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Cooperative NHC/LA Catalysis for Stereoselective Strain-Release Difunctionalization of Bicyclo[1.1.0]butanes to 1,1,3,3-Tetrasubstituted Cyclobutanes

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Article

Keywords:

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11634085/v1

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Additional Declarations: Yes there is potential Competing Interest. Provisional patent (Application number 202611102297, dated 24-08-2026) has been filed based on this chemistry.

Cooperative NHC/LA Catalysis for Stereoselective Strain-Release gem-Difunctionalization of Bicyclo[1.1.0]butanes to 1,1,3,3-Tetrasubstituted Cyclobutanes

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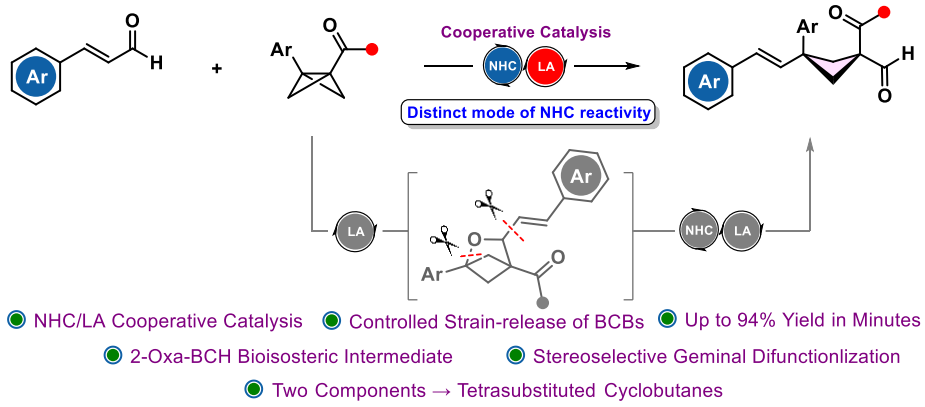
The stereoselective synthesis of densely substituted cyclobutanes and the development of efficient strategies to access them have emerged as important frontiers in contemporary molecular synthesis, owing to their value as three-dimensional building blocks and bioisosteric motifs. Here we report a cooperative N-heterocyclic carbene (NHC)/Lewis acid catalytic strategy for the strain-release difunctionalization of bicyclo[1.1.0]butanes (BCBs) with α,β-unsaturated aldehydes, affording 1,1,3,3-tetrasubstituted cyclobutanes in up to 94% yield with excellent syn-diastereoselectivity across a broad substrate scope. Most reactions reach completion within 15 min at room temperature. Mechanistic studies, including isolation of a 2-oxabicyclo[2.1.1]hexane intermediate and its subsequent conversion to the cyclobutane product under the catalytic conditions, establish its involvement in the reaction pathway. The data support Lewis acid-assisted C–O σ-bond cleavage followed by NHC-mediated ring opening and rearrangement. Beyond the synthesis of substituted cyclobutanes, this transformation reveals an unconventional mode of NHC reactivity in an unusual oxygenated system and demonstrates how Lewis acid cooperation can redirect NHC reactivity to enable new reaction pathways.



The increasing demand for structurally complex, sp^3-rich molecular architectures has reshaped modern medicinal chemistry, as saturated three-dimensional (3D) frameworks can offer favorable physicochemical and pharmacokinetic properties compared with their planar counterparts.[1-4] In the pursuit of 'escaping from flatland',[5-9] cyclobutanes have emerged as valuable structural motifs owing to their rigid, conformationally constrained frameworks, which enable precise spatial orientation of substituents and impart distinct three-dimensional character to molecular architectures. Consequently, cyclobutane-containing scaffolds have found widespread applications in medicinal chemistry,[10-15] and several pharmaceuticals incorporating 1,3-disubstituted cyclobutane motifs have advanced to clinical evaluation. These applications have stimulated the development of efficient and versatile strategies for the synthesis of increasingly complex and densely functionalized cyclobutanes (Fig. 1A).

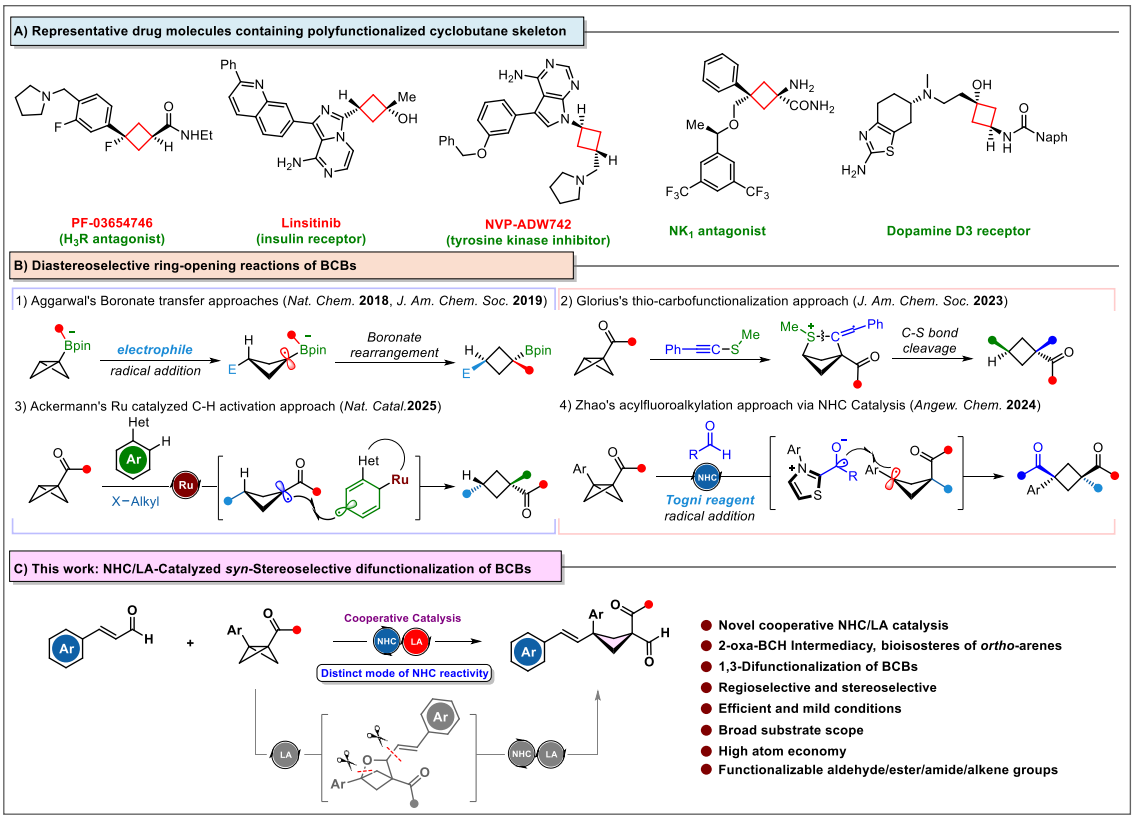


Fig. 1 The difunctionalization of BCBs to access 1,1,3-trisubstituted and 1,1,3,3-tetrasubstituted cyclobutanes. A) Representative drug molecules containing polyfunctionalized cyclobutane skeleton. B) Strategies for the synthesis of highly functionalized cyclobutanes via strain release. C) Our protocol for the synthesis of 1,1,3,3-tetrasubstituted cyclobutanes via NHC/Lewis acid cooperative catalysis

BCBs have recently emerged as versatile strain-release synthons for the rapid construction of functionalized cyclobutanes.[16-18] Their exceptionally weak and highly strained central C–C σ-bond exhibits pronounced π-bond-like character, rendering it susceptible to activation by nucleophilic, electrophilic, and radical species.[19-28] Cleavage of this 'spring-loaded' bond releases substantial strain energy, enabling the efficient conversion of readily

accessible BCBs into structurally diverse cyclobutane frameworks. This distinctive reactivity has led to the development of diverse catalytic strain-release functionalization and polyfunctionalization reactions with high levels of regio- and stereocontrol across a range of catalytic manifolds.[29-32] Nevertheless, controlling the reactivity of BCBs to achieve highly substituted cyclobutanes with defined relative stereochemistry remains challenging, particularly when multiple bond-forming events are coupled to strain release.[21,22,27,28] These challenges highlight the need for catalytic strategies that not only activate the strained C–C bond, but also redirect its inherent reactivity along new and stereochemically controlled reaction pathways.

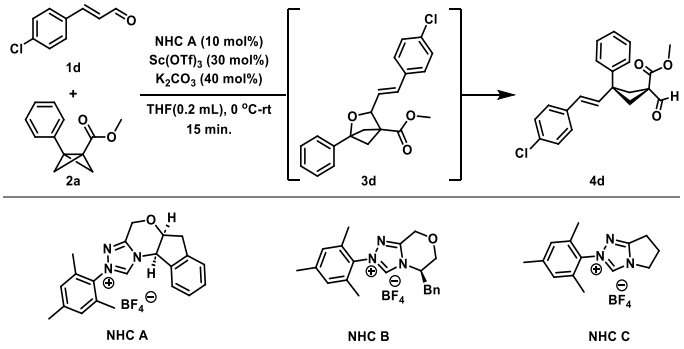
Several recent studies have highlighted the potential of BCBs for stereoselective access to highly substituted cyclobutanes.[17] Aggarwal and co-workers established an electrophilic radical-induced ring opening of boronate-substituted BCBs (Fig. 1B, path 1), in which radical addition generates an α-boryl radical that undergoes stereospecific 1,2-boron migration to furnish highly functionalized cyclobutanes with excellent diastereoselectivity.[24,33,34] Subsequently, Glorius and co-workers disclosed a photoredox-enabled thio-carbofunctionalization of BCBs using sulfur-containing bifunctional reagents (Fig. 1B, path 2). In this process, strain-release ring opening followed by C–S bond cleavage of a cyclic radical cation intermediate provides *syn*-functionalized cyclobutanes with high stereocontrol.[35] Although these approaches demonstrate the versatility of BCB strain-release chemistry, they are largely centered on monosubstituted BCBs, limiting their direct application to more substituted cyclobutane architectures. Ackermann and co-workers reported an interesting Ru(II)-catalyzed C–C/C–H functionalization of BCBs, integrating strain-release ring opening, halogen-atom transfer, and site-selective C–H functionalization to access functionalized tri- and tetrasubstituted cyclobutanes (Fig. 1B, path 3).[36] More recently, Zhao and co-workers reported an N-heterocyclic carbene (NHC)-catalyzed acylfluoroalkylation of BCBs through an NHC-derived ketyl radical, providing access to 1,1,3,3-tetrasubstituted cyclobutanes with high diastereoselectivity (Fig. 1B, path 4).[37] This transformation utilize fluoroalkyl radical precursor, such as a Togni's reagent, to achieve tetrasubstitution, with most of the substrates providing excellent diastereoselectivity. Despite these advances, a general catalytic strategy for the direct conversion of readily accessible BCBs into stereodefined 1,1,3,3-tetrasubstituted cyclobutanes through a simple two-component coupling remains underdeveloped. More broadly, new catalytic modes that redirect BCB strain-release reactivity toward stereoselective geminal difunctionalization remain elusive.

In recent years, cooperative catalysis with NHC has emerged as a powerful strategy for the development of diverse synthetic transformations.[38] Here, we report a cooperative NHC/Lewis acid catalytic strategy for the stereoselective strain-release geminal difunctionalization of BCBs, enabling rapid access to 1,1,3,3-tetrasubstituted cyclobutanes (Fig. 1C). The two-component protocol directly couples readily accessible BCBs with α,β-unsaturated aldehydes to furnish densely functionalized cyclobutanes in very good yield and with excellent diastereoselectivities. Beyond providing a direct route to highly substituted cyclobutanes, this cooperative strategy enables an unconventional mode of NHC reactivity with an unusual substrate, in which Lewis acid cooperation redirects strain-release reactivity toward a stereoselective bond-forming pathway.

Results and Discussion

We began our investigation using 4-chlorocinnamaldehyde (**1d**) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (**2a**) as reaction partners for the optimization of the reaction conditions (Table 1, selected entries, see SI).

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from Standard Condition[a]	Yield of **3d** (%)[b]	Yield of **4d** (%)[b]
1.	**None**	**n.d.**	**85%**
2.	20 mol% $Sc(OTf)_3$ instead of 30 mol%	20%	57%
3.	NHC B instead of NHC A	7%	71%
4.	NHC C instead of NHC A	45%	33%
5.	1.5 equiv. of **2a** instead of 2 equiv.	15%	40%
6.	Cs_2CO_3 instead of K_2CO_3	n.d.	24%
7.	DBU instead of K_2CO_3	n.d.	18%
8.	Toluene instead of THF	n.d.	49%
9.	$CHCl_3$ instead of THF	10%	48%
10.	CH_3CN instead of THF	89%	n.d.
11.	Without NHC	78%	5%
12.	Without $Sc(OTf)_3$	n.d.	n.d.

[a]Reaction conditions: **1d** (0.16 mmol), **2a** (2.0 equiv.), **NHC A** (10 mol%), $Sc(OTf)_3$ (30 mol%), K_2CO_3 (40 mol%), THF (0.2 mL), Temp. = 0 °C to rt, t = 15 min. [b]Yield of isolated products, n.d. = Not detected.

Gratifyingly, the reaction proceeded smoothly under the optimized cooperative catalytic conditions, employing 10 mol% of NHC A, 30 mol% $Sc(OTf)_3$, and 40 mol% K_2CO_3 in THF. Conducting the reaction from 0 °C to room temperature enabled rapid conversion within just 15 min, furnishing the desired 1,1,3,3-tetrasubstituted cyclobutane **4d** in 85% isolated yield (Table1, entry 1). A reduction in the $Sc(OTf)_3$ loading to 20 mol% resulted in a significant decrease in the product yield to 57%, along with formation of **3d** in 20% yield (Table 1, entry 2). Several NHC catalysts featuring triazolium-, imidazolium-, and thiazolium-derived carbene frameworks were initially screened for this transformation (see SI). Among them, NHC catalysts based on the triazolium scaffold proved to be the most effective, affording the desired product in good yields. Notably, decreasing the steric bulk of the NHC catalyst resulted in a noticeable reduction in reaction efficiency and, consequently, lower expected product yields (Table 1, entries 3 and 4). Screening of various Lewis acids identified $Sc(OTf)_3$ as uniquely effective for this transformation (see the Supporting Information). When the amount of BCB was reduced from 2.0 to 1.5 equivalents, the yield of **4d** decreased to 40%, with **3d** formed in 15% yield (Table 1, entry 5). The nature of the base was found to have a pronounced impact on the reaction efficiency (see the Supporting Information). Substitution of K_2CO_3 with either Cs_2CO_3 or DBU led to a dramatic erosion in the yield of the desired product (Table 1, entries 6 and 7). Evaluation of various solvents identified THF as the optimal medium for this transformation (Table 1, entries 8 and 9). The use of ACN as the solvent interestingly resulted in the formation of **3d** exclusively in 89% yield, with no detectable formation of the desired product **4d** (Table 1, entry 10). When the reaction was performed in the absence of the NHC catalyst, **3d** was formed in 78% yield, whereas the desired product **4d** was obtained in only 5% yield (Table 1, entry 11). In contrast, in the absence of $Sc(OTf)_3$, neither **3d** nor **4d** was detected (Table 1, entry 12). Interestingly, the reaction proceeded even in the absence of K_2CO_3, with the NHC catalyst and $Sc(OTf)_3$ alone, although the yields were slightly lower (see SI). Further investigations are required to elucidate the possible alternative pathways for carbene generation under these conditions.

With the optimized reaction conditions in hand, we next investigated the generality of this bifunctionalization protocol using a diverse range of α,β-unsaturated aldehydes and BCBs (Fig. 2). We initially examined the substrate scope with respect to the α,β-unsaturated aldehyde component. The cooperative NHC-Lewis acid catalytic system exhibited broad applicability, efficiently converting a variety of α,β-unsaturated aldehydes into the corresponding 1,1,3,3-tetrasubstituted cyclobutane derivatives in good to excellent yields and with consistently high diastereoselectivities (**4a-4j, 4m-4o**). Cinnamaldehyde worked well to provide the desired

product **4a** in excellent yield and stereoselectivity. Substrates bearing halo substituents at the para, meta and ortho positions, as well as dihalo substituted derivative underwent smooth transformation to furnish the corresponding products **4b-4g** in moderate to very good yields (20-85%).

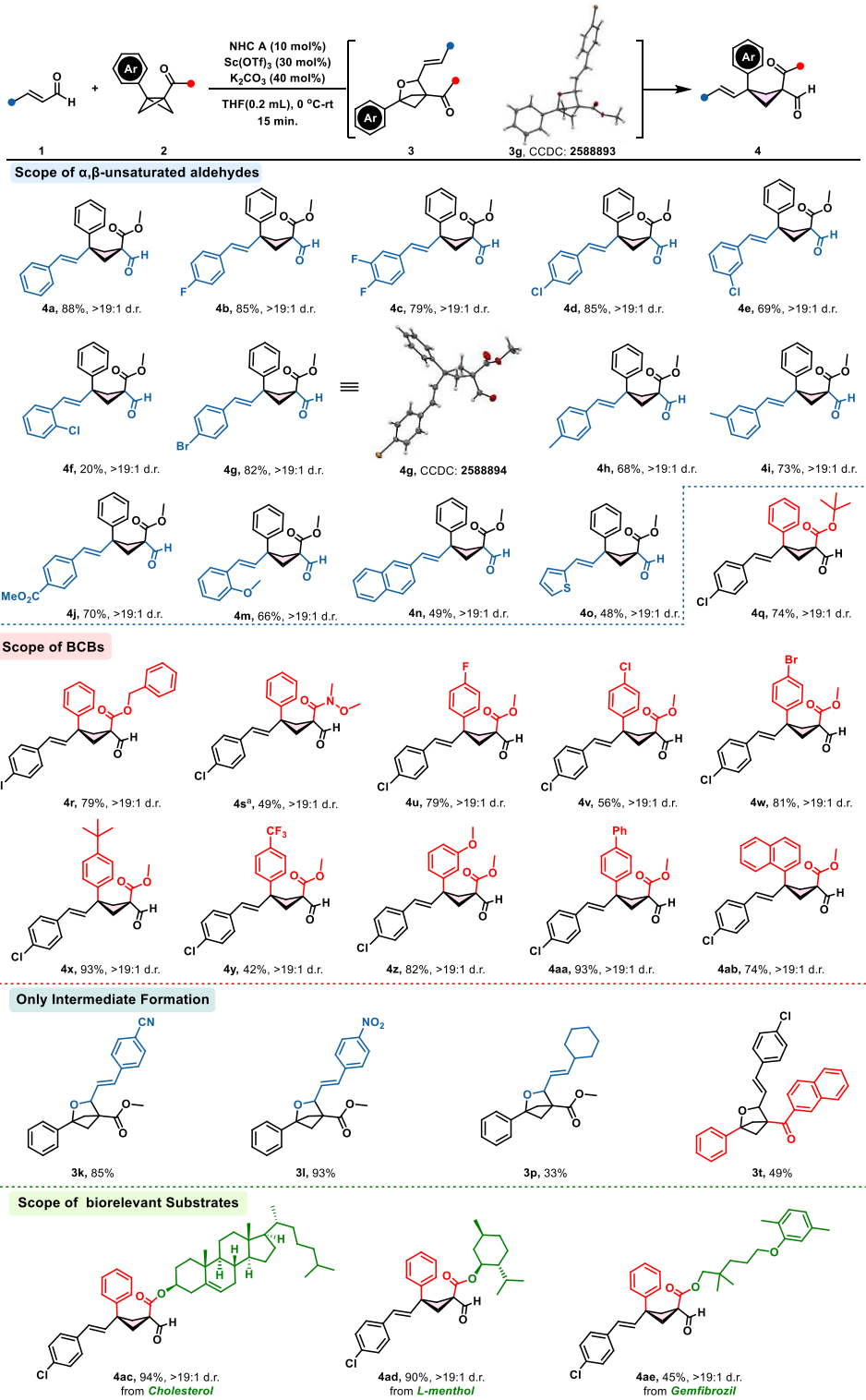


Fig. 2 Substrate scope of α,β-unsaturated aldehyde and BCBs. Reaction condition: **1** (0.16 mmol), **2** (2 equiv.), NHC A (10 mol%), $Sc(OTf)_3$ (30 mol%), K_2CO_3 (40 mol%), THF (0.2 mL), T = 0 °C-rt, t = 15 min. Isolated product yields. Diastereomeric ratio (d.r.) values were determined by ^1H NMR. [a]Reaction mixture heated to 50 °C for 10 h.

The molecular structure of intermediate **3g**, corresponding to the proposed intermediate **3**, was unambiguously confirmed by single-crystal X-ray diffraction analysis (see SI). The relative stereochemistry of compound **4g** was established by single-crystal X-ray diffraction analysis, confirming the cis arrangement of the styryl and aldehyde groups on the cyclobutane framework (see SI). Para and meta methyl substituted enals were also readily accommodated, affording products **4h** and **4i** in 68% and 73% yields, respectively. Furthermore, the electron-withdrawing methyl ester substituted cinnamaldehyde was well tolerated, delivering the corresponding product **4j** in a good yield of 70%. However, the protocol didn't work well with cyano and nitro substituted cinnamaldehydes probably due to lesser nucleophilicity of the NHC-enolate. Only the corresponding intermediates **3k** and **3l** were observed in good yields. The influence of ortho-methoxy substitution was also examined, which furnished the corresponding product **4m** in 66% yield. In addition, 2-naphthyl-substituted and β-heteroaryl enals were compatible with the reaction conditions, providing the corresponding products **4n** and **4o** in moderate yields and with good diastereoselectivities. Aliphatic enal afforded only the corresponding intermediate **3p,** while the expected product **4p** was not observed.

Having established the scope of the α,β-unsaturated aldehyde component, we next investigated the effect of structural variation in the BCB substrates **2q**-**2ab**. We first explored variations in the ester functionality of the BCB substrate. Both *tert*-butyl and benzyl ester-substituted BCBs were readily accommodated, furnishing products **4q** and **4r** in good yields of 74% and 79%, respectively. The Weinreb amide-substituted BCB also participated in the reaction, affording the desired product **4s** in 49% yield, however it requires higher temperature and longer reaction time. In contrast, the keto-substituted BCB did not furnish the desired product **4t** and proceeded only to the corresponding intermediate **3t**. We subsequently examined the influence of substituents present on the aryl group of the BCB substrates. Para halo-substituted phenyl BCB derivatives underwent efficient transformation under the cooperative NHC-Lewis acid catalytic conditions, affording the corresponding cyclobutane products **4u**-**4w** in moderate to good yields (56-81%). Notably, the para *tert*-butyl-substituted phenyl BCB delivered the corresponding product **4x** in an excellent yield under the optimized reaction conditions. In contrast, the presence of a strongly electron-withdrawing CF_3 group at the para position resulted in the reduced yield of the corresponding product **4y**. The meta methoxy-substituted phenyl BCB was also well tolerated, providing the desired product **4z** in 82% yield. Furthermore, the biphenyl BCB exhibited excellent reactivity, furnishing the corresponding product **4aa** in 93% yield. The 1-naphthyl-substituted BCB **4ab** also afforded the desired product in a good yield of 74%. Encouraged by the excellent tolerance of diverse

functional groups, we evaluated the applicability of this protocol to the substrates featuring structurally complex and biologically relevant molecules. Accordingly, BCB substrates derived from cholesterol, *L*-menthol, and the drug gemfibrozil were subjected to the optimized reaction conditions. The corresponding cyclobutane products **4ac**-**4ae** were obtain in 45-94% yield. Among these substrates, the cholesterol-derived BCB displayed particularly high reactivity, delivering the corresponding 1,1,3,3-tetrasubstituted cyclobutane derivative **4ac** in an excellent yield of 94%. These results highlight the excellent functional group tolerance and potential utility of this methodology for the late-stage diversification of structurally complex and biologically relevant molecules.

To gain insight into the mechanism of this transformation, a series of control experiments were performed (Fig. 3A). The importance of the α,β-unsaturated aldehyde functionality for the protocol was investigated by replacing enal **1a** with 3-phenylpropanal **1a′**. When **1a′** and BCB **2a** were subjected to the standard reaction conditions, **1a′** remained unreacted, and neither the corresponding intermediate **3a′** nor the desired cyclobutane product **4a′** was detected (Fig. 3A-i). In contrast, BCB **2a** was completely consumed, with formation of the corresponding cyclobutene derivative. These observations suggest that the α,β-unsaturated aldehyde functionality plays a crucial role in the reaction with the $Sc(OTf)_3$-activated BCB substrate. The corresponding 2-oxa-bicyclo[2.1.1]hexane **3a′** has previously been synthesized by the Huang group through a cobalt-promoted photocatalytic [2π + 2σ] cycloaddition of BCBs with aldehydes under visible-light irradiation.[39] To examine whether the intermediate **3d** could serve as a precursor to the final product. It was subjected to the standard reaction conditions. Complete consumption of **3d** was observed within 15 mins, affording the corresponding 1,1,3,3-tetrasubstituted cyclobutane **4d** in 93% isolated yield (Fig. 3A-ii). This outcome clearly supports **3d** as a competent intermediate in the formation of the final product. In a separate experiment, hydrogenation of intermediate **3a** led to reduction of the alkene along with C–O bond cleavage, affording compound **3a″** in 95% yield (Fig. 3A-iii). These observations suggests that coordination of $Sc(OTf)_3$ to the oxygen atom may facilitate C–O bond cleavage during the conversion of **3d** to the corresponding cyclobutane product.

Finally, two additional control experiments were performed to investigate the individual roles of $Sc(OTf)_3$ and the NHC catalyst in the conversion of intermediate **3d** into the product **4d**. When **3d** was subjected to the optimized reaction conditions in the absence of $Sc(OTf)_3$, no conversion to **4d** was observed and omission of the NHC catalyst also failed to promote the formation of **4d** (Fig. 3A-iv). Taken together, these results indicate that both $Sc(OTf)_3$ and the NHC catalyst are required for the conversion of intermediate **3d** into product

4d. Overall, these observations are consistent with the involvement of cooperative NHC/Lewis acid catalysis in facilitating the transformation.

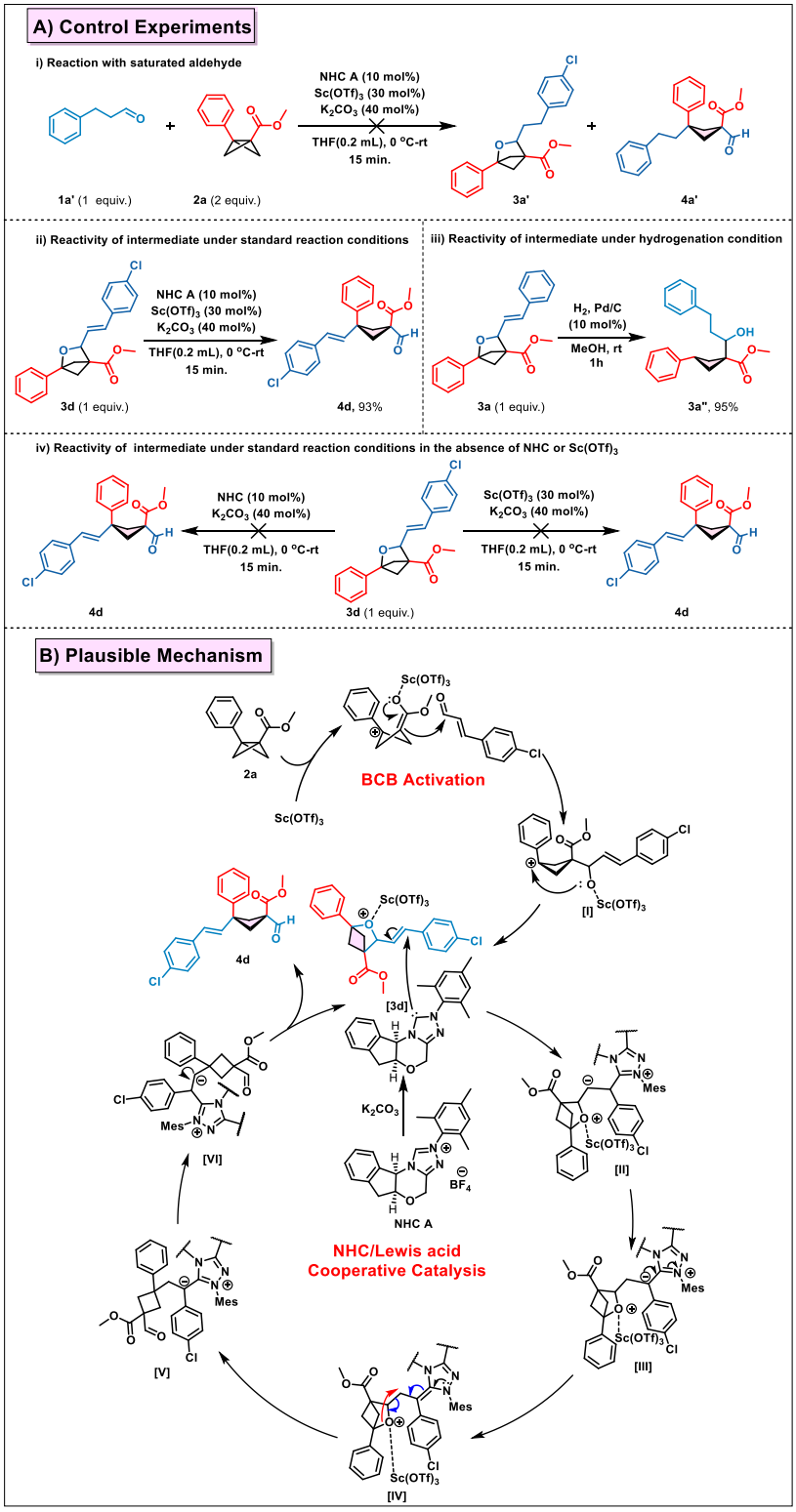


Fig. 3 A) Control Experiments: i) Reaction using saturated aldehyde ii) Reactivity of intermediate under standard reaction condition. iii) Reactivity of intermediate under hydrogenation condition. iv) Reactivity of intermediate under standard reaction conditions in the absence of NHC or $Sc(OTf)_3$ B) Plausible Mechanism.

On the basis of the control experiments and relevant literature reports,[40-42] a plausible reaction pathway for this transformation is proposed (Fig. 3B). Initially, the BCB is activated through coordination with the Lewis acid $Sc(OTf)_3$, which facilitates cleavage of its highly strained central C–C bond.[42] The resulting activated BCB intermediate then reacts with the enal, followed by intramolecular cyclization to furnish the bioisosteric[43,44] 2-oxabicyclo[2.1.1]hexane intermediate **3d**. Meanwhile, the NHC catalyst is generated *in situ* through deprotonation of the triazolium salt in the presence of a base. The generation of NHC might be facilitated by THF in the absence of a base.[45] The resulting NHC attacks the double bond of intermediate **3d**, generating intermediate **II**, which subsequently undergoes proton transfer to afford intermediate **III**, followed by the formation of intermediate **IV**. To investigate the possible existence of intermediate **IV**, we analyzed aliquots of the reaction mixture by HRMS after 3, 5, and 10 min (see SI). Subsequently, coordination of the oxygen atom with $Sc(OTf)_3$ and the presence of the NHC in intermediate **IV** facilitates the simultaneous cleavage of the C–C and C–O bonds, giving rise to intermediate **V**. The intermediate **V** upon proton transfer, affords intermediate **VI**. Finally, release of the NHC catalyst from intermediate **VI** furnishes the 1,1,3,3-tetrasubstituted cyclobutane product **4d**.

To demonstrate the scalability and practical applicability of the developed methodology, two independent scale-up experiments were conducted under the optimized reaction conditions using cinnamaldehyde **1d** as the α,β-unsaturated aldehyde component. The reaction of **1d** (3 mmol, 500 mg) with BCB **2x** furnished the corresponding bifunctionalized cyclobutane product **4x** in an excellent yield of 90%. The reaction was subsequently performed on a larger 6 mmol scale using BCB **2a**, affording the corresponding product **4d** in 71% yield (Fig. 4A). The stereoselectivity was not hampered even on bigger scale demonstrating the robustness of the protocol.

The synthetic versatility of product **4x** was further demonstrated through complementary downstream transformations (Fig. 4B). Catalytic hydrogenation of the styryl moiety in **4x** using H_2 and Pd/C smoothly afforded the corresponding saturated cyclobutane derivative **5** in 85% yield. Chemoselective reduction of the aldehyde functionality in **4d** with $NaBH_4$ furnished the corresponding primary alcohol **6** in an excellent yield of 96%. Reduction of **4x** with excess of $LiAlH_4$ afforded the corresponding diol **7** in 94% isolated yield. We further demonstrated the utility of **4d** by oxidizing the aldehyde group to carboxylic acid **8** via Pinnick oxidation. The alcohol and acid derivatives of product **4** were used for late-stage functionalization with bioactive molecules and drugs (Fig. 4C). Through amidation or esterification, we successfully conjugated ciprofloxacin, estrone and isoxepac. These reactions

furnished a diverse library of biologically relevant 1,1,3,3-tetrasubstituted cyclobutane analogs in good to excellent yields (46-95%). Collectively, these transformations demonstrate the synthetic versatility of the polyfunctionalized cyclobutane products and further highlight the utility of the present methodology as a versatile platform for accessing structurally diverse and synthetically valuable molecular scaffolds.

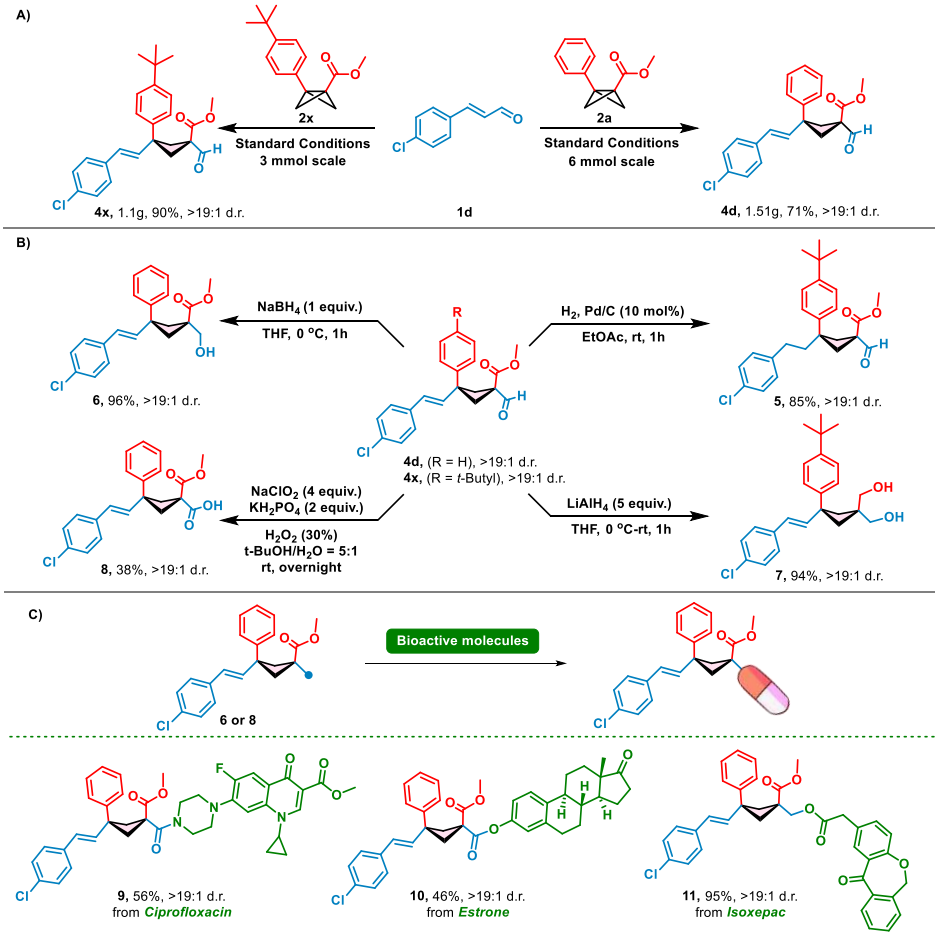


Fig. 4 A) Gram Scale synthesis. B) Product functionalization. C) Late-stage modification of bioactive molecules.

Conclusion

In summary, we have developed a cooperative NHC/Lewis acid catalytic strategy for the stereoselective strain-release difunctionalization of bicyclo[1.1.0]butanes with enals, providing rapid access to 1,1,3,3-tetrasubstituted cyclobutanes under mild conditions. The transformation accommodates electronically and structurally diverse enals and BCBs, delivering high efficiency, high regioselectivity and excellent syn-diastereoselectivity. The resulting cyclobutanes contain synthetically versatile geminal aldehyde and ester or amide functionalities at highly substituted stereogenic centres, providing opportunities for further molecular diversification. Beyond its synthetic utility, this transformation reveals an

unconventional mode of NHC reactivity enabled by Lewis acid cooperation. The isolation and independent conversion of the 2-oxabicyclo[2.1.1]hexane intermediate under the catalytic conditions provide compelling evidence for its role as a mechanistic gateway to the substituted cyclobutane products. This reactivity highlights how Lewis acid cooperation can unlock C–O bond cleavage and redirect the fate of strained oxygenated intermediates through NHC-mediated rearrangement. More broadly, this work expands the reactivity landscape of NHC catalysis and establishes cooperative activation as a platform for accessing new NHC-mediated transformations.

Methods

General optimized procedure for the synthesis of polyfunctionalised cyclobutane derivatives 4: An oven-dried schlenk tube equipped with a magnetic stirring bar was charged with the NHC precatalyst-**A** (10 mol%) and K_2CO_3 (40 mol%). The reaction vessel was evacuated and backfilled with argon three times. Under an argon atmosphere, α,β-unsaturated aldehyde **1** (1 equiv.) and bicyclobutane derivative **2** (2 equiv.) were added followed by addition of THF. The reaction vessel was evacuated and backfilled with argon three times. The schlenk tube was placed in an ice bath and the reaction mixture was stirred for 5 minutes. After this, $Sc(OTf)_3$ (30 mol%) was added and the tube was tightly closed with a glass stopper. The resulting mixture was kept for stirring at rt for completion of the reaction. Upon completion of the reaction as observed by TLC, the reaction mixture was directly subjected to column chromatography using ethyl acetate:pet ether over 230-400 flash silica gel to afford the desired products **4** in good to excellent yields**.**

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Acknowledgment
S.B.M. acknowledges financial support from CSIR, India. S.G.J. thanks DST-Inspire, India and G.J.B. thanks CSIR, New Delhi.

Author contribution
S.B.M. conceived the project. S.G.J. and G.J.B. performed the synthetic experiments. R.G.G. carried out single crystal X-Ray diffraction analysis of compounds **3g** and **4g**. S.B.M. supervised the project.

Competing interest
Provisional patent (Application number 202611102297, dated 24-08-2026) has been filed based on this chemistry.

Data availability statement
All data supporting the findings of this study are available in the main text of the paper and/or its Supplementary Information files.

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