Enolate addition to bicyclobutanes enables expedient access to 2-oxo-bicyclohexane scaffolds

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We report the synthesis of 2-oxo-bicyclo[2.1.1]hexanes (2-oxo-BCHs) from bicyclobutanes (BCBs) and readily available enolate precursors. We propose this reaction proceeds *via* initial enolate addition to the bicyclobutane, followed by an intramolecular acyl substitution by the resulting enolate intermediate. Glycine-derived enolates directly give protected 2-oxo-3-amino-BCH derivatives that can be further functionalized. Arylacetate derivatives are also suitable enolate precursors, giving 2-oxo-3-aryl-BCH scaffolds from readily available starting materials.

Accessing C*sp*^{3}-rich molecular scaffolds is increasingly important in modern medicinal chemistry.[1-3] Drug candidate molecules with a higher fraction of C*sp*^{3} sites (F*sp*^{3}) often have more favourable drug-like properties, including solubility, metabolic stability, and/or lipophilicity.[4-7] One class of C*sp*^{3}-rich scaffolds of current interest are bicyclo[2.1.1]hexanes (BCHs). These structures are relevant benzene bioisosteres, mimicking a variety of substitution patterns.[8] Until recently, syntheses of substituted BCHs were scarce, and relied on intramolecular photochemical [2+2] cycloaddition.[9-13] Building on seminal work from Cairncross and Blanchard,[14] a flurry of recent reports demonstrate the feasibility of intermolecular formal [2+2] cycloadditions with bicyclobutanes (BCBs), through either radical-based mechanisms[15-18] or Lewis acid catalysis[19,20] (Fig. 1A).

To effectively use BCHs as versatile scaffolds for medicinal chemistry, access to molecules with synthetic handles for vector elaboration is critical. 2-Oxo-bicyclohexanes, which contain a carbonyl group in the bicyclic system, provide such a handle. The initial direct route to these motifs, reported by Carpenter, requires UV photochemical intramolecular [2+2] of oxygen-functionalized dienes.[10,21] Fessard and Salomé reported a modification that uses a photocatalyst to enable lower energy light.[22] For intermolecular cycloaddition, Studer recently reported a Lewis acid catalyzed [2+2] cycloaddition of ketenes to bicyclobutanes, enabling access to 2-oxo-BCHs with quaternary stereocenters α to the carbonyl.[23]

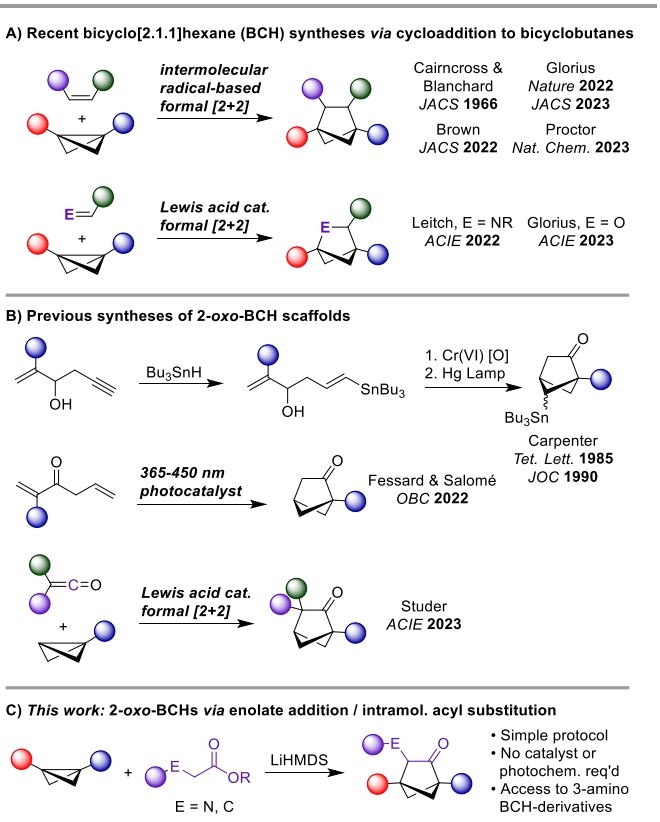


Figure 1. **(A)** Recent syntheses of bicyclo[2.1.1]hexanes from bicyclobutanes *via* formal cycloaddition approaches. **(B)** Previous syntheses of 2-oxo-bicyclo[2.1.1]hexanes, either through photochemical [2+2] cycloaddition, or Lewis acid catalyzed formal [2+2] cycloaddition with ketenes. **(C)** This work on the synthesis of bicyclo[2.1.1]hexanes through tandem enolate addition / cyclization with bicyclobutanes.

Here, we report intermolecular enolate addition to BCBs which enables direct access to 2-oxo-BCHs through difunctionalization of the central C–C bond (Fig. 1C). Nucleophile addition to bicyclobutanes is common, with many nucleophile classes reported.[24] These include organometallics,[25,26] azides,[27] phosphines,[28] thiols and alcohols,[29,30] amines,[31-32] and boronates.[33] Surprisingly, enolate additions to bicyclobutanes have not been

previously reported (to the best of our knowledge). We hypothesized that the combination of ester-derived enolates and bicyclobutanes could result in 2-oxo-BCHs via the mechanism in Figure 2. Nucleophilic attack of an enolate – generated *in situ* from ester **2** – to the electrophilic carbon of a bicyclobutane **1** would result in ring opening and generation of another enolate intermediate. This enolate could then undergo intramolecular acyl substitution at the pendant ester to form the 2-oxo-bicyclo[2.1.1]hexane product. Many reactions of bicyclobutanes are analogous to the reactivity of alkenes or donor-acceptor (DA) cyclopropanes.[34] In the present case, we were unable to find corresponding cyclizations to generate cyclobutanones (after conjugate addition to electron-deficient alkenes) or cyclopentanones (from enolate addition to DA-cyclopropanes). Nevertheless, we reasoned that the proposed 5-*exo*-*trig* cyclization would be viable.

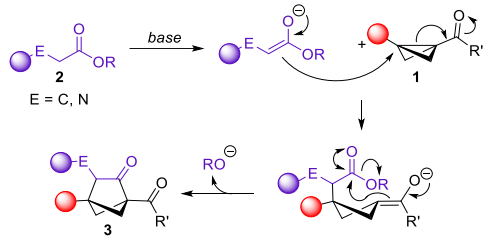


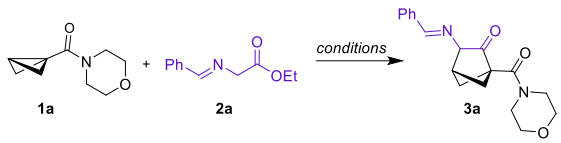
Figure 2 – Proposed mechanism for synthesis of bicyclo[2.1.1]hexanes **3**.

To assess the viability of the proposed addition/cyclization sequence, a variety of conditions were tested using monosubstituted bicyclobutane containing a morpholine amide (**1a**), and an ethyl glycinate derivative with the nitrogen protected as the benzaldimine (**2a**) (Table 1). We used the amide electron-withdrawing group on the BCB to avoid competitive 1,2-addition to that carbonyl, and the benzaldimine was used as a convenient protected NH_2 equivalent without acidic hydrogens. Soft enolization using Lewis acid / weak base combinations failed to generate any desired product (entry 1 and 2). Hard enolization using lithium diisopropylamide (LDA), sodium hydride (NaH), and potassium bis(trimethylsilyl)amide (KHMDS) also failed to generate **3a** (entry 3, 4 and 5). In these cases, decomposition of **1a** and/or **2a** was instead observed.

Switching to lithium bis(trimethylsilyl)amide (LiHMDS) gave a 20% solution yield of **3a** on a 0.05 mmol scale (entry 6). On larger scale (0.30 mmol of bicyclobutane), keeping all other variables constant, the yield of **3a** dropped to 11% (entry 7). Using a slight excess of LiHMDS and enolate (1.5 and 1.2 equiv respectively), the yield increased to 39% (entry 8). Finally, increasing the reaction concentration from 0.05 M to 0.30 M of **1a** further improves the yield of **3a** to 47% (entry 9).

These conditions were carried forward to explore the reactivity of **3a** toward functionalization of the amine and ketone synthetic handles (Fig. 3). A solution of **3a** was generated using conditions from Table 1, entry 9, and then subject to a mild aqueous workup ($NaHCO_3$) prior to functionalization; yields of the resulting products are calculated over two steps from **1a** (solution yield of **3a** ~50%).

Table 1 – Reaction optimization for synthesis of bicyclo[2.1.1]hexane **3a** from **1a** and **2a**.



Entry	Conditions[a]	1a[b]	2a[b]	3a[b]
1	AgOAc (10 mol%), NEt_3, DCM	72	25	**0**
2	$Ga(OTf)_3$ (15 mol%), NEt_3, THF	100	78	**0**
3	LDA (1.1 equiv), -78°C, THF	0	0	**0**
4	NaH (2 equiv), THF, 1.5 equiv **2a**	99	68	**0**
5	KHMDS (1.5 equiv), THF, 1.2 equiv **2a**	67	35	**0**
6	LiHMDS (1 equiv), THF	0	17	**20**
7	LiHMDS (1 equiv), THF, (**0.30 mmol 1a**)	15	9	**11**
8	LiHMDS (**1.5 equiv**), THF, **1.2 equiv 2a**, (0.30 mmol **1a**)	11	17	**39**
9	LiHMDS (1.5 equiv), THF**, 0.30 M**, 1.2 equiv **2a**, (0.30 mmol **1a**)	21	0	**47**

[a]Unless otherwise noted, reactions are performed at room temperature for 24 hours with 0.05 mmol of **1a**, 1 equiv of **2a**, and 1 mL of solvent ([**1a**] = 0.05 M). [b]Amounts of **1a**, **2a**, and **3a** are obtained by ^{1}H NMR spectroscopy by relative integration vs. internal standard, 1,3,5-trimethoxybenzene (TMB).

To reveal the protected primary amine, imine hydrolysis was performed by stirring **3a** over silica to give **4a** in 35% yield over two steps. Both imine and ketone were reduced using sodium borohydride to give aminoalcohol product **4b** in 35% yield. Notably, **4b** was obtained as a single diastereomer, with *syn* relative stereochemistry between amino and hydroxyl groups (determined by 2D NOESY NMR spectroscopy, see ESI). Tandem acylation/hydrolysis of the imine was achieved using either benzyl chloroformate (Cbz-Cl) or *p*-toluoyl chloride, giving the corresponding carbamate **4c** and amide **4d** in 47% and 28% yield, respectively. Single crystals of 4b and **4d** have been analyzed by X-ray diffraction, confirming the proposed relative stereochemistry and connectivity (CCDC 2290171 & 2298459).

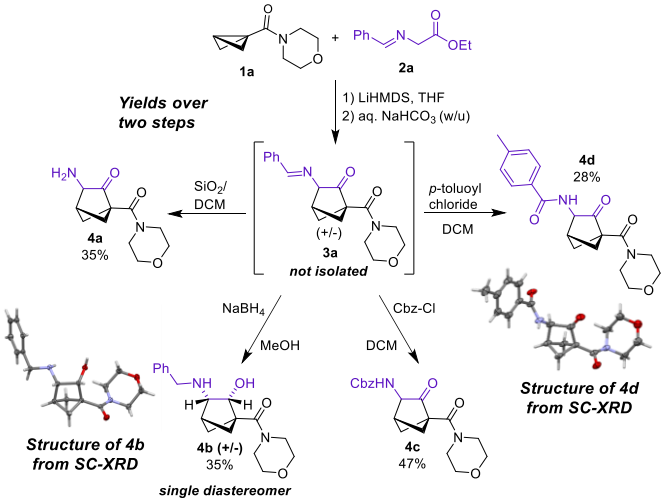


Figure 3 – Synthesis of **3a** followed by modifications of the imine (and ketone) synthetic handles. All yields are for isolated compounds and are calculated over two steps. **4b** was obtained as a single diastereomer (see ESI for 2D NOESY details). Ellipsoids for single crystal X-ray diffraction structures (SC-XRD) of **4b** and **4d** are plotted at 50%.

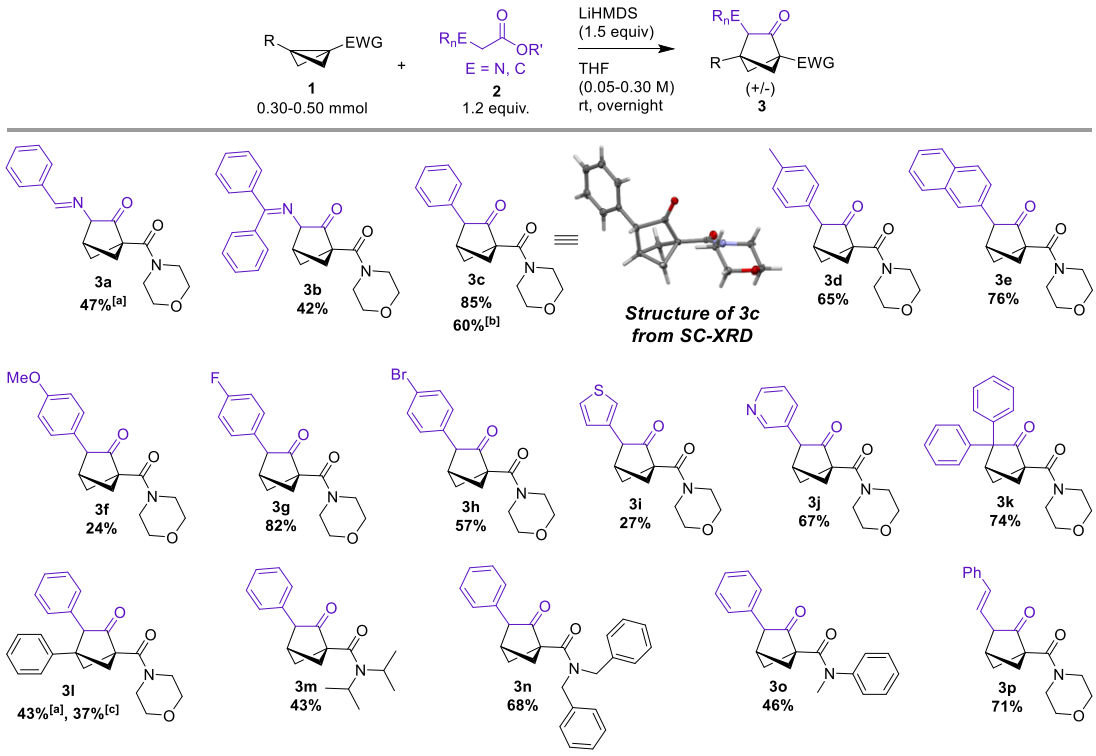


Figure 4 – Scope of 2-oxo-bicyclo[2.1.1]hexanes enolate addition to bicyclobutanes. Unless otherwise noted, yields are for isolated compounds following automated purification. Ellipsoids for single crystal X-ray diffraction structure (SC-XRD) of **3e** are plotted at 50%. [a]Yields determined by ^{1}H NMR spectroscopy (rel. integration vs. internal standard TMB). [b]Isolated yield on 3.0 mmol **1** scale, 0.60 M. [c]Isolated yield as part of a mixture with unreacted bicyclobutane (32%), which could not be separated by column chromatography.

Using the optimized enolate-addition conditions, we performed an initial survey of the reaction scope with respect to BCB (**1**) and enolate precursor (**2**) (Fig. 4). Imine-containing product **3a** is acid labile, and decomposes during chromatography on silica, so the reported yield is obtained by ^{1}H NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Using the more stable benzophenone imine as a protecting group, we were able to isolate analogue **3b** in 42% yield.

In addition to enolates from glycinate ester derivatives, we assessed a variety of readily available arylacetate esters as enolate precursors. Ethyl phenylacetate is an excellent reactant, giving BCH **3c** with an isolated yield of 85% on 0.5 mmol scale, and 60% on 3.0 mmol scale. Single crystal X-ray diffraction of **3c** confirmed the proposed structure (CCDC 2290170). We also tested other arylacetates with a variety of (hetero)aromatic substituents. Electron rich aromatics including *p*-tolyl (**3d**), 3-naphthyl (**3e**), and *p*-methoxyphenyl (**3f**) were all successfully incorporated. In addition, halobenzenes *p*-fluorophenyl (**3g**) and *p*-bromophenyl (**3h**) as well as heterocycles 3-thiophenyl (**3i**) and 3-pyridyl (**3j**) are also compatible with moderate to good isolated yields.

An α,α-disubstituted enolate precursor was also added successfully to give product **3k** with a 74% yield, despite the additional steric bulk. A disubstituted BCB is also compatible with this reaction, giving **3l** in 43% solution yield (determined by ^{1}H NMR spectroscopy); however, attempts to purify this compound by column chromatography under multiple conditions led to isolation of a mixture of **3l** (37% yield) and unreacted bicyclobutane (32 mol%). Other tertiary amides are supported, such as *N,N*-diisopropyl (**3m**), dibenzyl (**3n**) and *N,N*-methylphenyl (**3o**) with good yields. Finally, an alkenyl-substituted enolate was successfully added (**3p**); however, attempts to use alkyl-substituted enolates (e.g. from ethyl propionate) led to no product formation. A bicyclobutane substituted with a benzyl ester was also tested, leading to multiple products; we were able to isolate the corresponding ethyl ester BCH (presumably formed via transesterification with ethoxide, see ESI).

Finally, we noted that the strongly basic reaction conditions to generate **3a** should be compatible with the formation of BCB **1a** itself from the tosylcyclobutane precursor **1aa**. Therefore, we explored two alternative pathways to prepare BCH **3a** via *in situ* formation of **1a** (Fig. 5). Starting from **1aa**, product **3a** can be made in 54% solution yield using 1.5 equiv of LiHMDS, followed by the addition of **2a** (1.2 equiv) and more LiHMDS (1.5 equiv) in a telescoped, one-pot procedure. BCH **3a** can even be formed by simply mixing **1aa** and **2a** in THF, and adding excess LiHMDS (2.5 equiv) to both generate **1a** and the enolate of **2a**. This avoids the need to isolate bicyclobutane **1a**, and has the potential to enable reactions involving less stable and/or difficult to isolate BCBs. Further work to explore and optimize this approach is currently underway.

With respect to the reaction mechanism, we also considered the possibility of *in situ* ketene formation and formal [2+2] cycloaddition catalyzed by Li^+ as a Lewis acid, analogous to Studer's system (though notably those reactions do not proceed with amide-based BCBs, nor with disubstituted BCBs, nor with *in situ* ketene formation).[23] We therefore tested phenylacetyl chloride as a ketene precursor toward **3e** (eq. 1). Performing a

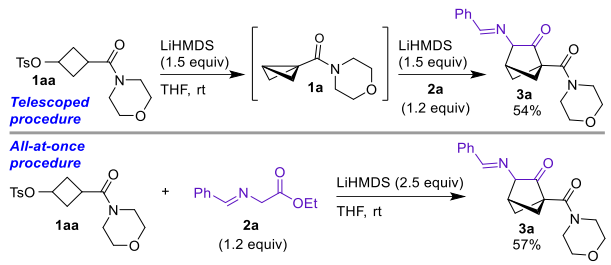
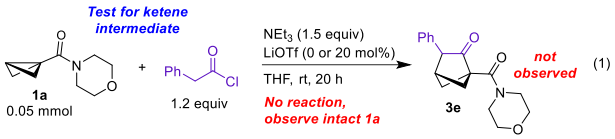


Figure 5 – Alternative synthetic pathways to access bicyclo[2.1.1]hexanes without isolation of bicyclobutane **1a**. **Top:** Telescoped synthesis with *in situ* formation of **1a**. **Bottom:** All-at-once procedure with simultaneous formation of BCB **1a** and enolate of **2a**. Yields of **3a** are obtained by ^{1}H NMR spectroscopy (rel. integration vs. internal standard TMB).

reaction in THF with NEt_3 (with or without LiOTf present as a potential Lewis acid catalyst) led to complete consumption of the acyl chloride, but no conversion of **1a**, ruling out a ketene-based mechanism. In addition, during larger scale preparation of **3c**, we isolated and characterized a byproduct where only the first enolate addition occurred (**3cc**, see ESI for details), further supporting the stepwise mechanism from Fig. 2.



In summary, we have developed a straightforward and expedient synthesis of functionalized 2-oxo-bicyclo[2.1.1]hexanes through enolate addition to bicyclobutanes. This reaction supports imine containing enolates, which provides a protected primary amine synthetic handle on the BCH ring for further derivatization. The reaction is also compatible with a variety of aromatic enolate derivatives, as well as other amide bicyclobutane derivatives, and can even be performed in one-pot procedures with *in situ* formation of the BCB substrate. Further studies on the scope and mechanism of this and related transformations toward the synthesis of C*sp*^{3}-rich molecular scaffolds are underway in our laboratories, and will be reported in due course.

Conflicts of interest

There are no conflicts to declare

Author contributions

K. J. W.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. K. D. D.: investigation, methodology. N. D. S.: formal analysis (XRD). D. C. L.: conceptualization, funding acquisition, project administration, supervision, writing – review & editing.

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