Chemical Science

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Cite this: *Chem. Sci.*, 2025, **16**, 18255

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 22nd July 2025
Accepted 26th August 2025

DOI: 10.1039/d5sc05468k

rsc.li/chemical-science

Regiodivergent Lewis acid catalysis of bicyclo[1.1.0]butanes with 2-naphthols

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Enhancing drug efficacy often involves increasing the proportion of sp^3-hybridized carbons. Three-dimensional polycyclic frameworks, such as bicyclo[1.1.1]pentanes (BCPs) and bicyclo[2.1.1]hexanes (BCHs), serve as excellent benzene bioisosteres, improving bioavailability and reducing toxicity while retaining biological activity. However, synthetic routes to 2D/3D-ring-fused BCHs *via* dearomatization are scarce, previously limited to cycloadditions of bicyclobutanes (BCBs) with indoles, bicyclic aza-arenes, or naphthalenes. Herein, we achieve Lewis acid-catalyzed dearomatization of BCBs with 2-naphthol. $Eu(OTf)_3$ catalysis provides dearomatized tertiary alcohols, while $AgBF_4$ promotes dearomatization/aromatization to directly access naphthalene-fused BCHs, showcasing remarkable reaction selectivity. Mechanistic studies definitively identify cyclobutyl carbocations as key intermediates. This strategy is anticipated to accelerate the exploration of fused BCH scaffolds in medicinal and synthetic chemistry.

Introduction

The benzene ring is a highly significant structural motif in drug molecules, present in approximately 45% of marketed small-molecule drugs, and can be readily transformed into a variety of functionalized two-dimensional (2D) scaffolds.[1–3] However, it has been found that the benzene ring is still associated with limitations in terms of solubility, metabolic liabilities, and stability.[4] The augmentation of sp^3-carbon atoms within the molecular structure of compounds has been demonstrated to be an effective method of enhancing the clinical efficacy.[5] Three-dimensional polycyclic (3D) frameworks are emerging as attractive non-planar bioisosteric replacements for the benzene ring in medicinal chemistry. Replacement of the benzene ring with its bioisosteres often enables drug molecules to retain their biological activity, while also enhancing bioavailability and reducing inherent toxicity.[6–8] Based on these advantages, it has garnered significant attention from the chemistry community in recent years.

Inspired by the "escape from flatland" concept proposed by Lovering and colleagues,[9–11] three-dimensional (3D) saturated bicyclic scaffolds, such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs) and bicyclo[3.1.1]heptanes (BCHeps), have been developed as novel replacements for arenes (Scheme 1a).[12] Bicyclo[2.1.1]hexanes (BCHs) are a class of highly strained cyclic compounds, which have been extensively studied due to their unique three-dimensional structure and could be used as mimics of *meta*- or *ortho*-substituted arenes (Scheme 1b).[13] Furthermore, fused rings incorporating both 2D and 3D fragments have attracted attention from scientists. Such molecules can enhance biological topological diversity and allow conformational adjustment for improved receptor/ligand complementarity. Consequently, fused rings containing 2D and 3D motifs have become important skeletons in medicinal chemistry (Scheme 1c).[14] Several synthetic methods for constructing BCHs have been developed. However, dearomative cycloaddition reactions involving bicyclo[1.1.0]butanes (BCBs) typically require high activation energy, and consequently, only limited examples have been reported (Scheme 1d). Furthermore, developing dearomative cycloaddition reactions of BCBs to synthesize complex fused rings incorporating both 2D and 3D fragments remains challenging. In 2022, Glorius reported an intermolecular $[2\pi + 2\sigma]$-photocycloaddition that used bicyclo[1.1.0]butanes as 2σ-electron reactants.[15] In 2023, Deng and Feng independently reported Lewis acid-catalyzed $[2\pi + 2\sigma]$ cycloadditions of available indoles with BCBs, affording indoline-fused BCHs.[16,17] In the same year, Glorius and Houk reported an ortho-selective intermolecular photocycloaddition of bicyclic aza-arenes including (iso)quinolines, quinazolines, and quinoxalines by utilizing a strain-release approach, enabling the direct assembly of $C(sp^3)$-rich BCHs.[18] In 2025, the You group reported a Gd(III)-catalyzed dearomative $[2\pi + 2\sigma]$ photocycloaddition reaction between naphthalene derivatives and BCBs.[19] These reports facilitated the synthesis of fused rings containing 2D/3D motifs. Notably, there was only one example of constructing BCHs from phenol through dearomative cyclization. In 2024, the Glorius group developed

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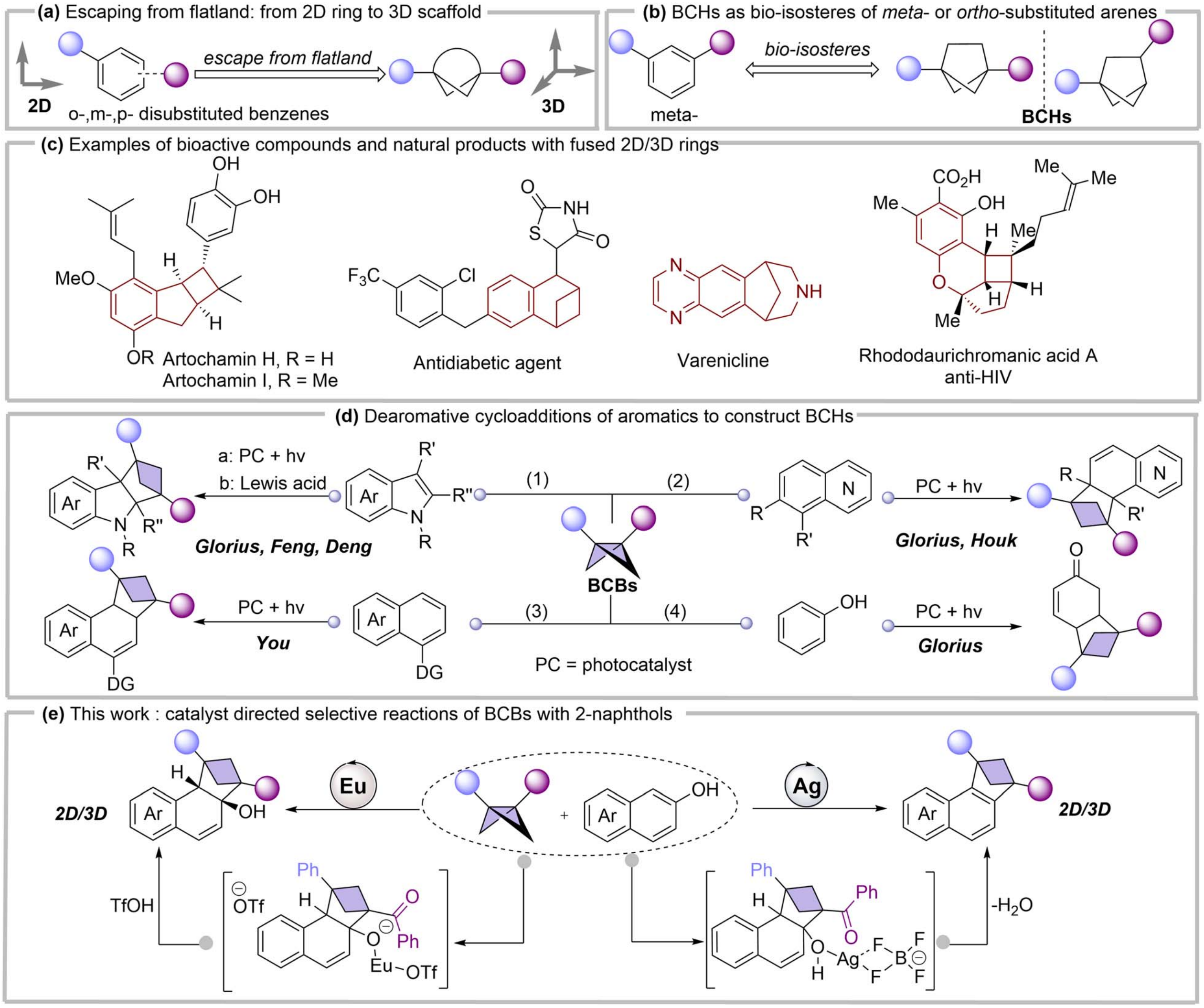
photoredox-promoted dearomative [$2\pi + 2\sigma$] cycloaddition of phenolic compounds with BCBs, enabling the synthesis of BCHs fused with cycloalkenones.[20] In 2025, Feng and Wang reported a silver-catalyzed cycloaddition reaction of BCBs and naphthol.[21] Naphthols have been attractive substrates for the syntheses of functionalized benzenes or naphthalene derivatives, demonstrating significant value in the pharmaceutical and agrochemical industries.[22] The transformation of planar naphthols into complex polycyclic compounds comprising 2D and 3D fragments is both significant and challenging.

In this work, we outline the Lewis acid-catalyzed [$2\pi + 2\sigma$] cycloaddition reaction of BCBs with 2-naphthols (Scheme 1e). This transformation exhibits high tunability, yielding distinct fused rings incorporating 2D/3D motifs, which are selectively synthesized dictated by Lewis acid catalysts. When Eu(OTf)$_3$ is used as the catalyst, dearomatized products can be obtained. The reaction follows a dearomatization/aromatization strategy catalyzed by AgBF$_4$, yielding alternative naphthalene-fused bicyclic[2.1.1]hexanes (BCHs).

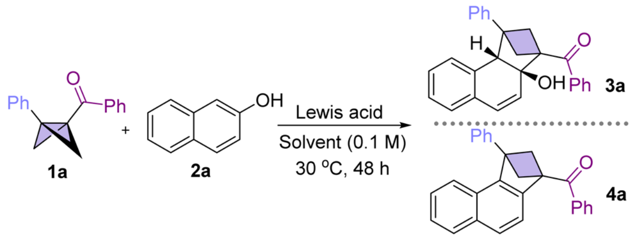
Results and discussion

To explore the feasibility of the dearomative [$2\pi + 2\sigma$] cycloaddition reaction, we preliminarily selected keto-substituted BCBs (**1a**; Table 1; see the SI for details) and 2-naphthol (**2a**) as standard substrates. We initially investigated the effect of Lewis acids on the [$2\pi + 2\sigma$] cycloaddition reaction of BCBs with 2-naphthol. Pleasingly, the desired BCH containing tertiary alcohol (**3a**) was obtained with Sc(OTf)$_3$ as the catalyst, exhibiting excellent regioselectivity, despite the moderate yield (46%, entry 1). At the same time, another product bearing the naphthalene-fused BCH (**4a**) could be obtained from the reaction with low yield (19%, entry 1). Encouraged by this result, we further screened other Lewis acid catalysts and observed that Yb(OTf)$_3$ and Bi(OTf)$_3$ could also afford compounds **3a** and **4a** (entries 2–3). More remarkably, In(OTf)$_3$ failed to produce **3a**, whereas Tm(OTf)$_3$ was able to catalyze the reaction more effectively and synthesize **3a** in 26% yield with high



Scheme 1 (a) Escaping from flatland: from 2D rings to 3D scaffolds; (b) BCHs as bio-isosteres of *meta*- or *ortho*-substituted arenes; (c) examples of bioactive compounds and natural products with fused 2D/3D rings; (d) dearomative cycloadditions of aromatics to construct BCHs; (e) this work: catalyst directed selective reactions of BCBs with 2-naphthols.

Table 1 Optimization of the reaction conditions[a]



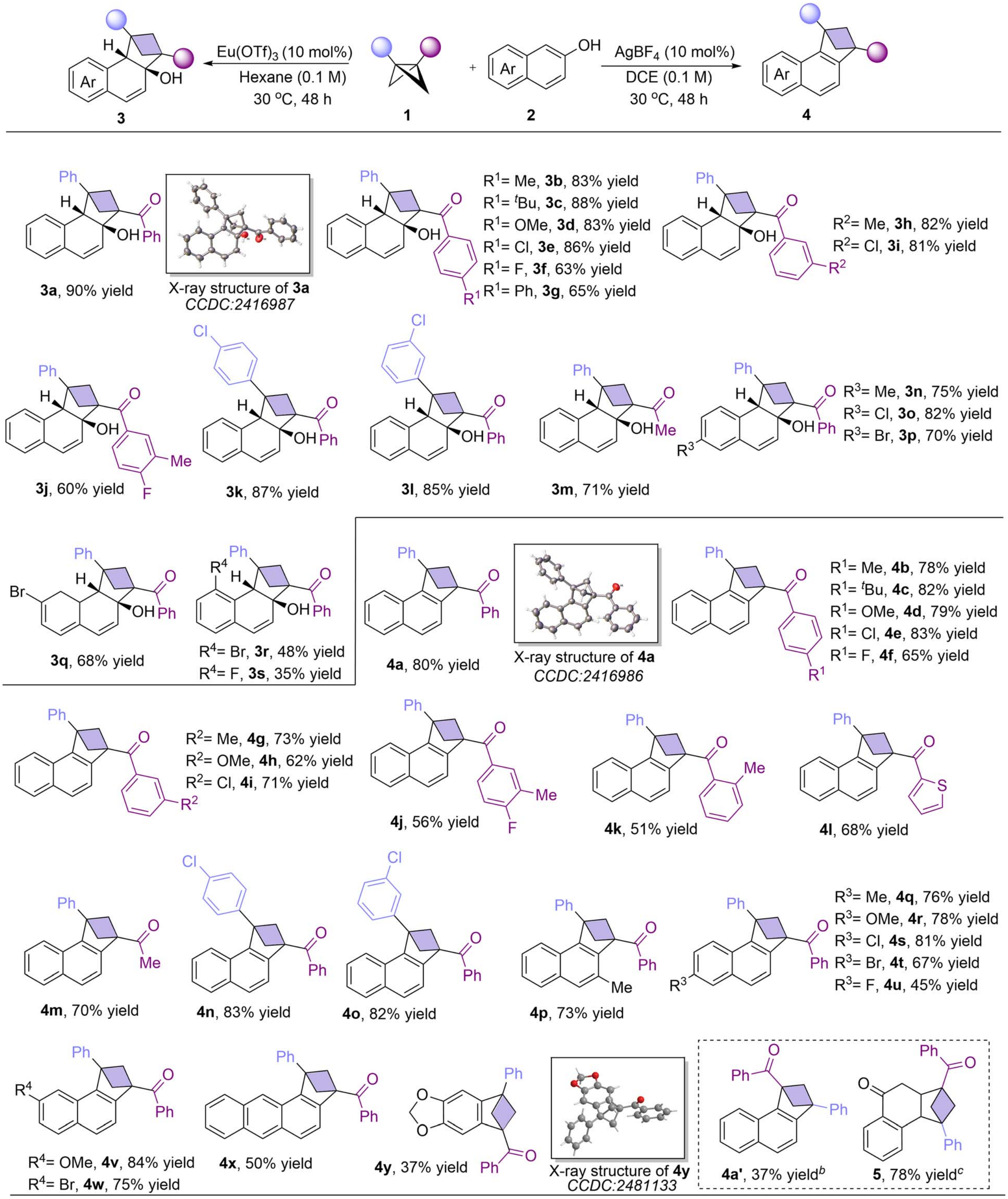
Entry	LA	Solvent	Yield of[b] 3a	Yield of[b] 4a
1	$Sc(OTf)_3$	DCE	46%	19%
2	$Yb(OTf)_3$	DCE	47%	20%
3	$Bi(OTf)_3$	DCE	28%	52%
4	$In(OTf)_3$	DCE	nd	57%
5	$Tm(OTf)_3$	DCE	26%	nd
6	$Eu(OTf)_3$	DCE	53%	nd
7	$AgPF_6$	DCE	nd	57%
8	$AgBF_4$	DCE	nd	78%
9	$Eu(OTf)_3$	DCM	43%	nd
10	$Eu(OTf)_3$	CCl_4	45%	nd
11	$Eu(OTf)_3$	CyH	67%	nd
12	$Eu(OTf)_3$	Hexane	88%	nd
13	$AgBF_4$	DCM	nd	76%
14	$AgBF_4$	Toluene	nd	44%
15	$AgBF_4$	DMF	nd	17%
16[c]	$Eu(OTf)_3$	Hexane	90%	nd
17[c]	$AgBF_4$	DCE	nd	80%

[a] **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), Lewis Acid (10 mol%), solvent (0.1 M), 30 °C, 48 h. [b] NMR yield with CH_2Br_2 as an internal standard. [c] reaction was carried out using a 1.5 : 1 ratio of **1a** and **2a**. LA = Lewis acid, DCE = dichloroethane, DCM = dichloromethane, DMF = *N*,*N*-dimethylformamide, CyH = cyclohexane.

chemoselectivity (entries 4–5). Following further screening, we were pleased to observe that $Eu(OTf)_3$ emerged as optimal, affording **3a** in moderate yield (53%) with high selectivity (entry 6). In addition, $AgBF_4$ proved highly effective for synthesizing **4a** in 78% yield with excellent chemoselectivity (entry 8). These results demonstrated that Lewis acid played a critical role in governing the chemoinductive effect of the reaction (entries 1–8). Next, the effect of solvents on the reaction was investigated (entries 9–12). When $Eu(OTf)_3$ was used as a catalyst in this reaction, the polarity of the solvent had a significant effect on this reaction. As solvent polarity decreased, the yield of **3a** progressively increased, with hexane identified as the optimal solvent that significantly elevated the yield to 88%. When $AgBF_4$ was employed as the catalyst, attempts to promote the cyclization of keto-substituted BCB **1a** using various solvents (DCM, toluene and DMF) proved futile (entries 13–15). Furthermore, adjusting the ratio of **1a** to **2a** to 1.5 : 1 further enhanced the reaction efficiency, affording **3a** in 90% yield and **4a** in 80% yield (entries 16–17). The optimized conditions for synthesizing **3a** were established as: **1a** (1.5 equiv.), **2a** (1.0 equiv.), $Eu(OTf)_3$ (10 mol%), hexane (0.1 M), 25 °C. Conversely, the optimal conditions for **4a** were determined to be **1a** (1.5 equiv.), **2a** (1.0 equiv.), $AgBF_4$ (10 mol%), DCE (0.1 M), 25 °C.

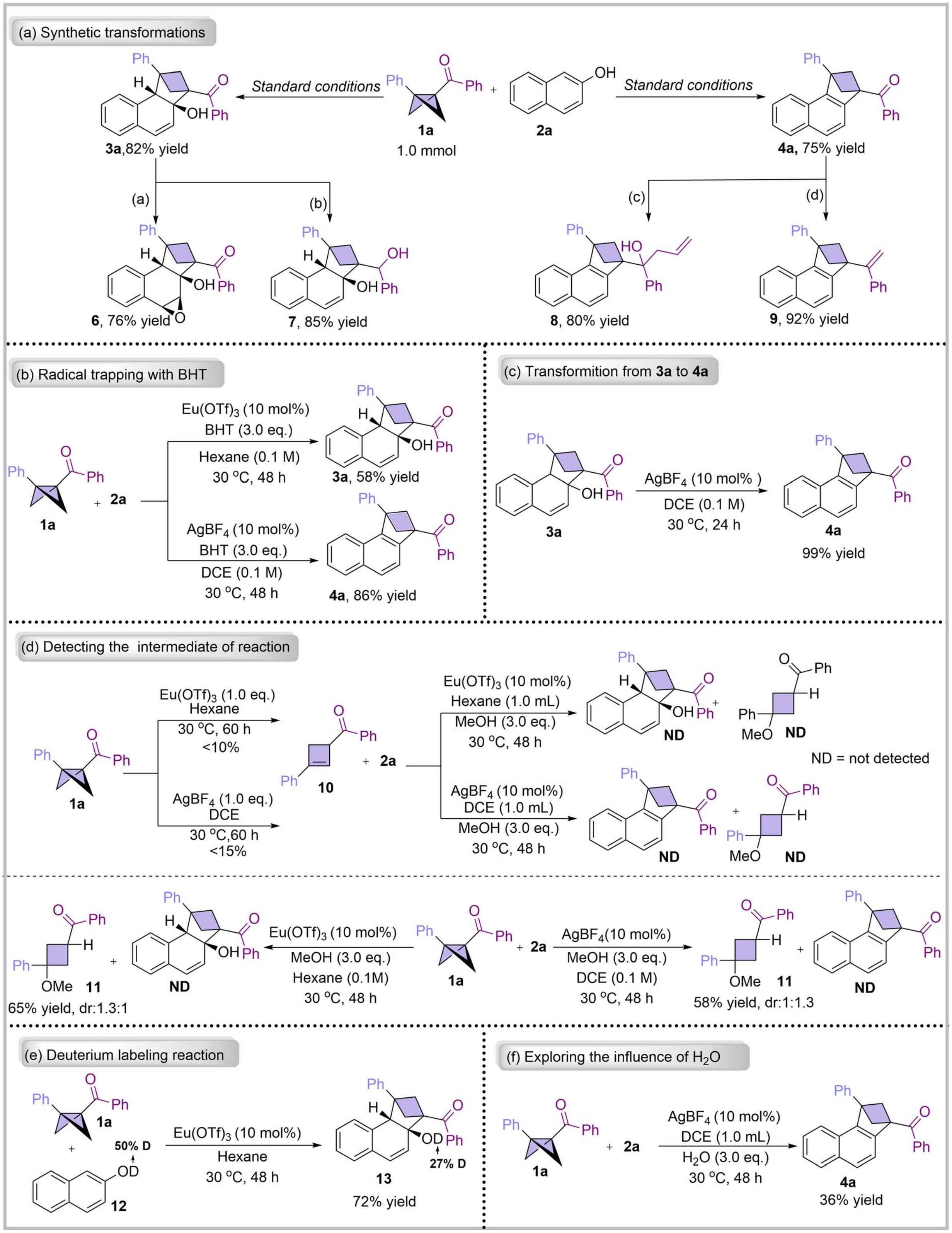
After establishing the optimal reaction conditions, we next investigated the substrate scope of the Lewis acid-catalyzed [2π + 2σ] cycloaddition reaction of BCBs with 2-naphthols (Table 2). First, we investigated substrate suitability for the dearomatization reaction catalyzed by $Eu(OTf)_3$. Initially, a series of BCBs featuring aryl ketone substituents with various groups on the benzene ring were investigated. Electron-donating groups (Ar′ = 4-Me-phenyl, 4-^{t}Bu-phenyl, 4-OMe-phenyl) and electron-withdrawing groups (Ar′ = 4-Cl-phenyl, 4-F-phenyl) afforded dearomatized BCHs containing tertiary alcohols (**3b–3f**) in good to excellent yields. The biphenyl BCB (Ar′ = 4-Ph-phenyl), which had a larger conjugated and more delocalized system, also afforded compound **3g** in 65% yield. Furthermore, meta-substituents on the benzene ring of the aryl ketone substituent, such as Me and Cl, also demonstrated good compatibility (**3h–3i**). When two substituents were present on the benzene ring of the aryl ketone substituent, a satisfactory result was obtained (**3j**). However, the BCB with *ortho*-tolyl ketone substitution failed to afford the dearomatized product, probably due to the influence of the steric effect and Lewis acid. BCBs substituted with Cl at the *para*- or *meta*-position proved to be suitable substrates, affording the desired BCHs **3k–3l** in 87% and 85% yields, respectively. Notably, the alkyl ketone-substituted BCB could also react with 2-naphthol under standard conditions to form **3m** with good yield (71%). Subsequently, we turned our attention to examining the compatibility of 2-naphthol. Various substituents at position 6 of 2-naphthol were well tolerated in the reaction, affording the desired products (**3n–3p**) in 70–82% yields, regardless of whether they were electron-donating or electron-withdrawing groups. Halogen-substituted substrates at positions 7 and 8 were compatible with the reaction, generating the corresponding cyclization products (**3q–3s**), despite the reaction yields being low, presumably due to steric hindrance. Next, we explored the substrate tolerance of the $AgBF_4$-catalyzed dearomatization-aromatization reaction. A series of structurally and electronically diverse BCBs participated in the cycloaddition reaction, thus affording naphthalene-fused BCHs in good yields. For instance, BCBs featuring aryl ketone substituents exhibited good tolerance toward both electron-donating and electron-withdrawing groups on the aromatic ring (**4b–4i**), although the yields of *meta*-substituted substrates were slightly lower than those of *para*-substituted substrates. BCBs bearing two substituents on the benzene ring of the aryl ketone group afforded the target compound **4j**. Notably, even an *ortho*-methyl substituent on the aryl ketone's benzene ring did not significantly interfere with the reaction, delivering **4k** in 51% yield. When the groups on the benzene ring of the aryl ketone substituent were replaced with thiophene or methyl, the target products **4l** and **4m** were obtained in good yields. Encouraged by these results, we further evaluated the electronic and steric influences produced by substituents on the aromatic ring of 2-naphthol associated with this transformation. BCBs equipped with 4-Cl and 3-Cl phenyl groups also reacted with 2-naphthol, affording satisfactory results (**4n–4o**). When methyl was introduced at the C3 position of 2-naphthol, the dearomatization-aromatization product was obtained in 73% yield (**4p**). The

Table 2 Substrate scope investigation[a]



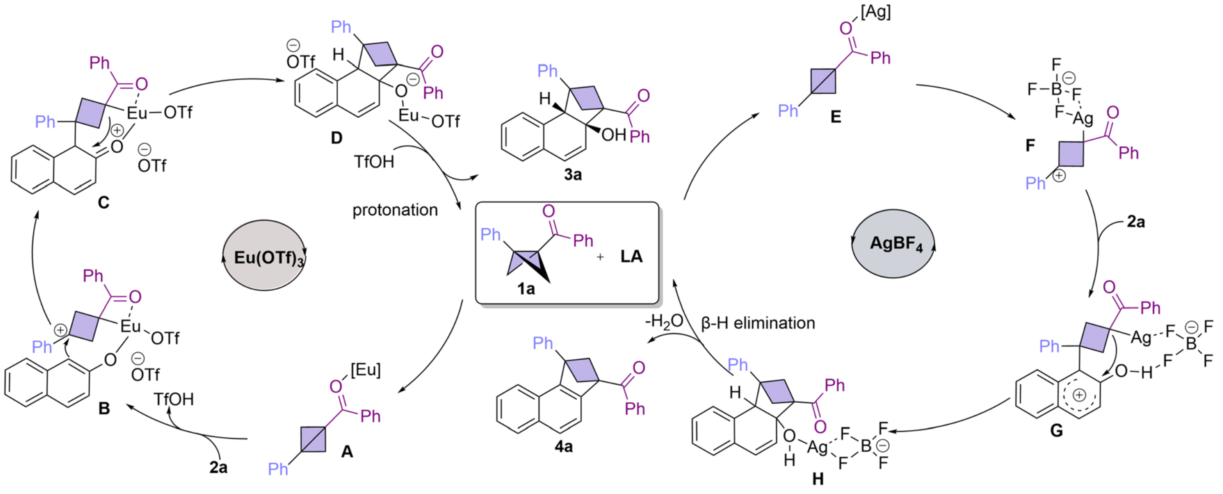
[a] Reaction conditions for synthesis of **3**: **1** (0.15 mmol, 1.5 equiv.), **2** (0.1 mmol, 1.0 equiv.), Eu(OTf)$_3$ (10 mol%), hexane (0.1 M), 30 °C, 48 h. Reaction conditions for synthesis of **4**: **1** (0.15 mmol, 1.5 equiv.), **2** (0.1 mmol, 1.0 equiv.), AgBF$_4$ (10 mol%), DCE (0.1 M), 30 °C, 48 h. [b] 1-Naphthol instead of 2-naphthol. The reaction procedure was based on the synthesis of **4**. [c] 1-Naphthol instead of 2-naphthol. The reaction procedure was based on the synthesis of **3**.

introduction of electron-donating or electron-withdrawing substituents at the C6 or C7 position of 2-naphthol had little impact on the reaction, delivering products in moderate to good yields (45–84%, **4q–4w**). However, no reaction occurred when 1-methyl-2-naphthol was employed. Both anthracenol and sesamol also participated in the reaction, albeit with lower yields



Scheme 2 Synthetic derivatizations and mechanistic studies.

(**4x–4y**). Additionally, the structures of compounds **3a**, **4a** and **4y** were confirmed by X-ray diffraction (see the SI for details). BCBs featuring pyrazole amide, an ester group and a sulfonyl group, unsubstituted BCB ketones and BCB with a methyl substituent were investigated, none of which afforded the corresponding target BCHs (see the SI for details). The reactivity of 1-naphthol



Scheme 3 Proposed mechanism.

has been investigated. When $AgBF_4$ was used as the catalyst, **4a′** could be obtained in 37% yield, which was lower than that of 2-naphthol. Dearomative (3 + 2) cycloaddition product **5** could be afforded in 78% yield catalyzed by $Eu(OTf)_3$.

To demonstrate the practicality of the reaction, we performed a mmol-scale [2π + 2σ] cycloaddition experiment under standard reaction conditions using **1a** and **2a**, yielding **3a** and **4a** in 82% yield and 75% yield, respectively. Subsequently, several transformations were performed on compounds **3a** and **4a** to highlight the application potential of 2D/3D ring fused BCHs (Scheme 2a). The epoxidation of **3a** was achieved using *meta*-chloroperoxybenzoic acid (*m*-CPBA), affording epoxidized BCH **6** in 76% yield. The carbonyl group of **3a** was efficiently reduced to secondary alcohol **7** using $NaBH_4$ (85% yield). Nucleophilic addition of **4a** with the allyl Grignard reagent afforded tertiary alcohol **8. 4a** underwent nucleophilic addition with phosphorus ylide (Wittig reaction) to afford alkene product **9.** In order to gain deeper insights into the reaction mechanism, a series of mechanistic investigations were conducted. Initially, when the radical scavenger BHT was introduced to the standard reaction system, product formation was not completely suppressed, indicating that the reaction does not proceed *via* a radical pathway (Scheme 2b). We attempted to use **3a** as a substrate in the $AgBF_4$-catalyzed reaction and found that it was almost completely converted to **4a,** indicating that **3a** serves as an intermediate in the formation of **4a** (Scheme 2c). The reaction of **1a** with $AgBF_4$ or $Eu(OTf)_3$ at 30 °C led to the formation of cyclobutene product **10,** indicating the generation of a cyclobutyl carbocation intermediate along the reaction pathway. When methanol was employed as an external nucleophile in the reaction between BCB **1a** and 2-naphthol **2a,** nucleophilic addition product **11** was obtained. In contrast, cyclobutene product **10** with methanol did not afford nucleophilic addition product **11.** These observations strongly supported the carbocation mechanism and excluded the possibility of cyclobutene serving as an intermediate (Scheme 2d). Additionally, deuterium labeling experiments were conducted to deepen the understanding of the reaction mechanism. Subjecting naphthol **12** with 50% deuterium incorporation to the $Eu(OTf)_3$-catalyzed dearomative [2π+2σ] reaction afforded deuterated product **13** with 27% deuterium retention (Scheme 2e). This deuterium labeling study confirmed the critical role of the naphthol hydroxyl group in the dearomative cycloaddition. Finally, 3.0 equiv. of water was added to the reaction and significant inhibition of the reaction was observed (Scheme 2f).

Based on mechanistic studies and previous literature reports,[21,23] a feasible mechanism is proposed (Scheme 3). In the initial stage, the coordination between $Eu(OTf)_3$ and **1a** forms the intermediate **A.** 2-Naphthol **2a** then coordinates with intermediate **A** to generate the cationic intermediate **B.** The carbocation moiety in **B** is attacked by the C1 position of naphthol, yielding intermediate **C.** Subsequent intramolecular electrophilic addition and cyclization of **C** affords intermediate **D,** which is then protonated to deliver the dearomatized tertiary alcohol product **3a,** completing one catalytic cycle. In addition, $AgBF_4$ coordinates with bicyclobutane **1a** to form intermediate **E. E** undergoes 1,3-silver migration to generate the zwitterionic intermediate **F.** Intramolecular nucleophilic attack of **F** then forms intermediate **G.** Cyclization of **G** yields intermediate **H,** which undergoes dehydration *via* β-hydride elimination to afford the dearomatized/aromatized product **4a.**

Conclusions

In summary, we have integrated two types of Lewis acid to catalyze the [2π + 2σ] cycloaddition reactions between BCBs and 2-naphthol ingeniously, yielding dearomatized tertiary alcohols and dearomatized/aromatized naphthalene-fused BCHs, respectively. These products enrich fused rings containing both 2D and 3D structural fragments. Serving as potential bioisosteres of meta-substituted arenes, these frameworks exhibit broad substrate scope and excellent functional group tolerance. We foresee that these mild and highly efficient catalytic methods will open new avenues for developing dearomatization of phenolic compounds while enabling access to sp^3-rich architectures, showing promising applications in drug discovery.

Author contributions

L. Fan carried out most of the experiments and wrote the initial manuscript draft. G.-F. Zhong directed the project and finalized the manuscript. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Crystallographic information files (CIF) have been deposited with the Cambridge Crystallographic Data Centre.

CCDC 2416986 2416987 and 2481133 contain the supplementary crystallographic data for this paper.[24]

General information, detailed experimental procedures, characterization data for compounds and NMR spectra are available in the SI.

Supplementary information: supplementary methods, tables, experimental procedures, NMR figures and X-ray structure. See DOI: **https://doi.org/10.1039/d5sc05468k**.

Acknowledgements

Financial support was provided by the Start-Up Funding for scientific research of EIT and the 2024 Ningbo Yongjiang Talent Program.

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