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Review

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Synthetic developments and functionalization approaches for bicyclo[1.1.1]pentanes via [1.1.1]propellane

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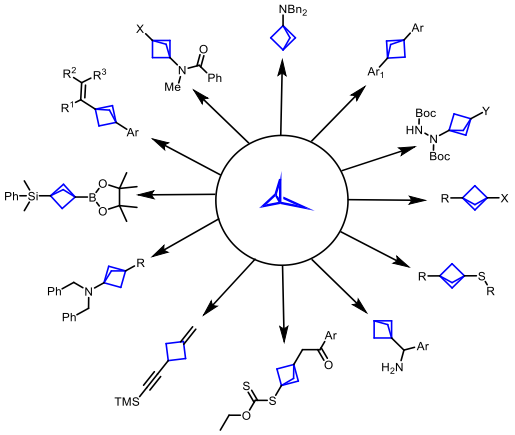
The manuscript is dedicated to the 71th birth anniversary of Prof. Satyaban Jena

Received 08-17-2025 **Accepted** 10-06-2025 **Published on line** 11-04-2025

Abstract

The bicyclo[1.1.1]pentane (BCP) scaffold has emerged as a versatile and increasingly valuable bioisostere in medicinal chemistry, offering a rigid, three-dimensional framework that enhances metabolic stability, membrane permeability, and aqueous solubility in drug candidates. Central to the synthetic accessibility of BCP derivatives is [1.1.1]propellane, a highly strained small ring system that serves as a pivotal precursor for diverse functionalization strategies. This review provides an in-depth look at recent advancements in the synthesis and functionalization of BCP motifs via [1.1.1]propellane, with a particular focus on nucleophilic, anionic, and radical-based transformations. Key methodological innovations, mechanistic insights, and scope of reactivity are discussed, highlighting how these developments have enabled the rapid and modular assembly of structurally complex and pharmaceutically relevant BCP-containing molecules.



Keywords: [1.1.1] Propellane; strain ring; bicyclo[1.1.1]pentane; radical reaction; BCP Grignard reagent

Cite as *Arkivoc* **2025** (1) 202512457

DOI: https://doi.org/10.24820/ark.5550190.p012.457

Table of Contents

1. Introduction

Three-dimensional cyclic scaffolds have gained considerable attention in modern pharmaceutical chemistry for their ability to improve the physicochemical and pharmacokinetic properties of therapeutic agents [1-7]. Among these, the bicyclo[1.1.1]pentane (BCP) motif has emerged as a compelling isosteric replacement for 1,4-disubstituted phenyl rings in various biologically active compounds (Figure 1).[8] Notable applications include its use in α-secretase inhibitors, [9] mGlu1 receptor antagonists, [10] and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) inhibitors. [11]

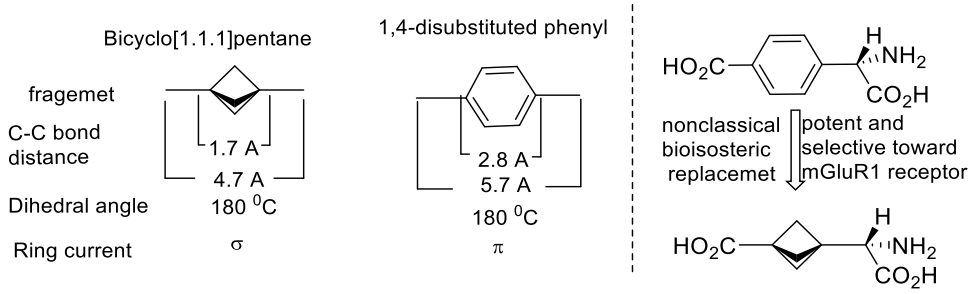


Figure 1. Bicyclo[1.1.1]pentane as a Phenyl bioisostere.

BCP-containing molecules often retain biological activity comparable to their aromatic counterparts, while exhibiting improved metabolic stability, enhanced aqueous solubility, and increased membrane permeability.[9]

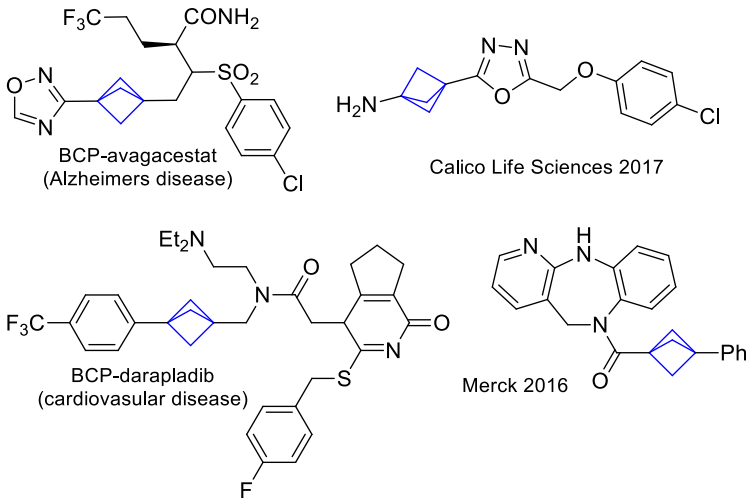


Figure 2. BCP-containing lead compounds.

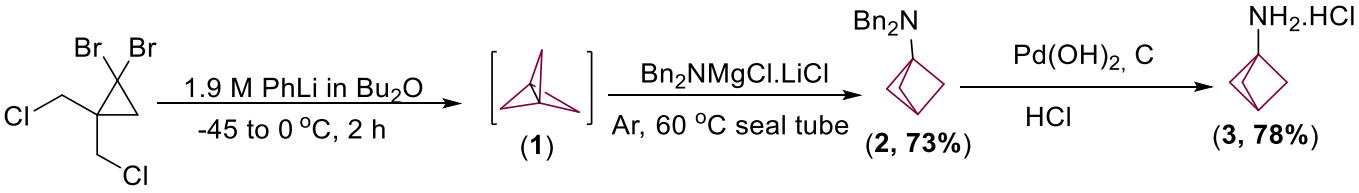
The introduction of this sp^3-rich scaffold as a bioisosteric surrogate for para-substituted benzene rings is not only chemically intriguing but also advantageous from an intellectual property standpoint.[9,12,13] Bicyclo[1.1.1]pentane was first synthesized by Wiberg and co-workers in 1964.[12-13] BCP, which can be described as a cyclobutyl-bridged cyclobutane, exhibits a strain energy of 66.6 kcal mol^{-1} compared to the straight-chain hydrocarbon pentane. Despite its high strain, BCP has proven to be a synthetically accessible and functionally valuable motif. A pivotal advancement came in 1982 with the synthesis of [1.1.1]propellane by Wiberg and Walker[14] [1.1.1]Propellane has since garnered significant interest due to its unique bonding and reactivity profile, particularly its ability to undergo strain-release ring-opening reactions with a variety of nucleophiles, radicals, and electrophiles to afford BCP derivatives.[15-19] The most widely adopted method for preparing [1.1.1]propellane was developed by Szeimies and co-workers[20] and involves the cyclopropanation of dichlorobutene followed by bromine–lithium exchange. This sequence induces intramolecular cyclization of the resulting carbanions to furnish the strained [1.1.1]propellane.[21] A significant enhancement in this synthesis was reported by the Baran group,[22] who demonstrated that phenyllithium serves as an efficient reagent for improving yield, scalability, and purity. Notably, the resulting [1.1.1]propellane can be stored in ethereal solvents for several months without appreciable decomposition. Its capacity to undergo efficient strain-release transformations makes it an ideal precursor for the modular synthesis of BCP-containing molecules.

In this perspective, we discuss the most significant recent advances in BCP synthesis, focusing on general and versatile strategies for the construction and functionalization of this structurally and pharmacologically important framework.

2. Turbo Grignard Reagent-Promoted Synthesis of BCP-Substituted Amines via Direct Propellane Functionalization

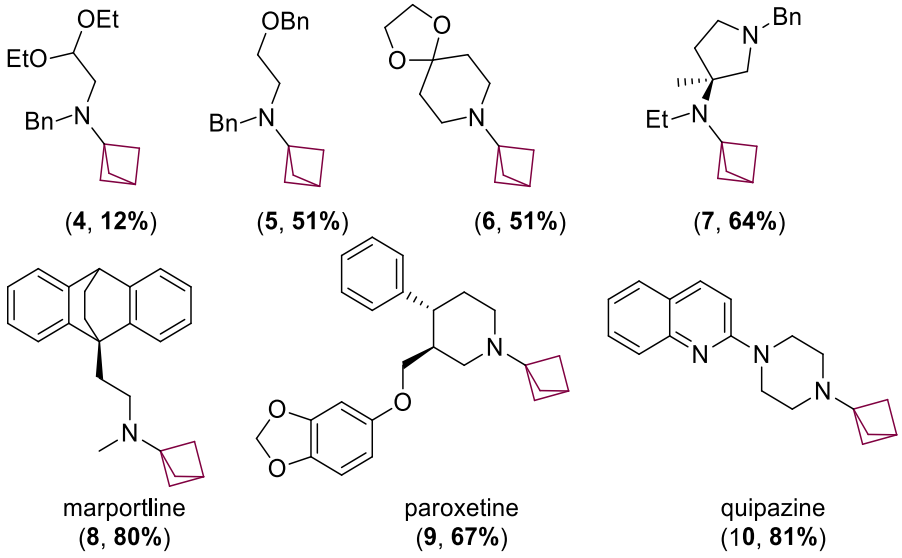
A notable advancement in the direct functionalization of amine substrates was reported by the Baran group. In this study, dibenzylamine was converted into the corresponding magnesium amide complex (Bn_2N–MgCl·LiCl) through treatment with a turbo Grignard reagent (i-PrMgCl·LiCl). The resulting Turbo-amide" exhibited enhanced

nucleophilicity and reacted efficiently with [1.1.1]propellane (**1**), furnishing the bicyclo[1.1.1]pentylamine intermediate (**2**) in 73% yield. Subsequent catalytic hydrogenolysis using $Pd(OH)_2/C$ in methanol removed the benzyl protecting groups, affording the free amine derivative (**3**) in 78% yield (Scheme 1)[22]. This transformation highlights the utility of turbo-amide chemistry in enabling the modular incorporation of bicyclo[1.1.1]pentyl motifs into amine-containing scaffolds.



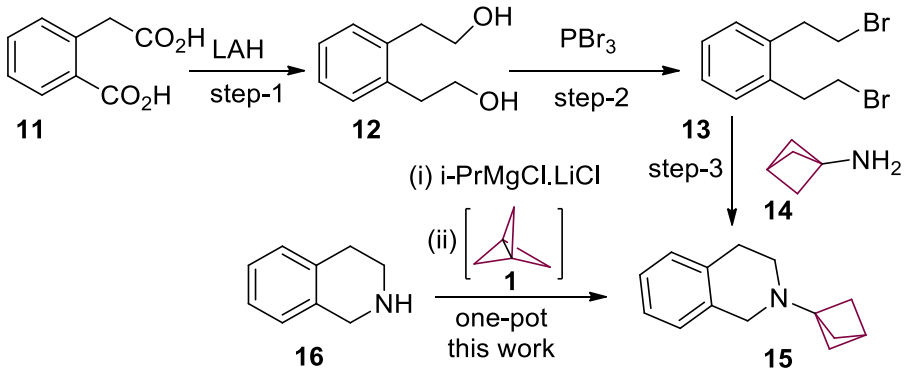
Scheme 1. Strain release amination.

This strain-release amination protocol was successfully applied to a variety of substrates, including acetals (**4**), benzyl ethers (**5**), ketals (**6**), and several commercial drugs (**8**–**10**), thereby eliminating the need for laborious multistep sequences and enabling efficient access to these analogues (Scheme 2)[22]



Scheme 2. Strain release amination of early and late-stage groups.

Notably, this method was also employed in the synthesis of BCP-tetrahydroisoquinoline **15**, providing a compelling example of how tedious multi-step syntheses can be circumvented. As shown in Scheme 3, the conventional synthesis of tetrahydroisoquinoline derivative **15** required three steps, starting from diacid **11**. In contrast, compound **15** was efficiently obtained from tetrahydroisoquinoline **16** using the Baran strain-release amination strategy (Scheme 3),[22,] highlighting the significant simplification of the synthetic route.

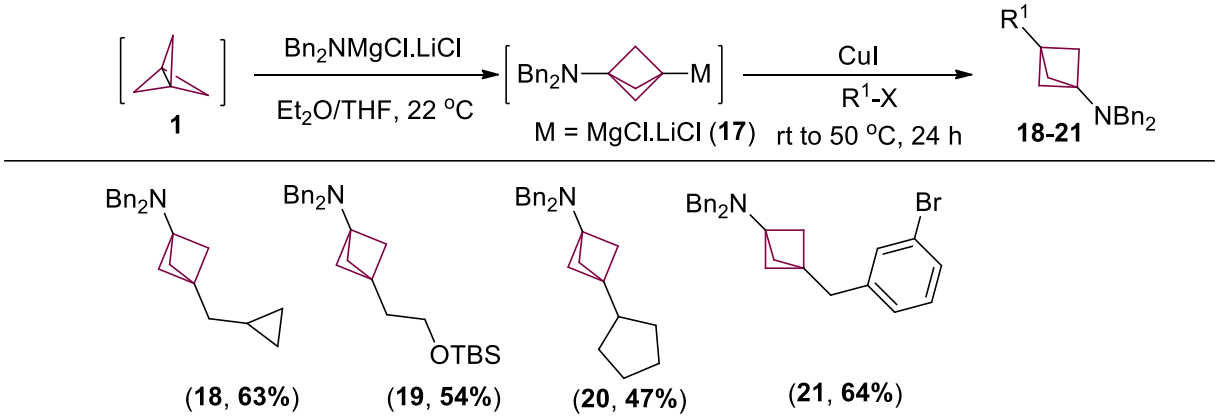


Scheme 3. Synthesis of the BCP tetrahydroisoquinoline unit.

2.1. Turbo amide-mediated aminoalkylation of [1.1.1]propellane: efficient access to 1,3-disubstituted BCP-amines and key building blocks

Gleason and co-workers developed a protocol for the direct addition of " Turbo-amide " (Bn_2N–MgCl·LiCl) to [1.1.1]propellane, presumably generating a metalated intermediate **17**, which could be efficiently trapped with various alkyl electrophiles in the presence of CuI as a catalyst to afford 1,3-disubstituted BCP-amines **18**–**21** (Scheme 4).[23]

This method also proved highly effective for incorporating the BCP unit as a terminal group.



Scheme 4. *In situ* generated Cu-BCP moiety trapping with alkyl electrophiles.

Furthermore, the in situ-generated intermediate **17** was successfully quenched with ethyl cyanoformate to furnish the corresponding amino ester **22**. Oxidation of **17** with Davis oxaziridine reagent provided the amino alcohol **23** in 54% yield. Additionally, a 1,4-addition of intermediate **17** to 2-cyclohexene-1-one afforded the cyclohexanone-substituted BCP-amine **24** (Figure 3).[23]

The significance of this strategy was further underscored by its application in the synthesis of a key building block, compound **27**. The synthetic route proceeded as follows: alkylated BCP-amine **25** underwent oxidative cleavage of the alkene to yield the corresponding acid **26**. Subsequent Fischer esterification of **26**, followed by deprotection at the benzyl position, efficiently furnished compound **27** in 84% yield. Overall, this newly developed aminoalkylation approach enabled the synthesis of **27** in only five steps (four pots) from [1.1.1]propellane (**1**) with a 38% overall yield[23] (Scheme 5), representing a significant improvement compared to the previous synthetic route.[24]

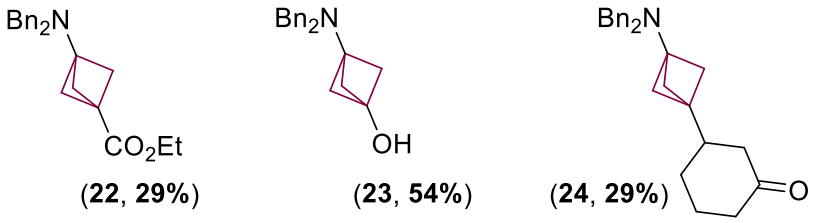
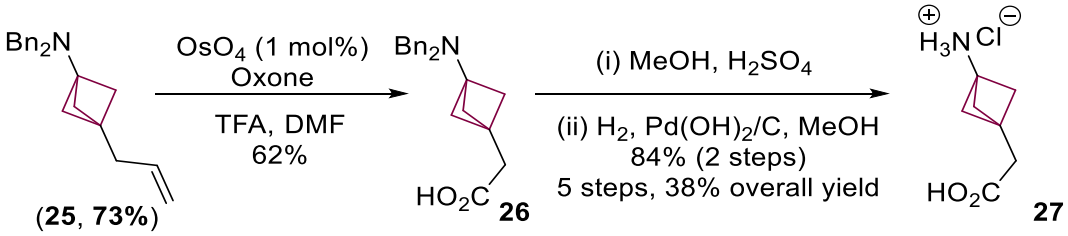


Figure 3. Trapping of *in situ*-generated Cu-BCP moiety with alkyl electrophiles.

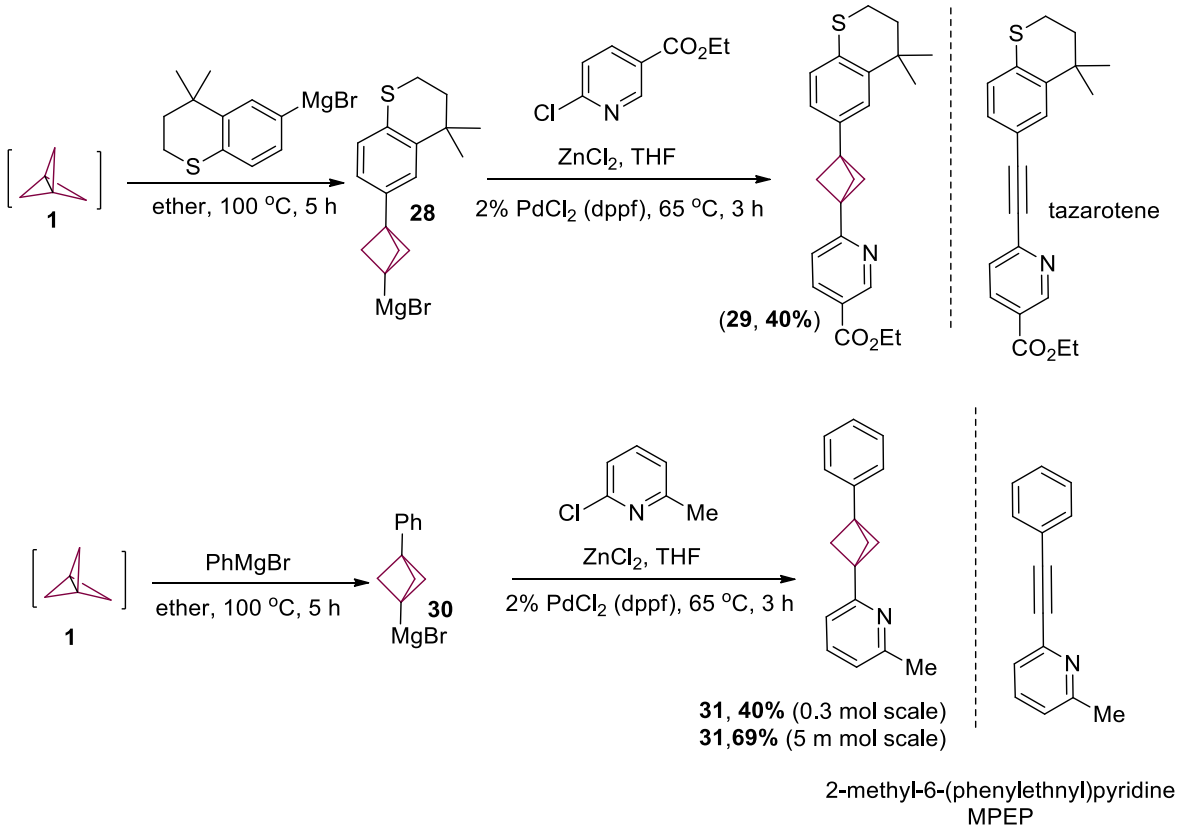


Scheme 5. Synthesis of the BCP derivative amino ester.

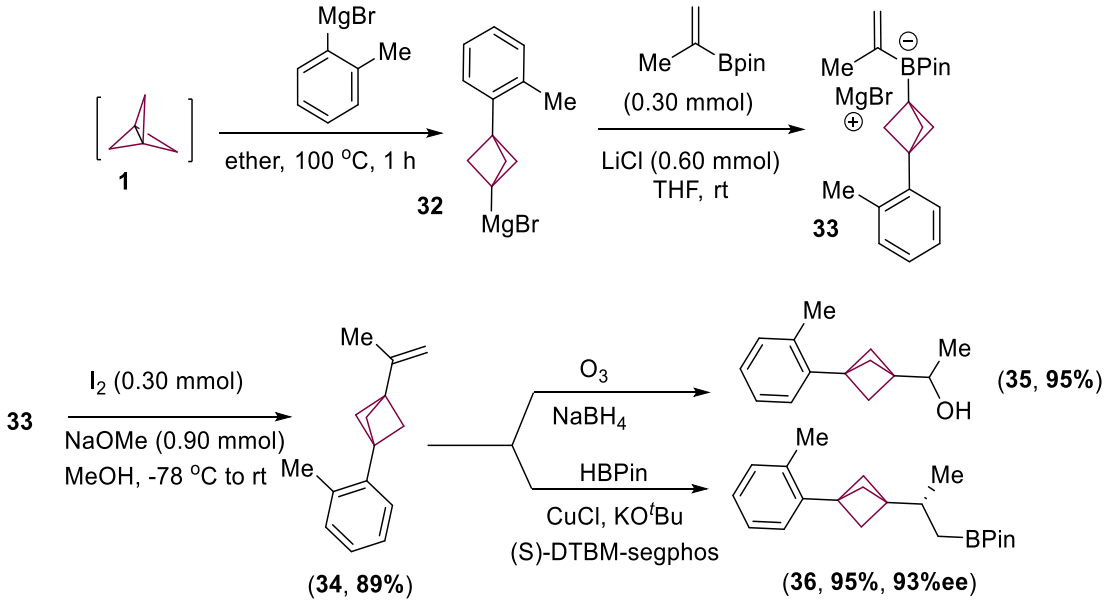
3. Synthesis of Functionalized Bicyclo[1.1.1]pentanes via Grignard Reagents and Subsequent Cross-Coupling Strategies"

The Paul Knochel group developed a unique strategy for the preparation of bicyclo[1.1.1]pentane (BCP) Grignard reagents through the reaction of [1.1.1]propellane (**1**) with arylmagnesium halides in the presence of ether at 100 ^{0}C. The resulting BCP Grignard reagents subsequently underwent transmetalation with zinc chloride ($ZnCl_2$), followed by Negishi cross-coupling with aryl and heteroaryl halides to afford bis-arylated bicyclo[1.1.1]pentane derivatives[25]. For instance, bis-arylated bicyclo[1.1.1]pentanes **29** and **31**, considered bioisosteres of internal alkynes present in tazarotene, were synthesized using this method. Moreover, this approach enabled the successful synthesis of the metabotropic glutamate receptor 5 (mGluR5) antagonist 2-methyl-6-(phenylethynyl)pyridine (Scheme 6).[25]

Subsequently, Aggarwal and co-workers disclosed an efficient protocol for the synthesis of alkenyl-BCP products[26], wherein the BCP-Grignard reagent **32** was reacted with a 2-propenyl boronic ester to generate boronate complex **33**. This intermediate underwent Zweifel olefination[24] (1,2-migration and boron elimination) in the presence of iodine and sodium[27], furnishing the desired alkenyl-BCP product **34** (Scheme 7). Furthermore, compound **34** was transformed into alcohol 35 and boronic ester **36** through reductive ozonolysis and enantioselective hydroboration reactions, respectively[27].



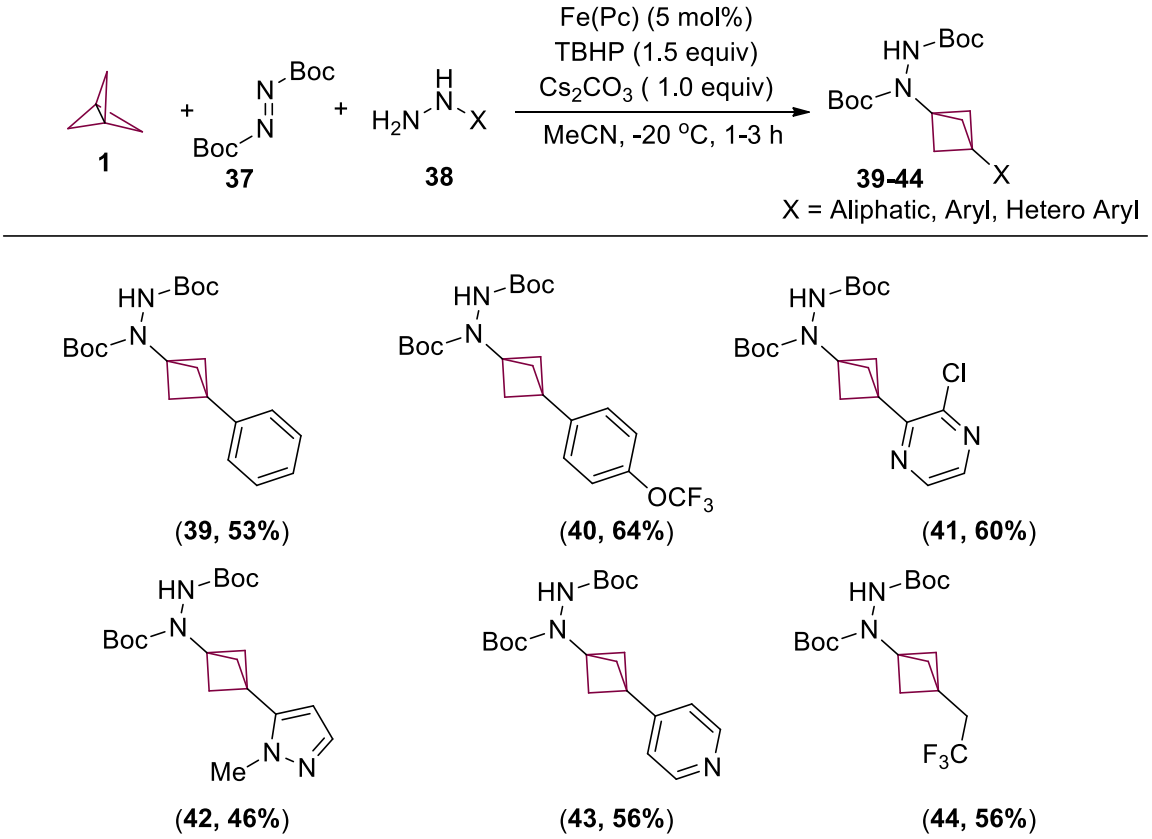
Scheme 6. Synthetic pathways of Bioactive compounds **29** and **31.**



Scheme 7. Formation of 1,3-functionalized bicyclo[1.1.1]pentanes.

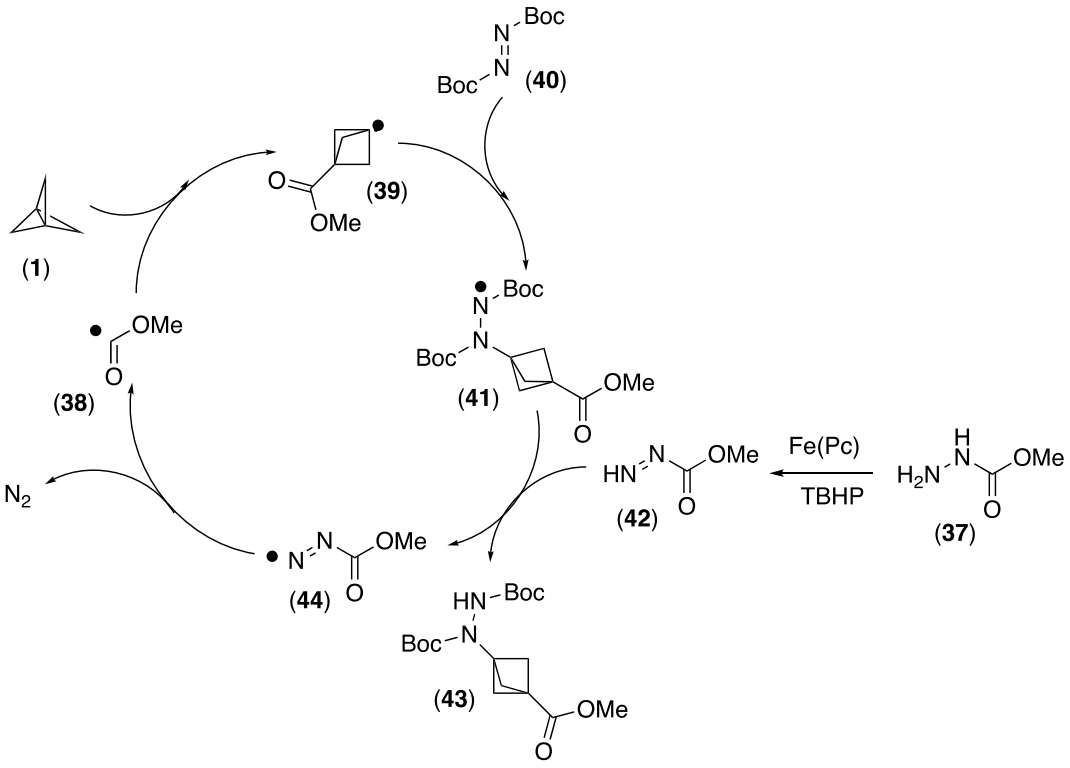
4. Radical Multicomponent Carbonation of [1.1.1]propellane: Synthesis of 1,3-Disubstituted BCP Derivatives

The bicyclo[1.1.1]pent-1-yl radical (BCP-radical) is generated through the opening of the central bond of [1.1.1]propellane via a radical pathway and is kinetically stable,[28,29] with an energy barrier to ring opening of approximately 26 kcal/mol. Uchiyama and co-workers developed a one-pot radical multicomponent carbonation of [1.1.1]propellane, enabling the synthesis of 1,3-disubstituted BCP hydrazine dicarboxylates.[30] This method simultaneously constructs C–C and C–N bonds in a single step through a sequence of radical addition, central bond cleavage[30], and radical trapping processes[31] (Scheme 8).



Scheme 8. 1,3- functionalized BCP-amines.

Mechanistically, the addition of a methoxycarbonyl radical **46** generated in situ by the oxidative denitrogenation of methyl carbazate **45** to [1.1.1]propellane (**1**) induces cleavage of the central bond, furnishing the BCP-radical intermediate **47**. Di-tert-butyl azodicarboxylate **48** acts as an excellent radical acceptor, trapping intermediate **47** to form a stable amidyl radical **49**. Subsequent hydrogen abstraction from compound **50** by radical **49** yields the unsymmetrically disubstituted BCP product **51**[30] and the diazinyl radical **52**. Finally, smooth release of molecular nitrogen from radical **52** regenerates methoxycarbonyl radical **46**, thus completing the catalytic cycle.[32] (Scheme 9)

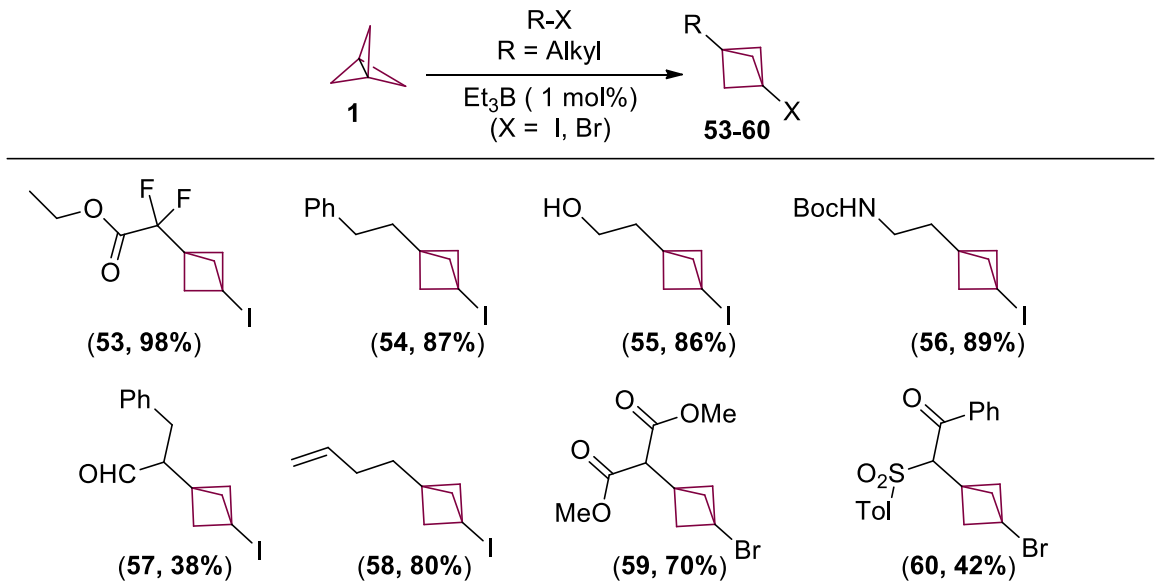


Scheme 9. The mechanism cycle for the transformation of 1,3-functionalized BCP-amines.

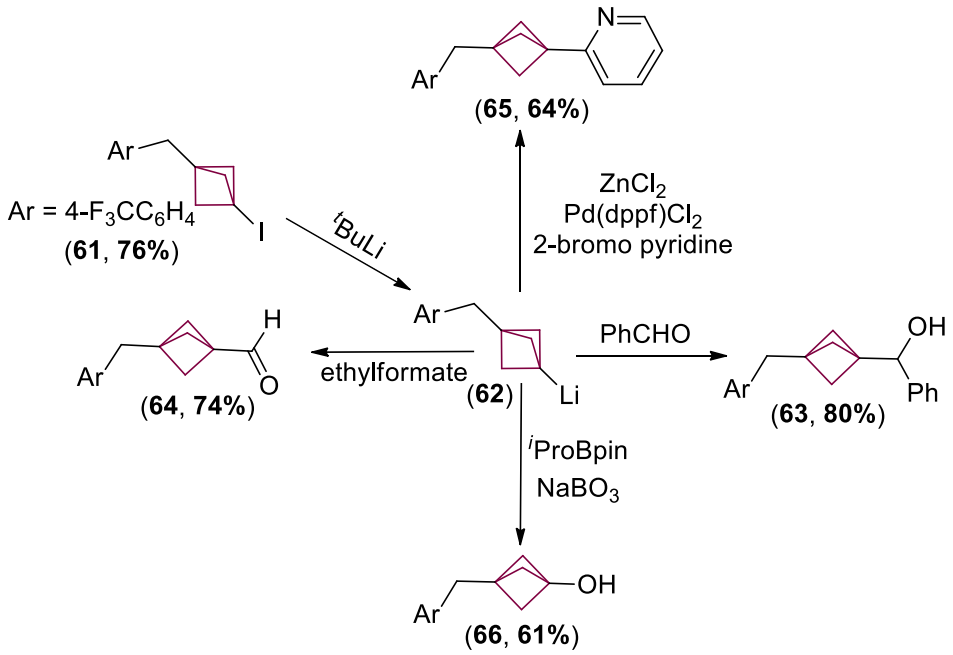
5. Atom Transfer Radical Addition (ATRA) Approach for the Synthesis and Functionalization of Bicyclo[1.1.1]pentane (BCP) Derivatives

The atom transfer radical addition (ATRA) process has emerged as an alternative strategy for opening the tricyclo[1.1.1.0]pentane (TCP) ring. The Anderson group employed this method to synthesize BCP derivatives bearing carbon and halogen substituents under exceptionally mild reaction conditions. Ring-opening of TCP with alkyl halides was achieved via a triethylborane-initiated ATRA reaction[33] (Scheme 10). This method demonstrated broad substrate scope and excellent functional group tolerance, enabling the incorporation of BCP motifs into various biologically relevant targets, including pharmaceuticals, nucleosides, and peptide cores.

The transformation of BCP-iodide **61** into diverse products is illustrated in (Scheme 11). Lithiation of **61** generated the corresponding organolithium species **62**[34], which underwent nucleophilic addition to benzaldehyde and ethyl formate to afford alcohol **63** and aldehyde **64**, respectively. Furthermore, cross-coupling of organozinc species (prepared in situ via transmetalation of **62**) with 2-bromopyridine provided pyridyl-substituted BCP **65** in 64% yield. The synthesis of the phenol bioisostere[35] **66** was achieved by borylation quench of **62**, followed by oxidation with sodium perborate.

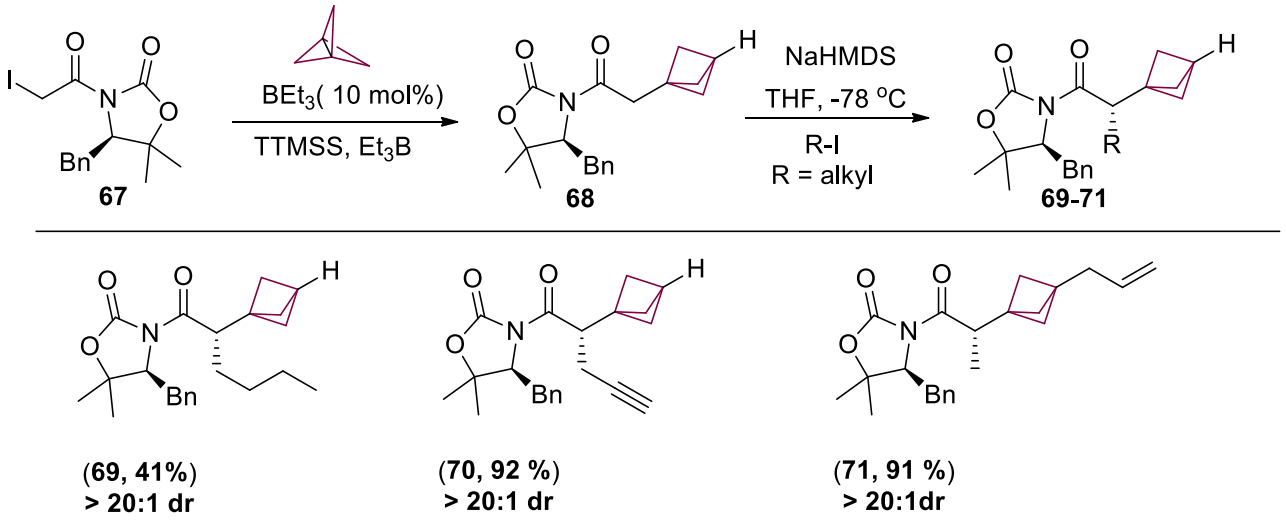


Scheme 10. Ring opening involving the ATRA process.



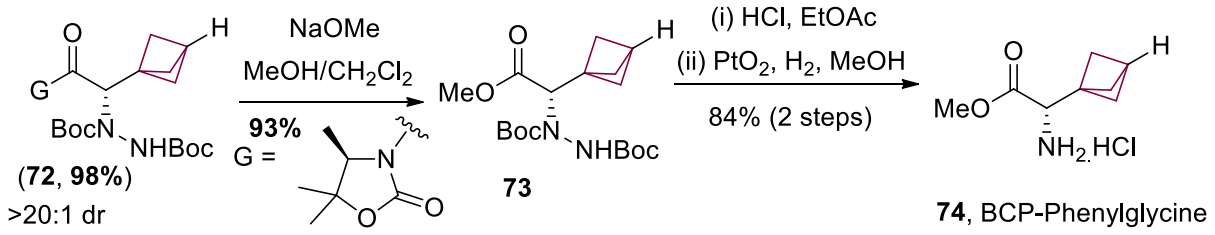
Scheme 11. The application of BCP-iodide.

Additionally, the ATRA process proved effective for the synthesis of α-chiral BCPs, including oxazolidinone derivatives, via highly diastereoselective asymmetric enolate functionalization of α-halo carbonyl compounds[36] (Scheme 12).



Scheme 12. ATRA process involves TCP ring-opening.

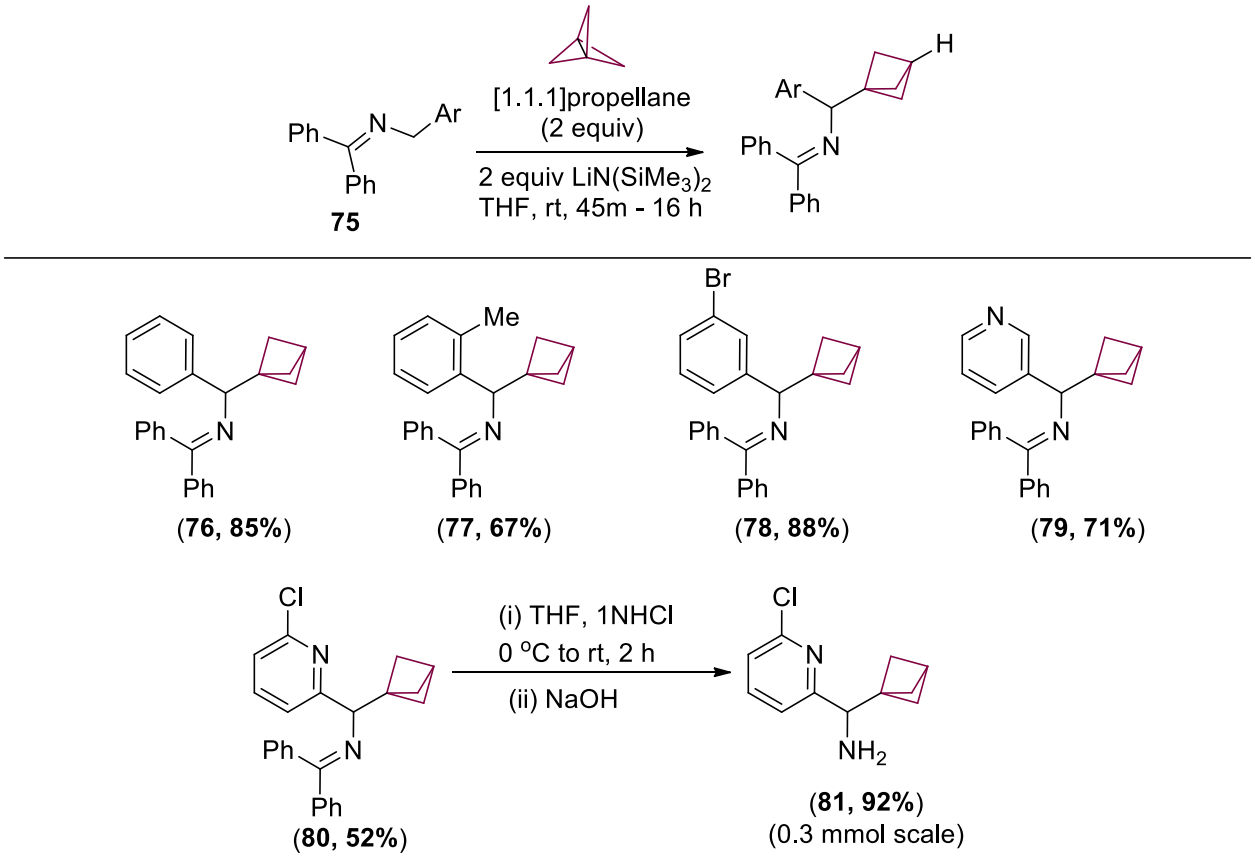
This method was further utilized in the synthesis of a BCP analogue of phenyl glycine (Scheme 13). Methanolysis of **72** afforded the desired ester **73**, which, upon Boc deprotection and subsequent Pt-catalyzed hydrogenation,[29,37] delivered the BCP analogue of L-(+)-α-phenylglycine methyl ester hydrochloride **74** in 78% yield.



Scheme 13. Synthesis of L-(+)-α- phenylglycine methyl ester hydrochloride.

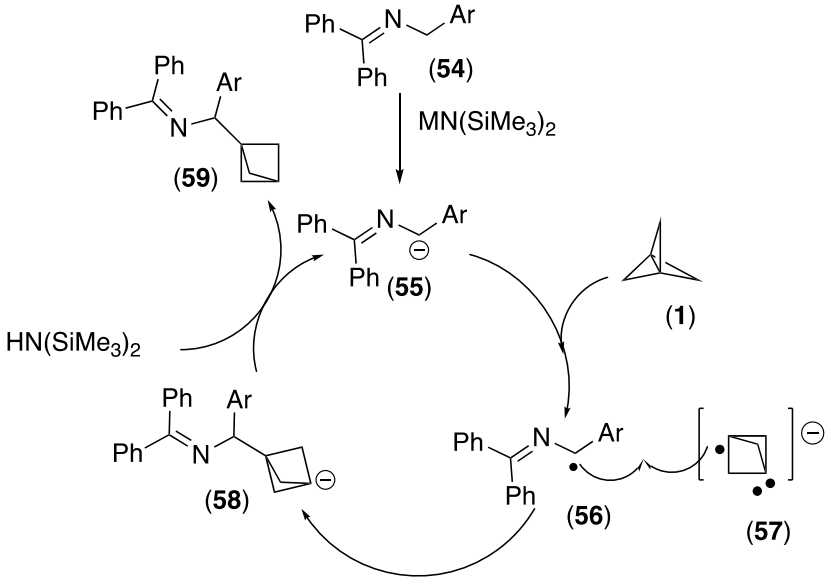
6. Super Electron-Donating 2-Azaallyl Anions for [1.1.1]Propellane Functionalization via Single-Electron Transfer

Walsh and co-workers developed an innovative method utilizing super electron-donating (SED) 2-azaallyl anions, which were generated by the deprotonation of N-benzyl ketimines using $LiN(SiMe_3)_2$ as the base. The resulting 2-azaallyl anions engaged in single-electron transfer (SET) with [1.1.1]propellane to furnish the corresponding ketimine-BCP products[38-39] (Scheme 14). Subsequent acidic hydrolysis of these ketimine intermediates provided the desired BCP benzylamines [38]



Scheme 14. Synthesis of BCP benzylamines.

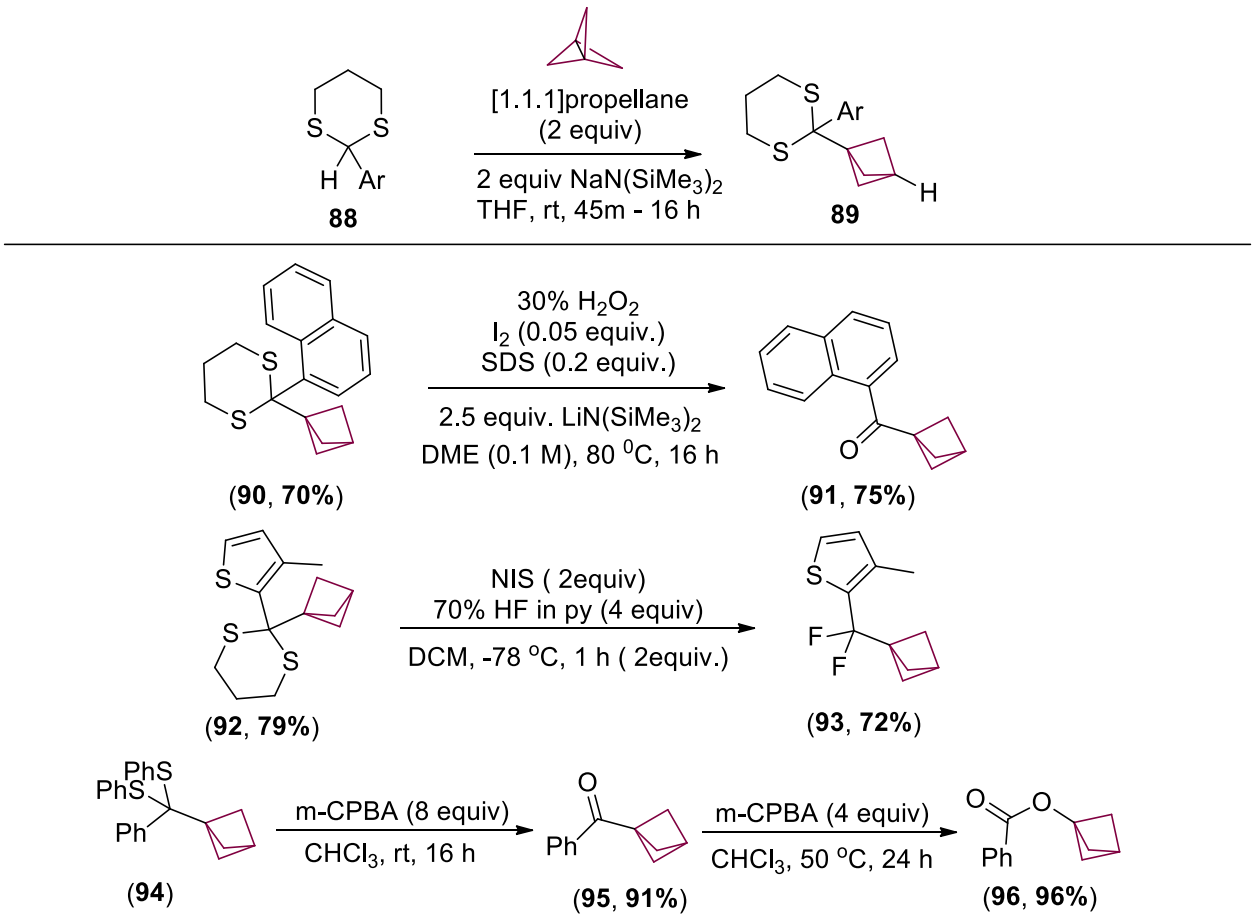
The proposed mechanistic cycle for this transformation is as follows: deprotonation of ketimine **82**[40] with $LiN(SiMe_3)_2$ generates the 2-azaallyl anion **83**. This anion undergoes a SET process with [1.1.1]propellane, resulting in the formation of the azaallyl radical **84**. Radical–radical coupling between **84** and the [1.1.1]propellane radical anion **85** affords the key intermediate **86**. Finally, protonation at the bridgehead carbon—either by unreacted ketimine **82** or by $HN(SiMe_3)_2$[41]—yields the ketimine-BCP product **87**[38] along with regeneration of **83** (Scheme 15).



Scheme 15. Mechanism of the synthesis of BCP Benzylamines.

7. Ring-Opening of [1.1.1]Propellane with Dithiane Anions and Downstream BCP Functionalization

The Walsh group reported that 2-aryl-1,3-dithiane anions act as competent nucleophiles capable of selectively cleaving the highly strained central bond of [1.1.1]propellane, resulting in the formation of a C–C bond at the bridgehead position of the bicyclo[1.1.1]pentane (BCP) framework[42] (Scheme 16). Subsequent deprotection of the resulting BCP dithiane **90**, following the protocol developed by Barik,[43] furnished the corresponding ketone **91**. In a related transformation, the aryl dithiane–thiophene derivative **92** was successfully converted into the BCP aryl difluoromethane derivative **93** using the procedure described by Katzenellenbogen[44]. Additionally, hydrolysis of dithioacetal **94** with 8 equivalents of m-chloroperoxybenzoic acid (m-CPBA) in chloroform at ambient temperature afforded ketone **95**. This intermediate was further subjected to Baeyer–Villiger [45] oxidation employing 4 equivalents of m-CPBA at 50 °C, yielding the corresponding ester 66 (Scheme 16).

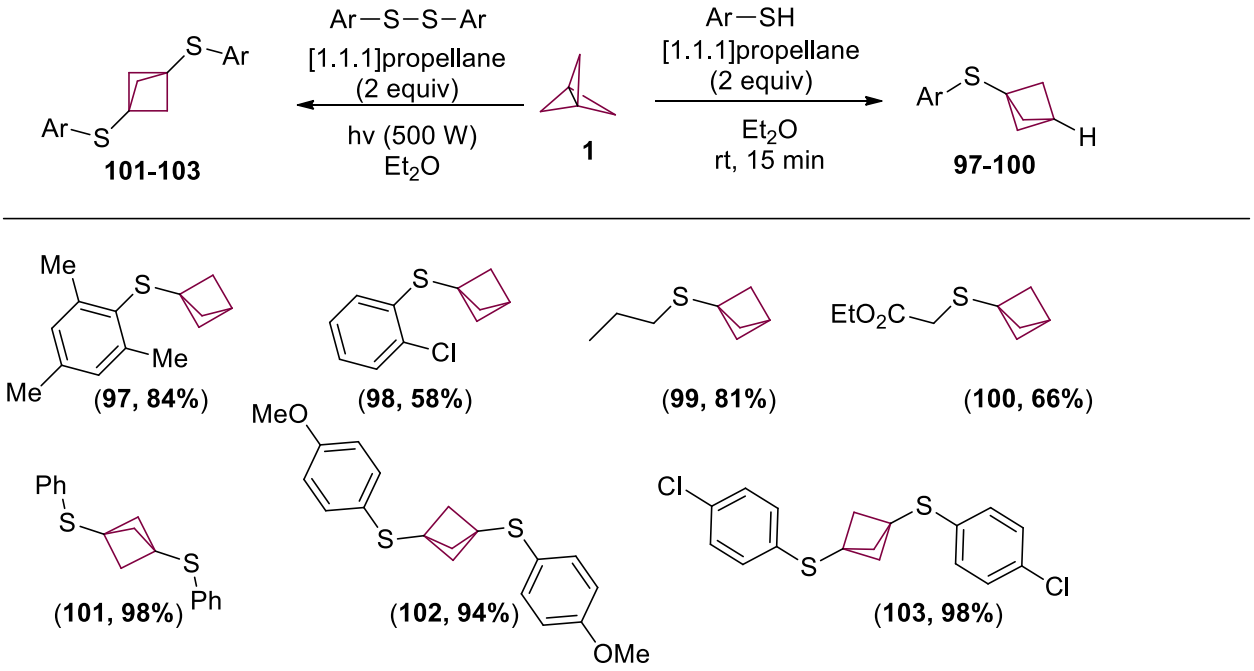


Scheme 16. Synthesis of BCP products and their transformation.

8. Radical Addition of Thiols and Disulfides to [1.1.1]Propellane: Access to Functionalized BCPs

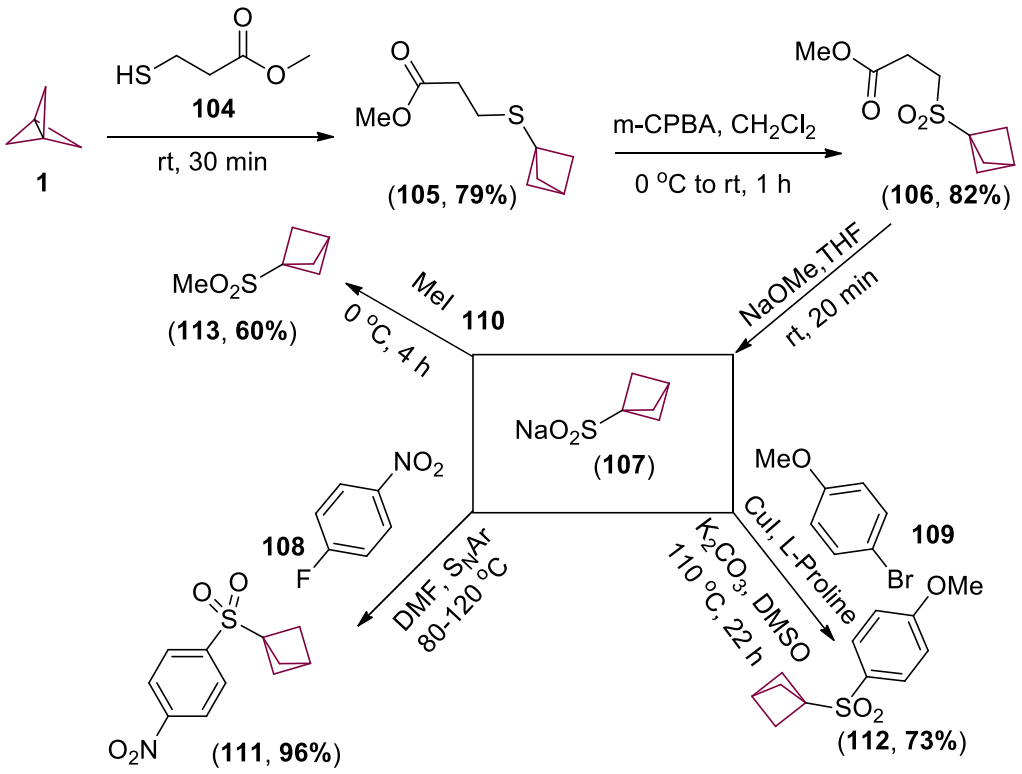
Bräse and co-workers developed an efficient protocol for the synthesis of sulfur-containing bicyclo[1.1.1]pentane (BCP) derivatives, wherein aromatic and aliphatic thiols were reacted with [1.1.1]propellane (**1**) at room temperature for 15 minutes to afford the corresponding BCP products.[46] The

reaction proceeded via a radical chain mechanism, as confirmed by various deuterium labelling experiments[45] (Scheme 17). Additionally, [1.1.1]propellane was treated with disulfides under UV irradiation to access both symmetrical and unsymmetrical BCP sulfides[47] (Scheme 17).



Scheme 17. Thiol addition to sulphides and disulphides.

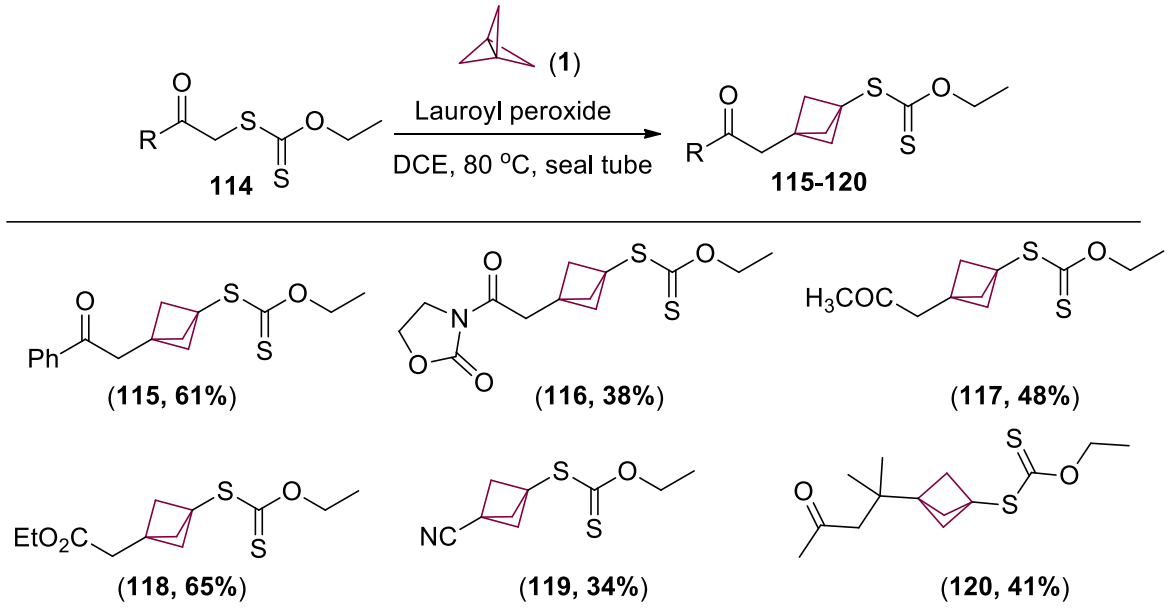
These protocols demonstrated broad substrate scope, tolerating both electron-donating and electron-withdrawing groups on aromatic and aliphatic thiols. For example, thiol **104** was added to [1.1.1]propellane at room temperature, and subsequent washing with an aqueous sodium hydroxide solution yielded pure BCP sulfide **105** in an isolated yield[46] of 79%. Oxidation of **105** with meta-chloroperoxybenzoic acid (m-CPBA) provided sulfone **106** in 82% yield. The sulfone **106** underwent a retro-Michael reaction upon treatment with sodium methoxide to generate the corresponding sulfinate **107** in good yield[48] (Scheme 18). This versatile intermediate was subjected to several further transformations: (i) nucleophilic aromatic substitution (SNAr) with electron-deficient aryl fluorides furnished sulfones **111** in good yields (Scheme 18); (ii) a copper(I)-catalyzed reaction with electron-rich aryl substrates **109** efficiently delivered BCP sulfones **112** (Scheme 18)[46] and (iii) simple alkylation product 113 was successfully performedwith methyl iodide at low temperature without the addition of a base,[49] Overall, these strategies highlight the versatility and broad applicability of sulfur-functionalized BCP building blocks in organic synthesis.



Scheme 18. Transformation of various sulfonate BCP derivatives.

8.1. Degenerative radical exchange strategy for the functionalization of [1.1.1]propellane using xanthate derivatives

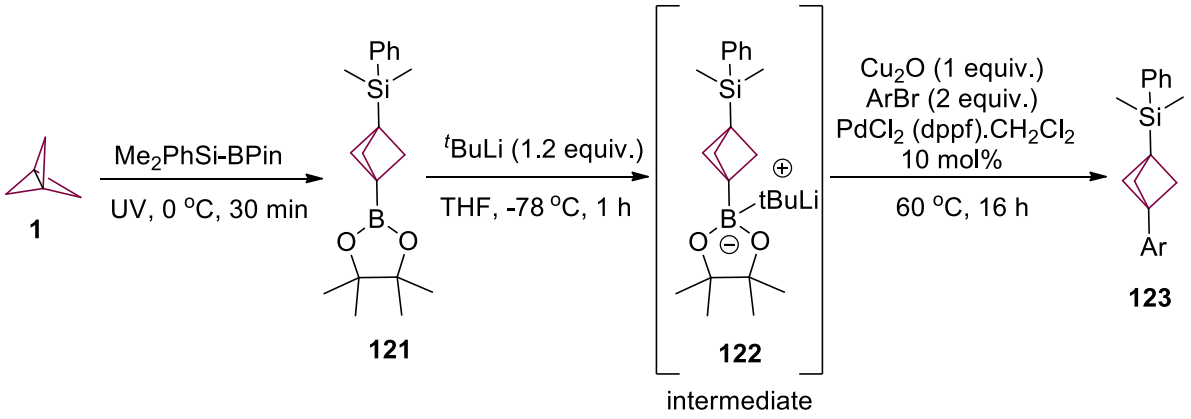
The development of degenerative radical exchange of thiocarbonylthio derivatives, particularly xanthates, marked a significant breakthrough in the field of radical chemistry.[50-51] Building on this concept, the Riant group successfully employed this strategy to incorporate xanthate substrates into the highly strained [1.1.1]propellane framework, thereby synthesizing BCP O-ethyl carbonodithioates. The reaction was carried out in a sealed tube using substoichiometric amounts of dilauroyl peroxide (DLP) as a radical initiator[52-53] (Scheme 19). Notably, this method demonstrated broad substrate scope, tolerating a wide range of xanthate derivatives, including keto-, ester-, heterocyclic-, cyano-, and β-keto-substituted xanthates, among others, thereby underscoring the versatility and robustness of this approach.



Scheme 19. BCP moiety of xanthates.

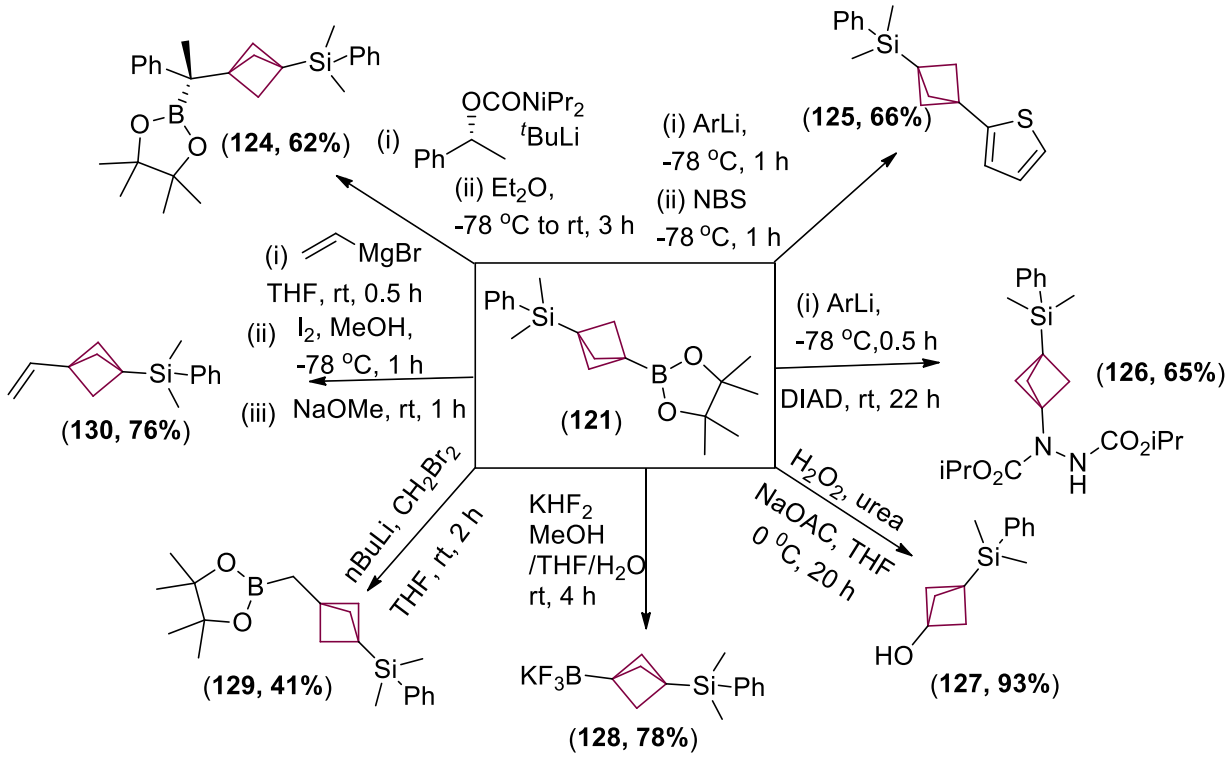
9. Synthetic Strategy and Functionalization of Bicyclo[1.1.1]pentane (BCP) for Structural Diversification and Application in Advanced Organic Synthesis

Uchiyama's group developed a straightforward method for the direct introduction of boron (B) and silicon (Si) functional groups onto the bicyclo[1.1.1]pentane (BCP) scaffold under mild, additive-free conditions[54] (Scheme 20). The resulting C–B/C–Si BCP scaffold **121** was further transformed into highly reactive BCP boronic esters **122** through treatment with *tert*-BuLi in THF at –78 °C. Subsequently, the Suzuki–Miyaura cross-coupling reaction of **122** was successfully performed at the sterically hindered bridgehead sp³-carbon centre of the BCP framework using a combination of copper(I) oxide and $PdCl_2$(dppf) as the catalyst system, yielding compound[54] **123** (Scheme 20).



Scheme 20. Silaboration of [1.1.1] Propellane.

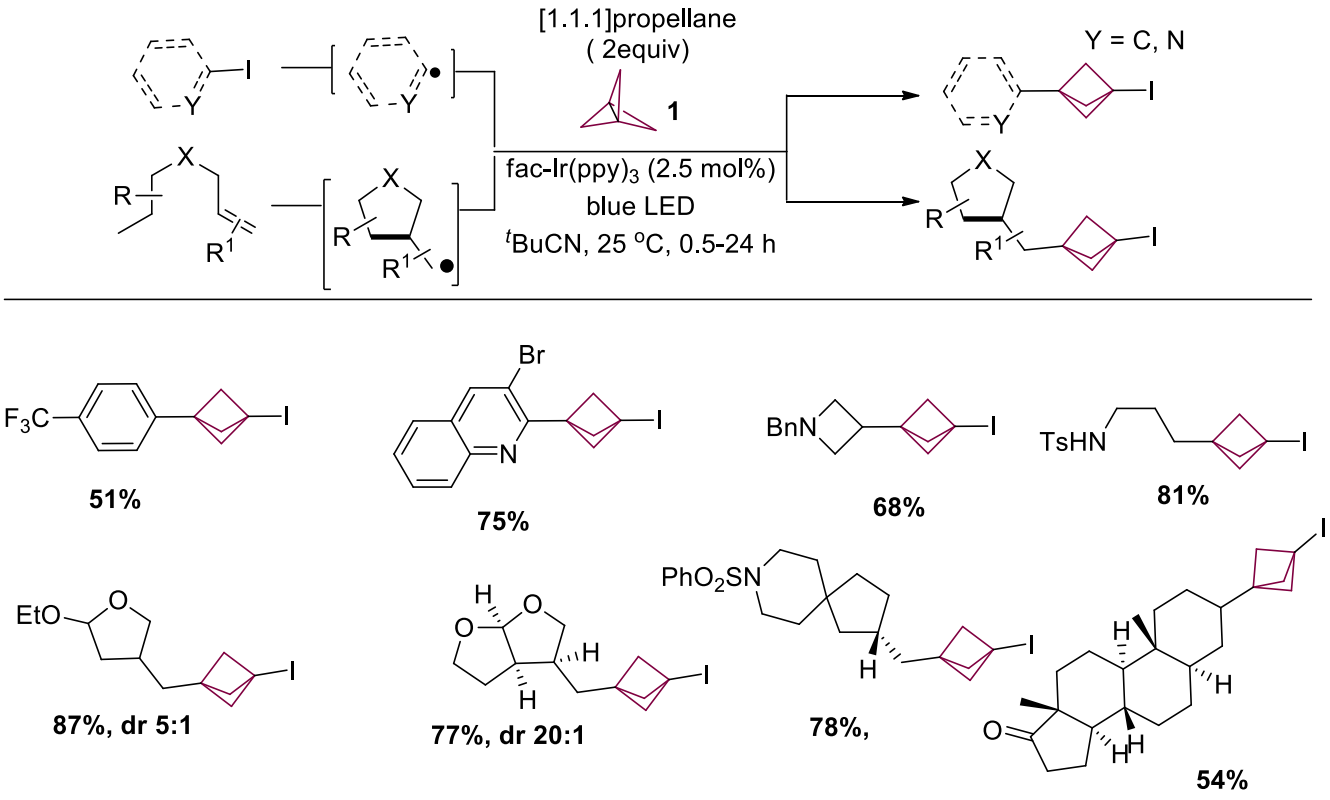
The synthetic utility of the silaboration adduct **121** was further explored by adopting Aggarwal's procedures[55] via borate intermediates (Scheme 21). This strategy enabled: (1) the stereospecific incorporation of a chiral C(sp^3) center to generate the previously inaccessible tetrasubstituted, chiral carbon-containing BCP framework **124** with high enantiospecificity[55]; (2) the introduction of a thiophene heteroaromatic moiety into the BCP skeleton to furnish compound **125** through lithiation followed by bromination of heteroaryl compounds;[56-58] and (3) the formation of scaffold **126** via an intermolecular C–N bond-forming reaction with diisopropyl azodicarboxylate. Furthermore, the versatility of adduct **121** was demonstrated through several additional transformations:[59] (4) oxidation to afford alcohol **127**; (5) conversion to the corresponding potassium trifluoroborate salt[60] **128**; (6) Matteson homologation[61] to yield boronic ester **129**; and (7) Zweifel olefination[62] to access alkene **130**.



Scheme 21. Synthetic utility of the silaboration.

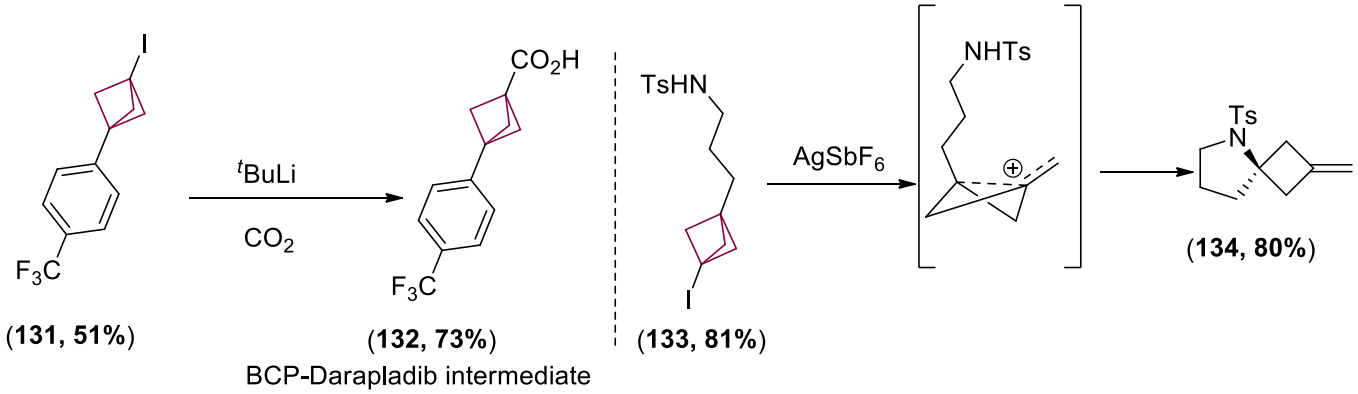
10. Bicyclo[1.1.1]pentanes Synthesis Through Photo Redox Catalysis

Photoredox catalysis has emerged as a powerful tool in synthetic organic chemistry.[63] Anderson et al. described the first example of atom transfer radical addition (ATRA) reactions of organic halides with the TCP ring using photoredox catalysis for carbon−carbon σ-bond functionalization[64]. This protocol not only enabled the addition of aryl and (hetero)aryl radicals but also facilitated the capture of non-stabilized alkyl radicals, providing access to a diverse range of bicyclo[1.1.1]pentane (BCP) products. Furthermore, the authors extended this method to two-component atom transfer radical cyclization (ATRC) processes, in which one or more carbocyclic rings were formed before the intermolecular radical capture by TCP[64] (Scheme 22).



Scheme 22. Photoredox-catalyzed ATRA reactions of organic halides with TCP.

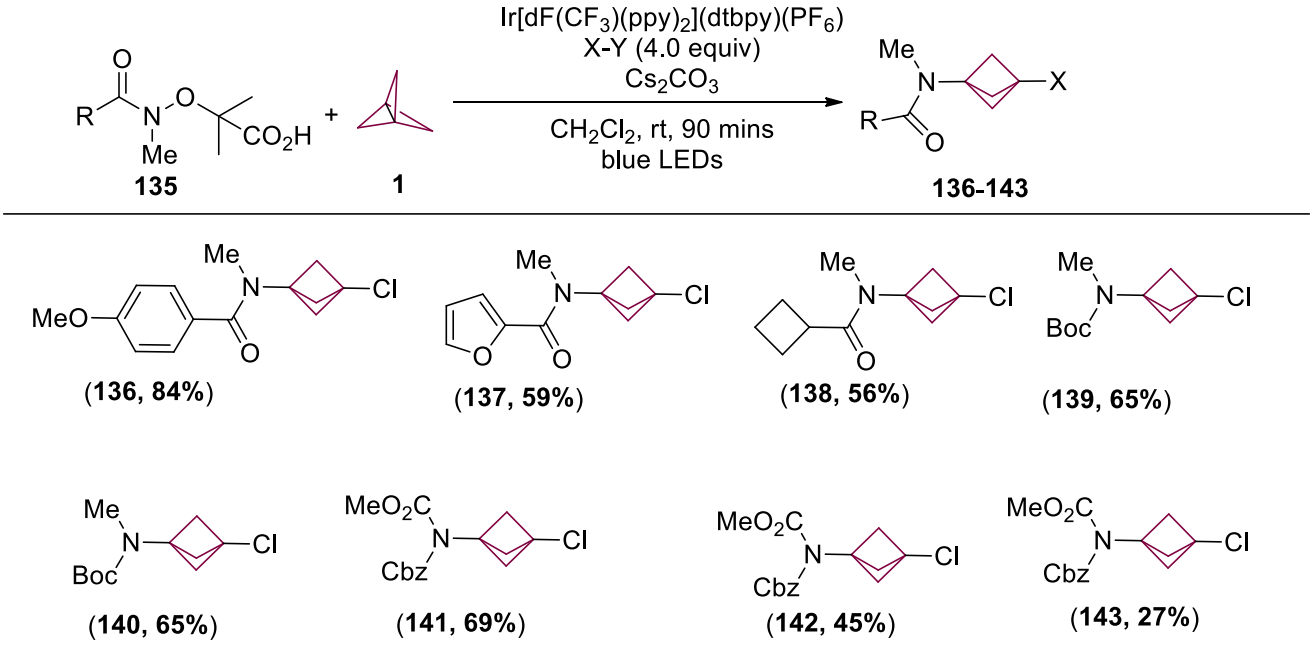
This approach also facilitated a more efficient two-step synthesis of the BCP-darapladib intermediate **132**, a key compound in the cardiovascular drug moiety. In this method, the lithiation of **131** followed by electrophilic trapping with CO_2 produced intermediate **132**, offering a more favourable alternative to the previously reported seven-step synthesis[10]. The iodo-BCP framework **133** was further explored as a potential precursor for the formation of spirocyclic cyclobutene **134**, achieved through Ag(I)-promoted iodide abstraction, rearrangement, and cyclization[64] (Scheme 23).



Scheme 23. Transformation of BCP Iodide product.

11. Photocatalytic Strain-Release Functionalization of Bicyclo[1.1.1]pentylamines Using Nitrogen Radicals

The Leonori group developed a photocatalytic strategy for the preparation of functionalized bicyclo[1.1.1]pentylamines, utilizing nitrogen radicals as a strain-release source for [1.1.1]propellane in the presence of N-chlorosuccinimide (NCS)[65] (Scheme 24). This protocol proved effective in engaging nitrogen-radical species containing two carbonyl substituents (**141–143**), resulting in the desired products[66-73] (Scheme 24).



Scheme 24 [1.1.1]- Propellane with various electrophilic nitrogen radicals.

The optimal conditions for strain-release aminochlorination were subsequently investigated with other SOMOphiles[65] (Figure 4). For instance, the use of N-bromosuccinimide (NBS) led to a complex reaction mixture containing Br–CCl_3 (**144**) alongside the amino-bromination product **148** in a 20% yield. Phthalimide-based SOMO reagents (**145–147**) were applied under optimized conditions to introduce -SCF_3, -S, and -Se functionalities at the bridgehead position of BCP scaffolds, leading to the formation of compounds **149–151** (Figure 4).

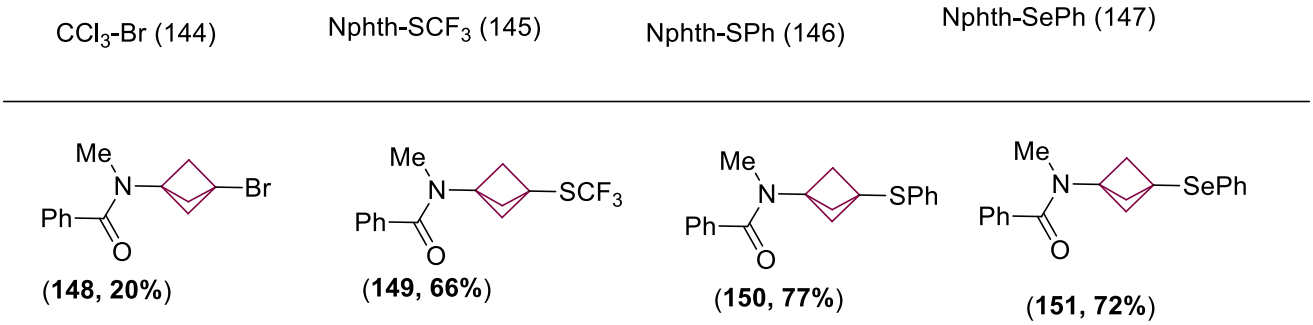
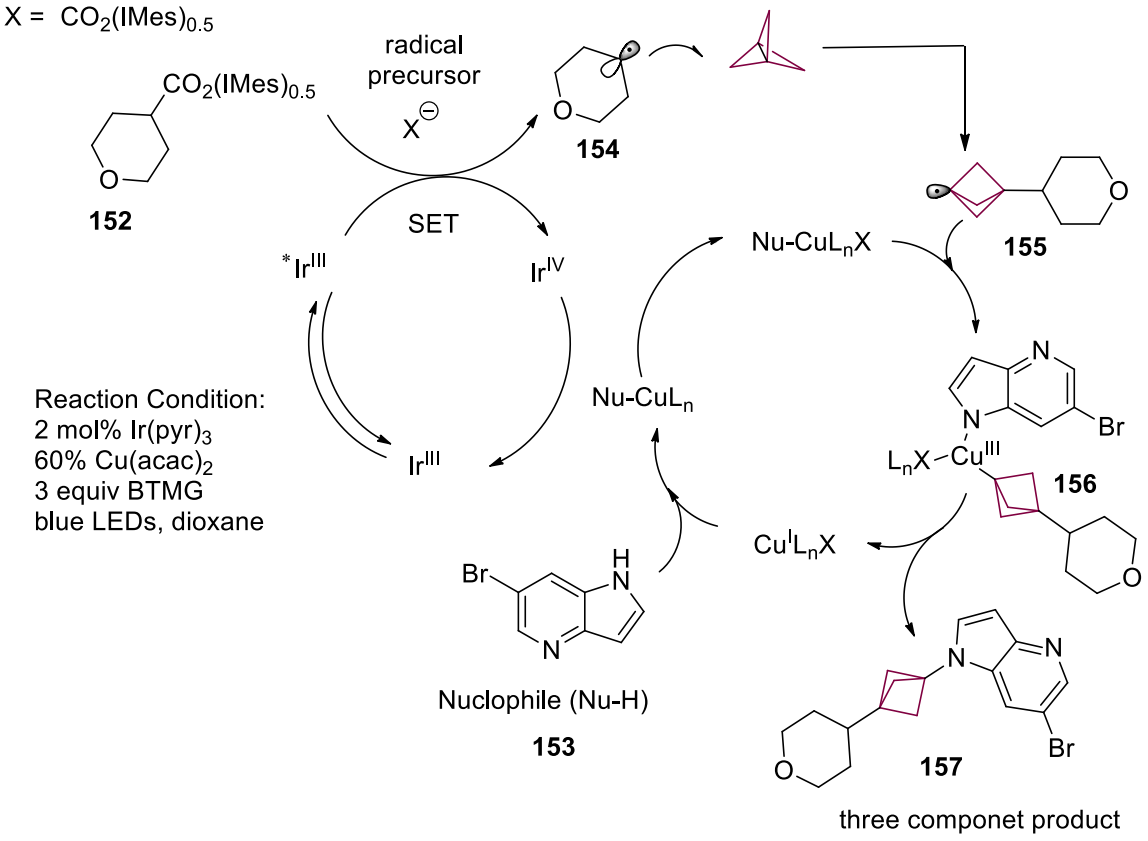


Figure 4. Transformation of various electrophilic nitrogen radicals.

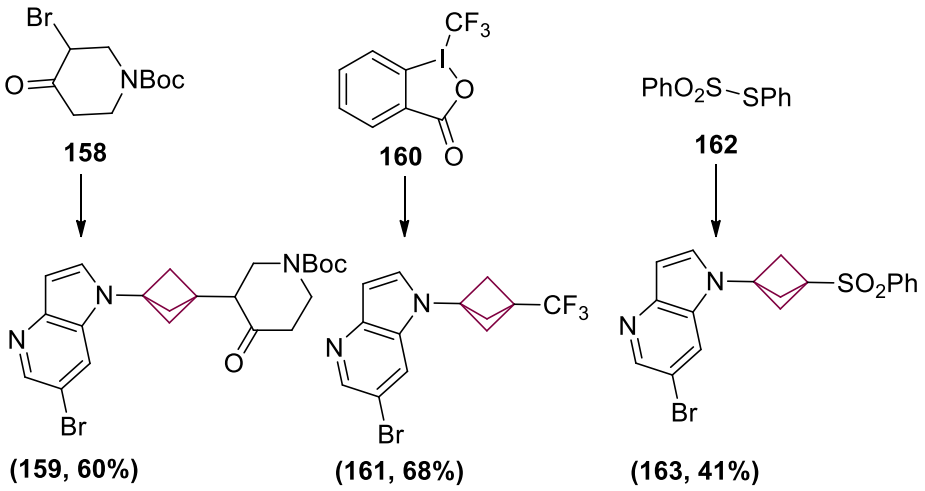
12. Metallaphotoredox-Catalyzed Three-Component Radical Coupling of BCP Analogues

The Macmillan group developed a three-component radical coupling reaction of functionalized bicyclo[1.1.1]pentane (BCP) analogues utilizing various radical precursors and heteroatom nucleophiles through metallaphotoredox catalysis[74] (Scheme 25). For instance, the reaction of carboxylic acids (via iodonium dicarboxylates **152**, generated in situ without purification) and 7-bromo-4-azaindole **153** with [1.1.1]propellane resulted in the formation of the three-component product **157** in the presence of an iridium photocatalyst.
The proposed mechanism for this transformation is as follows: The alkyl radical **154** is generated by the reductive radical generation of **152**, facilitated by the triplet state of the Ir catalyst. Radical **154** then reacts with [1.1.1]propellane (**1**), causing the strain ring to open and form the BCP radical **155**.



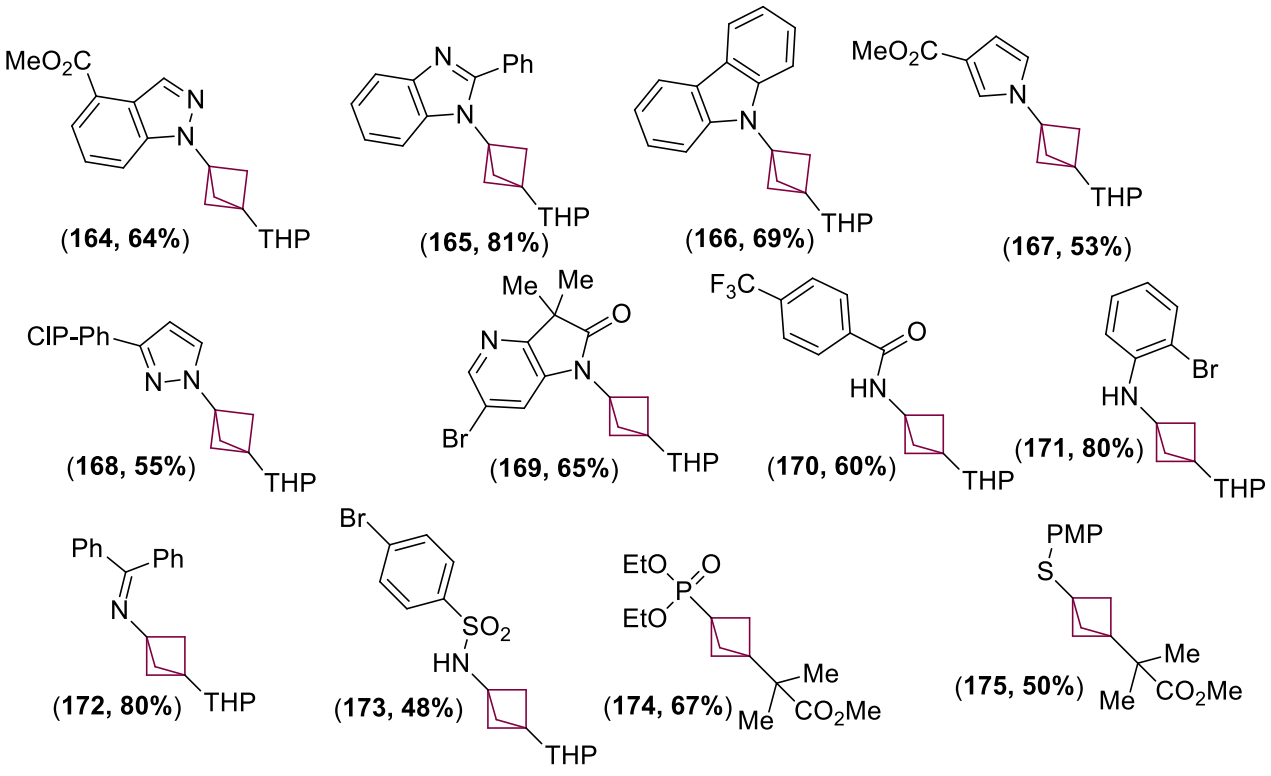
Scheme 25. Mechanism of copper-mediated three-component reaction.

Oxidative addition of the copper complex to the **155** intermediate leads to the formation of the copper(III) species **156**. Finally, reductive elimination of **156** yields the desired three-component BCP product **157** (Scheme 25).[74] This method also explored various other radical precursors in combination with 7-bromo-4-azaindole, identifying α-bromo carbonyl **158**, Togni reagent II **160**, and thiosulfonates **162** as effective radical precursors, yielding functionalized BCP products **159**, **161**, and **163** under optimized conditions (Scheme 26).[66-73]



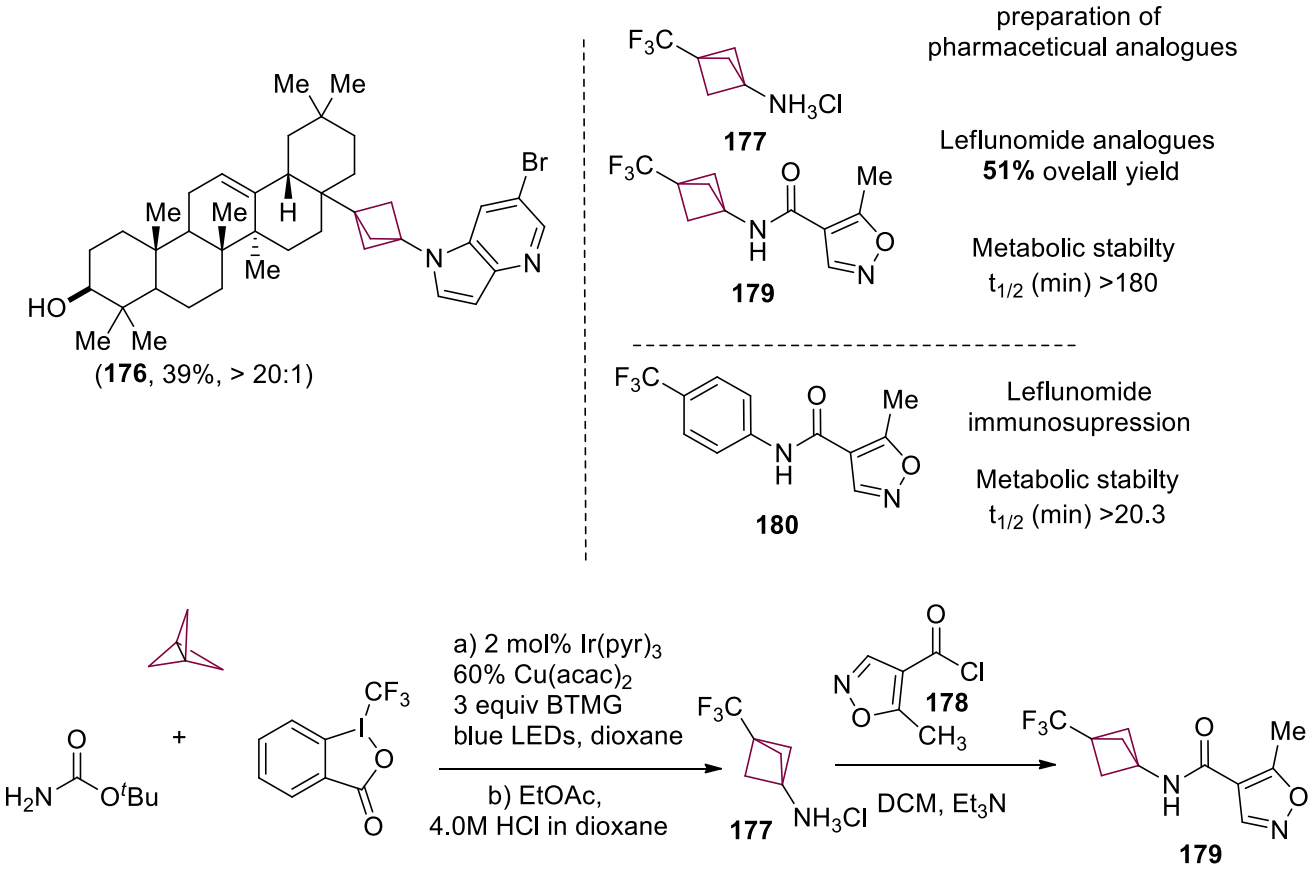
Scheme 26. Scope of the substrate with different radical partners.

The scope of this approach was extended to encompass a wide range of medicinally relevant N-heterocyclic compounds. Examples include indazole **164**, benzimidazole **165**, carbazole **166**, pyrrole **167**, pyrazole **168**, and oxazaindole **169**, all of which were successfully coupled with [1.1.1]propellane to afford the corresponding BCP products with good to excellent yields, as depicted in Scheme 27. Furthermore, this three-component C–N coupling method was not restricted to N-heterocycles; it was also compatible with a diverse range of other N-nucleophiles, such as amides **170**, anilines **171**, imines **172**, and sulfonamides **173**, which underwent smooth reactions with [1.1.1]propellane to give their respective products. Notably, P-nucleophiles **174** and S-nucleophiles **175** demonstrated remarkable reactivity within this platform, enabling access to a broad array of chemically diverse compounds (Scheme 27).



Scheme 27. Three-component radical reaction with different heterocycles

The synthetic utility of this new method was further demonstrated through the late-stage modification of readily available natural products and pharmaceutical moieties.[74] As shown in Scheme 28, a direct installation of an azaindole-bearing BCP unit into the commercially available oleanolic acid **176** was achieved, enabling a single-step access to vicinal quaternary centres within a multicyclic product with synthetically useful yields. The incorporation of carbocyclic aryl rings plays a critical role in the metabolic action of cytochrome P450 (CYP) enzymes. BCP isosteric motifs, being less prone to oxidative degradation, were found to be beneficial in this context. Substitution of the BCP moiety significantly reduced compound clearance and increased metabolic half-life building on these findings, the Macmillan group synthesized bioisosteric compounds and evaluated the in vitro metabolic stability of MCR product **179** (Scheme 28).



Scheme 28. Late-stage functionalization and pharmaceutical analogues.

A gram-scale synthesis of compound **177** was achieved in just two steps (60% combined yield) using amino-trifluoromethylation conditions. Acylation of the amine compound with commercially available acid chloride produced the leflunomide analogue **179**. In vitro stability studies revealed that analogue **179** exhibited markedly improved metabolic stability and a significantly longer half-life in both rat and human liver microsomes compared to the parent leflunomide[74] (Scheme 28).

Conclusion

In conclusion, this review has provided a comprehensive summary of recent advancements in the synthesis of bicyclo[1.1.1]pentane (BCP), focusing on its direct synthesis from strain [1.1.1]propellane via one-pot reactions.

These methods enable the facile formation of C-C, C-N, C-O, C-X (X = Br, I), and C-S bonds at the bridgehead position of BCP scaffolds. The incorporation of the BCP unit into target molecules plays a crucial role in modulating pharmacophore properties, thereby influencing medicinal chemistry applications. Nevertheless, the development of novel, efficient, practical, atom-economical, and environmentally friendly protocols for the synthesis of these valuable compounds remains an ongoing challenge and a key area for future research.

Acknowledgements

We gratefully acknowledge the financial support from OSHEC under the Mukhyamantri Research Innovation (MRI) Extramural Research Funding-2024 (24EM/CH/34), Department of Higher Education, Government of Odisha, and B.J.B. Autonomous College, Bhubaneswar, for providing the necessary research facilities.

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