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Dual Lewis Acid/Photoredox-Catalyzed Addition of Ketyl Radicals to Vinylogous Carbonates in the Synthesis of 2,6-Dioxabicyclo[3.3.0]octan-3-ones

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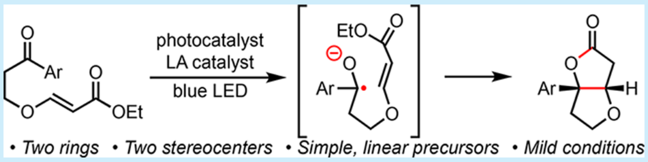
Supporting Information

ABSTRACT: A combined Lewis acid/photoredox catalyst system enabled the intramolecular umpolung addition of ketyl radicals to vinylogous carbonates in the synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-ones. This reaction proceeded on a variety of aromatic ketones to provide THF rings in good yield (up to 95%). Although diastereoselectivity was found to be modest (1.4−5:1) for the C-C bond forming reaction, the minor diastereomers were converted to 2,6-dioxabicyclo[3.3.0]-octan-3-ones by an efficient Lewis acid-mediated epimerization cascade in up to 90% yield.



Tetrahydrofuran fused γ-lactones, specifically 2,6-dioxabicyclo[3.3.0]octan-3-ones (**1**), are a prevailing structural feature in a number of biologically active natural products (Figure 1). For instance, the plakortones are a large family of natural products with applications in cardiac arrhythmia, and it is hypothesized that the oxabicylic "head" is central to its function.[1] More highly substituted forms have been found as key components of other natural products such as the pallambins[2] and the rubriflordilactones.[3] Of particular interest is the presence of this moiety in both polyketide and terpenoid natural products. The prevalence and congested complexity of this core structure call for efficient methods for its construction. The most common method for the synthesis of these bicyclic structures is by conjugate addition of a pendant alcohol to an already constructed unsaturated γ-lactone.[4−11] Other assemblies of this moiety include palladium-catalyzed carbonylative oxidation,[12−16] iodolactonization of a dihydrofuran,[17] and by ionic rearrangement cascades.[18,19] These methods focus primarily on the formation of C-O bonds in the core structure; methods that center around C-C bond formation remain lacking.

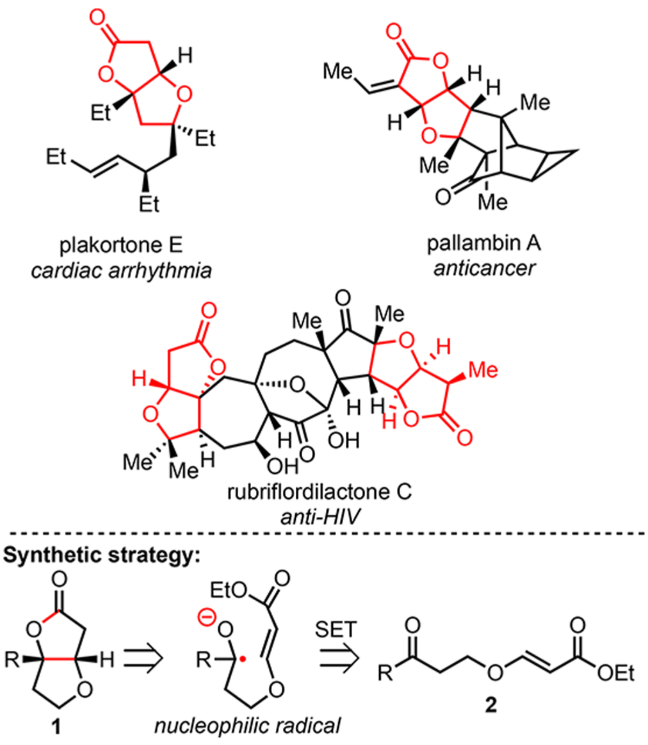


Figure 1. Example of bioactive natural products bearing 2,6-dioxabicyclo[3.3.0]octan-3-one cores.

Although these methods provide access to the key oxabicyclic structure, they require at least one stereocenter of the ring fusion to be established prior to construction of the ring system. We anticipated that the simultaneous construction of the ring-fusion C-C and the lactone C-O bonds of the bicyclo[3.3.0]octane would greatly simplify their synthesis by generating both of these stereocenters in a single step (Figure 1). Stereoselectivity would then be under reagent control, and it would allow for deconstruction to a highly simplified linear precursor that is readily available from β-hydroxy ketones. We hoped to employ the intramolecular umpolung addition of a ketyl radical from a linear vinylogous carbonate (**2**) to achieve the direct synthesis of the ring-fusion C-C bond. Ketyls are powerful nucleophilic radical intermediates that have been used widely in C-C bond forming processes.[20,21] However, the challenging single electron reduction of ketones has made ketyl radical chemistry difficult to render catalytic. To date, addition of ketyl radicals to vinylogous carbonates has been limited to tin hydride,[22−24] or samarium-(II) mediated processes.[25−27] These reagents can be toxic or

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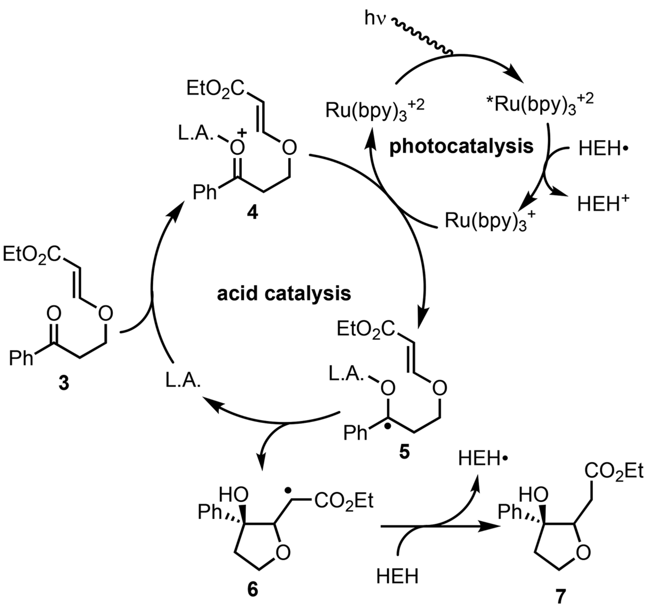
highly sensitive to adventitious water and O_2, further reducing their practical use. Although samarium(II) is a convenient reagent for this transformation, reduction of samarium(III) to the active samarium(II) is rare in catalysis.[28−31] We aimed to effect this transformation with mild, catalytic conditions that would avoid toxic intermediates or stoichiometric transition metals.

Photoredox catalysis has enabled a growing and powerful family of reactions that harvest visible light to achieve often-challenging electron transfer reactions.[32−34] The combination of photoredox catalysts such as $Ru(bpy)_3^{+2}$ and $Ir(ppy)_3$ with acids has enabled the mild reduction of carbonyl derivatives to the corresponding ketyl. Recent reports by Knowles,[35−37] Rueping,[38−40] and others[41−43] have shown that activated carbonyl compounds can accept an electron from the reduced form of the photocatalyst. These catalyst systems provide an exciting opportunity for the reductive umpolung reactivity of ketones and aldehydes in C-C bond forming reactions. In these systems, a Brønsted or Lewis acidic cocatalyst lowers the effective reduction potential of the carbonyl, enabling electron transfer from photoexcited transition metal complexes.[44,45] This approach could serve as a general catalytic strategy for the reductive umpolung reactions of carbonyls in place of systems requiring full equivalents of transition metal.

Inspired by these recent studies, we were interested in their application to the cyclization of γ-ketovinylogous carbonates (**2**). We anticipated some additional challenges for the proposed substrates relative to previously reported reactions. The sensitivity of the vinylogous carbonate to hydrolysis under acidic conditions were of primary concern. Additionally, vinylogous carbonates are much more sluggish electrophiles than α,β-unsaturated esters. In light of these two considerations, a full re-evaluation of the reaction conditions was warranted.

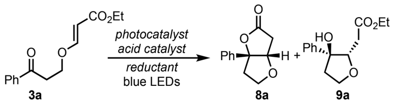
The proposed catalytic cycle for the synthesis of furan-fused lactones **1** involves cooperation between an acid and a transition metal photocatalyst (Scheme 1). In this cycle, photoexcited $Ru(bpy)_3^{+2}$ would be reduced by a terminal reductant to provide the super-reductant $Ru(bpy)_3^{+}$. This complex would then transfer an electron to a ketone that has been activated by coordination to a Lewis acid (**4**) or by protonation by a Brønsted acid. The resulting ketyl radical (**5**) would add to the pendant vinylogous carbonate to provide THF **6** followed by H atom transfer from a terminal reductant such as Hantzsch ester (HEH) to provide 3-hydroxytetrahydrofurans such as **7**. *Syn*-THF **7** could cyclize to the corresponding 2,6-dioxabicyclo[3.3.0]octan-3-one.

Scheme 1. Proposed Dual-Catalytic Cycle



Vinylogous carbonate **3a** was chosen for the optimization of THF synthesis (Table 1). Initial studies began by investigating proton-coupled electron transfer (PCET) to β-keto vinylogous carbonate **3a**. Under the conditions reported by Knowles, cyclization to **8**/**9a** was observed in low yield (entry 1).[4] It was found that 2,3-dihydro-2-phenylbenzothiazole was too active as a terminal reductant, and the predominant side product was the direct reduction of the ketone to the alcohol. Changing to Hantzsch ester (HEH) was found to reduce this undesired reactivity (entry 2). Although changing reductants did not significantly impact the yield, the mass balance in this case was now found to be predominantly unreacted **3a**. $Ru(bpy)_3^{+2}$ proved to be the optimal photoredox catalyst for this process (entry 3). Increasing the amount of Hantzsch ester and acid catalyst dramatically improved the yield (entry 4). After a survey of protic acids, it was found that Lewis acids provided superior conversion, with $SnCl_2$ and $La(OTf)_3$ having the best performance (entries 5−7). Acetonitrile was determined to be the optimal solvent (entries 8 and 9). Ultimately, 2 mol % of photocatalyst, combined with 40 mol % of Lewis acidic $La(OTf)_3$ in acetonitrile with 3 equiv Hantzsch ester irradiated with blue LED light proved to be the optimal conditions (entry 7). Control experiments proved that the combined action of the photocatalyst, Lewis acid, and light to be necessary for sufficient reactivity (entries 10−12). Interestingly, in the absence of photocatalyst, a small amount of cyclization was observed (entry 12). It is thought that the photoexcited state of Hantzsch ester (ca. −2.0 V) could directly reduce activated complex **4**, albeit at a reduced rate than photoexcited $Ru(bpy)_3^{+2}$.[46] Although it was anticipated that Lewis acids might preferentially template a

Table 1. Discovery and Optimization of THF Synthesis[a]



entry	photocat	acid (mol %)	solvent	yield[b] (%)	dr[c] 8a:9a
1[d]	$Ir(ppy)_3$	p-TSA (10)	THF	28	2.2:1
2[e]	$Ir(ppy)_3$	p-TSA (10)	THF	22	1.4:1
3[e]	$Ru(bpy)_3$	p-TSA (10)	THF	21	1.4:1
4	$Ru(bpy)_3$	p-TSA (20)	THF	41	1.7:1
5	$Ru(bpy)_3$	p-TSA (20)	MeCN	44	1.7:1
6	$Ru(bpy)_3$	$SnCl_2$ (20)	MeCN	51	2.1:1
7	$Ru(bpy)_3$	$La(OTf)_3$ (40)	MeCN	75	2.4:1
8	$Ru(bpy)_3$	$La(OTf)_3$ (40)	DCM	49	2.1:1
9	$Ru(bpy)_3$	$La(OTf)_3$ (40)	DMF	59	2.4:1
10	$Ru(bpy)_3$		MeCN	trace	nd[g]
11[f]	$Ru(bpy)_3$	$La(OTf)_3$ (40)	MeCN	trace	nd[g]
12		$La(OTf)_3$ (40)	MeCN	21	nd[g]

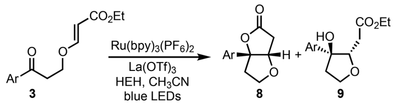
[a] 0.2 mmol **3a**, 2 mol % photocatalyst, 3 equiv HEH, [**3a**] = 0.05 M. [b] Combined yield of **8a** and **9a** after chromatography. [c] Determined by relative yields of isolated material after chromatography. [d] 2,3-Dihydro-2-phenylbenzothiazole (1.5 equiv) used in place of HEH. [e] 1.5 equiv of HEH. [f] Conducted in the absence of light. [g] Not determined.

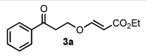
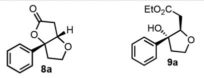
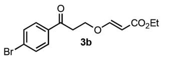
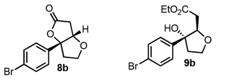
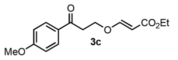
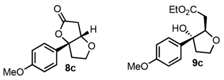
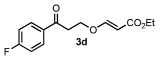
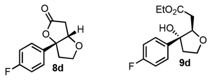
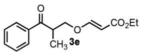
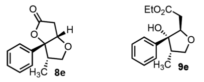
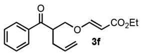
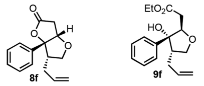
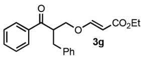
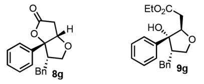
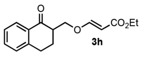
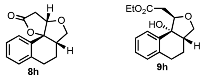
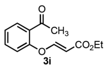
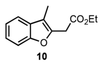
single diastereomeric transition state, no experimental conditions were found that significantly improved the diastereoselectivity of the C-C bond formation.

In general, we found vinylogous carbonates **3** to be sluggish to react compared to other α,β-unsaturated carbonyl electrophiles. These substrates therefore required up to 48 h to achieve full consumption of starting material. However, the vinylogous carbonates were surprisingly stable to the reaction conditions, with no byproducts of carbonate hydrolysis observed, and predominantly starting material (**3**) was recovered from slow reactions. Additives that have been found to be beneficial for combined photoredox/Lewis acid catalysts, such as 2,2′-bipyridyl,[41] had little effect on reactivity in our case. Although it is possible that the enhanced reactivity of Lewis acids when compared to Brønsted acids is due to additional Lewis acid activation of the vinylogous carbonate, we have no additional evidence to support this hypothesis.

A number of vinylogous carbonates were investigated in this THF synthesis (Table 2). The reaction could be scaled to 1 mmol of **3a** without a significant impact on overall yield (entry 1). Aromatic substitution did not dramatically impact the yield or selectivity of cyclization, and the reaction was tolerant of electron-donating and electron-withdrawing aromatic substituents (entries 2−4). α-Substituted ketones proved to be excellent substrates for this reaction (entries 5−8), providing the highest yields of cyclized products **8** and **9**. Interestingly, these substituents also had an effect on the diastereoselectivity of the reaction. Larger substituents increasingly favored the *anti*-diastereomer, with benzyl substrate **3g** completely inverting the selectivity. Furthermore, the diastereoselectivity relative to the 4-position was typically high, with only small amounts of other diastereomers visible by ^{1}H NMR. The alkene and aromatic functionality of **3f** and **3g** were also well-tolerated (entries 7 and 8), and no products of radical addition to these functional groups were observed. Tetralone derivative **3h** provided tetracyclic products **8h** and **9h** in good yield. Salicylate-derived vinylogous carbonate was also cyclized, however the product readily aromatized under the acidic conditions to provide benzofuran **10** (entry 9). It is also important to note the general stability of the resulting 3° benzylic alcohol products to the reaction conditions, which underscores their mild nature. Overall, substituted tetrahydrofurans could be obtained in good yields from a variety of linear vinylogous carbonates.

Table 2. Scope of Ketyl Cyclization[a]

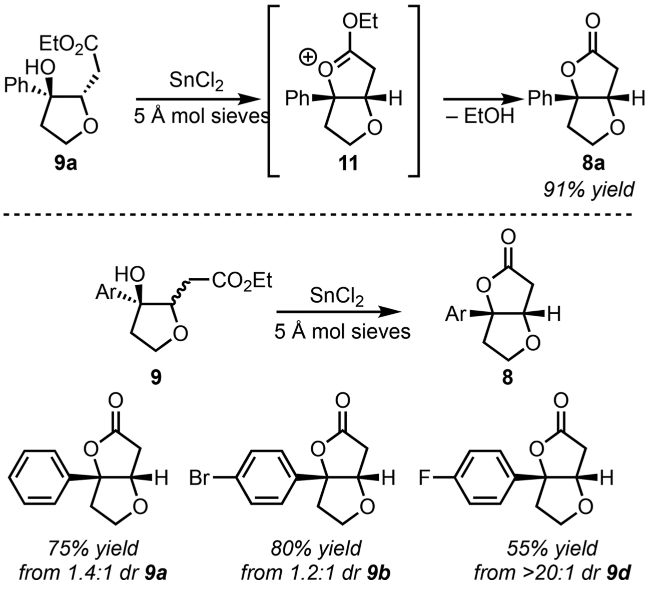


entry	substrate	products	yield (%) **8**:**9**[b]
1[c]			65 2:1
2			48 1.3:1
3			62 1.5:1
4			60 1.6:1
5			85 23:3:17:1[d,e]
6			86 5:1:11:2[d,e]
7			95 5:1:27:5[d,e]
8			54 1.9:1[d]
9			77

[a] 0.20 mmol **3**, 2 mol % $Ru(bpy)_3(PF_6)_2$, 40 mol % $La(OTf)_3$, 3 equiv HEH, [**3**] = 0.05 M, 48 h. [b] Determined by relative yields of isolated material after chromatography. [c] 1 mmol **3a**. [d] Configuration of major 4-substituent diastereomer determined by 1D NOE analysis of **8g** and **9g**, others assigned by analogy. [e] Ratio of **8**:4-*epi*-**8**:**9**:4-*epi*-**9**

Although the diastereoselectivities of the C-C bond formation remained modest, a strategy for converting the minor diastereomer to the desired lactone was developed (Scheme 2). It was initially proposed that epimerization could proceed through β-elimination of the THF oxygen atom, attempts to epimerize **9a** under basic conditions were met with only moderate success.[47] It was eventually found that Lewis acids were capable of mediating the desired transformation, with $SnCl_2$ performing the best. Under the optimized conditions, **9a** was converted to 2,6-dioxabicyclo[3.3.0]octan-3-one **8a** in the presence of $SnCl_2$ and 5 Å molecular sieves in high yield. The Lewis acid likely ionizes the alcohol to generate a benzylic cation, ablating the C3 stereocenter, or the stereocenter is inverted by anchimeric assistance from the neighboring ester (i.e., **11**). Lactone **8** would then be generated either by lactonization of an epimerized alcohol or by loss of ethanol from **11**. Sequestration of ethanol by molecular sieves then drives the equilibrium to 2,6-dioxabicyclo[3.3.0]octan-3-one **8**.

Scheme 2. Epimerization of Tetrahydrofurans 9 to Lactones 8



This epimerization approach proved to be general for the conversion of the *anti* cyclization diastereomer (**9**) to the corresponding 2,6-dioxabicyclo[3.3.0]octan-3-one in good yield. Furthermore, diastereomeric mixtures of **9** could be converted to a single isomer of **8** using these conditions. Although electronic substitution of the aromatic ring affected the rate, the yield did not suffer. Overall, this two-step process renders this synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-ones from vinylogous carbonates **3** to be highly diastereoselective.

In conclusion, a new dual Lewis acid/photoredox catalyst system has been developed for the umpolung reactivity of ketones. This method has been specifically applied to the intramolecular addition to vinylogous carbonates to provide polysubstituted tetrahydrofurans in good yield. Although the diastereoselectivity of the C-C bond formation was modest, a strategy to convert the minor *anti* diastereomer to the bicyclic lactone product was implemented. Overall, this two-step procedure provides ready access to 2,6-dioxabicyclo[3.3.0]-octan-3-ones from a linear precursor where the relative stereochemistry of the product can be controlled.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02442.

Experimental details, NOE studies of **8g** and **9g**, ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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