounds are essential for a successful reaction (Table S2). Overall, our assumption is that under the reaction conditions, $TiBn_4$, $Ph_3C[B(C_6F_5)_4]$, and **LH4** in situ form a cationic titanium complex that acts as the catalytically active species.[10]



Scheme 2. Investigated intermolecular hydroaminoalkylation of diphenylacetylene (**2**) with *N*-methylpiperidine (**1**, top) and the investigated ligand precursors **LH1**-**LH4** (bottom). Reaction conditions: 1) *N*-methylpiperidine (**1**, 20 mg, 0.2 mmol), diphenylacetylene (**2**, 53 mg, 0.3 mmol), $TiBn_4$ (8 mg, 0.02 mmol, 10 mol%), ligand precursor (0.02 mmol, 10 mol%), $Ph_3C[B(C_6F_5)_4]$ (16 mg, 0.016 mmol, 8 mol%), toluene (1 mL), rt-140 °C, 24–72 h; 2) *p*-cymene (0.02 mmol, internal standard), GC analysis.

With the optimized conditions in hand, a corresponding 1 mmol-scale experiment was performed in a sealed 5 mL ampoule, and ***E*-3** could be isolated in 68% yield as the sole hydroaminoalkylation product. To demonstrate that the reaction can also be carried out in more common glass ware, an additional control experiment on a 1 mmol-scale was carried out in a Schlenk tube ($V = 5$ mL, Teflon stopcock) under otherwise identical conditions with regard to catalyst loading, borate loading, temperature, and time. In this case, product ***E*-3** was isolated in comparable yield of 75%. The structure of ***E*-3** could subsequently be assigned by comprehensive NMR studies (HMBC, HMQC, NOE, Figures S6-S8) and after conversion into the corresponding hydrochloride ***E*-3·HCl**,[14] it was possible to obtain crystals suitable for single-crystal X-ray diffraction.[15] Figure 1 proves that the two phenyl groups of ***E*-3·HCl** are *cis* to each other which means that the configuration of the trisubstituted double bond is *E*. In good agreement with mechanistic studies of the Sc-catalyzed hydroaminoalkylation of alkenes with tertiary amines[10a–e] and the results of Zr- and Ti-catalyzed hydroaminoalkylation reactions of alkynes with secondary amines,[5c,d] it is assumed that a cationic titanaaziridine acts as the catalytically active species of the new reaction (Scheme 3). The stereoselective formation of the trisubstituted double bond of the allylamine product can then easily be understood by a C–C bond forming insertion of the alkyne into the Ti–C bond of the cationic titanaaziridine, which selectively gives a 2-titana-3-pyrroline in which the former alkyne substituents must be *cis*-oriented to each other.[5c,d]

As can be seen from Scheme 4, a wide variety of additional tertiary alkylamines could also be reacted successfully with diphenylacetylene (**2**) using the new catalyst system. However, at least for some substrates the reaction time had to be expanded to

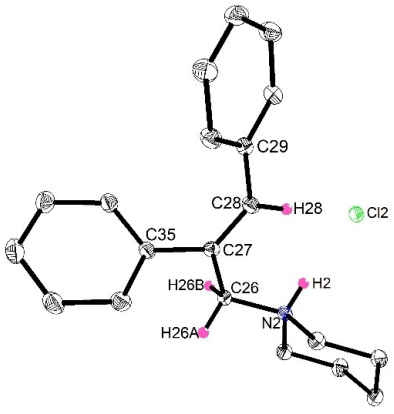
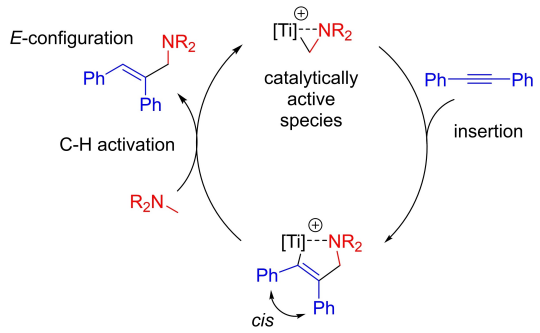
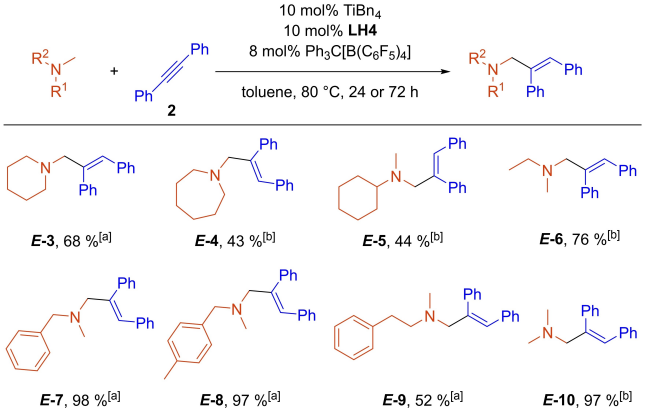


Figure 1. Molecular structure of ***E*-3·HCl**.[15] Hydrogen atoms (except H2, H26A, H26B, and H28) have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): N2–C26 1.506(2), C26–C27 1.513(3), C27–C28 1.342(3), $\Sigma_{(angles)}$(C27) 359.7, $\Sigma_{(angles)}$(C28) 359.9.



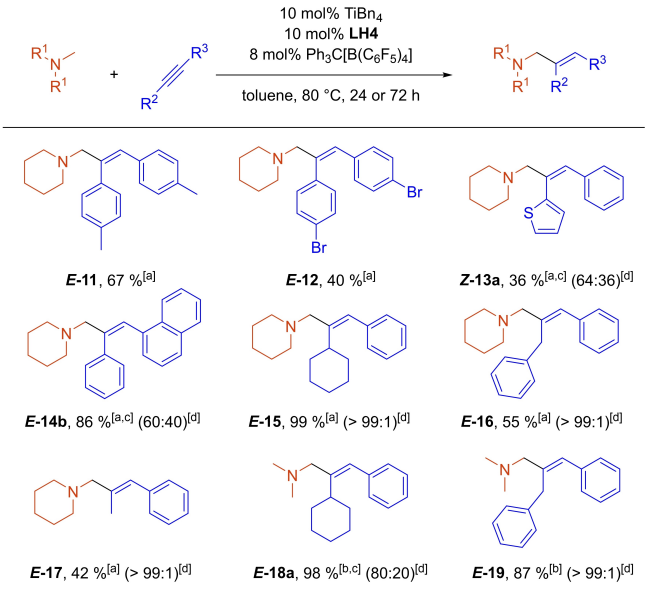
Scheme 3. Mechanistic hypothesis for the stereoselective formation of the trisubstituted double bond of the allylic amines.



Scheme 4. Ti-catalyzed hydroaminoalkylation reactions of diphenylacetylene (**2**) with various tertiary amines. Reaction conditions: amine (1.0 mmol), alkyne (1.5 mmol), $TiBn_4$ (0.10 mmol, 10 mol%), **LH4** (0.10 mmol, 10 mol%), $Ph_3C[B(C_6F_5)_4]$ (0.08 mmol, 8 mol%), toluene (4.5 mL), 80 °C, 24 h or 72 h, sealed ampoule ($V = 5$ mL). Yields refer to isolated pure compounds. [a] 24 h. [b] 72 h.

72 h to achieve acceptable yields. In all cases, C–H bond activation of the reacting amine exclusively occurred at *N*-methyl groups suggesting that the reaction is very sensitive to steric hindrance. This assumption is not only underlined by the selective formation of ***E*-4** from *N*-methylazepane but also by the formation of ***E*-7** and ***E*-8** from *N,N*-dimethylbenzylamine derivatives because in the latter cases, no reaction took place at the generally more reactive benzylic position. In addition, dihydroaminoalkylation of substrates possessing two *N*-methyl groups was not observed in any case and most impressively, *N,N*-dimethylethylamine reacted exclusively at one methyl group to selectively give product ***E*-6** in 76% yield. While *N,N*-dimethylcyclohexylamine and *N,N*-dimethyl-2-phenylethylamine gave products ***E*-5** and ***E*-9** only in modest yields of 44% and 52%, respectively, the most simple tertiary amine, trimethylamine delivered ***E*-10** in excellent yield of 97%. The latter result deserves particular attention because trimethylamine is a side product of the industrial production of methylamine and dimethylamine and according to the literature,[16] a lack of need for trimethylamine exists in the chemical industry because its conversion into useful products is difficult to achieve. With regard to substrate scope it must be mentioned that we did not observe any product formation with *N,N*-dimethylaniline, which is consistent with our previous observation that tertiary arylamines, do not undergo hydroaminoalkylation with alkenes in the presence of $TiBn_4$ and $Ph_3C[B(C_6F_5)_4]$.[10f]

Furthermore, we investigated the alkyne scope by reacting *N*-methylpiperidine (**1**) with a variety of symmetrical and unsymmetrical alkynes (Scheme 5). While during this study, diarylalkynes and alkylarylalkynes could be converted into the desired hydroaminoalkylation products ***E*-11**-***E*-17** with modest to excellent yields (36-99%), dialkyl-substituted alkynes and terminal alkynes did not give satisfactory results. The reaction tolerates methyl (***E*-11**), bromo (***E*-12**), and thienyl (***E*-13**) substitution and reactions of alkylarylalkynes exclusively deliver hydroaminoalkylation products that result from C–C bond formation at the alkyl-substituted carbon atom of the alkyne starting material (***E*-15**-***E*-17**). Particularly impressive was the reaction of 2-cyclohexyl-1-phenylacetylene which gave ***E*-15** in quantitative yield as a single regioisomer suggesting that electronic reasons are mainly responsible for the observed regioselectivity. In good agreement with this assumption, only modest regioselectivities were observed with unsymmetrically diaryl-substituted alkynes and as a result, mixtures of regioisomers could only be obtained from corresponding reactions of 2-(phenylethynyl)thiophene or 1-(phenylethynyl)naphthalene. In both cases, hydroaminoalkylation was slightly favored at the sterically less hindered side of the alkyne and correspondingly, ***Z*-13a** and ***E*-14b** were identified to be the major products of these reactions. Additional hydroaminoalkylation reactions of 2-cyclohexyl-1-phenylacetylene and 2-benzyl-1-phenylacetylene with sterically less demanding trimethylamine then revealed that



Scheme 5. Ti-catalyzed hydroaminoalkylation reactions of various alkynes with *N*-methylpiperidine (**1**) or trimethylamine. Reaction conditions: amine (1.0 mmol), alkyne (1.5 mmol), $TiBn_4$ (0.10 mmol, 10 mol%), **LH4** (0.10 mmol, 10 mol%), $Ph_3C[B(C_6F_5)_4]$ (0.08 mmol, 8 mol%), toluene (4.5 mL), 80 °C, 24 h or 72 h, sealed ampoule ($V = 5$ mL). Unless otherwise noted, yields refer to isolated pure compounds. If applicable, only the major regioisomer is shown. [a] 24 h. [b] 72 h. [c] The isolated product contained amounts of the other regioisomer. [d] Regioselectivity was determined by GC analysis prior to flash chromatography.

the steric bulk of the amine as well as the alkyl substituent of the alkyne does influence the regioselectivity of the reaction. Only in the case of 2-benzyl-1-phenylacetylene, a single regioisomer (***E*-19**) was formed (87% yield). The reaction of 2-cyclohexyl-1-phenylacetylene with trimethylamine gave both regioisomeric hydroaminoalkylation products in a ratio of 80:20 with ***E*-18a** as the major product. This result is in sharp contrast to the reaction of sterically more demanding *N*-methylpiperidine, which only gave ***E*-15** as a single regioisomer. Unfortunately, at the moment, we are not able to provide a reasonable explanation for the different behavior of *N*-methylpiperidine (**1**) and trimethylamine. With regard to stereoselectivity, it could finally be emphasized that during our entire study, only products that were formed by syn-addition of the amine across the C–C triple bond of the alkyne could be isolated and *E-Z* isomerization was not observed in a single case.

Conclusion

In summary, we have discovered that intermolecular hydroaminoalkylation reactions of symmetrical and unsymmetrical alkynes with tertiary amines can be achieved in the presence of a catalyst system that is generated in situ from $TiBn_4$, $Ph_3C[B(C_6F_5)_4]$, and a sterically demanding aminopyridinato ligand precursor. The resulting products, tertiary β,γ-disubstituted allylic amines, are stereoselectively formed by syn-addition and as a consequence, the configuration of the trisubstituted double bond of the allylic amines is *E*. In the case of unsymmetrical alkylarylalkynes, C–C bond-formation takes place regioselectively at the alkyl-substituted carbon atom of the alkyne starting material. Particularly promising for future applications for example for the synthesis of fine chemicals[17] is the fact that even the simplest tertiary amine, the industrial side product trimethylamine, can be used as a substrate.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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

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