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N-Heterocyclic Carbene-Catalyzed Umpolung of β,γ-Unsaturated 1,2-Diketones

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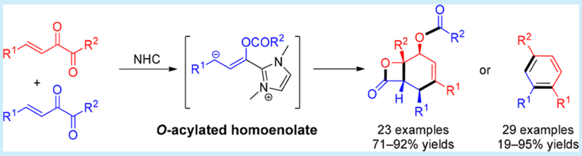
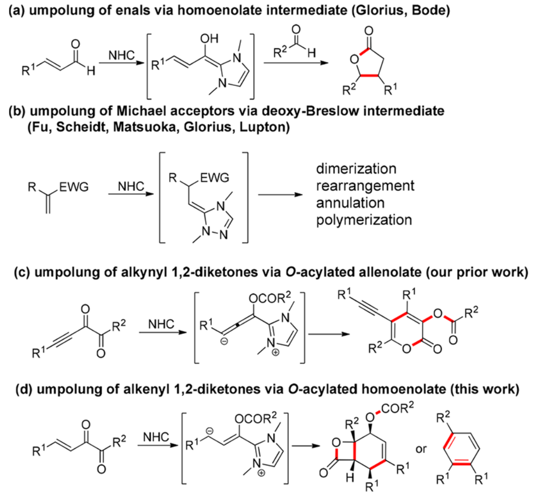
Supporting Information

ABSTRACT: The umpolung of β,γ-unsaturated diketones through N-heterocyclic carbene catalysis is described, which allows access to a variety of highly functionalized bicyclic cyclohexene-β-lactones and 1,3,4-triaryl benzenes. An unprecedented reaction pattern involving the catalytic formation of nucleophilic *O*-acylated homoenolate intermediate is proposed. A diverse set of transformations on the product further showed the synthetic potential of this protocol.



The unique and irreplaceable roles of umpolung (or polarity reversal) have attracted long-standing and global research interest among the chemical community.[1] Various approaches have been developed to facilitate the umpolung of different types of molecules. In this context, N-heterocyclic carbene (NHC) organocatalysis has been one of the most versatile and powerful methods to achieve this purpose.[2] Widely studied transformations are benzoin and Stetter reactions wherein the polarity reversal of aldehydes is realized via the formation of the Breslow intermediate, which have been well documented.[3] Furthermore, NHC-mediated umpolung of the remote β-position of an unsaturated substrate through conjugation has significantly expanded the domain of this chemistry. For instance, in 2004, Glorius and Bode independently reported the a^3-d^3 umpolung of enals through a homoenolate intermediate, which opened a new era for the whole field of NHC catalysis (Scheme 1a).[4] Furthermore, Fu, Scheidt, Matsuoka, Glorius, and Lupton have developed the umpolung of unsaturated esters/ketones/sulfones via a deoxy-Breslow intermediate (Scheme 1b).[5] Our group recently achieved the umpolung of alkynyl diketones via the formation of *O*-acylated allenolate, allowing rapid access to α-pyrones (Scheme 1c).[6] A noteworthy NHC-catalyzed reaction of cinnamils leading to 2,3,8-triaryl vinyl fulvenes was reported by the Nair group, but the mechanism features an initial [3,3]-rearrangement pathway, with no homoenolate type intermediate and umpolung of substrates claimed by the authors.[7] Considering the unique and irreplaceable roles of the remote position activation, the discovery of new unsaturated substrates that can participate in NHC-catalyzed novel umpolung remains challenging and necessary. In this report, we disclose the catalytic formation of an *O*-acylated homoenolate intermediate via an NHC-catalyzed umpolung of alkenyl 1,2-diketones, which could afford a series of cyclohexenyl β-lactones and 1,2,4-triaryl benzenes under mild conditions through an unprecedented pathway (Scheme 1d).

Scheme 1. Selected Umpolung Modes of Unsaturated Substrates via NHC Organocatalysis



The investigation commenced by subjecting easily available diketone **1a** to the conditions involving a series of carbene precursors **A**−**G** (Table 1). The initial test with imidazolium **A** and K_2CO_3 resulted in a product that was finally identified as **2a** by analogy to the single-crystal X-ray structure of **2h** (Scheme 2), a highly substituted bicyclic compound with a cyclohexene and β-lactone unit (Table 1, entry 1). Efforts to further improve the yield of **2a** indicated that bases played a crucial role with respect to the outcomes of the reaction. For instance, the organic base, DBU, led to a yield of 45% (Table 1, entry 2), and weak bases (Et_3N or NaOAc) did not show any reactivities (Table 1, entries 3 and 4). Strong inorganic bases such as KOH and ^{t}BuOK afforded **2a** in low to moderate yields (38% and 52%,

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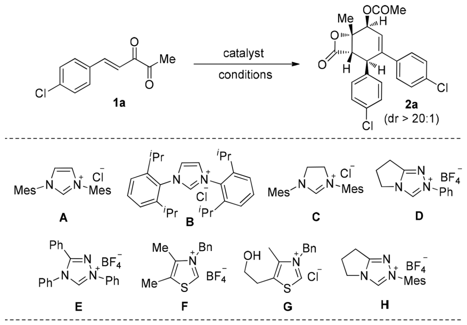
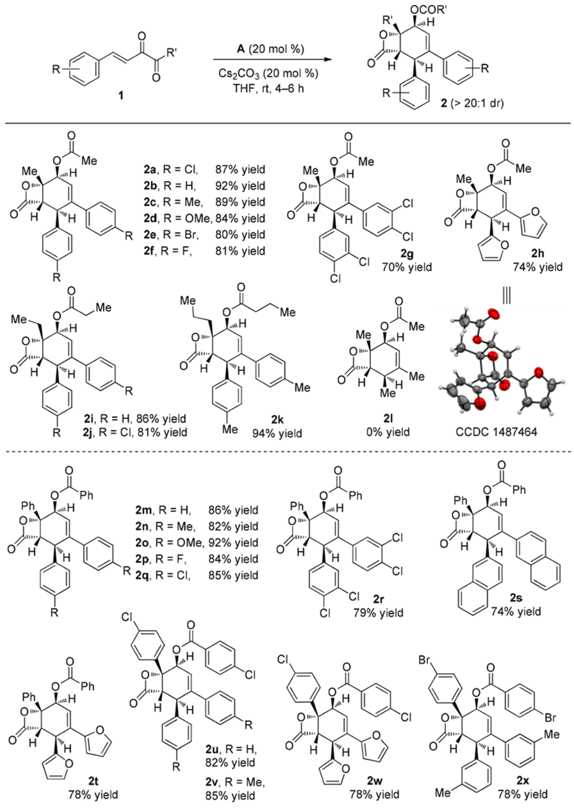
Table 1. Reaction Conditions Optimization[a]



entry	catalyst (mol %)	base	solvent	yield (%)[b]
1	**A** (20)	K_2CO_3	THF	74
2	**A** (20)	DBU	THF	45
3	**A** (20)	Et_3N	THF	0
4	**A** (20)	NaOAc	THF	0
5	**A** (20)	KOH	THF	38
6	**A** (20)	^{t}BuOK	THF	52
7	**A (20)**	**Cs_2CO_3**	**THF**	**86**
8[c]	**A** (20)	Cs_2CO_3	THF	82
9	**A** (10)	Cs_2CO_3	THF	69
10	**A** (20)	Cs_2CO_3	toluene	48
11	**A** (20)	Cs_2CO_3	CH_2Cl_2	36
12	none	Cs_2CO_3	THF	0
13	**A** (20)	none	THF	0
14	**B** (20)	Cs_2CO_3	THF	26
15	**C–G** (20)	Cs_2CO_3	THF	0
16	**H** (20)	Cs_2CO_3	THF	13

[a] Reaction conditions: **1a** (0.2 mmol), base (20 mol %), solvent (2 mL), argon protection, 4.5–24 h. [b] Isolated yields based on **1a**. [c] Cs_2CO_3 (1.0 equiv) was used.

Scheme 2. Substrate Scope for β-Lactone Formation[a]



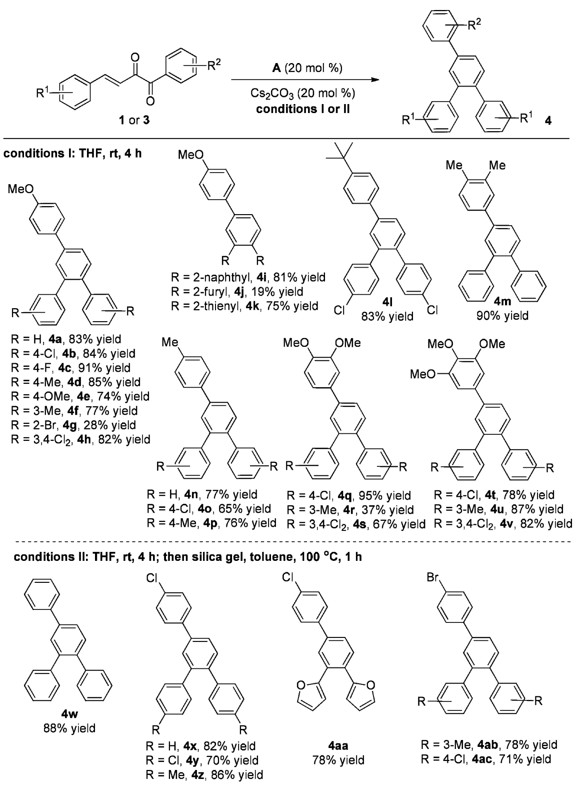
[a] All reactions were run on a 0.2 mmol scale; all yields were of isolated products based on **1**; ee values were determined via HPLC analysis on a chiral stationary phase.

respectively, Table 1, entries 5 and 6). To our delight, further screening of bases indicated that the employment of Cs_2CO_3 can promote the yield to an acceptable level (86%, Table 1, entry 7). Moreover, increasing the amount of Cs_2CO_3 showed little impact on the outcome (Table 1, entry 8), but a drop in the yield was detected when the catalyst loading was decreased to 10 mol % (Table 1, entry 9). Exchange of the solvent from THF to toluene or CH_2Cl_2 significantly retarded the reaction (Table 1, entries 10 and 11). The presence of catalyst **A** is necessary since Cs_2CO_3 itself could not initiate the transformation (Table 1, entry 13). Imidazolium **B** and triazolium **H** can also catalyze this annulation, however, in a very low efficiency (Table 1, entries 14 and 16, respectively), and catalysts **C–G** proved inert to this reaction (Table 1, entry 15).

Having established the optimal conditions, we focused on evaluating the scope and limitations of this transformation. Substrates with aliphatic ketone moieties were examined first. Removal of the electron-withdrawing chlorine atom in **1a** showed no influence on the yield, releasing **2b** in an excellent yield of 92% (Scheme 2, **2b**). Substrates with electron-donating methyl or methoxy groups at the aryl rings were also well tolerated (Scheme 2, **2c** and **2d**). Introduction of other electron-withdrawing groups such as Br, F, or 3,4-Cl was also possible, with very limited impact on the yields detected (Scheme 2, **2e**, **2f**, and **2g**). Furthermore, the phenyl ring can be changed to a heterocyclic furan group, and the product was determined unambiguously via single-crystal X-ray structure analysis (Scheme 2, **2h**, CCDC 1487464). Replacement of the methyl group at the ketone moiety with ethyl or *n*-propyl was also amenable under the standard conditions, generating the corresponding bicyclic products in high yields (Scheme 2, **2i**, **2j**, and **2k**). Unfortunately, the introduction of a methyl group into the alkene unit did not form the desired product, despite the full conversion of the starting material (Scheme 2, **2l**). The evaluation of the substrate scope was subsequently performed on aromatic 1,2-diketones. To our delight, phenyl diketone **1m** afforded the annulation product in 86% yield (Scheme 2, **2m**), and the variations of the substitution pattern on the Ar^1 group with additional electron-donating or -withdrawing groups were feasible, providing the annulation products with diversely substituted aromatic groups in 74–92% yields (Scheme 2, **2n–2s**). A heteroaromatic ring substituted substrate was also amenable under the standard conditions (Scheme 2, **2t**). Moreover, the introduction of electron-withdrawing groups such as Cl or Br on the Ar^2 ring did not encumber the reaction, delivering **2u–2x** in 78–85% yields (Scheme 2, **2u–2x**).

Further examination of the substrates with electron-rich aryl groups at the ketone units showed somewhat unexpected results because 1,2,4-triarylbenzenes were obtained, probably through a late-stage decarboxylation–release of the acyloxy group pathway (Scheme 3). A similar electron-donating substituent-assisted decarboxylation has also been observed in Scheidt's report of dynamic kinetic resolution of β-keto esters.[8] Triaryl benzenes have found wide applications in material sciences, including liquid crystals, microporous organic solids, molecular rotors, and molecular wires.[9] NHC-mediated formation of benzene derivatives has been reported by Chi, Lupton, Ye, and Wang, respectively.[10] In these reports, the substrates were usually enals

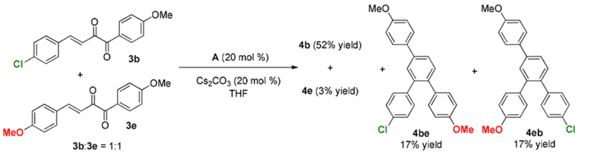
Scheme 3. Substrate Scope for Benzene Formation[a]



[a] All reactions were run on a 0.2 mmol scale; all yields were of isolated products based on 3.

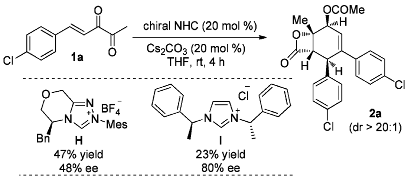
and the products were mainly 1,2,3,5-tetrasubstituted and 1,3,5-trisubstituted benzenes; methods of using ketones in benzene construction and reactions leading to 1,2,4-triarylbenzens are still underdeveloped. Thus, we expanded the substrate scope and a series of 4-OMe-C_6H_4 group substituted diketones were surveyed; the reaction proved insensitive to the electronic properties of the Ar^3 ring (Scheme 3, **4a**−**4k**). Besides the 4-OMe group, the substrates with 4-^{t}Bu, 3,4-Me_2, 3,4-$(OMe)_2$, 3,4,5-$(OMe)_3$, and even 4-Me substituents were all compatible under the standard conditions (Scheme 3, **4l**−**4v**). Further study revealed that stable products obtained in Scheme 2 can also be transferred to benzene derivatives via a simple operation, thus affording **4w**−**4ac** in good yields (Scheme 3, **4w**−**4ac**). Using equal amounts of **3b** and **3e** under standard conditions I, cross-coupling products **4be** and **4eb** could be produced in similar yields (Scheme 4).

Scheme 4. Cross-coupling Reaction



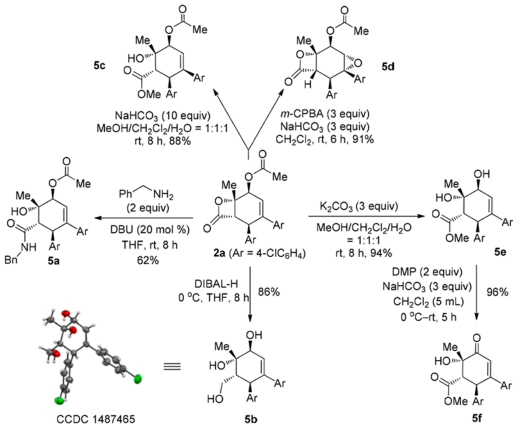
Attempts to realize an enantioselective transformation in this study revealed that triazolium catalyst **H**[11] can afford product **2a** in moderate yield with 48% ee. A promising 80% ee was perceived when imidazolium **I**[12] was utilized, albeit in a low yield (Scheme 5).[13]

Scheme 5. Enantioselective Transformation



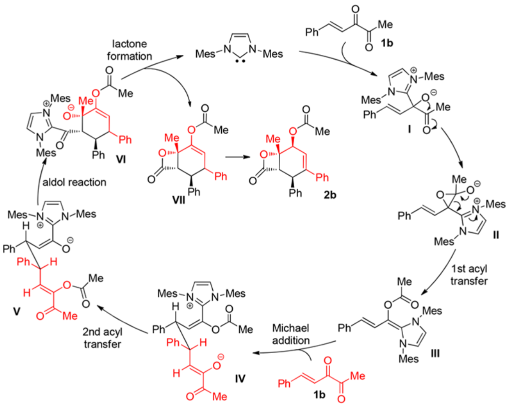
The synthetic potential of the annulation products is demonstrated in Scheme 6. For instance, reaction of **2a** with benzyl amine afforded amide **5a** in 62% yield, and a global reduction of **2a** by DIBAL-H allowed access to the heavily substituted cyclohexene **5b** (CCDC 1487465). The β-lactone unit of **2a** can be selectively hydrolyzed under $I_2/NaHCO_3$ conditions to generate ester **5c** in excellent yield. Oxidation of the double bond resulted in epoxide **5d** in excellent yield.[14] Furthermore, highly substituted cyclohexenone **5f** can be obtained in an excellent yield through a two-step pathway.[15]

Scheme 6. Derivatizations of Product 4a



The possible mechanism of this unique transformation is shown in Scheme 7. The nucleophilic attack of the α-carbonyl group of **1a** by a carbene catalyst leads to intermediate **I**, and an intramolecular rearrangement happens to allow the formation of *O*-acylated homoenolate **III** possibly via epoxy intermediate **II**.[7] Then, a Michael addition of **III** to another molecule of substrate **1b** is proposed to produce enolate **IV**, and the second acyl transfer occurs to afford a new enolate **V**. Then, after the

Scheme 7. Proposed Reaction Mechanism



intramolecular aldol reaction and the regeneration of carbene catalyst, **VII** is formed. The final product **4b** is obtained probably through the double bond migration under the basic reaction conditions. A series of acyl transfer and rearrangements feature this process, and two C−C bonds and two C−O bonds are newly constructed in this catalytic cycle.

In conclusion, the umpolung of β,γ-unsaturated diketones via NHC catalysis was achieved, allowing access to a broad range of highly substituted cyclcohexene-β-lactones and triaryl substituted benzene derivatives in a concise and efficient fashion. The synthetic applications of the products were further demonstrated by a series of highly selective transformations. Moreover, an unprecedented catalytic cycle involving *O*-acylated homoenolate was proposed on the basis of experimental results. Further studies on the mechanistic details of this transformation and new applications of unsaturated diketones are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03358.

> Experimental procedures, optimization details, data for all new compounds, NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1487464−1487465 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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