Pyridine-Boryl Radical-Catalyzed [3π + 2σ] Cycloaddition for the Synthesis of Pyridine Bioisosteres

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The exploration of C(sp^3)-rich three-dimensional (3D) scaffolds as bioisosteres for planar aromatics has garnered increasing attention. While the bioisosterism of benzenes has been extensively studied, the bioisosterism of pyridines, the second most prevalent aromatic compounds in pharmaceuticals, faces additional challenges and has encountered surprisingly limited success. In this study, we propose unprecedented 2-azabicyclo[3.1.1]heptenes as effective bioisosteres of 1,3,5-trisubstituted pyridines in terms of not only 3D conformation but also basicity. We develop a pyridine-boryl radical-catalyzed [3π + 2σ] cycloaddition reaction of vinyl azides with bicyclo[1.1.0]butanes (BCBs) as an efficient synthetic approach. Synthetic manipulation of the products reveals valuable synthetic handles, allowing for the modular synthesis of various pyridine bioisosteres.

INTRODUCTION

In recent years, chemists have been captivated by the concept of "escaping from flatland"[1,2]. The utilization of C(sp^3)-rich three-dimensional (3D) scaffolds as bioisosteres for planar aromatic ring structures has provided practical solutions to various developability challenges encountered in drug discovery[3,4]. This bioisosteric substitution often leads to enhanced potency, solubility, and metabolic stability[5-8]. In this context, the invention and synthesis of benzene bioisosteres have been actively explored in organic synthesis[4,9], primarily due to the widespread use of benzene in a vast array of bioactive compounds (Fig. 1a)[10]. Through these efforts, a diverse range of bicyclic or polycyclic hydrocarbon scaffolds has been synthesized[5,7,11], enabling the precise mimic of ortho-[12-18], meta-[19-25], and para-disubstituted benzenes[26-32].

In sharp contrast, the bioisosteres of pyridine, the second most common aromatic ring appearing in drugs[10,33], have received less attention and surprisingly encountered trivial success. A notable example was recently disclosed by Mykhailiuk, wherein a novel type of 3-azabicyclo[3.1.1]heptanes was synthesized through the reduction of spirocyclic oxetanyl nitrile. The resulting fragment was proposed to mimic 3,5-disubstituted pyridines (Fig. 1a)[34].

As the most common six-membered aromatics, pyridine and benzene should, in principle, share a similar strategy for 3D bioisosterism. However, it is crucial to bear in mind that the basicity of the sp^2-N in pyridine plays a vital role in ligand-protein recognition[35]. The complete saturation of pyridine would alter the hybridization of the nitrogen atom

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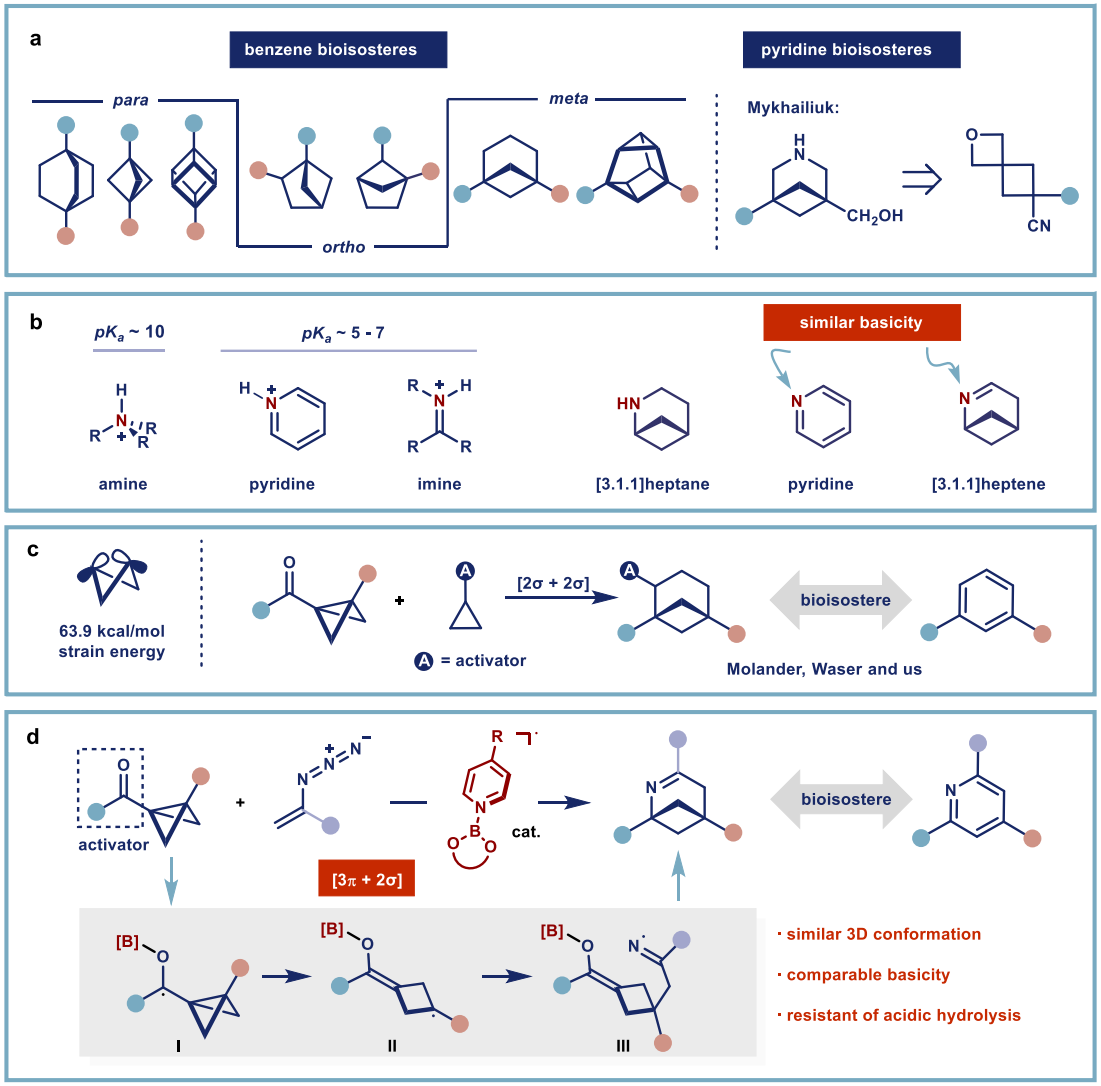


Fig 1. Pyridine-boryl radical-catalyzed [3π + 2σ] cycloaddition for the synthesis of pyridine bioisosteres. a, Selected benzene and pyridine bioisosteres. The development of pyridine bioisosteres has received less attention and surprisingly encountered trivial success compared to benzene bioisosteres. **b**, The difference in basicity among different N-centered bases emphasizes the importance of maintaining the sp2-hybridized N in the bioisosteres. **c**, strain-release induced intermolecular [2σ + 2σ] cycloaddition of BCBs with activated cyclopropane leads to the construction of fully-saturated bicyclo[3.1.1]heptanes (BCHeps), a valuable bioisostere of benzene. **d**, This work: intermolecular [3π + 2σ] cycloaddition of BCBs with vinyl azides. The coordination of boryl radical with the carbonyl group of BCB lead to the ring-opening to form a cyclobutyl radical. This species adds to vinyl azide to deliver an iminyl radical. Subsequent 6-exo-trig radical cyclization furnishes 2-azabicyclo[3.1.1]heptene bearing a flat-imine moiety. The synthesized skeletal structure resembles pyridine in terms of 3D conformation, basicity and stability upon acidic hydrolysis, rendering it an ideal bioisostere for pyridine.

($sp^2 \rightarrow sp^3$), resulting in a significant difference in basicity (Fig. 1b)[36]. Therefore, achieving a balance between the fraction of sp2 and sp3 is essential for the precise mimic of pyridines. We regard the nitrogen-embedded BCHeps as promising bioisosteres for

pyridines (Fig. 1b). To better mirror the basicity of pyridine, preserving a planar sp2-hybridized N was believed to be important, given the analogous basicity shared between pyridines and imines. This partial flatness confers an additional advantage by introducing a novel in-plane exit vector. To the best of our knowledge, however, methods for synthesis of azabicyclo[3.1.1]heptenes have not been reported before, largely due to the complexity.

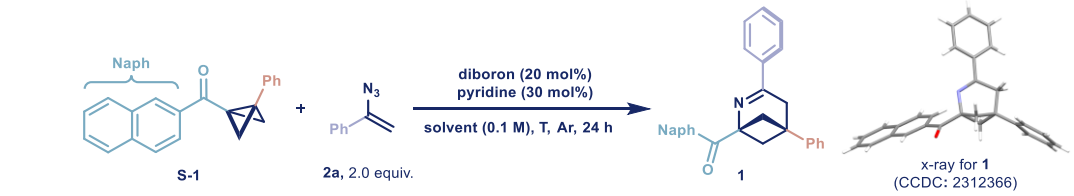
In recent years, bicyclo[1.1.0]-butanes (BCBs) have garnered attention as intriguing synthons capable of engaging in diverse ring-opening reactions, thanks to the significant strain present in BCBs (Fig. 1c)[6,37-47]. Of particular interest is their involvement in cycloaddition reactions, where the selective cleavage of the bridgehead C–C bond facilitates the assembly of ring-enlarged, yet conformationally restricted bridged bicycles. To achieve this, carbenes[28,32,48-50], and unsaturated bonds such as alkenes[14-18,51,52], alkynes[53], ketenes[54], carbonyls[55,56], imines[57], triazolinediones[58], and even aromatic rings[59-63] have been successfully employed as coupling partners, yielding diverse and valuable 3D scaffolds. Of note, by using BCBs as radical acceptors, Molander[21], Waser[19] and us[23] independently realized the [2σ + 2σ] cycloaddition of activated cyclopropanes with BCBs. The reactions led to the formation of substituted bicyclo[3.1.1]heptanes (BCHeps), which can precisely reproduce the geometrics of meta-substituted benzenes and have been a central focus of recent synthetic endeavors (Fig. 1c)[20,22,25].

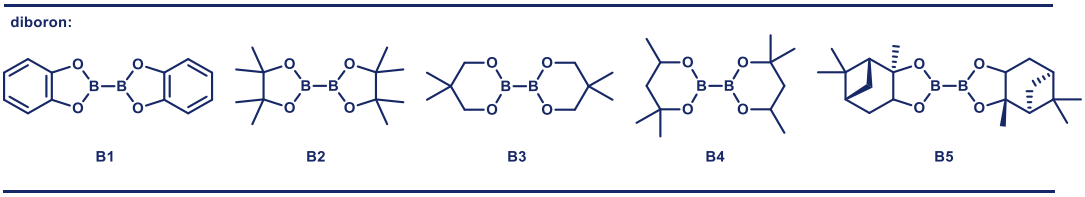
To develop an efficient method for azabicyclo[3.1.1]heptenes, we envisioned that vinyl azides could serve as intriguing 3π radical acceptors[64,65], engaging in a [3π + 2σ] cycloaddition with BCBs (Fig. 1d). Recently, we uncovered a pyridine-boryl-radical catalyzed [2π + 2σ] cycloaddition of BCBs with alkenes. Consequently, we reasoned that the addition of the cyclobutyl radical **II**, formed via a boryl-mediated ring-opening of BCB, to vinyl azide would lead to the formation of an iminyl radical **III**. Subsequent 6-*exo*-trig radical cyclization would then furnish a bicyclic system bearing a flat-imine moiety (Fig. 1d). Notably, although removal of a heteroatom to carbonyl groups is usually facile via radical processes, installation of a heteroatom to carbonyl groups has been rare. In this report, we present that in the presence of a pyridine-boryl radical catalyst, the reaction of BCBs with vinyl azides allows for the facial synthesis of 2-azabicyclo[3.1.1]heptene, a skeletal structure previously unknown. Conformation analysis demonstrates that this scaffold perfectly mimics 1,3,5-substituted pyridine, and the imine moiety exhibits similar basicity to pyridine rings. Furthermore, surprisingly, this skeleton remains stable upon acidic hydrolysis, rendering it an ideal bioisostere for pyridine.

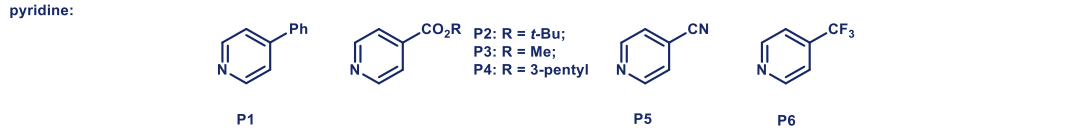
RESULTS AND DISCUSSION

Initially, BCB **S-1** and vinyl azide **2a** (2.0 equiv.) were chosen as model substrates for reaction optimization (Table 1). In the presence of 4-Ph-pyridine (30 mol%)/B2cat2 (20 mol%) in toluene at room temperature, a catalytic system previously employed in our cycloaddition reaction of BCBs with alkene[17], a [3π + 2σ] adduct 2-azabicyclo[3.1.1]heptene 1 was formed, showing an encouraging yield of 50% (entry 1). The structure of 1 was unambiguously confirmed by X-ray analysis. Further exploration involving different diborons (B1-B5) and substituted pyridines (P1-P6) revealed that

Table 1 Reaction optimization





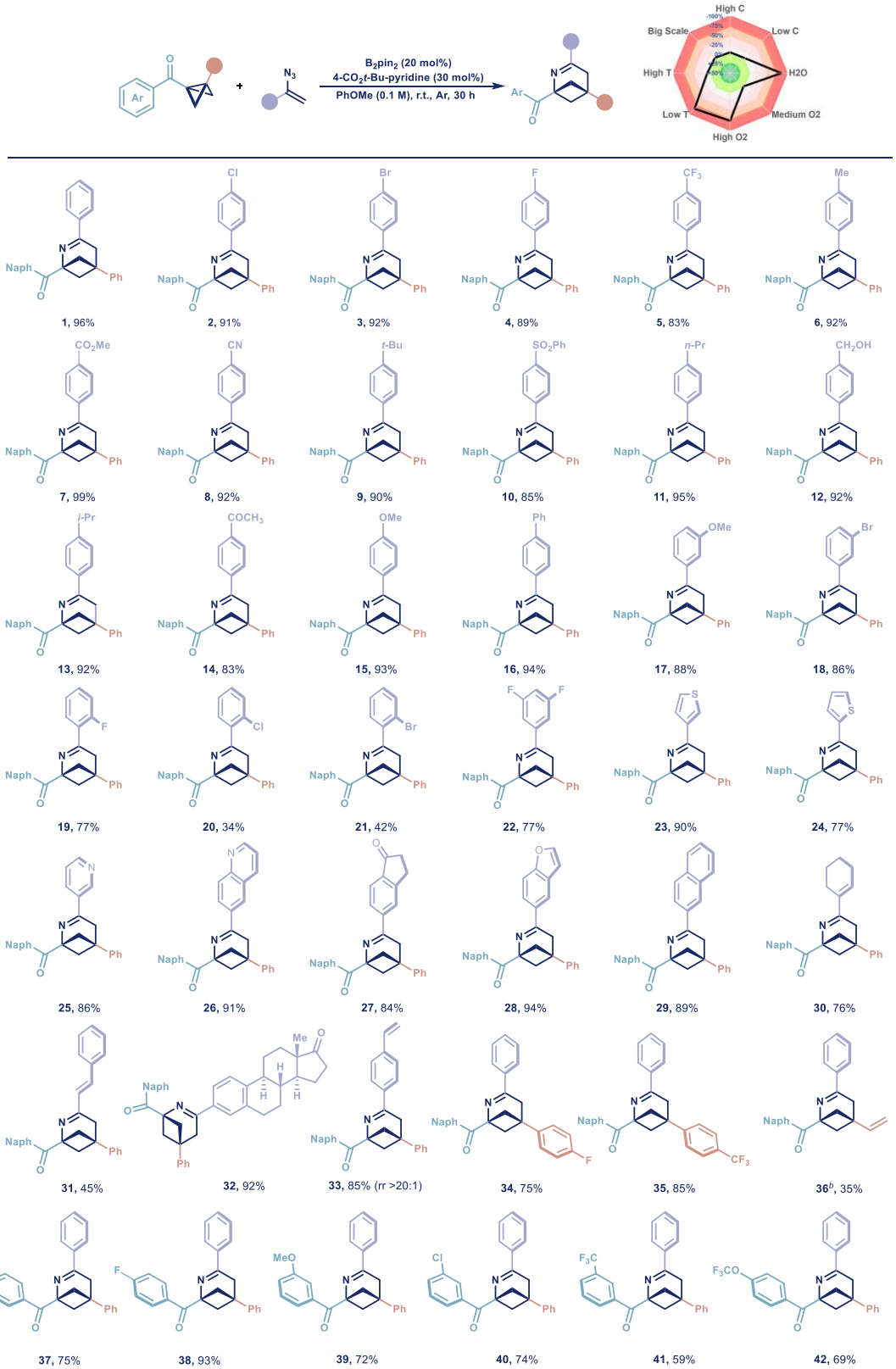


entry	solvent	boron	T (^{o}C)	pyridine	Yield
1	toluene	B1	25 ^{o}C	P1	50%
2	toluene	B1	25 ^{o}C	P2-P6	0
3	toluene	B3	25 ^{o}C	P1	70%
4	toluene	B4, B5	25 ^{o}C	P1	0
5	toluene	B2	25 ^{o}C	P4	75%
6	toluene	B2	25 ^{o}C	P2	83%
7	**anisole**	**B2**	**25 ^{o}C**	**P2**	**91%/96%^{b}**
8^{c}	anisole	B2	45 ^{o}C	P2	84%
9	anisole	-	25 ^{o}C	P2	0
10	anisole	B2	25 ^{o}C	-	0
11^{d}	anisole	B2	25 ^{o}C	P2	0

^{a}Reaction conditions: S-1 (0.1 mmol), 2a (0.2 mmol), B_2pin_2 (20 mol %), 4-CO_2tBu-pyridine (30 mol %), solvent (1.0 mL), Ar atmosphere, and 30 h. ^{b}Yield of isolated product. ^{c}B_2pin_2 (10 mol %), 4-CO_2tBu-pyridine (15 mol %) and 48 h. ^{d}Reaction as in entry 7 but in the presence of 3.0 equiv of TEMPO.

several catalyst combinations, such as B3/P1, B2/P4, and B2/P2, were also effective in this transformation, with B2/P2 providing the highest yield of 83% (entries 2-7). Substituting toluene with anisole, a solvent of choice in our recent [2σ + 2σ] cycloaddition reaction, resulted in an excellent isolated yield of 96% (entry 7)[23]. By slightly raising the reaction temperature and extending the reaction time, it was possible to reduce the amount of catalyst used with minimal loss in yield (entry 8). Control experiments demonstrated that neither B2 nor P2 alone could catalyze the reaction (entries 9, 10). Additionally, the use of the radical scavenger TEMPO in the reaction completely inhibited reactivity, suggesting a radical reaction pathway (entry 11). Intriguingly, a wide variety of catalytic systems employed in the cycloaddition reaction of BCBs were also attempted, but none proved effective in this specific reaction (see SI for details).

Table 2. Substrate scope.



[a]All values indicate the yield of the isolated product. Unless otherwise noted: BCB (0.1 mmol), B_2pin_2 (20 mol%), 4-CO_2t-Bu-pyridine (30 mol%), vinyl azides (2.0 equiv.), PhOMe (1.0 mL), 25 °C, Ar atmosphere, 30 h. [b]conditions: B_2pin_2 (30 mol%), 4-CO_2t-Bu-pyridine (40 mol%), vinyl azides (2.0 equiv.), PhOMe (1.0 mL), 40 °C, Ar atmosphere, 48 h.

With the optimized conditions in hand (entry 7, Table 1), we initially assessed the compatibility of various vinyl azides in this reaction (Table 2). For 1-aryl vinyl azides, it was observed that the reaction is not sensitive to the electronic properties of the phenyl ring. Numerous valuable functional groups, irrespective of whether they are electron-donating or electron-withdrawing, such as halogens (**2**-**4**), trifluoromethyl (**5**), ester (**7**), nitrile (**8**), sulfonyl (**10**), ketone (**14**), ether (**15**), and even unprotected hydroxyl (**12**) were all well tolerated. Vinyl azide derived from estrone, also proved to be a competent coupling partner (**32**). While styrenes are known to react with BCBs under boryl radical catalysis, we observed that the vinyl group remained intact after the reaction (**33**), indicating that the vinyl azide moiety is more reactive towards cyclization. Increasing steric hindrance at the ortho position had a negative impact on the yield (**19-21**). Importantly, besides phenyl rings, heteroaromatics such as thiophenes (**23, 24**), pyridine (**25**), quinoline (**26**), and benzofuran (**28**) were also compatible. Substituting aryl rings with a cyclohexenyl or styryl group also yielded successful results (**30, 31**), providing valuable handles for subsequent skeleton modifications. Exploring variations in the aryl group (**34, 35, 37-42**) and replacing the benzene ring with a vinyl group (**36**) on the BCBs proved to be fruitful as well.

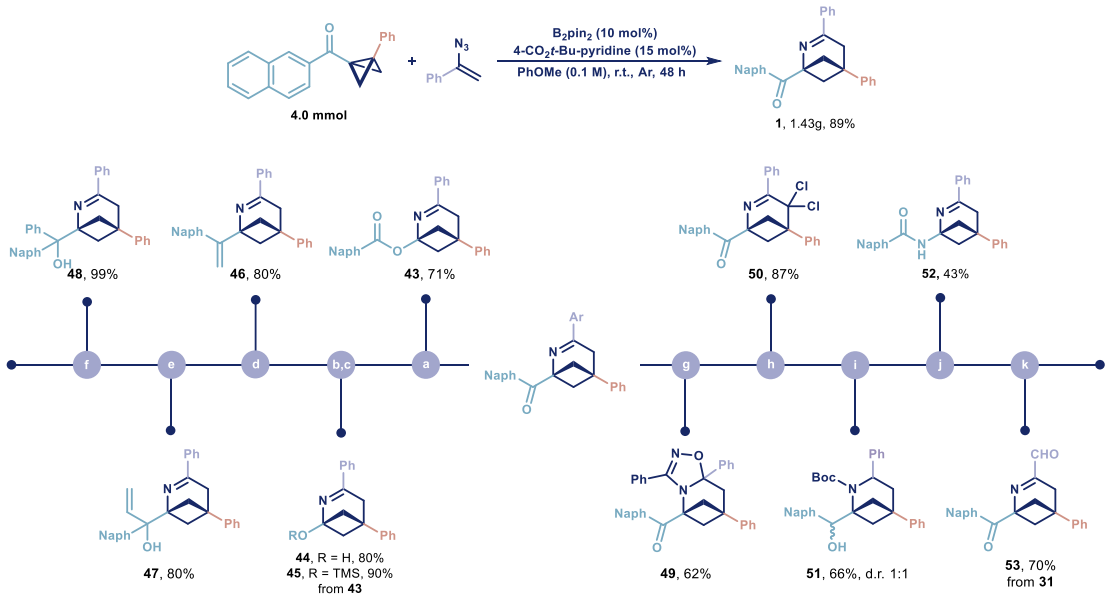


Fig. 2 Gram-scale synthesis and synthetic applications. Reaction conditions: [a] m-CPBA (2.0 equiv), DCM, 0 °C; [b] LiOH (10.0 equiv.), THF-MeOH-H_2O, rt; [c] TMSOTf (2.0 equiv.), Et_3N (4.0 equiv), DCM, 0°C to rt; [d] (i) *n*-BuLi (1.6 equiv), Methyltriphenylphosphonium bromide (1.6 equiv), THF, 0 °C to rt; [e] $CH_2CHMgBr$ (2.0 equiv) and THF, rt; [f] PhMgBr (2.0 equiv) and THF, rt; [g] N-hydroxybenzimidoyl chloride (2.2 equiv), Et_3N (2.5 equiv) and DCM, rt; [h] NCS (4.0 equiv) and CCl_4, 80°C; [i] (1) $NaBH_4$ (1.2 equiv) and THF, rt; (2) DIBAL-H (4.0 equiv) and THF, reflux; (3) Boc_2O (2.0 equiv), Et_3N (3.0 equiv) and THF, rt; [j] (1) NaOAc (4.0 equiv), $NH_2OH{\cdot}HCl$(2.0 equiv), and MeOH, 80°C; (2) DAST (1.5 equiv), THF, rt; [k] O_3, Me_2S, THF, -78 °C to rt, For more details, see the Supporting Information.

The protocol proved suitable for gram-scale synthesis. We observed that compound 1 could be obtained in a yield of 89% (1.43 g) with reduced catalyst loading (Fig. 2). To enhance the functional group diversity on the molecular framework, we carried out various derivatization experiments as illustrated in Scheme 3. The Baeyer–Villiger rearrangement of 1 with m-CPBA yielded carboxylate-substituted 2-azabicyclo[3.1.1]heptene **43** in a satisfactory yield. Hydrolysis of the newly formed ester group was achievable under both basic and acidic conditions. Surprisingly, the hydroxyl-decorated 2-azabicyclo[3.1.1]heptene **44** remained stable during silica gel chromatography, exhibiting no signs of ring-opening.

Similarly, the condensation of the carbonyl group with NH_2OH in heated MeOH followed by treatment of diethylaminosulfur trifluoride (DAST) led to the Beckmann rearrangement, yielding a product with an amide functionality (**52**). The Witting olefination reaction facilitated the synthesis of vinyl-substituted 2-azabicyclo[3.1.1]heptene **46**. Nucleophilic addition to the carbonyl group with Grignard reagents provided tertiary alcohols **47** and **48** in high yields without backbone deconstruction. The [3+2] cycloaddition reaction with N-hydroxybenzimidoyl chloride offered a convenient route to fused 1,2,4-oxadiazol **49**. Treating **1** with N-chlorosuccinimide (NCS) resulted in the formation of dichloro-substituted imine **50** in excellent yield. Subsequent reduction of the carbonyl and imine groups with $NaBH_4$ and DIBAL-H, respectively, afforded compound **51**. Finally, ozonolysis of **31** produced aldehyde **53**.

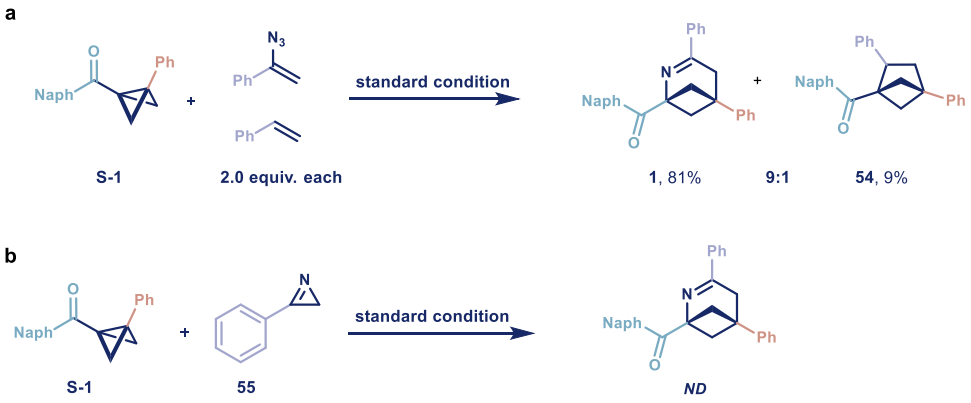


Fig. 3. Mechanistic studies. a, competition experiments show that vinyl azide is more reactive than styrene as coupling partner. **b**, 2H-azirine is not an intermediate in the reaction.

Competition experiments between vinyl azide and styrene revealed the preferential formation of 2-azabicyclo[3.1.1]heptene **1** (Fig. 3a). This observation suggests the activating role of N_3 on the double bond, aligning with the reaction outcome of product **33** as depicted in Table 2. Typically, vinyl azides undergo thermolysis or photolysis to generate 2H-azirines, which serve as intermediates in various transformations. However, in our specific case, 3-phenyl-2H-azirine **55**, synthesized following a literature procedure, exhibited no reactivity (Fig. 3b).

The geometric characteristics of the core structure in our synthesized 2-azabicyclo[3.1.1]heptene were meticulously compared with those of the 1,3,5-

trisubstituted pyridine drug, Zatolmilast. Our focus centered on evaluating the two-carbon distances, denoted as r and d, as well as the angles (ϕ) formed by the three exit vectors. These values were derived from X-ray data obtained for compounds 1 and Zatolmilast. Intriguingly, it was observed that both the r and d values on the bridgehead side of 1 were approximately 0.3 Å shorter than those in pyridine. Apart from this distinction, all other parameters exhibited a precise match with those found in pyridine. The visual representation of their superposition further underscores the accurate bioisosterism between pyridine and 2-azabicyclo[3.1.1]heptene.

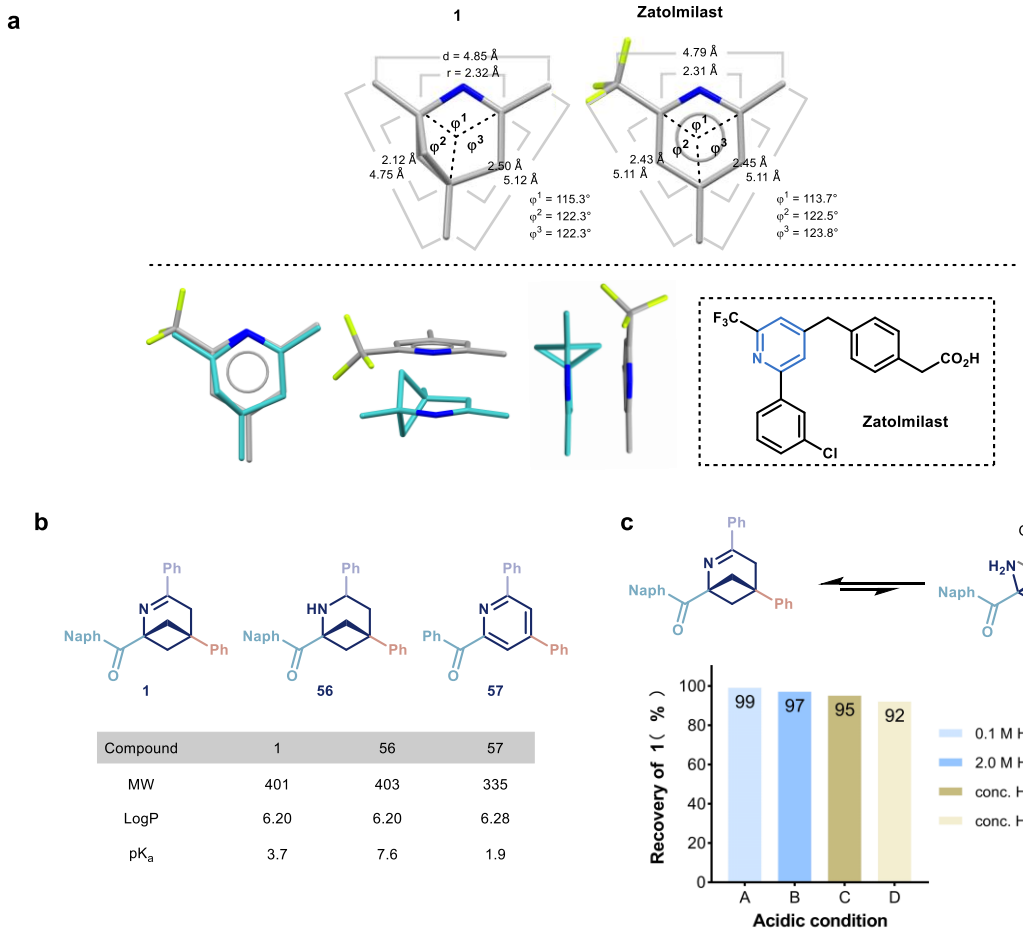


Fig. 4. Bioisostere analysis. a, Visualized comparison of **1** and Zatolmilast; **b**, predicted pK_a and LogP values. **c**, stability testing of **1,** A: 1 (0.1 mmol), 0.1M HCl (2.0 mL), THF (0.5 mL), r.t. 24h; B: 1 (0.1 mmol), 2.0M HCl (2.0 mL), THF (0.5 mL), r.t. 24h; C: 1 (0.1 mmol), conc. HCl (2.0 mL), THF (0.5 mL), r.t. 24h; D: 1 (0.1 mmol), conc. HCl (2.0 mL), THF (0.5 mL), 60 °C, 24h.

The perturbation of pKa and LogP can significantly influence the binding affinity, pharmacokinetic properties, and/or bioavailability of a pharmaceutical agent. Therefore, we calculated the basicity of the nitrogen atom in 2-azabicyclo[3.1.1]heptene, its hydrogenated form piperidine **56**, and pyridine. As depicted in Fig. 4b, piperidine **56** exhibits a notable difference in basicity compared to pyridine **57**, while 2-azabicyclo[3.1.1]heptene **1** demonstrates a much closer resemblance. Additionally, acidic stability is a crucial parameter in the development of orally administered drugs. The imine moiety is typically susceptible to hydrolysis under aqueous acidic conditions. Remarkably,

we observed exceptional stability in 2-azabicyclo[3.1.1]heptene, even under concentrated HCl at 60 °C for 24 hours (Fig. 4c). One possible explanation for this stability is that, upon hydrolysis, the amino and carbonyl groups, located on the same side of the cyclobutane ring, are in close proximity, thereby facilitating rapid intramolecular cyclization to reform 2-azabicyclo[3.1.1]heptene.

In summary, taking advantage of the great stain of BCBs, we report herein a stain-release [3π + 2σ] cycloaddition of BCBs with vinyl azides as catalyzed by a pyridine-boryl radical. The reaction lead to the synthesis of 2-azabicyclo[3.1.1]heptenes in high efficiency in an atom-economic manner. The mildness of this protocol also ensures excellent functional group tolerance and the reaction can be performed on a preparative scale. The partial flatness of the 2-azabicyclo[3.1.1]heptane core render it a perfect pyridine bioisostere in terms of 3D conformation and basicity. Considering the popularity of pyridine rings in bioactive compounds, we anticipate our protocol will find application in drug development.

Data availability Materials and methods, experimental procedures, mechanistic studies, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Crystallographic data for compound **1** have been deposited with the Cambridge Crystallographic Data Centre under accession code CCDC 2312366.

Supplementary Information is linked to the online version of the paper at www.nature.com/nchem.

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Author contributions Z.D., P.L. and H.W. conceived the project. Y.L., S.L., Y.L. and Y.-J.T. designed and performed the experimental work. Y.L. and J.-H.X. contributed to the analysis and interpretation of data. P.L. and H.W. wrote the manuscript. All authors contributed to or approved the final version of the paper.

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