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Eu(OTf)$_3$-Catalyzed Formal Dipolar [4π + 2σ] Cycloaddition of Bicyclo-[1.1.0]butanes with Nitrones: Access to Polysubstituted 2-Oxa-3-azabicyclo[3.1.1]heptanes

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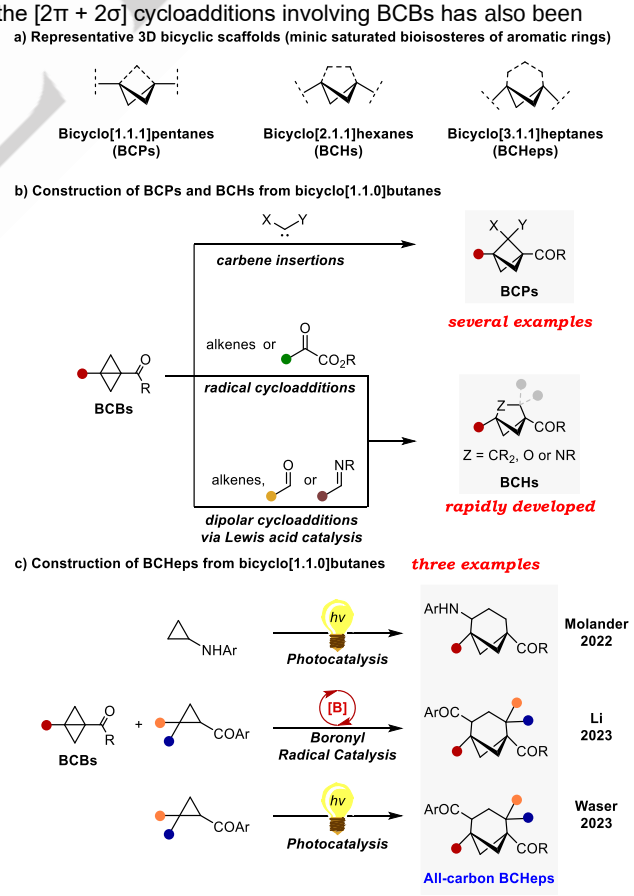
Abstract: Herein, we have synthesized multifunctionalized 2-oxa-3-azabicyclo[3.1.1]heptanes, which are considered potential bioisosteres for *meta*-substituted arenes, through Eu(OTf)$_3$-catalyzed formal dipolar [4π+2σ] cycloaddition of bicyclo[1.1.0]butanes with nitrones. This methodology represents the initial instance of fabricating bicyclo[3.1.1]heptanes adorned with multiple heteroatoms. The protocol exhibits both mild reaction conditions and a good tolerance for various functional groups. Computational density functional theory calculations support that the reaction mechanism likely involves a nucleophilic addition of nitrones to bicyclo[1.1.0]butanes, succeeded by an intramolecular cyclization. The synthetic utility of this novel protocol has been demonstrated in the concise synthesis of the analogue of Rupatadine.

The paradigm shift towards substituting planar arene moieties with three-dimensional (3D) saturated bicyclic analogues (a concept popularly referred to as "escape from flatland") has garnered considerable scholarly interest over recent decades.[1] These captivating 3D scaffolds, particularly the bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]-hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHeps), function as bioisosteric replacements for substituted aromatic rings and are posited to confer distinctive biological activities, metabolic profiles, and physicochemical characteristics, owing to their inherent rigid conformation and metabolic stability (Scheme 1a).[2] The increasing awareness of this phenomenon has prompted a surge of interest in access to these chemical entities.[3-7] Notably, bicyclo[1.1.0]butanes (BCBs) have gained significant attention due to their outstanding ability to construct these 3D bicyclic frameworks through cycloadditions with diverse partners.[8] For example, the integration of carbenes into BCBs provided numerous BCPs (Scheme 1b).[9] Besides, the synthesis of BCHs through the intermolecular thermally-driven cycloaddition of BCBs with alkenes[10] was pioneered by Blanchard[10a] in 1966, with Wipf[10c] subsequently achieving the intramolecular version in 2006. Apart from these thermally induced conversions, the seminal contributions of Glorius[11] and Brown[12] in the realm of radical BCB-alkene cycloadditions, facilitated by triplet energy transfer, led to the expeditious advancement of radical [2π + 2σ] cycloadditions between BCBs and alkenes (ketones) over the past two years, providing a copious array of enticing (oxa)-BCHs.[13] Furthermore, the employment of Lewis acid catalysis for the [2π + 2σ] cycloadditions involving BCBs has also been



Scheme 1. Construction of three-dimensional bicyclic mimetics from BCBs.

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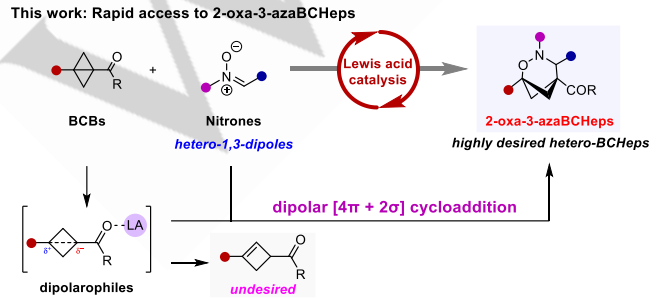
substantiated as a potent strategy for the assembly of (hetero)BCHs, as described by Leitch,[14] Glorius,[15] Studer,[16] Deng,[17] and Feng[18] respectively (Scheme 1b). Despite extensive preceding studies, access to bicyclo[3.1.1]heptanes (BCHeps), which function as *meta*-substituted arene bioisosteres, via cycloadditions of BCBs remains scarce. The first successful synthesis of unique functionalized BCHeps via photoinduced cycloaddition utilizing BCBs and cyclopropyl amines was achieved by Molander last year.[19] Soon after, Li reported the pyridine-boryl radical [2σ + 2σ] cycloaddition between BCBs and cyclopropyl ketones, generating highly substituted BCHeps.[20] These two synthetic transformations are characterized by their progression through oxidative and reductive electron transfer mechanisms. Remarkably, the radical [2σ + 2σ] cycloaddition for the creation of BCHeps from BCBs and cyclopropyl ketones could also occur with photocatalyzed homolytic cleavage of the latter, which was discovered simultaneously by Waser (Scheme 1c).[21] This outcome serves as a significant complement to the methodologies proposed by Molander and Li (homolytic cleavage and redox activation). Collectively, the aforementioned synthetic routes all utilize cyclopropanes as three-carbon synthons and undergo radical pathways to afford the rare all-carbon BCHeps.

Significantly, heteroatom incorporated analogs of 3D saturated bicyclic mimetics (hetero-BCPs, BCHs, and BCHeps) have been proven frequently confer improved water solubility, enhanced metabolic stability, and reduced lipophilicity.[5a,5c,7] Nevertheless, application of hetero-BCHeps in medicinal chemistry were limited due to the restricted synthetic methods. Consequently, there is a great need to develop novel protocols for constructing hetero-BCHep frameworks, especially those incorporating multiple heteroatoms. Based on our previous studies in dipolar cycloadditions[22] and interest in BCB chemistry, we envisaged constructing the highly desired hetero-BCHeps via dipolar cycloadditions of BCBs with hetero-1,3-dipoles. Nitrones[23] might be the ideal choice of hetero-1,3-dipoles for their widespread use in synthesizing *N*,*O*-heterocycles. Notably, nitrones have been successfully involved in a strain-release driven reaction with housane at high temperatures, which was developed by Tanner and Jessing,[24] providing oxaza-bicyclo[3.2.1]octanes. We hypothesize that nitrones could trap the BCBs, serving as dipolarophiles upon activation by Lewis acid,[14-18] and afford a series of structurally novel and biologically interesting 2-oxa-3-azaBCHep skeletons (Scheme 2). According to the literature,

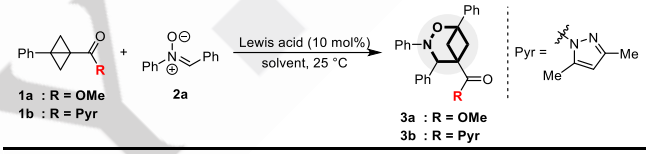


Scheme 2. Lewis acid-catalyzed formal dipolar [4π + 2σ] cycloaddition of BCBs with nitrones for synthesis of 2-oxa-3-azabicyclo[3.1.1]heptanes.

BCBs are prone to isomerize upon Lewis acid activation to cyclobutenes.[14] As a consequence, matching the reactivity of the Lewis acid-activated BCBs with nitrones will be crucial for the dipolar cycloaddition. Herein, we report the first example of a formal dipolar [4π + 2σ] cycloaddition of BCBs with nitrones in the presence of $Eu(OTf)_3$, providing a novel 2-oxa-3-azaBCHep scaffold with broad substrate scope.

We initiated our studies by employing bicyclo[1.1.0]butane with ester **1a** (0.10 mmol, 1.0 equiv.) and nitrone **2a** (0.15 mmol, 1.5 equiv.) as model substrates in the presence of $Ga(OTf)_3$ (0.01 mmol, 10 mol%) in CH_2Cl_2 (1.5 mL) at 25 °C (Table 1, entry 1). However, the reaction resulted in a complex mixture. No desired product **3a** was detected and the undesired cyclobutene was isolated in 22% yield. We thought that this may be attributed to facile decomposition of **1a** and lower reactivity towards cycloaddition. Thus, the bicyclo[1.1.0]butane equipped with an acyl pyrazole group **1b**,[15] which was developed by Glorius and exhibits better stability and higher cycloaddition reactivity, was employed. Gratifyingly, the reaction of **1b** proceeded efficiently, yielding the polysubstituted 2-oxa-3-azabicyclo[3.1.1]heptane **3b**

Table 1. Optimization of the reaction conditions.[a]



Entry	Lewis acid	Solvent	Yield (%)[b]
1[c]	$Ga(OTf)_3$	CH_2Cl_2	-
2	$Ga(OTf)_3$	CH_2Cl_2	31
3	$Er(OTf)_3$	CH_2Cl_2	60
4	$Lu(OTf)_3$	CH_2Cl_2	67
5	$In(OTf)_3$	CH_2Cl_2	38
6	$Sc(OTf)_3$	CH_2Cl_2	33
7	$Eu(OTf)_3$	CH_2Cl_2	87
8	$Dy(OTf)_3$	CH_2Cl_2	52
9	$Yb(OTf)_3$	CH_2Cl_2	82
10	AgOTf	CH_2Cl_2	19
11	$BF_3{\cdot}Et_2O$	CH_2Cl_2	-
12	TMSOTf	CH_2Cl_2	-
13	$Eu(OTf)_3$	DCE	82
14	$Eu(OTf)_3$	THF	95
15	$Eu(OTf)_3$	toluene	61
16	$Eu(OTf)_3$	MeCN	26
17	$Eu(OTf)_3$	1,4-dioxane	71
18[d]	$Eu(OTf)_3$	THF	-
19[e]	$Eu(OTf)_3$	THF	90
20	-	THF	-
21[f]	-	THF	-
22[f]	-	toluene	-

[a] Reaction condition: **1b** (0.10 mmol), **2a** (0.15 mmol), Lewis acid (0.01 mmol, 10 mol%), solvent (1.5 mL), N_2 atmosphere, 25 °C, 24 h. [b] Isolated yield. [c] with **1a** (0.10 mmol). [d] with 20 mol% H_2O. [e] with 100.0 mg 4 Å molecular sieves. [f] at 100.0 °C. Abbreviation: THF = tetrahydrofuran.

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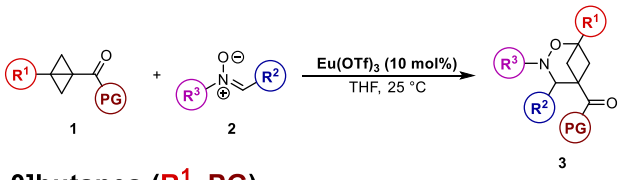
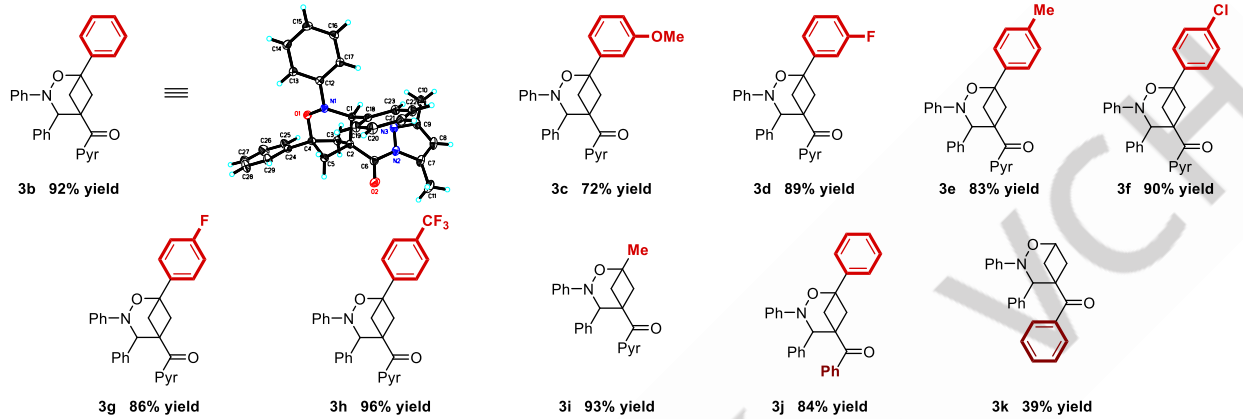
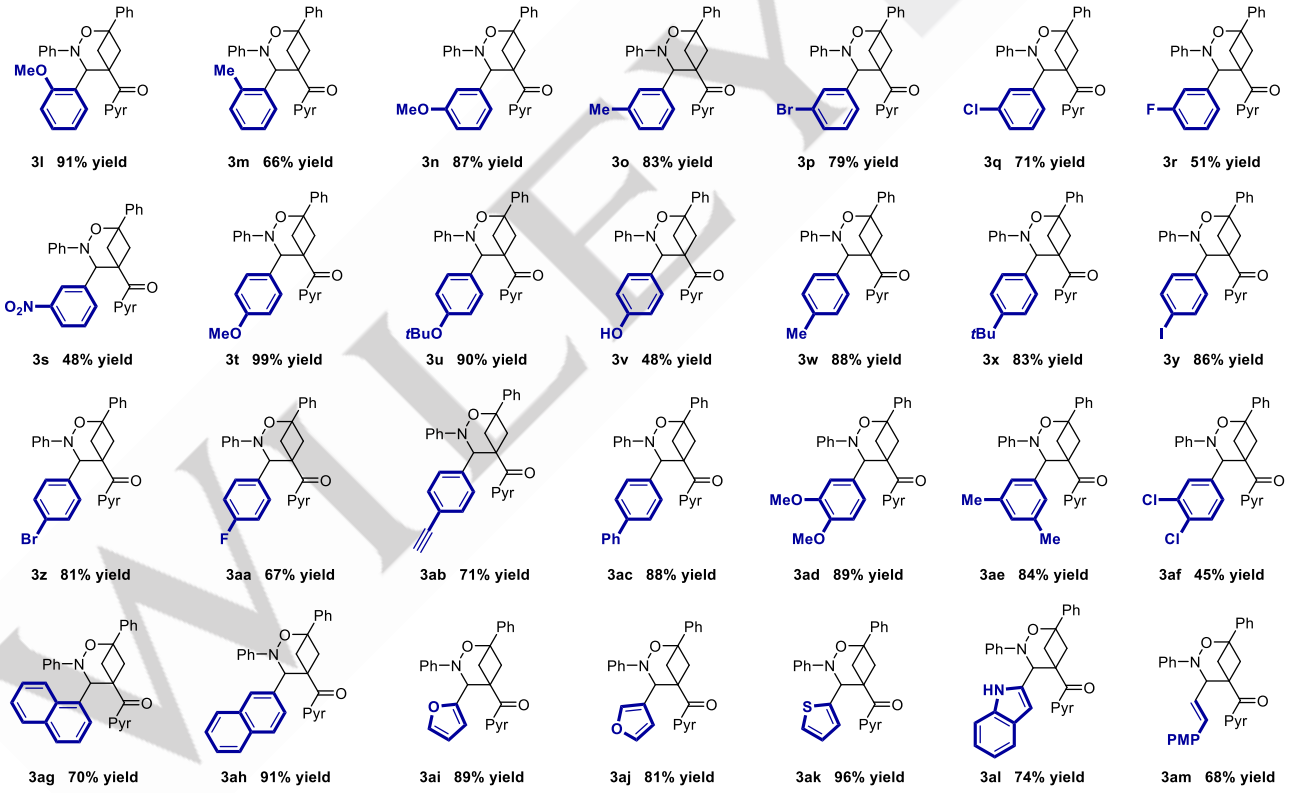
Table 2. Substrate scope investigation.[a][b]



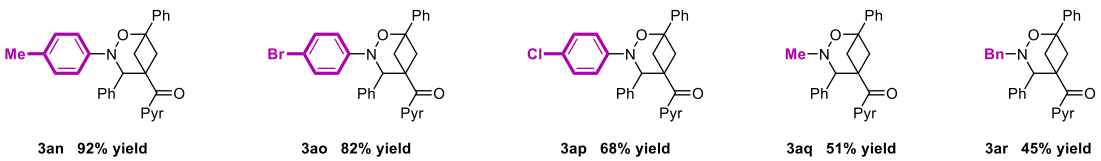
Variation of bicyclo[1.1.0]butanes (R^1, PG)



Variation of nitrones (R^2)



Variation of nitrones (R^3)



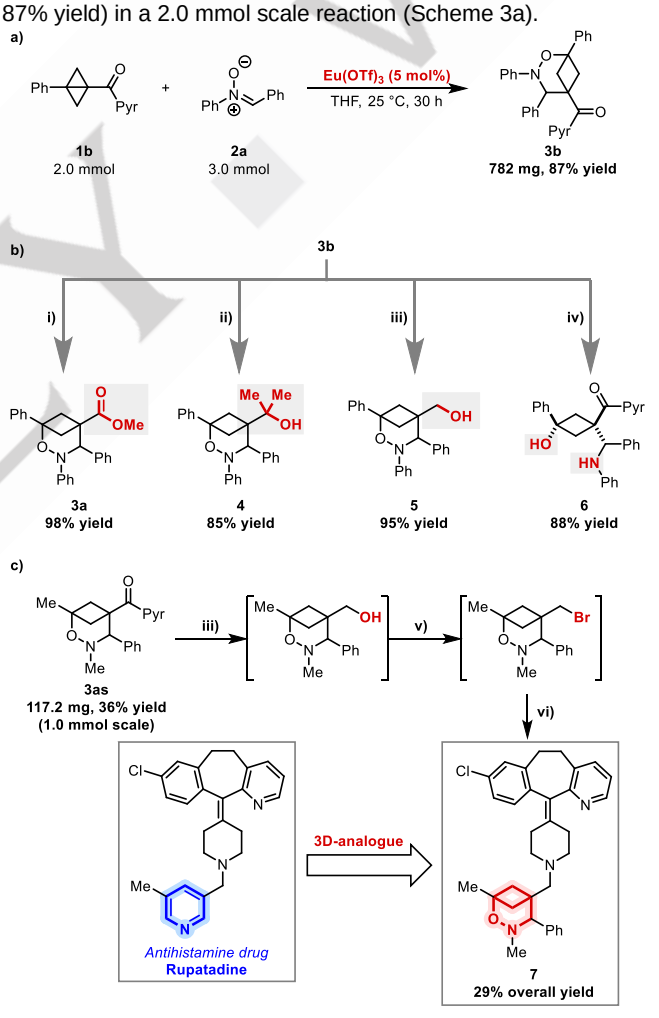
[a] Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), $Eu(OTf)_3$ (0.02 mmol, 10 mol%), THF (3.0 mL), N_2 atmosphere, 25 °C. [b] isolated yields.

10.1002/anie.202318476

in a 31% yield (Table 1, entry 2). Encouraged by the result, multiple Lewis acids were evaluated in an attempt to enhance the yields (entries 3-10). All the selected Lewis acids were effective in the reactions, and the results uncovered that $Eu(OTf)_3$ was optimal (entry 7, 87% yield). Additionally, two common nonmetal Lewis acids ($BF_3{\cdot}Et_2O$, TMSOTf) were evaluated as well, and the reactions became messy, and neither produced the target product **3b** (entries 11-12**)**. Subsequent screening of various solvents (entries 13-17) revealed tetrahydrofuran as the superior solvent, achieving a 95% yield. The reaction failed to proceed in the presence of 20 mol% water (entry 18). Moreover, the introduction of 4 Å molecular sieves slightly reduced the yield of **3b** to 90% (entry 19). The control experiments showed that the reaction could not occur even at 100 °C in the absence of the Lewis acid, indicating the necessity of the Lewis acid (entries 20-22). Ultimately, the optimum conditions identified were based on the use of **1** (1.0 equiv.), **2** (1.5 equiv.) in THF at 25 °C in the presence of $Eu(OTf)_3$ (10 mol%).

With the optimal conditions in hand, we next investigated the substrate scope, starting with diverse BCBs **1** through reactions with nitrones **2a**. As summarized in Table 2, BCBs **1c**-**1h** featuring various substituted phenyl rings (*m*-OMe, *m*-F, *p*-Me, *p*-Cl, *p*-F, *p*-CF_3) furnished the corresponding products (**3c**-**3h**) in good to high yields (72%-96%). Notably, the methyl-substituted BCB **1i** also reacted smoothly, as demonstrated by product **3i**, delivering 93% yield under the optimized conditions. Other BCBs were also evaluated. Phenyl(3-phenylbicyclo[1.1.0]butan-1-yl)methanone **1j** furnished the product **3j** in a high yield (84%), and monosubstituted BCB ketone **1k** yielded the desired cycloadduct **3k** though with a low yield (39%). Besides, monosubstituted BCB sulfone and *N*,*N*-dimethyl-3-phenylbicyclo[1.1.0]butane-1-carboxamide did not yield the desired cycloadducts. Attention was then paid to the nitrones **2**. An array of nitrones **2b-2s** bearing either electron-donating or electron-withdrawing groups on the *ortho* (*o*-OMe, *o*-Me), *meta* (*m*-OMe, *m*-Me, *m*-Br, *m*-Cl, *m*-F, *m*-NO_2), and *para* positions (*p*-OMe, *p*-O*t*Bu, *p*-OH, *p*-Me, *p*-*t*Bu, *p*-I, *p*-Br, *p*-F, *p*-ethynyl, *p*-Ph) of phenyl rings (R^2), participated smoothly in the reaction (**3l**-**3ac**, 48%-99% yields). It should be noted that nitrone **2l**, containing an exposed phenolic hydroxyl group, afforded **3v** with a reduced yield of 48%. The above results revealed that electron-rich substituents were markedly beneficial for the yields of products than the electron-deficient ones on the same positions of phenyl rings, and exposed the significant influence of steric effect on the output in some degree. Additionally, nitrones with disubstituted aryl groups at R^2, such as **2t** (3,4-diOMe), **2u** (3,5-diMe), and **2v** (3,4-diCl), were also accommodated (**3ad** 89% yield; **3ae** 84% yield; **3af** 45% yield). Nitrones **2w** and **2x**, featuring fused-ring R^2 groups (*α*- or *β*-naphthyl), also reacted efficiently, producing **3ag** and **3ah** with yields of 70% and 91%. Furthermore, heteroaryl R^2 groups, including 2-furyl, 3-furyl, 3-thienyl, and 2-indolyl, were well tolerated, leading to the formation of **3ai**, **3aj**, **3ak**, and **3al** in good to excellent yields (74%-96%). Significantly, *p*-methoxy styryl nitrone **2ac** also showed good reactivity in this reaction, giving product **3am** in reasonable yield (68%). The influence of the R^3 group on the nitrones was also investigated. Nitrones **2ad**-**2af**, with a methyl, Br, or Cl group on the *para* site of the benzene ring at R^3, all behaved well under optimal conditions to afford desired products **3an**-**3ap** in good to high yields (68%-92%). Altering the R^3 group from a phenyl to a methyl or benzyl group resulted in lower reactivity for **2ag**-**2ah**, but they still engaged in the reaction to produce **3aq**-**3ar**, albeit with reduced yields (51%, 45%). However, nitrones with other aliphatic R^2 groups (cyclohexyl, cyclopropyl, and *tert*-butyl) resulted in only trace amounts of the desired cycloadducts with a cyclobutane as the byproduct, and ketone-derived ketonitrone (*α*,*β*-unsaturated *N*-phenyl ketonitrone) and pyridine *N*-oxide failed to yield the desire products (more details were shown in Supporting Information). The structure of **3b** was unambiguously determined through *X*-ray single crystal diffraction, and the configurations of other products were assigned by analogy.[25]

To demonstrate the synthetic potential of the current protocol, scale-up synthesis and several transformations were carried out as depicted in Scheme 3. Remarkably, reducing the catalyst loading to 5 mol% caused a limited decrease in the yield (782 mg, 87% yield) in a 2.0 mmol scale reaction (Scheme 3a).

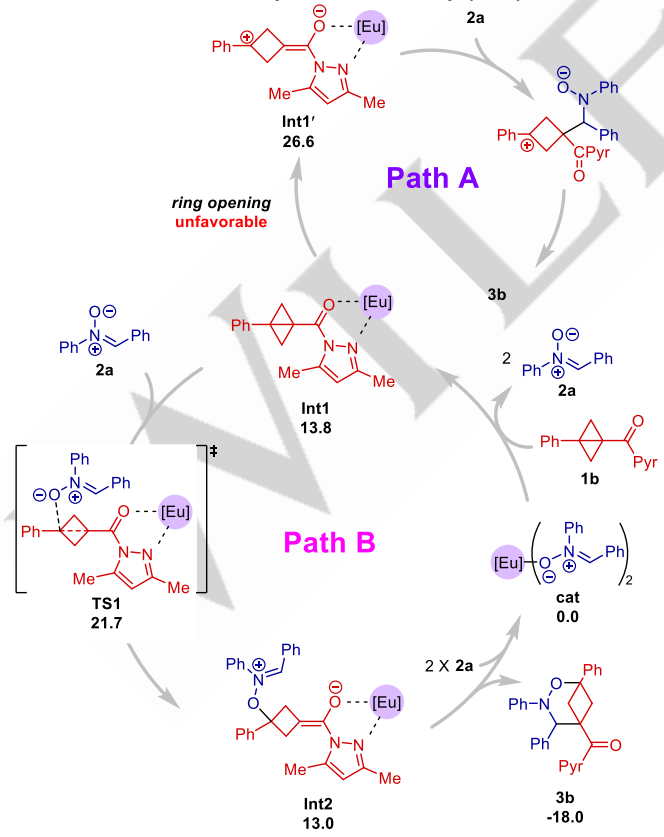


Scheme 3. Scale-up synthesis, synthetic transformations, and synthesis of the analogue of Rupatadine. i) Et_3N (2.0 equiv.), MeOH, 50 °C, 12 h. ii) MeMgBr (3.0 equiv., 3.0 M in Et_2O), THF, 25 °C, 0.5 h. iii) $NaBH_4$ (2.0 equiv.), MeOH, 0 to 50 °C, 0.5 h. iv) Pd/C (palladium on activated carbon, 5% Pd basis,10 mol%), H_2, MeOH, 25 °C., 2 h. v) NBS (1.0 equiv.), PPh_3 (1.0 equiv.), CH_2Cl_2, 0 to 25 °C, 1.0 h. vi) desloratadine (1.0 equiv.), K_2CO_3 (1.0 equiv.), DMF, 50 °C, 8.0 h. Abbreviation: DMF = *N*,*N*-dimethylformamide.

10.1002/anie.202318476

Subsequently, several transformations of **3b** were conducted (Scheme 3b). Nucleophilic substitution of the acyl pyrazole unit with alcohol proceeded smoothly, leading to the formation of ester **3a** in excellent yield (98%). Additionally, the reaction of **3b** with MeMgBr produced the tertiary alcohol **4** in a high yield (85%). The acyl pyrazole group of **3b** was reduced to the hydroxyl group with $NaBH_4$ with high efficiency (**5**, 95% yield). Interestingly, the N-O bond in cycloadduct **3b** could be cleaved with H_2 in the presence of Pd/C, furnishing the functionalized cyclobutane **6** (88% yield). Moreover, we incorporated the 2-oxa-3-azaBCHep unit into the structure of the antihistamine drug Rupatidine[26] in 3 steps (29% overall yield from **3as**), instead of the pyridine ring, which demonstrated the synthetic practical utility of the obtained hetero-BCHep scaffolds (Scheme 3c). The smooth progress of these transformations highlighted the synthetic utility. Further investigation on the stability of product **3b** demonstrated that 2-oxa-3-azaBCHeps possess excellent thermal stability and good acid resistance (more details were shown in Supporting Information).

Then we focused on elucidating the mechanism of the formal dipolar [4π + 2σ] reaction. The transformation may proceed in two ways, 1) nucleophilic attack of nitrone by activated BCBs followed by ring-closing (Scheme 4, path A). 2) nucleophilic attack of BCBs, upon Lewis acid activation and enolization, to nitrone followed by ring-closing (Scheme 4, path B). Our experimental results indicated that electron-rich nitrones resulted in higher reaction efficiencies, suggesting that the nucleophilic attack of the nitrones on BCBs is the likely initial step (path B). To investigate the mechanistic details, density functional theory (DFT) calculations were performed (Scheme 4). Our results showcased that the ring opening of $Eu(OTf)_3$-complexed BCB **Int1** had an endergonic energy change of 12.8 kcal mol^{-1} (**Int1** to **Int1'**), which was even higher than that of the transition state for the nucleophilic attack of the nitrone to the BCB (**TS1**, 7.9 kcal mol^{-1}, for details, see the Supporting Information). These values are consistent with our hypothesized reaction pathway (path B). Based on these results, we proposed a plausible mechanism. Firstly, coordination of the Lewis acid $Eu(OTf)_3$ with the acyl pyrazole group occurs, activating the BCB **1b**. Subsequently, the nitrone **2a** nucleophilically attacks the activated **1b**, triggering the ring opening to furnish **Int2**. This key intermediate then undergoes intramolecular cyclization to form the target 2-oxa-3-azabicyclo[3.1.1]heptane **3b**.



Scheme 4. Density functional theory calculations and proposed mechanism.

In conclusion, we have demonstrated $Eu(OTf)_3$-catalyzed formal dipolar [4π + 2σ] cycloaddition of BCBs with nitrones, facilitating the efficient generation of a variety of polysubstituted 2-oxa-3-azabicyclo[3.1.1]heptanes. The resulting heteroatom-substituted 3D frameworks are brand-new and attractive, offering a distinctive platform for exploring new 3D drug candidates. Moreover, this straightforward approach proceeds under mild conditions and shows good functional group tolerance. DFT calculations support a stepwise pathway initiated by nucleophilic attack of the nitrones to BCBs and followed by ring-closing. Our results will not only broaden the challenging bicyclic frameworks greatly, but also enrich the cycloaddition chemistry of bicyclo[1.1.0]butanes. Further studies are ongoing to construct 3D hetero-cyclic scaffolds from BCBs in our lab.

Acknowledgements

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Keywords: Bicyclic Compounds • Bioisosteres • Dipolar Cycloaddition • Bicyclo[1.1.0]butanes • Strained Molecules

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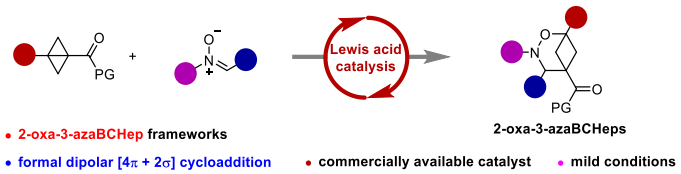

Rapid access of diverse polysubstituted 2-oxa-3-azabicyclo[3.1.1]heptanes, which were not readily accessible by known methods, has been realized through $Eu(OTf)_3$-catalyzed formal dipolar [4π + 2σ] cycloaddition of bicyclo[1.1.0]butanes with easily accessible nitrones.