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Calcium-Catalyzed Dynamic Multicomponent Reaction

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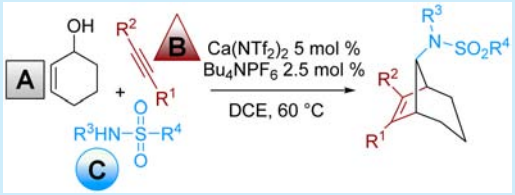
Supporting Information

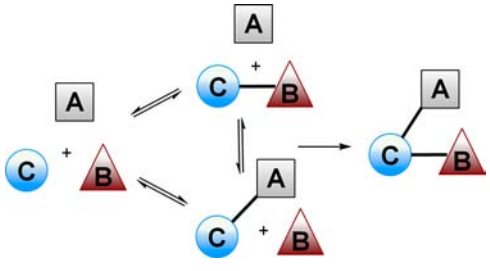
ABSTRACT: The reversible formation of covalent bonds enabled by the remarkably high Lewis acidity of our calcium-based catalyst system was used for the development of a new type of multicomponent reaction. Accordingly, a pharmacologically interesting bicyclic amine was amplified from a highly efficient dynamic equilibrium. The product is formed with full diastereoselectivity, and as typical for our calcium-catalyzed reactions, precautions for the exclusion of air and moisture are unnecessary.



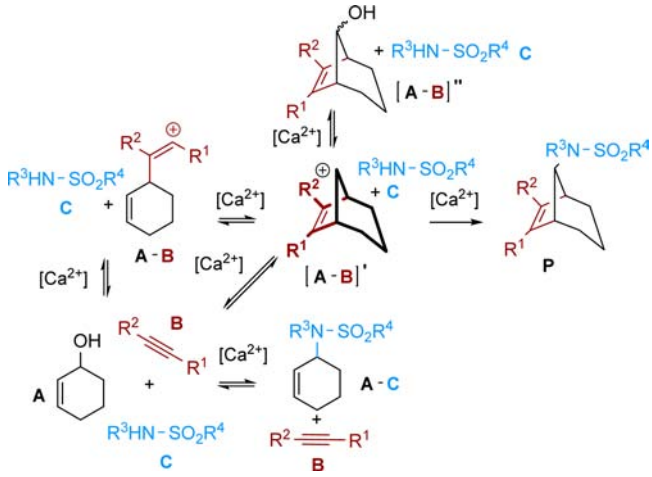
Multicomponent reactions (MCRs) are a powerful tool for the assembly of complex molecules in a single synthetic operation, and the discovery of new MCRs is vital to address the ever-growing demand for compound collections with maximum scaffold diversity.[1] In a classical MCR, the various reaction partners, all present in the mixture from the onset of the transformation, generally react in succession; hence the product of reaction A engages in reaction B, the product of which participates in reaction C, and so on, thereby determining the product outcome. A similar, yet mechanistically different, approach might be seen in the concept toward dynamic combinatorial libraries (DCLs; Scheme 1), in which all constituents can react or interact in multiple ways and are therefore in equilibrium through a reversible chemical process involving noncovalent interactions or reversible covalent bonding.[2] In most DCLs, an external selection pressure, such as biological targets, metal templates, or other stimuli including pH and light, is exploited to amplify a set of library members. The control of a DCL by an internal trigger, might be seen as a combination of both approaches and certainly leads to the discovery of conceptually new MCRs.

Apart from the intramolecular reaction of a specific constituent in the dynamic equilibrium that was recently used as such a trigger,[3] the simple fact that one of the library members features superior thermodynamic stability might be used to amplify this most stable component upon prolonged reaction times. Ideally, to ensure a maximum of complexity being generated during the process, this most stable compound forms upon reaction of all the compound classes present. An obvious requirement for the creation of such an internally triggered selection process is to find an appropriate reversible chemical process, which has to allow for the equilibration of all library members on a reasonable time scale, while, at the same time, being mild enough to ensure stability of the product and avoid decomposition of the equilibrating species.

Scheme 1. Dynamic Multicomponent Reaction



Scheme 2. Ca^{2+}-Catalyzed Dynamic Equilibrium



Over recent years, our group developed a simple calcium catalyst as a more sustainable alternative to expensive and highly toxic noble metal catalysts, which can be used for a variety of synthetic applications.[4] The high Lewis acidity of this catalyst was found to efficiently transform a range of precursors into reactive carbocations, a reactive species that is known for its ability to engage in reversible/equilibrating transformations. Furthermore, in many of our previously published reactions, product formation was found to be accompanied by reversible background reactions.[5] This reversibility of covalent bond formation, presumably derived from its high potency as a Lewis acid,

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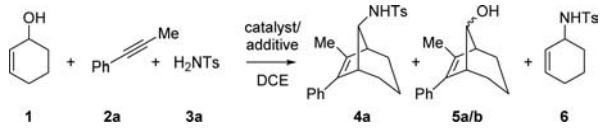
Table 1. Optimization of the Reaction Conditions



			yield[a] (%)		
entry[b]	catalyst	additive	4a	5a/b	6
1	$Al(NTf_2)_3$	Bu_4NPF_6	—	—	15
2	$LiNTf_2$	Bu_4NPF_6	13	9/10	40
3	$Ca(NTf_2)_2$	Bu_4NPF_6	88	—	—
4	$Ca(OTf)_2$	Bu_4NPF_6	trace	—	40
5	$Ca(NTf_2)_2$	Bu_4NBF_4	52	4/13	19
6	$Ca(NTf_2)_2$	$PhMe_2HN^+$ $B(C_6F_5)_4^-$	6	10/—	78
7	$HNTf_2$	Bu_4NPF_6	19	5/13	60
8	HOTf	Bu_4NPF_6	7	5/3	36
9[c]	$Ca(NTf_2)_2$	NH_4PF_6	32	—/13	26

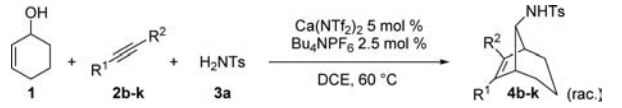
[a]Isolated yield. [b]Cyclohexenol **1** (0.3 mmol), alkyne **2a** (0.2 mmol), sulfonamide **3a** (0.4 mmol), additive (2.5 mol %), catalyst (5.0 mol %), DCE (1 mL), 60 °C, 12 h. [c]15 mol % of NH_4PF_6 and cyclopentanone (1.0 mmol) were added.

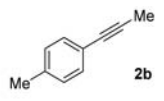
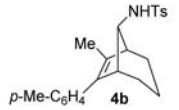
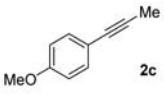
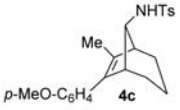
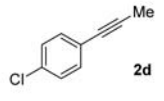
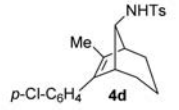
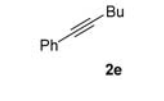
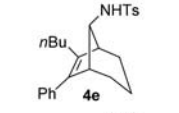
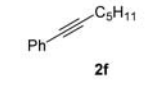
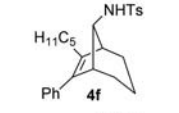
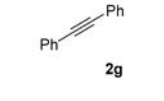
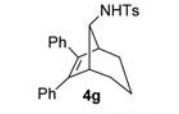
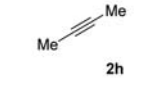
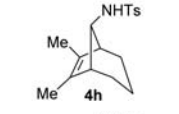
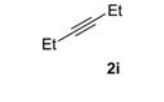
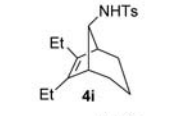
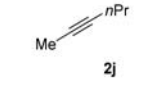
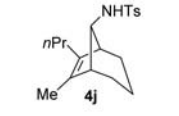
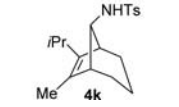
being a distinctive property of the calcium catalyst, encouraged us to line out the following scenario as a new type of MCR.

The bicyclic cation [A−B]′ (see Scheme 2) was chosen as the trigger compound, as it combines several benefits. It forms with superior stability over the other equilibrating species due to the formation of a delocalized nonclassical cation embedded in a rigid frame.[6] It ensures diastereoselective product formation as the cation−π interaction inducing its stabilization is only highly effective in a single, optimal geometry. Finally, it provides pharmacologically interesting three-dimensional bicyclic scaffolds from very simple two-dimensional precursors and thereby ensures a maximum of complexity being generated in the process.[7] Knowing that all three, the formation of A−B, A−C, and [A−B]″, are reversible in the presence of the Ca^{2+} catalyst, we set out for a proof of concept and exposed cyclohexenol **1**, phenylpropyne **2a**, and *p*-toluenesulfonamide **3a** to the calcium-based catalyst system (Table 1).

Initial screenings (not shown) revealed that, compared to our earlier work,[5b] in the presence of sulfonamide **3a**, a change of the additive, necessary for the formation of the catalytically active calcium catalyst,[4] from NH_4PF_6 to Bu_4NPF_6 as well as the omission of cyclopentanone as a cation-stabilizing electron pair donor ensured maximum reversibility and the most efficient dynamic equilibrium and allowed for the isolation of the desired product **4a** in 88% yield as a single diastereomer. Furthermore, the calcium catalyst showed distinctly higher reactivity in comparison with that of other Lewis acids (entries 1−3). While $Al(NTf_2)_3$ afforded only the direct amination product **6** in 15% yield (entry 1), $LiNTf_2$ gave the bicyclic sulfonamide **4a** in poor yield with a diastereomeric mixture of the bicyclic alcohol **5a/b** and, again, irreversibly formed direct amination product **6** (entry 2). The use of other calcium sources (entry 4) led to highly diminished reactivity, as did the change to other additives (entries 5 and 6). Notably, commonly used Brønsted acids also proved unable to efficiently reverse the direct amination of the initially formed cyclohexadienyl cation, even after prolonged reaction times, and hence afforded inferior yields of the desired product (entries 7 and 8). Interestingly, under the previously reported reaction conditions for the direct addition of alcohols to

Table 2. Scope of Alkynes



entry[a]	alkyne	product	yield[b] (%)
1	 2b	 4b	82
2	 2c	 4c	63
3	 2d	 4d	78
4	 2e	 4e	83
5	 2f	 4f	80
6	 2g	 4g	70
7	 2h	 4h	92
8	 2i	 4i	90
9	 2j	 4j	86
10	 2k	 4k	77

[a]Cyclohexenol **1** (0.3 mmol), alkynes **2b−k** (0.2 mmol), sulfonamide **3a** (0.4 mmol), Bu_4NPF_6 (2.5 mol %), $Ca(NTf_2)_2$ (5.0 mol %), DCE (1 mL), 60 °C, 12 h. [b]Isolated yield.

alkynes, **4a** was formed only in low yield and 26% of the direct amination product **6** remained in the reaction mixture. Also, 2-cyclohexenyl phenylpropanone, which forms upon the addition of water to the vinyl cation A−B as the main product in the presence of cyclopentanone as an electron pair donor,[5b] was formed only in small amounts under these reaction conditions. In conclusion, it might be stated that, even though other Lewis and Brønsted acids are capable of catalyzing the initial ionization of cyclohexenol **1**, the reversible formation of covalent bonds, necessary for an efficient equilibrium between the species formed after this initial ionization, is enabled solely by the remarkably high Lewis acidity of our calcium-based catalyst system.

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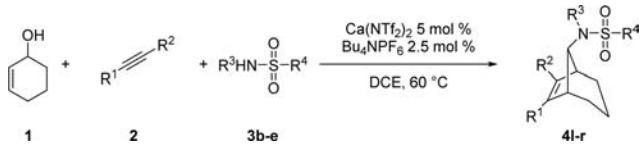
Table 3. Scope of Sulfonamides



1 2 3b-e 4l-r

entry[a]	alkyne	sulfonamide	product	yield[b] (%)
1		3b	4l	95
2	2a	3c	4m	95
3		3d	4n	83
4		3e	4o	96
5	2i	3d	4p	82
6	2k	3d	4q	80
7	2i	3e	4r	93

[a]Cyclohexenol **1** (0.3 mmol), alkyne **2** (0.2 mmol), sulfonamides **3b–e** (0.4 mmol), additive (2.5 mol %), catalyst (5.0 mol %), DCE (1 mL), 60 °C, 12 h. [b]Isolated yield.

With the optimized reaction conditions in hand, the substrate scope of this new type of MCR was examined. To our delight, a broad range of alkynes readily afforded the bicyclic products (Table 2). Phenylacetylene derivatives bearing electron-donating (**2b,c**) and electron-withdrawing (**2d**) substituents on the phenyl ring were well-tolerated under the reaction conditions. Similarly, alkynes bearing longer aliphatic chains (**2e,f**) as well as the sterically more demanding diphenylacetylene **2g** gave the desired products in excellent yields.

Notably, also simple nonaromatic alkynes (**2h–k**) reacted smoothly under the reaction conditions. This fact not only emphasizes the versatility of this transformation but also constitutes a rare example for the successful use of aliphatic alkynes as nucleophiles in carbocation cascade reactions. Thus, 2-butyne **2h** and 3-hexyne **2i** provided the corresponding bicyclic products in excellent yields. Moreover, the use of alkynes with more bulky substituents such as **2k**, bearing an isopropyl group, was possible without interfering 1,2-H shifts, affording the desired product in 70% yield. Diastereoselectivity was found to be excellent throughout the study, with no trace of the minor diastereomer being detected in any case.

Next, we turned our attention to the variation of the sulfonamide component. Here, the substitution pattern on the aromatic ring (**3b,c**) had no influence on the reactivity, and the corresponding bicycles were isolated in excellent 95% yield (Table 3). Also, disubstituted sulfonamides **3d**, as well as aliphatic sulfonamides **3e**, reacted smoothly under the reaction conditions. Diastereoselectivity was again excellent in all cases.

In summary, we demonstrated that the remarkably high Lewis acidity of our calcium-based catalyst system allows for the reversible formation of covalent bonds, resulting in a highly efficient dynamic equilibrium. Amplification of the most stable compound of this equilibrium, a pharmacologically interesting bicyclic amine, was used for the development of a new type of MCR. Furthermore, the product is formed with full diastereoselectivity, as the high stability of the nonclassical cation that is directly preceding its formation can efficiently delocalize only in a single geometry embedded in a rigid frame. Further investigations of the reversible covalent bond formation triggered by our calcium catalyst are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02593.

Experimental procedures, full characterization of products, NMR spectra, and additional information (PDF)

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Author Contributions

†S.G. and T.S. contributed equally to this paper.

Notes

The authors declare no competing financial interest.

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