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Metal Free Carboamination of Internal Alkynes – an Easy Access to Polysubstituted Quinolines

T. Stopka and M. Niggemann*

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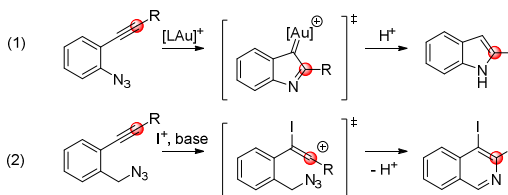
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A metal free carboamination of unactivated alkynes towards highly substituted quinolines was realized in the persence of a synergistic Brønsted acid catalyst system. Supported by mechanistic probes, the reaction proceeds via a highly reactive vinyl cation in a C-C bond formation - Schmidt reaction sequence. The irreversible extrusion of N₂, as a powerful driving force, allows for a general conversion of poorly nucleophilic aliphatic alkynes.

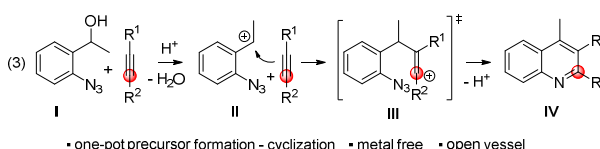
Substituted quinolines represent an important structural motif in numerous biologically active natural products and pharmaceuticals.¹ Due to their wide utility much effort has been devoted to the efficient synthesis of these compounds. Traditional condensations, such as the Friedlander reaction and related protocols,² have been extensively studied. Nevertheless, harsh reaction conditions such as the necessity for extended heating in strongly basic or acidic media severely limit functional group tolerance and often impart modest reaction selectivity. Allowing for milder reaction conditions, and avoiding self-condensation side reactions associated with classical Friedlander substrates, the coupling of alkynes with anilines and derivatives has recently become increasingly popular.³ Despite remarkable progress, most protocols are still confined to terminal⁴ or activated alkynes bearing one or two carboxylate groups.⁵ Therefore, new procedures, providing general access to highly substituted quinolines from internal alkynes under mild reaction conditions are highly desirable.

The activation of alkynes by noble metal catalysts lately established powerful concepts for the synthesis of complex structures also from unactivated internal alkynes.⁶ Here especially, the acetylenic Schmidt reaction, catalyzed by cationic Au(I)-species, drew our attention, as it is highly effective for the synthesis of nitrogen heterocycles (f. ex. Scheme 1, eqn. 1).⁷ Alternatively, strong electrophiles, such as iodine donors have been successfully applied (f. ex. Scheme 1, eqn. 2).⁸ Apart from the obvious drawbacks of these methods - the need of expensive TM-catalysts, or a stoichio-

Au(I)-catalyzed or I⁺-mediated acetylenic Schmidt reaction:



This work:



Scheme 1 Reaction of azides with internal, unactivated alkynes.

metric electrophile - they call for the preformation of alkyne tethered azide building blocks.

In this context, we reasoned, that in an ideal synthetic strategy towards highly substituted quinolines from alkynes the C-C bond formation for the synthesis of the cyclization precursor is combined with the activation of the alkyne for the subsequent Schmidt reaction, resulting in a bifunctionalizing formal carboamination of the unactivated, internal alkyne (Scheme 1, eqn. 3). In this reaction alcohol I is ionized to a benzylic carbocation II which is readily reacting with the alkyne to form a vinylcation III.⁹ Nucleophilic addition of the azide to the vinylcation induces the loss of nitrogen and a simple deprotonation yields the corresponding quinoline IV. Addressing the above mentioned shortcomings of the existing quinoline syntheses, our new protocol adds not only a valuable transformation to the toolbox of scarcely explored carboamination reactions of alkynes¹⁰ but also combines several further benefits. Expensive, sensitive and potentially toxic metal catalysts are unnecessary. Water and N₂ are the only byproducts of the process. Last but not least, from a more fundamental view point, merging the intermolecular vinyl cation forming C-C bond formation process with a powerful driving force, such as the irreversible expelling of nitrogen in the Schmidt reaction, represents an ideal playground for

^a Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany. Email: niggemann@oc.rwth-aachen.de

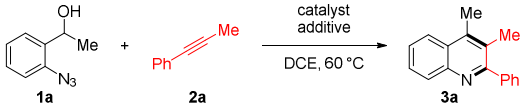
[†] Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data. See DOI: 10.1039/x0xx00000x

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a further expansion of the knowledge on highly reactive vinyl cations.

We started our investigation reacting 2-azido phenylethanol (**1a**) with 1-phenylpropyne (**2a**, Table 1). To our delight, a first attempt in the presence of our calcium-based catalyst system afforded the corresponding quinoline **3a** in 36% yield (Table 1, entry 1). Other Lewis acid catalysts proved less effective, and provided the desired product in diminished yield, or not at all (Table 1, entries 2-6). As no catalyst was able to produce the desired product in a satisfying yield and we generally recovered larger amounts of unreacted starting material, we suspected product inhibition being responsible for the incomplete conversion. To substantiate this hypothesis, we carried out a reaction in the presence of stoichiometric $\text{BF}_3 \cdot \text{OEt}_2$ and indeed obtained the quinoline in 74% yield (Table 1, entry 7). Searching for milder options, equally effective at preventing product inhibition, we tested Brønsted acid additives, among which *p*-toluenesulfonic acid (pTSA) proved most efficient. Using 10 mol% of calcium catalyst in the presence of pTSA, the conversion of the starting material proceeded to completion and we isolated the product in 58% yield (Table 1, entry 8). The role of the acid might be seen in the formation of a hydrogen bond to the quinoline's nitrogen atom, thereby liberating the catalyst for turnover.¹¹

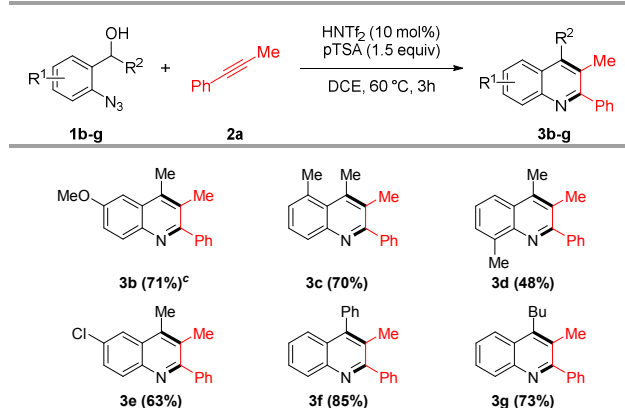
Table 1 Optimization of the reaction conditions.

				
Entry	Catalyst (mol%)	Additive (mol%)	Time	Yield (%) ^a
1	$\text{Ca}(\text{NTf}_2)_2$ (10)	Bu_4NPF_6 (5)	23h	36
2	$\text{Zn}(\text{OTf})_2$ (10)	---	23h	nr
3	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10)	Bu_4NPF_6 (5)	23h	nr
4	$\text{Bi}(\text{OTf})_3$ (10)	---	23h	25
5	$\text{Sc}(\text{OTf})_3$ (10)	Bu_4NPF_6 (5)	23h	15
6	$\text{BF}_3 \cdot \text{OEt}_2$ (25)	---	23h	26
7	$\text{BF}_3 \cdot \text{OEt}_2$ (120)	---	1h	74
8	$\text{Ca}(\text{NTf}_2)_2$ (10)	Bu_4NPF_6 (5) + pTSA (150)	3h	58
9	---	pTSA (150)	3h	19
10	---	TFA (150)	3h	11
11	HNTf ₂ (10)	pTSA (150)	3h	89 ^b
12	HNTf ₂ (150)	---	3h	82

Reaction conditions: Catalyst and additive were added to azide **1a** (0.25 mmol) and phenyl propyne **2a** (0.75 mmol), dissolved in DCE (2.5 mL) and stirred at 60 °C for the indicated time.^a NMR-yield based on mesitylene as internal standard.^b Isolated yield.

Brønsted acids such as *p*-TSA or TFA alone proved ineffective, even in overstoichiometric amounts, due to their poor ability for alcohol ionization (Table 1, entries 9-10). Remarkably, the desired product was isolated in excellent 89% yield, when we used a synergistic mixture of two Brønsted acids, 10 mol% HNTf₂ for an efficient ionization of the alcohol and pTSA as a hydrogen bond donor to prevent product inhibition (Table 1, entry 11). In contrast, HNTf₂ alone, in stoichiometric amounts, lead to a diminished yield, due to the rise of side reactions, an effect that is even much more pronounced with more sensitive substrates (Table 1, entry 12).

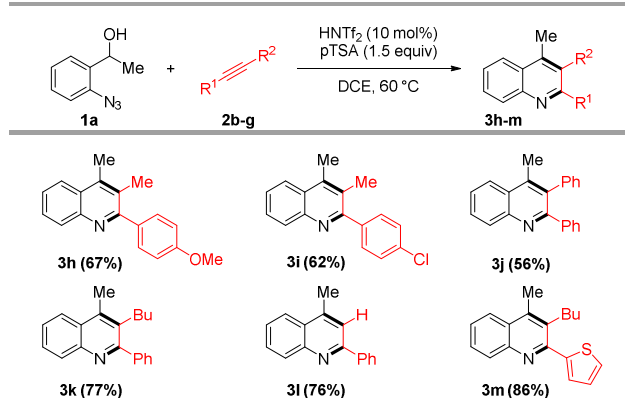
Table 2 Scope of azides^{a,b}.



^a Reaction conditions: HNTf₂ (10 mol%) and pTSA (1.5 equiv) were added to the corresponding azide **1b-g** (0.25 mmol) and phenyl propyne **2a** (0.75 mmol), dissolved in DCE (2.5 mL) and stirred at 60 °C for 3h. ^b Isolated yield. ^c 2h reaction time.

With the optimized reaction conditions in hands, the generality of the transformation was investigated. Therefore, we first reacted different azides with propyne **2a** (Table 2). A wide range of azido phenylethanol derivatives was tolerated under the reaction conditions. Substrates bearing an electron-donating group (**3b-3c**) lead to the desired products in good yields (71% and 70%). A substitution in the 3-position, interferes with the Schmidt-type cyclization and an only moderate yield was observed (**3d**). On the other hand, even the more challenging electron-withdrawing derivative (**3e**) reacted smoothly to the corresponding quinoline in an acceptable 63% yield. Furthermore, the reaction easily tolerated starting materials with sterically more demanding and electronically varying substituents for R² (**3f-3g**).

Table 3 Scope of aromatic alkynes^{a,b}.

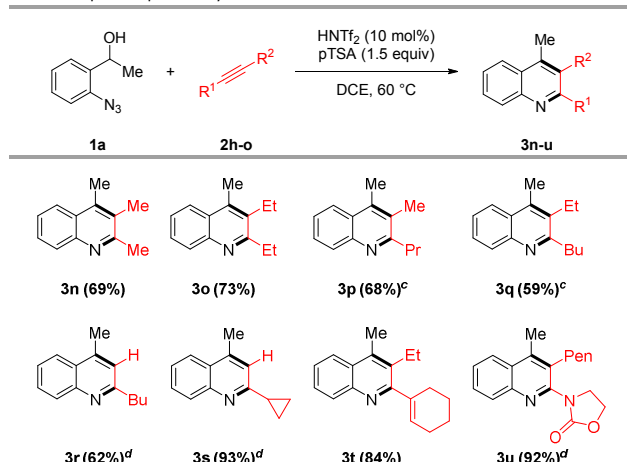


^a Reaction conditions: HNTf₂ (10 mol%) and pTSA (1.5 equiv) were added to azide **1a** (0.25 mmol) and the corresponding alkyne **2b-g** (0.75 mmol), dissolved in DCE (2.5 mL) and stirred at 60 °C for 3h. ^b Isolated yield.

Next, we turned our attention to the investigation of different alkynes (Table 3). A range of different alkynes gave the quinoline products in good to excellent yields. Alkynes bearing electron donating as well as electron withdrawing substituents in the arene moiety (**3h-3i**) were well tolerated. Noteworthy, also terminal alkynes reacted smoothly to the desired quinolines (**3l**), and heterocyclic alkynes (**3m**) were readily incorporated.

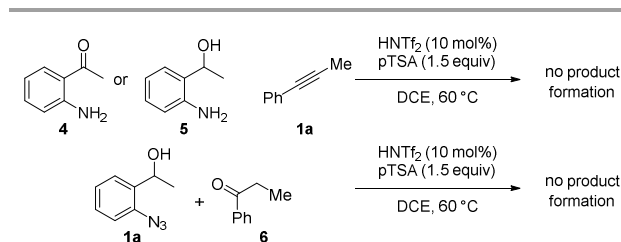
Inspired by the results shown above, we were interested if the intermolecular vinyl cation forming C-C bond formation process could be sufficiently promoted by the irreversible expelling of nitrogen in the subsequent Schmidt reaction that non-stabilized vinyl cations intermediates were accessible. Intermolecular reactions proceeding via vinyl cations that are not stabilized by an adjacent phenyl group are extremely scarce. Given the fact that both reactions are extremely fast, we reasoned that the reaction of the benzylic cation with the alkyne might be merged into a single (quasi)-concerted process with the subsequent Schmidt rearrangement – so that the developing cationic character on the alkyne is already stabilized by an interaction with the azide. To our delight, a wide range of aliphatic alkynes afforded the corresponding quinolines in good to excellent yields (Table 4). Symmetric aliphatic alkynes (**3n-o**) reacted to the corresponding quinolines in good yields. When aliphatic alkynes with two different, yet electronically similar substituents (**3p-q**) were used, the products were obtained in good yields but as a mixture of regioisomers.¹² Terminal aliphatic alkynes (**3r-s**) were found to be more challenging. Here, the use of stoichiometric $\text{BF}_3 \cdot \text{OEt}_2$ proved more efficient. In addition, the presence of double bonds (**3t**) and oxazolidone moieties (**3r**) did not interfere with the desired pathway.

Table 4 Scope of aliphatic alkynes^{a,b}.



^a Reaction conditions: HNTf_2 (10 mol%) and pTSA (1.5 equiv) were added to azide **1a** (0.25 mmol) and the corresponding alkyne **2h-o** (0.75 mmol) dissolved in DCE (2.5 mL) and stirred at 60 °C.^b Isolated yield.^c Mixture of regioisomers (see Supporting Information).^d $\text{BF}_3 \cdot \text{OEt}_2$ (1.2 equiv) was used instead of HNTf_2 and pTSA .

To exclude other potential reaction pathways involving a preceding hydrolysis of the alkyne to the corresponding ketone or the conversion of the azide to an amine moiety, that would overall result in two step Friedlander-type reactions,¹³ the mechanistic probes summarized in Scheme 2 were accomplished. Neither the reactions of aniline derivatives **4** and **5** with alkyne **2a**, nor the exposure of ketone **6** to the azido phenylethanol **1a** gave any significant conversion to the corresponding quinolones. A direct reaction of an ionized alkyne with the azide moiety would lead to an entirely different product. Therefore, the carboamination protocol presented herein is best accommodated by a mechanism proceeding via the ionization of the alcohol, vinyl cation formation and subsequent Schmidt reaction, such as outlined in Scheme 1.



Scheme 2 Mechanistic investigations.

In conclusion, a new and straightforward route toward polysubstituted quinolines, allowing a very general substitution pattern was developed. Addressing the limitation to terminal or carboxylate activated alkynes in previously published procedures using alkynes as a building block, an acetylenic Schmidt reaction was envisaged. To avoid the preformation of an azide tethered alkyne a C-C bond formation process was combined with the azide addition - rearrangement sequence. Thereby a challenging, formal carboamination reaction of internal, unactivated alkynes was realized. The reaction design does not require the use of expensive, sensitive and potentially toxic transition metal catalysts and water and N_2 are formed as the only byproducts. Proceeding also via unstabilized vinyl cation intermediates, this new protocol is highly interesting also from a more fundamental viewpoint. Therefore, the presented work is intriguing for both, industry as well as academia.

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