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Cyclopentanone as a Cation-Stabilizing Electron-Pair Donor in the Calcium-Catalyzed Intermolecular Carbohydroxylation of Alkynes

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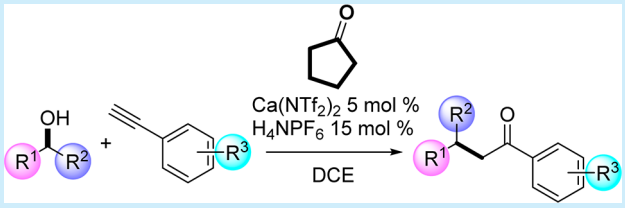
Supporting Information

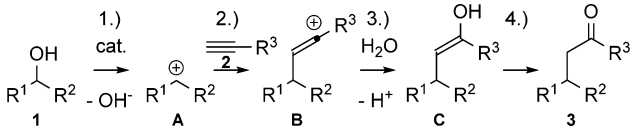
ABSTRACT: Although they have been used as reactivity-controlling additives in cationic polymerizations for decades, Lewis basic "electron pair donor" (ED) compounds were never used for the stabilization of cationic intermediates in transformations of small molecules. As such an ED, cyclopentanone proved highly efficient for the stabilization of allyl and vinyl cations in combination with our calcium-based catalyst system. Therefore, the first general transition-metal-free intermolecular carbohydroxylation of alkynes with allyl and propargyl alcohols was realized.



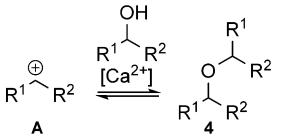
The direct functionalization of alkynes with carbon-centered electrophiles represents a highly desirable yet scarcely explored C−C bond-formation reaction.[1] A challenging model transformation for this type of chemistry is the carbohydroxylation with inexpensive and readily available alcohols resulting in the formation of ketones.[1d,2] As outlined in Scheme 1, this process consists of four elementary steps: (1) ionization of the alcohol; (2) nucleophilic attack of the alkyne and formation of a vinyl cation intermediate; (3) interception of the vinyl cation with a water molecule; (4) keto enol tautomerization.

Even though fundamentally simple and benefiting from full atom economy, the process suffers from major limitations related to the first two of these elementary steps. First, only very few catalysts have been found competent for the direct ionization of alcohols **1** other than benzylic alcohols; the scope of the process with regard to the carbon electrophile **A** remains therefore severely limited,[1d,2f−l] and stoichiometric use of "catalyst" is often necessary. Even more difficulties are associated with the low nucleophilicity of the alkyne moiety in **2**.[3] Due to this low nucleophilicity, the addition of the alkyne **2** to the previously generated carbocation **A** tends to be relatively slow, particularly in intermolecular transformations, so that the cation **A** is very likely to be entangled in unproductive side reactions especially when highly reactive due to the absence of stabilizing substituents. Furthermore, the reactive intermediate that is formed upon the successful addition, the vinyl cation **B**, is in any case even more reactive than **A** and its fate, hence, even more difficult to control.

Scheme 1. Carbohydroxylation of Alkynes



Scheme 2. Ether Cation Equilibrium



In recent years, our group has focused on the development of a simple calcium catalyst as a more sustainable alternative to expensive and highly toxic noble metal catalysts in synthetic chemistry.[4] Decorated with a carefully balanced combination of noncoordinating anions, the Ca^{2+} ion was found to be a highly efficient Lewis acid catalyst for the direct ionization of readily available and also nonbenzylic alcohols. In addition, cation formation was found to be generally accompanied by a reversible background reaction in which the cation was found to form ethers **4** (see Scheme 2),[5] thereby maintaining the effective cation concentration at a low level that might be highly beneficial to avoid unproductive side reactions of cation **A**.

Thus, having in hand a competent catalyst for the formation of an unprecedented scope of carbocations from alcohols and to maintain an equilibrium between these and a stable resting state, we set out to identify further reaction parameters that also allow for a reversible stabilization of the vinyl cation **B**. An extensive survey of the literature pointed us toward a series of papers that discusses the beneficial influence of electron-pair donors (EDs) for the control of reactivity in cationic polymerizations reactions.[6] Although the exact mechanistic role of these EDs is still a subject of debate, it was uniformly found that the rate of polymerization was slowed in the presence of EDs and at the same time products of a more controlled process with fewer unwanted intramolecular self-alkylation and smaller molecular weight distributions were

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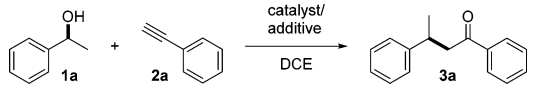
Table 1. Optimization of the Reaction Conditions



entry[a]	catalyst	additive	carbonyl-compound	temp (°C)	yield (%)[b]
1	$Ca(NTf_2)_2$	NH_4PF_6	---	rt	25
2	$Sc(OTf)_3$	---	---	rt	0
3	$FeCl_3{\cdot}6H_2O$	---	---	rt	10
4	$HNTf_2$	---	---	rt	16
5	$HNTf_2$	NH_4PF_6		40	39
6	TfOH	---	---	rt	5
7	$Ca(NTf_2)_2$	NH_4PF_6		rt	45
8	$Ca(NTf_2)_2$	Bu_4NPF_6		rt	traces
9	$Ca(NTf_2)_2$	$PhMe_2HN^+$ $B(C_6F_5)_4^-$		rt	0
10	$Ca(NTf_2)_2$	NH_4PF_6		40	85
11	$Ca(NTf_2)_2$	NH_4PF_6		40	69
12	$Ca(NTf_2)_2$	NH_4PF_6		40	57
13	$Ca(NTf_2)_2$	NH_4PF_6		40	0
14	$Ca(NTf_2)_2$	NH_4PF_6		40	0

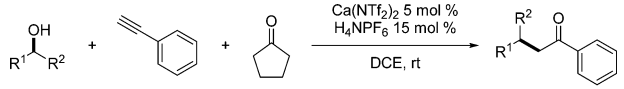
[a]Catalyst (5 mol %) and additive (15 mol %) were added to alcohol **1a** (0.25 mmol) and alkyne **2a** (0.75 mmol) in DCE (2.5 mL) and stirred for 16 h. [b]Isolated yield.

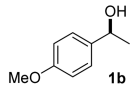
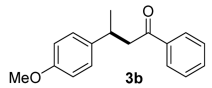
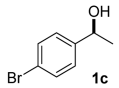
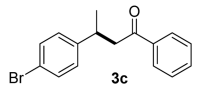
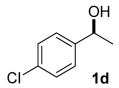
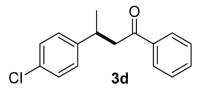
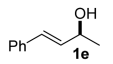
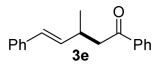
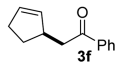
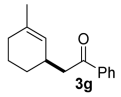
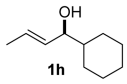
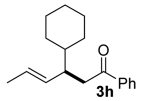
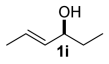
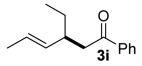
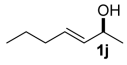
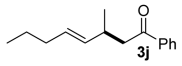
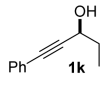
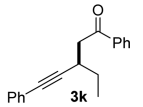
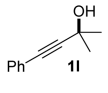
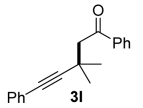
provided. This clearly points toward a reduction of reactivity of the cationic propagating species by the formation of Lewis acid/base pairs between the cation center and the lewis basic ED with more or less covalent character.[7]

Inspired by these findings from polymer chemistry, we chose the addition of phenylethanol (**1a**), yielding a still relatively stable benzylic cation, to phenylacetylene (**2a**) as a starting point to test the influence of EDs on the title transformation. In an initial set of screening reactions, 5 mol % of $Ca(NTf_2)_2$ in the presence of 15 mol % of NH_4PF_6 proved to be the most effective catalyst system in the absence of EDs, yielding the desired product in 25% yield (Table 1, entry 1).

Even though they are generally competent for the first ionization step in this particular case, as it is a benzylic alcohol, commonly employed Lewis acids (Table 1, entries 2 and 3) as well as Brønsted acids (Table 1, entries 4 and 5) were less efficient than the calcium-based system and led to complex reaction mixtures. The addition and variation of additives such as NH_4PF_6 had no significant impact in combination with these catalysts. Further optimization confirmed that the presence of cyclopentanone significantly improved the results, and the desired product was isolated in a much better yield (Table 1, entry 8). Notably, if the reaction was carried out in other solvents or with an additive different from NH_4PF_6 (Table 1, entries 9 and 10) the reaction became sluggish again. Finally, slightly higher reaction temperatures (40 °C) afforded the product with excellent yield (Table 1, entry 11).

Table 2. Addition of Alcohols to Phenylacetylene



entry[a]	alcohol	product	time	yield[b] (%)
1	 1b	 3b	3 h	87
2	 1c	 3c	19 h[c]	72
3	 1d	 3d	23 h[c]	53
4	 1e	 3e	2.5	71
5	 1f	 3f	2 h	56
6	 1g	 3g	2 h[c]	52
7	 1h	 3h	4 h	46[d]
8	 1i	 3i	3.5 h	62[d]
9	 1j	 3j	3 h	67[d]
10	 1k	 3k	3.5 h[c]	59[e]
11	 1l	 3l	10 h	68[e]

[a]$Ca(NTf_2)_2$ (5 mol %) and NH_4PF_6 (15 mol %) were added to alcohols **1b–l** (0.25 mmol), alkyne **2a** (0.75 mmol), and cyclopentanone (1.25 mmol) in DCE (2.5 mL) and stirred for the indicated time at room temperature. [b]Isolated yield. [c]Reaction at 40 °C. [d]Mixture of regioisomers (see the Supporting Information). [e]10 equiv of alkyne was used.

Although other carbonyl compounds had the ability to stabilize intermediates as well, inferior results were obtained in comparison with cyclopentanone (Table 1, entries 12 and 13). As these results reflect the carbonyl oxygens' binding affinity to Lewis acids, PhCHO ≈ PhCOMe < cyclopentanone, the influence of dimethylformamide and tetramethylurea was analyzed.[7,8] The presence of these two compounds with an even higher Lewis acid binding affinity resulted in the suppression of the formation of ether **4** (cf. Scheme 2), therefore leading to oligomerization of the initially formed cation A. This finding indicates once more the importance of a meticulous balancing of all stabilizing effects. Interestingly, the addition of carbonyl compounds had little influence in reactions catalyzed by the common Lewis/Brønsted acids in entries 2–5.

Having in hand the optimized reaction conditions, the generality and scope of the reaction were explored. Therefore, a

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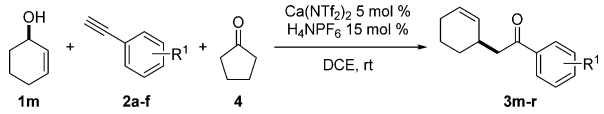
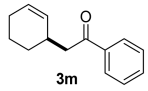
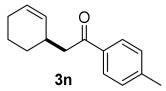
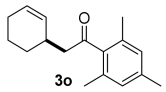
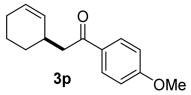
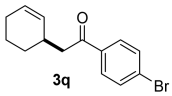
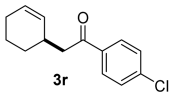
Table 3. Reaction of 2-Cyclohexenol with Phenylacetylenes



entry[a]	product	time	yield (%)
1	 3m	6 h	77
2	 3n	5 h	84
3	 3o	1.5 h	88
4	 3p	0.5 h	91
5	 3q	5 h	75
6	 3r	3.5 h	66

[a] $Ca(NTf_2)_2$ (5 mol %) and NH_4PF_6 (15 mol %) were added to 2-cyclohexenol **1m** (0.25 mmol), phenylacetylene **2a–f** (0.75 mmol), and cyclopentanone (1.25 mmol) in DCE (2.5 mL) and stirred for the time indicated at room temperature.

series of different π-activated alcohols was reacted with phenylacetylene (**2a**, Table 2). It was found that a wide range of various alcohols reacted readily under the reaction conditions. Benzylic alcohols bearing electron-rich or weakly withdrawing substituents afforded the corresponding products in good yields (Table 2, entries 1 and 2). With a more electron-deficient substrate the yield was slightly decreased (Table 2, entry 3). The linear allylic alcohol **1e** reacted smoothly within 2.5 h.

Next, a range of truly nonbenzylic alcohols were tested, as due to the low stability of the poorly stabilized corresponding cations they represent one of the aforementioned major limitations for this kind of transformations. To our delight, simple secondary and tertiary allylic alcohols afforded the corresponding aryl ketones even at room temperature (Table 2, entries 5–9). In some cases, the formation of regioisomers was observed due to double-bond isomerization of the initially formed cations **A** (Table 2, entries 7–9). Furthermore, secondary and tertiary propargylic alcohols also reacted readily with the desired products (Table 2, entries 10 and 11). Here, side reactions arising from the addition of the cation **A** to the alkyne moiety in the propargylic alcohol or the product could be avoided by using an excess amount of the alkyne.

Finally, the reactivity toward different kind of alkynes was explored. A wide range of phenylacetylenes was alkylated with 2-cyclohexenol (**1m**), thus further showcasing the generality of the transformation of its poorly stabilized corresponding allyl cation (Table 3). Electron-rich alkynes afforded the corresponding products in excellent yields (entries 2–4). Sterically hindered substrates bearing substituents in the *o*-position could be used without a drop in yield or expanded reaction times (entry 3). In addition, electron-deficient alkynes reacted smoothly, albeit with a slightly diminished yield.

In summary, we demonstrate that cyclopentanone, as a weakly Lewis basic electron-pair donor, proves to be highly efficient for the stabilization of allyl and vinyl cation intermediates in combination with our calcium-based catalyst system. Therefore, a transformation that is typically plagued by side reactions originating in the fleeting nature of poorly stabilized cationic intermediates, the intermolecular carbohydroxylation of alkynes, was realized with allyl and propargyl alcohols as alkylation agents for the first time. Further investigations in our laboratories of the stabilizing influence of electron-pair donors in other transformations of small molecules with cation participation will be reported due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, NMR spectra, and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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