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Calcium-Catalyzed Carboarylation of Alkynes

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Abstract: The first transition-metal-free carboarylation of alkynes with commercial and readily available alcohols as alkylating agents was realized in the presence of an environmentally benign calcium catalyst. Thereby, a novel protocol for the one-step synthesis of highly congested, all-carbon tetrasubstituted alkenes, as incorporated in potentially bioactive, complex dihydronaphthalene, chromene and dihydroquinoline structures, is provided. The reaction features an unprecedented, particularly wide substrate scope, good functional-group tolerance and simple experimental operation under mild reaction conditions.

All-carbon tetrasubstituted olefins are frequently found in natural products, pharmaceuticals, and materials and represent versatile starting materials for the synthesis of complex fine chemicals.^[1] However, the congested nature of these olefins encumbers their synthesis through classical procedures such as carbonyl olefination or olefin metathesis.^[1a] Although several methods have been developed to access them from alkynes in a stepwise fashion,^[1a,2] catalytic protocols for the one step assembly of these densely substituted building blocks remain a challenge to synthetic organic chemists. This is undoubtedly due to the fact that most procedures for the introduction of substituents to alkynes proceed via a carbometallation step, followed by further elaboration of the resulting vinyl-metal species A (Scheme 1). In catalytic one-step protocols this elaboration is often just a simple protodemetallation, consequently limiting the scope of accessible olefins to trisubstituted ones. In addition, air and moisture sensitive stoichiometric metal-organic reagents and transition-metal catalysts such as nickel,^[3] palladium,^[4] copper^[5] or iron salts^[6] are mandatory.

An ideal strategy towards all-carbon tetrasubstituted olefins engages the activation of the C=C triple bond for the subsequent introduction of a carbon nucleophile by an electrophilic carbon reagent, such as a carbocation, in analogy to the classical acid catalyzed hydroarylation of alkynes.^[7] In other words, the two carbon substituents are introduced concomitantly. The first one as an electrophile that generates an intermediary, highly reactive vinyl cation **B**, which is then trapped by the

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Scheme 1. Carbon electrophile-triggered carboarylation of internal alkynes.

second, being a carbon nucleophile (Scheme 1). Thereby, the need to proceed via a vinyl-metal intermediate is avoided from the outset. The feasibility of this approach was demonstrated recently with the development of a copper-catalyzed carboarylation of alkynes, in which the copper catalyst is used for the generation of aromatic electophiles from a diaryliodonium salt.^[5] In addition, iron salts have been shown to catalyze the annulation of benzylic alcohols with alkynes for the formation of indenes.^[8] Nevertheless, both of these methods are limited in scope as only aryl and benzyl cations are known to induce this highly valuable transformation, and transitions metal catalysts are still needed.

Calcium is one of the five most abundant elements in the earth's crust and it is therefore inexpensive and non-toxic even in substantial amounts. Over the last couple of years, our group has focused on developing an environmentally friendly calcium catalyst to replace expensive and highly toxic noble metal catalysts in synthetic chemistry.^[9] We have successfully utilized simple calcium salts as a highly efficient Lewis acid catalysts for the transformation of readily available alcohols into a broad variety of reactive carbocations.

The active Lewis-acidic calcium catalyst CaNTf₂PF₆, required for the ionizing deoxygenation of the alcohol, is formed in situ by anion exchange upon the combination of Ca(NTf₂)₂ and Bu₄NPF₆. Its particularly high reactivity originates presumably in a double role of the calcium catalyst. It activates the C–O bond for bond cleavage by withdrawing electron density via coordination to the hydroxy oxygen. At the same time a temporary leaving group, "NTf₂CaOH", is installed, due to the particular stability of Ca–O bonds.

Based on these hypotheses, we examined the reaction of acetylene **1a** with 4-hydroxyphenylethanol **2a** as model substrates, in the presence of 5 mol% $Ca(NTf_2)_2$ and 5 mol% Bu_4NPF_6 . To our delight, the reaction indeed occurred, and gave the isolated carboarylation adduct **3a** in 56% yield after 12 h reaction time (Table 1, entry 1). Inspired by this result, we started further optimization of the reaction conditions. Sol-

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vents had significant influence on the formation of **2a** and the yield was improved by using CH_3NO_2 instead of dichoroethene (DCE; Table 1, entry 2). We also found alternative organic salts, such as NH_4PF_6 and Bu_4NSbF_6 , to be equally efficient as cocatalysts (Table 1, entries 3 and 4). Notably, decreasing the additive loading to 2.5 mol% improved the yield of the reaction (Table 1, entry 5).



Mixed solvents and two equivalents of alcohol **2a** were also examined, but no better results were obtained (Table 1, entries 6 and 7). The absence of Bu₄NPF₆ resulted in no conversion (Table 1, entry 8). HNTf₂ (10 mol%) was identified to be a less efficient catalyst for the reaction (Table 1, entries 9 and 10). The superior levels of reaction efficiency with 5 mol% Ca(NTf₂)₂ and 2.5 mol%Bu₄NPF₆ in CH₃NO₂ at 40 °C for 12 h (Table 1, entry 5) were selected for further exploration.

We first examined the scope of the reaction towards a variety of readily available alcohols (Table 2). We found that electrondonating and -withdrawing groups, as well as reactive groups on the aromatic ring, such as OH, OCH₃, CH₃, or Cl at C4 positions and NHTs at C2 position, were well tolerated (Table 2, 3a-f). Some alcohols, such as 2b-m gave poor conversions in CH₃NO₂ as a reaction medium. The reactivity was found to be restored in DCE, albeit at the expense of product selectivity, as significant amounts of dihydronaphthalene 5 resulting from a direct hydroarylation of the alkyne (cf. discussion of the mechanism; see below) were formed alongside the desired carboarylation product 3. We were pleased to find that a mixed solvent system (DCE/CH₃NO₂ 1:1) allowed for a sufficient reactivity of the alcohol and at the same time suppressed the formation of the undesired hydroarylation product 5. Notably, even sterically hindered alcohols reacted smoothly in excellent yields (Table 2, 3 g and 3 h). In addition, not only alkenyl but also alkynyl groups were well tolerated by the reaction



(Table 2, **3***i*–**k**). Finally, the substrate scope was successfully extended to allylic alcohols (Table 2, **3***i* and **3***m*).

Secondly, we varied the substituents on the C=C triple bond. Both aryl and heteroaryl groups gave the desired adducts in excellent yields (Table 3, 3n-q). As an alternative, ynamides could also be used, thus providing access to more complex dihydronaphthalene derivatives (Table 3, 3r). Once more showcasing the robustness of the presented method towards steric hindrance, it is noteworthy that the preparation of axial chiral compounds using 2-anisyl and 1-naphthyl groups (Table 3, 3o and 3p) was highly efficient, albeit yielding racemic mixtures under the current reaction conditions.

Next, we examined the linking unit between the aryl nucleophile and the C=C triple bond. Apart from the ethylene linkage, oxygen and nitrogen substituents proved to readily yield chromene and dihydroquinoline derivatives (Table 3, **4a** and **4b**). The dihydroquinoline derivatives were obtained without chromatographic purification in 73% yield by simple filtration after reaction completion. The additional steric bulk of a substituent in the linking unit was again well tolerated (Table 3, **4c**). As typical for intermolecular carbocation additions,^[10] the diastereoselectivity was found to be mediocre, which might be attributed to the slenderness of the alkyne nucleophile. More importantly, seven-membered rings could be formed, due to the high reactivity of the vinyl cation, which further broadens the substrate scope (Table 3, **4d**).

Finally, we focused on our studies on the scope of nucleophilic arenes (Table 4). The reaction was very general with respect to the electronic properties of the substituent on the ring of nucleophilic arenes (Table 4, **3s-v**). Most notably, the

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[a] Additive and Ca(NTf₂)₂ were added to **1** (0.48 mmol) and **2a** (0.4 mmol) in CH₃NO₂ (2 mL) and stirred at 40 °C for 12 h; [b] yield of isolated product; [c] reaction at 80 °C for 12 h; d.r. determined by ¹H NMR spectroscopy of the crude mixture.



high reactivity of the vinyl cation intermediate allowed for smooth conversion of deactivated arenes bearing Br and even F (Table 4, 3u and 3v). In addition, naphthyl and heteroaromatic groups gave excellent yields (Table 4, 3w and 3x).

The mechanism of the calcium-catalyzed carboarylation can, in principle, proceed via two different pathways (Scheme 2, paths a and b). In the first, the calcium catalyst initially generates a carbocation **A** from the alcohol **2** that attacks the functionalized alkyne **1**. Thereupon, a trisubstituted highly reactive vinyl cation **B** is formed, which is attacked by the tethered aryl



Scheme 2. Proposed mechanisms for the carbon electrophile-triggered carboarylation of internal alkynes with alcohols by calcium catalysis.

nucleophile (ArH, path a). An alternative process (path b) is initiated by the activation of the alkyne by the Lewis-acidic calcium catalyst, resulting in the formation of a Lewis acid-bound vinyl cation and immediate protodemetallation with adventitious water, in analogy to the previously described activation of alkenes.^[11] The disubstituted vinyl cation **C** then reacts with the tethered aryl nucleophile (ArH), yielding a direct hydroarylation product 5. Product formation then occurs via a subsequent Friedel-Crafts type addition of the cation A that is once again generated from the alcohol 2 by the calcium catalyst. To gain insight into which of the two pathways is operative, especially due to the aforementioned fact that in some reactions 5 was formed as a byproduct, 5 was reacted with alcohols under the standard reaction conditions. The desired products 3a and 3b were obtained in 8% and 21% yield alongside unreacted dihydronaphthalene 5 (Scheme 3). These results clearly support the first, direct reaction pathway (Scheme 2, path a).

In conclusion, we have developed an alkyne carboarylation process that provides a concise route for the one-step preparation of all-carbon tetrasubstituted olefins in the presence of an environmentally benign calcium catalyst, using commercial and readily available alcohols as alkylation reagents. The reaction proceeds via a highly reactive trisubstituted vinyl cation and therefore allows for the use of deactivated, fluorine-substituted arenes as tethered nucleophiles and tolerates a great deal of steric congestion. In addition, the preparation of potentially bioactive chromene and dihydroquinoline derivatives makes this procedure particularly useful.

Experimental Section

General procedure for the carboarylation: **1** a (0.48 mmol) and **2** a (0.4 mmol) were dissolved in CH₃NO₂ (2 mL), then Bu₄NPF₆

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Scheme 3. Reactions of mechanistic probes.

(2.5 mol%) and Ca(NTf₂)₂ (5 mol%) were added and the reaction was stirred at 40 °C for 12 h. After completion, the reaction was stopped by addition of saturated NaHCO₃ solution (5 mL) and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over Na₂SO₄ and the crude product was purified by column chromatography (eluent = hexane/ethyl acetate, 15:1 to 7:1).

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Keywords: alkynes · calcium · carboarylation · synthetic methods · tetrasubstituted alkenes

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COMMUNICATION



Finally free: The first transition-metalfree one-step synthesis of highly congested, all-carbon tetrasubstituted olefins has been realized by a calcium-catalyzed carboarylation reaction. Internal alkynes react with alcohols as alkylating reagent under mild reaction conditions, which provides access to a variety of useful structural scaffolds via highly reactive trisubstituted vinyl cations.

Carboarylation

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An environmentally benign calcium catalyst...

...effects the first transition-metalfree carboarylation of alkynes with commercial and readily available alcohols as alkylating agents. In their Communication on page **I** ff., L. Fu and M. Niggemann report a novel protocol for the one-step synthesis of highly congested, allcarbon tetrasubstituted alkenes, with a wide substrate scope, good functional-group tolerance and simple experimental operation under mild reaction conditions.

