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Zinc-Catalyzed Domino Hydroamination–Alkyne Addition

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Abstract: The first zinc-catalyzed one-step synthesis of quaternary propargylamines with four different substituents is described. The domino hydroamination–alkyne addition reaction gives access to functionalized propargylamines under mild conditions.

Keywords: alkynes; domino reaction; hydroamination; metathesis; propargylamines; zinc

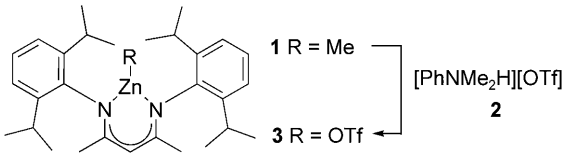
The synthesis of fine chemicals and natural products is often a multistep process including salt-generating reactions. Nowadays the modern synthesis design demands for efficient techniques to minimize the number of steps towards the product and to avoid the formation of by-products. Domino and cascade reactions allow an ecologically and economically favourable synthesis.[1–3] These procedures describe closely coupled individual reactions that yield a product in a single process.

The addition of an organic amine to C-C multiple bonds presents a challenging and demanding topic. The metal-catalyzed hydroamination has been studied with different types of catalysts.[4–7] We have reported the metal-catalyzed hydroamination reactions with a diversity of zinc complexes.[6] Hydroamination reactions of alkynes often resulted in the formation of unstable intermediates like enamines and imines and hence were reduced to the corresponding amines in a one-pot procedure.[7] Hydroaminations were also combined in a tandem process with several other reactions like Cope rearrangement,[8] hydroarylation,[9] hydrosilylation[10] and with diverse addition reactions.[11] We are interested in a combination of hydroamination and alkyne addition in a catalytic domino process yielding propargylamines. Such a sequence has not been described intensively and only a few cases are known. In the first report acetylene was converted in a copper-catalyzed reaction to propargylamines having a secondary carbon center.[12] These copper-catalyzed reactions have been recently described with diverse phenylacetylenes.[13] The hydroamination leads to anti-Markovnikov products and the following alkyne addition thus yields a propargylamine with a secondary carbon center. In case of a Zn/Cd catalyst the Markovnikov addition was observed but only propyne and dimethyl- or diethylamine were used under drastic conditions.[14] Herein we describe a flexible zinc-catalyzed one-step synthesis of quaternary propargylamines with four different substituents. The reaction proceeds under mild conditions and tolerates different functional groups.

During our studies on zinc-catalyzed hydroaminations we found that β-diiminate (BDI) complexes like **1** in presence of cocatalyst **2** lead to the catalytically active species **3** (Scheme 1). According to our results, the cocatalyst **2** protonates the precatalyst **1** irreversibly forming methane and generates the catalyst **3** as a cationic BDI-zinc complex with a low-coordinating triflate anion. We confirmed the molecular structure of **3**·THF by single crystal X-ray diffraction in the solid-state.

Compound **3** is a good catalyst for hydroamination of alkynes forming enamines, which should easily lead to imines or iminium salts. Since several zinc-catalyzed additions of monosubstituted acetylenes to special imines have been described,[15] we tested the intermediately formed **3** for the combined reactions.

In the initial experiments we used dibenzylamine and phenylacetylene. A 1/2.5 mixture was treated



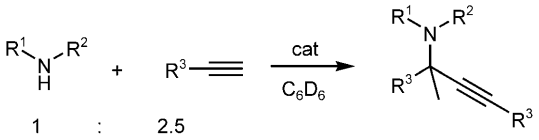
Scheme 1. Synthesis of the BDI-zinc catalyst **3**.

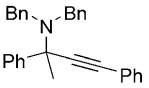
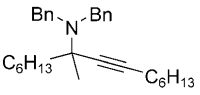
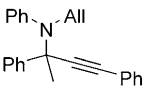
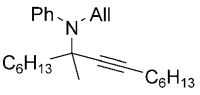
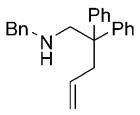
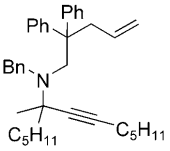
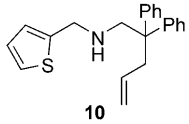
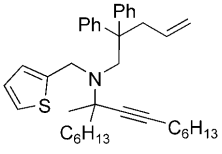
with 10 mol% precatalyst **1** and cocatalyst **2** in benzene-d_6 at 60 °C in a sealed tube. Dibenzylamine was completely consumed after 30 h and the corresponding propargylamine **4** was isolated by flash chromatography in 72% yield (Table 1, entry 1). When the temperature was increased to 80 °C, the reaction time was reduced to 18 h (Table 1, entry 2). The reactions were also performed with 1-octyne to verify the possibility of a tandem reaction with an aliphatic substituted alkyne and observed the formation of the corresponding propargylamines with high yields in a reduced reaction time. The double benzyl-protected propargylamine **5** having aliphatic groups was isolated in an even higher yield of 78% (Table 1, entries 3 and 4).

We next examined the use *N*-allylaniline in combination with phenylacetylene and observed the formation of product even at room temperature (Table 1, entry 5). The low isolated yield of the product **6** is attributed to its instability in the presence of moisture. It is proposed that this decomposition reaction is induced by the aromatic groups of product **6** introduced by phenylacetylene. We confirmed this assumption by using 1-octyne instead of phenylacetylene. The domino reaction of 1-octyne and with the *N*-allylic aniline delivered the propargylamine **7** in 8 h at 60 °C in a high yield of 86% (Table 1, entry 6). Decomposition reaction of the isolated enyne **7** was not observed.

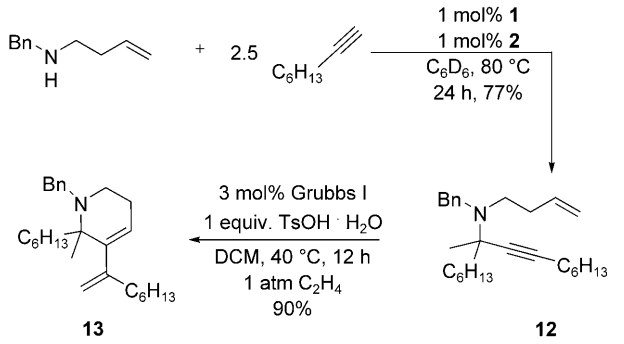
To expand the substrate scope, we studied more challenging substrates and converted amines **8** and **10** to the corresponding progargyl derivates **9** and **11** with 1-heptyne and 1-octyne (Table 1, entries 7 and 8). In this case the reaction took over 40 h at 80 °C and, interestingly, the reaction proceeded with complete selectivity, and no intramolecular alkene-hydroamination was observed.

Table 1. Intermolecular domino hydroamination–alkyne addition reactions.



Entry	Amine	Cat. loading [mol%]	Temp. [°C]	Time [h]	Yield [%]	Product
1		10	60	30	72	 **4**
2		10	80	18	73	
3		10	60	12	77	 **5**
4		1	80	34	78	
5		10	r.t.	53	87[a]	 **6**
6		10	60	8	86	 **7**
7	 **8**	10	80	40	61	 **9**
8	 **10**	10	80	40	76	 **11**

[a] Conversion determined by ^{1}H NMR.



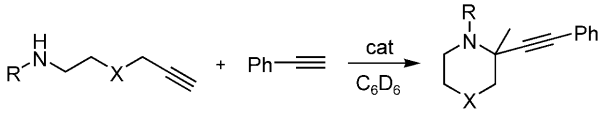
Scheme 2. Combination of domino hydroamination–alkyne addition with ring-closing metathesis.

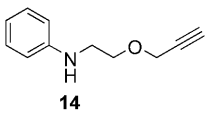
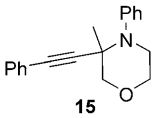
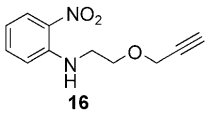
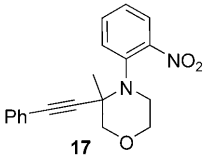
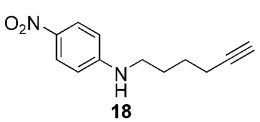
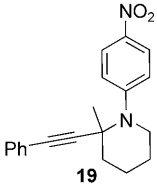
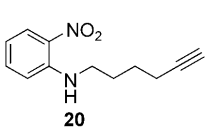
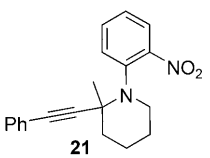
In order to exemplify the applicability of the presented methodology, we decided to combine this domino reaction with an enyne ring closing metathesis (RCM).[16] For this purpose, *N*-benzylbut-3-enylamine was reacted with 2 equivalents of 1-octyne and 1 mol% catalyst at 80 °C (Scheme 2). After 24 h the reaction was completed and the enyne **12** was isolated with 77% yield. Since tertiary amines are problematic substrates for Ru-catalyzed metathesis reactions, we performed the RCM in the presence of 1 equivalent of TsOH with 3 mol% of Grubbs' I catalyst under an ethylene atmosphere. After 12 h the expected diene **13**, which is a useful precursor for Diels–Alder reactions,[16c,d] was isolated after purification on column chromatography in 90% yield.

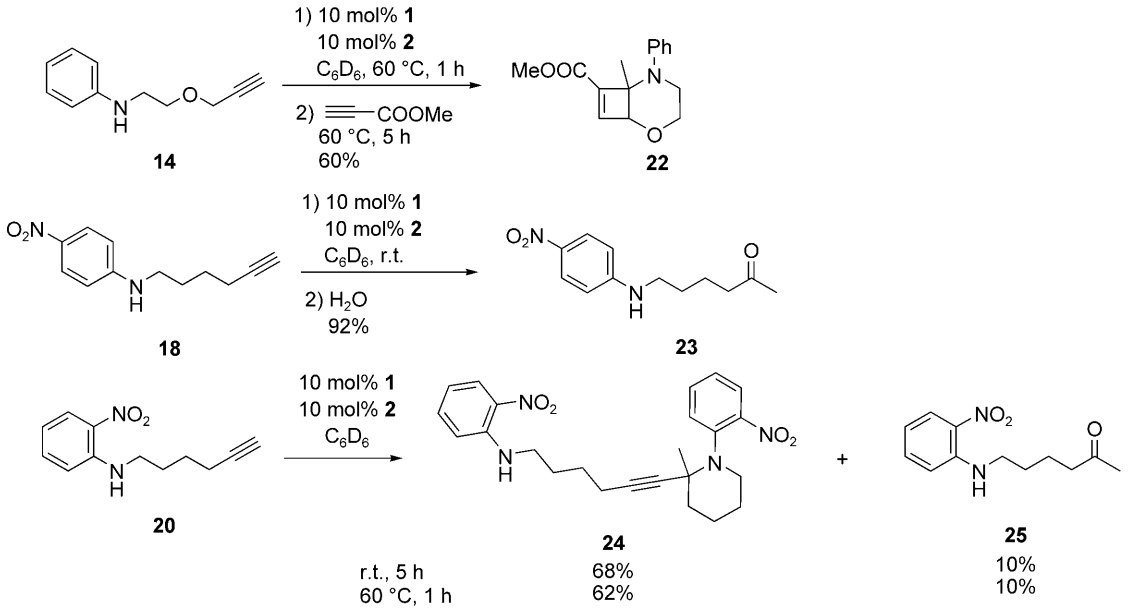
The mechanism of the zinc-catalyzed alkyne addition reaction is probably similar to that of the copper-catalyzed reaction.[13] In the first step of the domino hydroamination–alkyne addition reaction a zinc-catalyzed hydroamination to the corresponding Markovnikov product takes place. Subsequently, the resulting activated electrophilic enamine reacts with a second alkyne generating a quaternary propargylamine.

After the successful establishment of domino hydroamination–alkyne addition reactions, at which an amine molecule was reacted with two identical alkyne units, we were interested in the applicability of two different alkynes. Such cross-coupling reactions require different reaction rates of the alkyne derivatives in the individual reaction steps. As intramolecular hydroamination of alkynes to six-membered heterocycles compared to bimolecular reactions is considerably favored, we have studied the combination of the ring-closing reaction with the subsequent addition of a second alkyne. Our initial efforts focused on amino-

Table 2. Domino hydroamination–alkyne addition with two different alkynes.



Entry	Substrate	Cat. loading [mol%]	Temp. [°C]	Time [h]	Yield [%]	Product
9	 **14**	10	60	3	86	 **15**
10		1	80	54	76	
11	 **16**	10	60	4	66	 **17**
12	 **18**	10	r.t.	12	90	 **19**
13		10	60	1	90	
14	 **20**	10	r.t.	16	91	 **21**
15		10	60	1	91	



Scheme 3. Results obtained in the study of the Zn-catalyzed alkyne addition to the hydroamination intermediate.

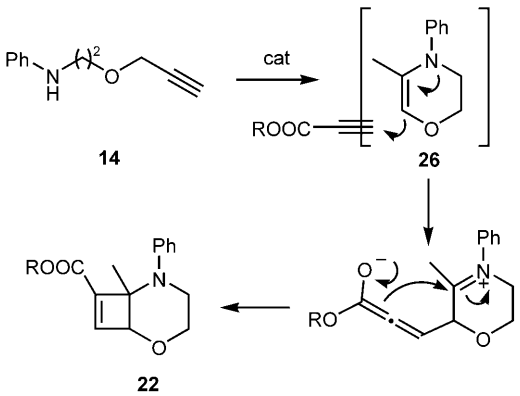
alkynes, which lead to instable cyclic products and which are converted to a stable amine *via* addition of the second alkyne. In a first experiment a 1/2.5 mixture of amine **14** and phenylacetylene was heated at 60 °C in benzene-d_6 with 10 mol% of catalyst. The reaction was completed after 3 h yielding the propargylamine **15** with 86% after chromatography (Table 2, entry 9). Next we tested the minimum of catalyst loading. With 1 mol% **1** and **2** we obtained 76% product, however the reaction needed 54 h at 80 °C. To analyze the tolerance of the zinc catalyst towards highly polar functional groups, we prepared substrates containing *para*- and *ortho*-nitro groups. The *ortho*-nitro containing substrate **16** led to propargylamine **17** in the presence of phenylacetylene at 60 °C in moderate yield in a short time (Table 2, entry 11). The *para*-nitro containing substrate **18** was converted to the corresponding product **19** at room temperature in the presence of phenylacetylene in 12 h in high yield (Table 2, entry 12). At 60 °C the reaction took only 1 h and provided the product **19** also in high yield (Table 2, entry 13). The *ortho*-substitued amine **20** gave similar results to furnish the *para*-analogue (Table 2, entries 14 and 15).

To gain insight into the substrate scope, phenylacetylene was substituted by propynoic esters. To our surprise, when propynoic acid ethyl[17] and methyl esters were used, bicyclic cyclobutene structures were isolated (Scheme 3). In this case, the cross-coupling is possible by doing the hydroamination of **14** first and adding the propynoic methyl ester after 1 h. The reaction was completed within 6 h at 60 °C and **22** was isolated as crude material in 60% yield.

We propose a domino hydroamination–Michael addition–Mannich reaction process as mechanistic explanation for the formation of **22** (Scheme 4) *via* enamine **26** as key intermediate. The presence of both oxygen and nitrogen should favor the formation of **26**, which undergoes Michael addition to the propynoic ester and consecutive intramolecular Mannich reaction. The whole process may also be activated *via* Lewis acid catalysis.

Since enamine **26** may be a reaction intermediate, we studied the same reaction for **16**, **18** and **20** without the addition of a second alkyne.

Exclusion of phenylacetylene in the case of substrate **16** did not result in the formation of any isolable product. When the reaction with amine **18** was performed in the absence of phenylacetylene, how-



Scheme 4. Proposed mechanism of the BDI-zinc-catalyzed hydroamination–Michael addition–Mannich cascade reaction.

ever, the acyclic ketone **23** was isolated as a single product (Scheme 3).

Unlike the *para*-nitro-containing substrate **18**, the corresponding *ortho*-nitro-containing analogue **20** showed a domino hydroamination–alkyne addition reaction even in the absence of phenylacetylene. The isolated product **24** showed that a second equivalent of the starting material **20** adds with its alkyne group to the *in situ* generated cyclic hydroamination intermediate. Along with obtained product **24**, the acyclic ketone **25** was isolated in low yield. This result is ascribed to the neighboring group effect of the *ortho*-nitro group that stabilizes the *in situ* generated cyclic iminium ion and allows the addition of alkynes having aliphatic substitution. In the presence of phenylacetylene, **24** and **25** were not observed and the cyclic product **21** was isolated in 91% yield (Table 2, entries 14 and 15).

During the preparation of this manuscript one report on a tandem amination–alkynylation reaction has been published.[13d] Hammond and co-workers report a copper-catalyzed N-heterocycles synthesis with similar yields as the ones presented in Table 2.

In summary, we have developed a highly efficient zinc-catalyzed domino hydroamination–alkyne addition reaction of secondary amines with terminal alkynes to furnish quaternary propargylamines with four different substituents. This method allows the access to bulky and highly functionalized amines from economic starting materials in one step. We have also reported the first Zn-catalyzed amination–Michael–Mannich cascade reaction to bicyclic cyclobutene derivatives. Further studies on the reaction scope, enantioselective methods, and combination of the methodology in novel cascade processes are currently under investigation in our group.

Experimental Section

General Tandem Hydroamination Procedure

Reactions were typically performed in NMR tubes and prepared in an N_2-filled glove-box. The substrate (0.36 mmol) and the alkyne (0.9 mmol) were dissolved in C_6D_6 (0.5 mL) and added to the precatalyst **1** (e.g., 36 μmol for 10 mol%) and then to the cocatalyst $[PhNMe_2H][OTf]$ (36 μmol for 10 mol%). In the case of 1 mol% catalyst loading the amount of substrates increased to 3.6 mmol. Subsequently, the mixture was injected into an NMR tube, removed from the glove-box, cooled to −196 °C and flame-sealed under vacuum. The reaction mixture was then heated in an oil bath for the stated duration of time.

Procedures and analytical data for all compounds are given in the Supporting Information.

Acknowledgements

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[17] For analytical data see Supporting Information.

