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Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane

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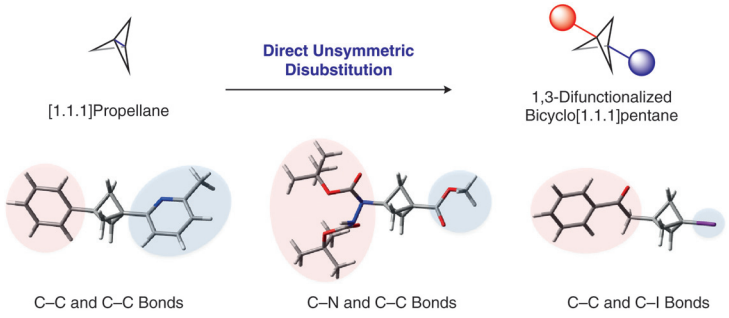

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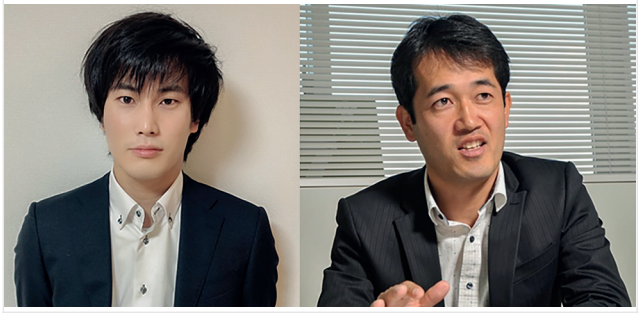
Abstract Utilization of three-dimensional cyclic scaffolds is important in modern drug discovery, both to provide greater opportunities for optimizing drug candidates and to expand the available chemical space of drugs. Among these scaffolds, bicyclo[1.1.1]pentane (BCP) is a high-value bioisostere for 1,4-disubstituted phenyl rings, internal alkynes, and the *tert*-butyl group, generally offering high passive permeability, high water solubility, and improved metabolic stability. However, the lack of methods for functionalizing BCP remains a significant challenge, and in particular, a versatile strategy for synthesizing a wide range of unsymmetrically 1,3-difunctionalized BCP derivatives has been lacking. In this account, we review recent advances in the synthetic chemistry of BCP, focusing especially on our recently developed radical multicomponent carboamination of [1.1.1]propellane.

Key words three-dimensional cyclic scaffolds, bioisosteres, radical multicomponent carboamination, density functional theory, propellanes, bicyclopentanes



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1 Introduction

A century after the synthesis of aspirin, the first artificial synthetic medicine, an enormous range of pharmaceutical drugs is now available. Even today, many newly approved drugs are small-molecule compounds that can be taken orally and can be produced at low cost.[1] However, compared with biopharmaceuticals, small-molecule drugs carry higher risks of toxicity due to their nonspecific interactions with off-target proteins. Because unexpected toxicities are a major reason for discontinuations of drug development,[2] great efforts have been made to analyze structural factors associated with toxicity. For example, statistical analyses indicate that as the number of aromatic ring structures is increased above three, various risks related to toxicity, such as target promiscuity or inhibition of the potassium-ion channel hERG, tend to increase. Moreover, important properties for orally available drugs, such as their aqueous solubility, passive permeability, and melting point,

also tend to get worse.[3] On the other hand, an increased three-dimensional character of compounds, as measured by Fsp^3 (sp^3-hybridized carbons to the total carbon count) has been found to be associated with a reduced risk of toxicity, as measured in terms of promiscuity in a panel of assays, especially for aminergic compounds.[3c] These analytical results therefore suggest that drug development is more likely to be successful for compounds having a small number of aromatic rings and a more-three-dimensional structure.

For these reasons, the importance of three-dimensional cyclic scaffolds in modern medicinal chemistry is increasing.[4] For example, bicyclo[1.1.1]pentane (BCP; **1**) was utilized as a bioisostere for a 1,4-disubstituted phenyl ring in the mGluR1 antagonists developed by Pellicciari et al. in 1996 (Figure 1B).[5a] Then, in 2012, Stepan et al. showed that BCP can be more broadly employed as a high-value bioisostere to improve aqueous solubility, permeability, metabolic stability, and other properties.[5b] Subsequently, additional advantages of converting a 1,4-disubstituted phenyl moiety into a BCP,[5c–f] such as decreased nonspecific binding,[5d] have been discovered. BCP has been also established as a high-value bioisostere for the *tert*-butyl group or for an internal alkyne (Figures 1C and 1D).[6,7]

2 Overview of the Synthetic Chemistry of [1.1.1]Propellane, the Most Promising Precursor of Bicyclo[1.1.1]pentane

Despite the usefulness of BCP as a bioisostere in drug development, it has proved difficult to establish a general procedure for the introduction of various functional groups at its bridgehead carbons. At present, [1.1.1]propellane (**2;** Scheme 1) (hereafter referred as to 'propellane') is considered to be the most promising precursor for synthesizing a broad range of BCP derivatives (Scheme 1A).[8]

Propellane was initially thought to be incapable of existence, due to its highly strained structure. However, Wiberg et al. theoretically predicted that it might be formed from 1,3-disubstituted BCP derivatives and would be relatively stable; it was then synthesized by the method shown in Scheme 1B.[9] Subsequently, Szeimies and co-workers dramatically improved and optimized the synthesis of propellane by using the commercially available starting material **3** (Scheme 1C).[10] This synthetic method can be scaled up for the synthesis of various BCP derivatives. It is also possible to synthesize BCP derivatives without using propellane; the method shown in Scheme 1D is a well-known representative example.[11] However, it is necessary to preinstall bicyclo[1.1.0]butane precursor substituents. Thus, the synthetic method that uses propellane offers much greater flexibility, in that various substituents can be efficiently introduced into the BCP scaffold.

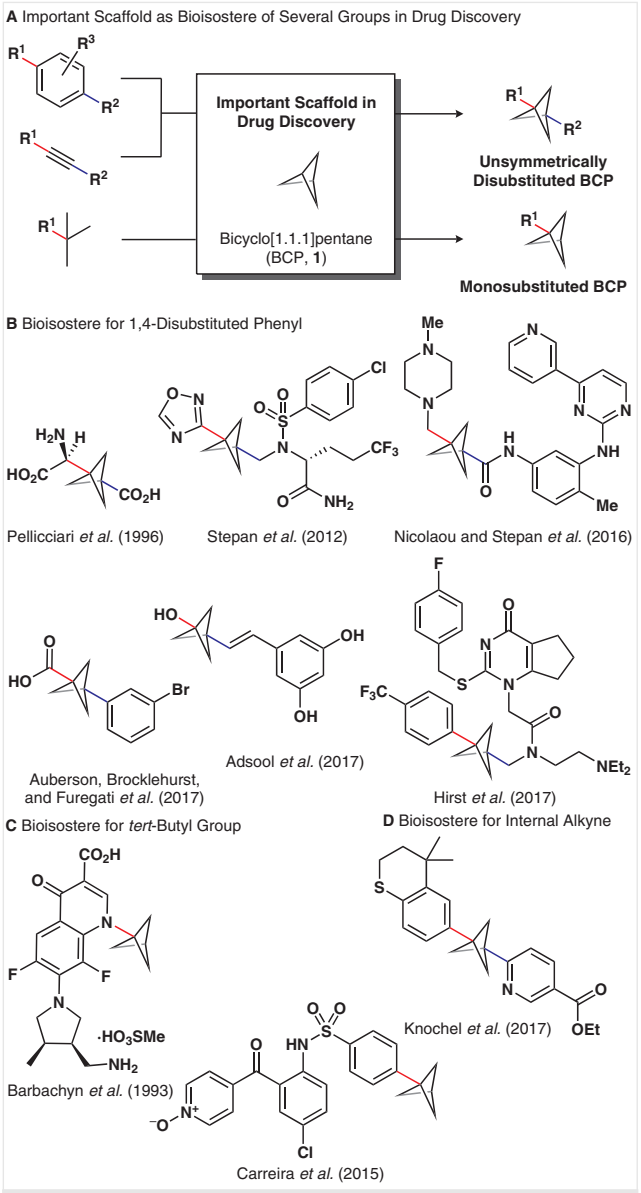
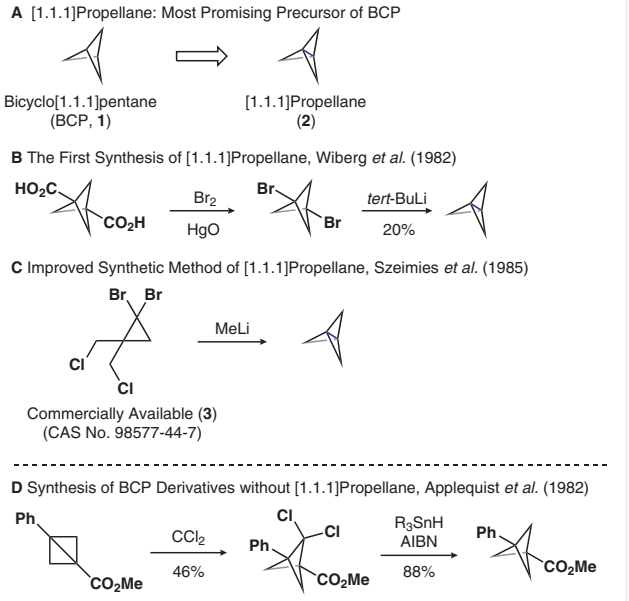
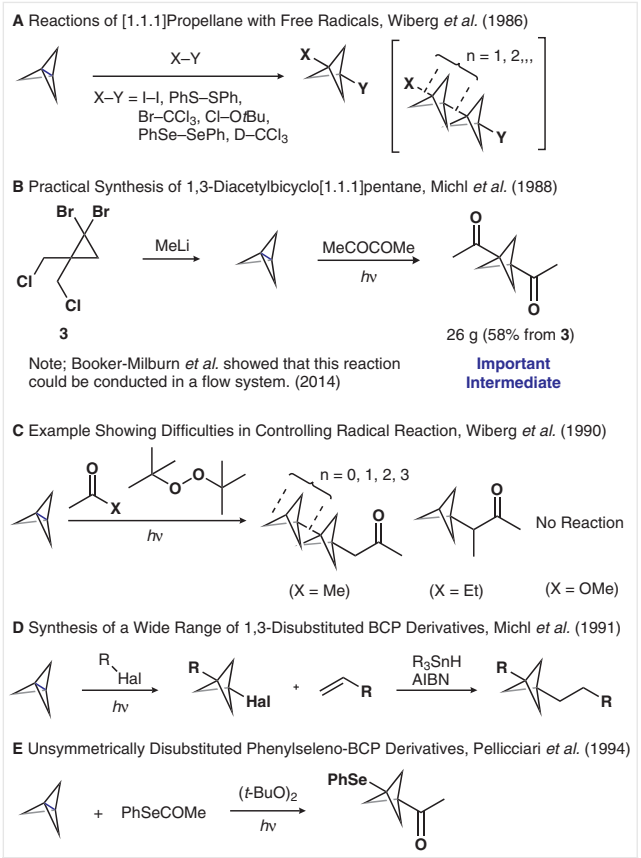


Figure 1 (A) BCP as a bioisostere for various groups. Examples include (B) a 1,4-disubstituted phenyl ring, (C) a *tert*-butyl group, and (D) an internal alkyne.

Propellane has a characteristic and fragile 'charge-shift bond' between the bridgehead carbons,[12] and ring-opening reactions of propellane with various reagents have been developed for the introduction of several functional groups into the BCP scaffold. The charge-shift bond can be cleaved with radical species to give a bicyclopentyl radical, which can be trapped with various reagents to give disubstituted products (Scheme 2A).[13] For example, the radical reaction of propellane with iodine gives 1,3-diiodobicyclo[1.1.1]pentane, which is a useful intermediate. However, in some other reactions, particularly in the addition of cyanogen bro-



Scheme 1 (A, B, C) History of the synthesis of propellane, the most promising precursor of BCP. (D) Synthesis of the BCP scaffold without propellane.



Scheme 2 Reactions of propellane with free radicals

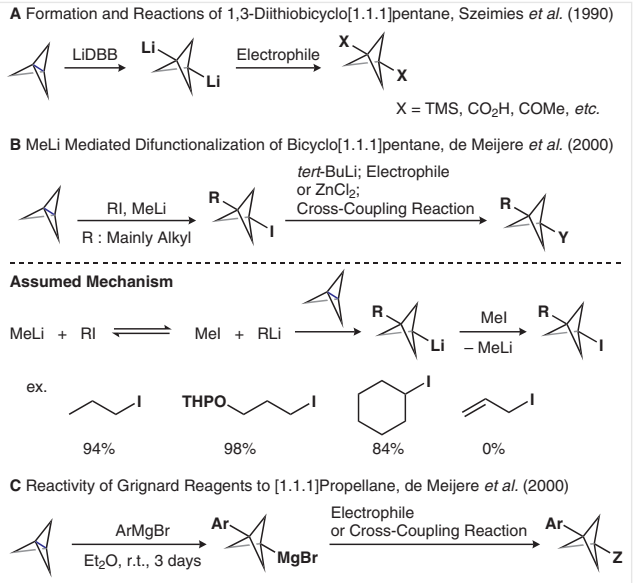
mide, oligomerization was observed. Subsequently, Kaszynski and Michl reported a practical synthesis of 1,3-diacetylbicyclo[1.1.1]pentane (Scheme 2B),[14] which is widely used as an intermediate in the synthesis of unsymmetrically disubstituted BCP derivatives, and can be synthesized in a flow system.[15] However, these intermolecular radical coupling reactions of propellane are generally limited by strict requirements for the reaction conditions, such as the concentration and/or the need for a low temperature to avoid oligomerization or self-condensation of propellane.[16,17] Further, it is often difficult to obtain the desired product in predictable way; for example, Wiberg and Waddell showed that subtle changes in the reactivity of reagents had a major influence on the product structure and the success or failure of the reaction (Scheme 2C).[17]

Michl and co-workers showed that some alkyl halides can be used as precursors of radical species for synthesizing BCP derivatives (Scheme 2D).[18] In addition, Pellicciari and co-workers reported a synthesis of unsymmetrically disubstituted phenylselenylated BCP (Scheme 2E).[19] As mentioned above, many different radicals and radical sources can be used if the reagents and conditions are appropriately chosen, so radical additions to propellane are frequently employed.

Bicyclo[1.1.1]pentyl metal reagents can also be used to synthesize 1,3-disubstituted BCP derivatives. Propellane is reduced by lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) to afford 1,3-dilithiated BCP (Scheme 3A),[20] which can react with various electrophiles. In 2000, de Meijere et al. reported a methyllithium-mediated addition of alkyl iodides to propellane (Scheme 3B),[21] in which alkyllithium generated in situ by a lithium–iodine exchange between methyllithium and an alkyl iodide adds to propellane. The resultant alkylated BCP lithium intermediate smoothly undergoes another lithium–iodine exchange with the alkyl iodide (or with methyl iodide).

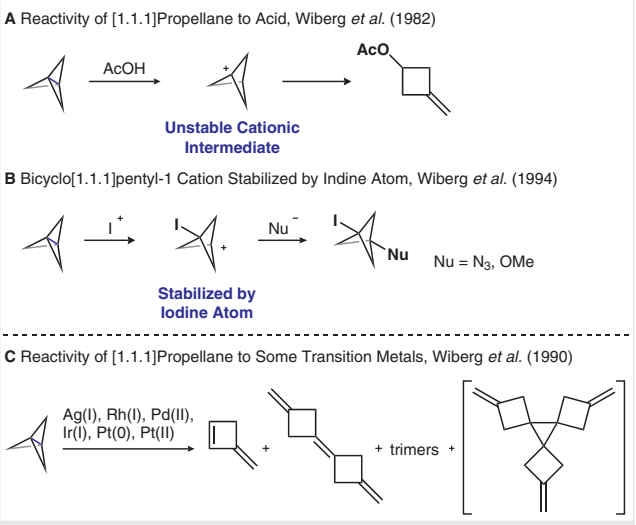
The fact that allyl iodide is not an effective reactant provides indirect support for this mechanism. That is, allyllithium should be less nucleophilic than alkyllithiums and thus less reactive in the addition to propellane. Grignard reagents can also be used for ring opening of propellane to give 1-substituted BCP–magnesium reagents.[21,22] The intermediate BCP–magnesium halides can react with electrophiles or can be used in cross-coupling reactions (Scheme 3C).

However, acidic conditions are not available for transformations of propellane, because the BCP cation is generally unstable and skeletal rearrangement readily occurs to yield four-membered ring-opened products exclusively (Scheme 4A).[9] On the other hand, Wiberg and McMurdie showed that installation of iodine at the 3-position significantly stabilized the BCP cation.[23] The resulting BCP cation can be trapped with a nucleophilic reagent such as the azide ion (Scheme 4B). Wiberg and Waddell also investigat-



Scheme 3 Reactions of propellane with organometallic reagents

ed the reactivity of propellane toward various transition metals and they obtained three- or four-membered ring derivatives (Scheme 4C).[17]

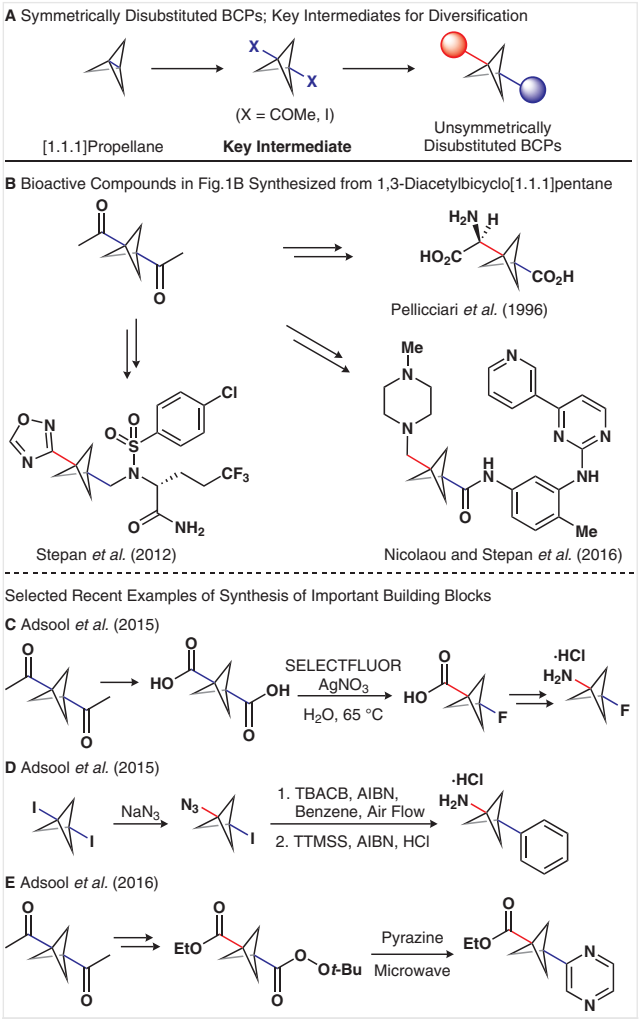


Scheme 4 Reactions of propellane with cationic species or transition metals

3 Recent Advances in the Synthetic Chemistry of Unsymmetrically 1,3-Disubstituted Bicyclo[1.1.1]pentane Derivatives

Access to unsymmetrically 1,3-disubstituted BCP derivatives remains a key challenge because the BCP radical/anion intermediates need to react with the appropriate reagents in preference to undergoing undesired oligomerization or skeletal rearrangement. Despite the importance of the above-mentioned pioneering studies on the synthesis of 1,3-disubstituted BCP derivatives, the available methods generally suffer from limitations of substrate scope, poor functional-group compatibility, and/or relatively harsh reaction conditions.

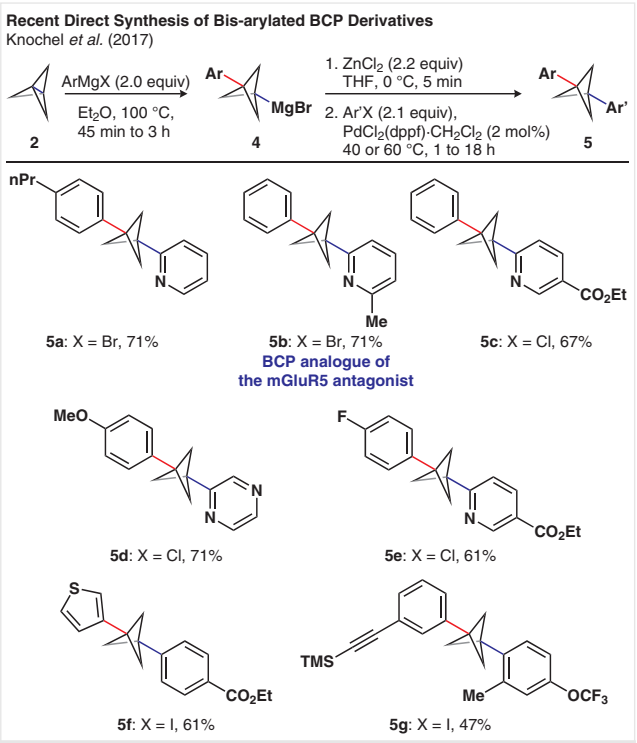
Therefore, structurally complicated BCP derivatives have generally been synthesized by using symmetrically disubstituted BCP derivatives as key intermediates (Scheme 5A). For example, some of the bioactive compounds containing unsymmetrically 1,3-disubstituted BCP scaffolds shown in Figure 1B were synthesized from 1,3-diacetyl compounds via multistep reactions (Scheme 5B).[5a–c] More recently, some building blocks have been synthesized by using a 1,3-diacetyl or 1,3-diiodo compound as a starting material. Adsool et al. have developed various practical re-



Scheme 5 (A) Symmetrically disubstituted BCPs: key intermediates. (B) Synthesis of bioactive compounds from 1,3-diacetylbicyclo[1.1.1]pentane. (C, D, E) Selected examples of syntheses of building blocks.

actions to afford 3-fluoro-BCP-1-amine (Scheme 5C)[24] and 3-aryl-BCP-amine/ester scaffolds (Schemes 5D and 5E),[25,26] which are of interest in modern drug discovery as bioisosteres of biaryl scaffolds to escape from the 'flatlands' of multiple aromatic rings.[3]

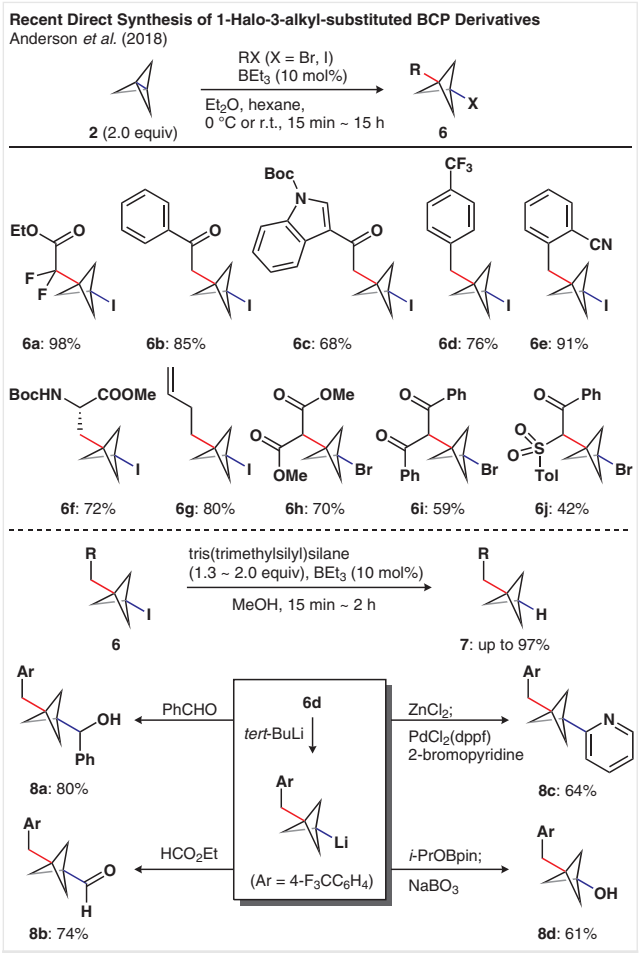
On the other hand, synthetic methods that do not use symmetrically disubstituted BCP derivatives as starting materials, that is, direct unsymmetrical disubstitution reactions of propellane, have been developed in increasing numbers. Knochel and co-workers developed an elegant method for synthesizing diarylated BCP derivatives **5** by combining Grignard reagent-mediated ring opening of propellane with Negishi cross-coupling after transmetalation with $ZnCl_2$ (Scheme 6).[7]



Scheme 6 Practical synthesis of diarylated BCP derivatives

The diarylated BCP derivatives obtained were shown to serve as potential bioisosteres of internal alkynes. Specifically, BCP analogues of tazarotene and an mGluR5 antagonist were prepared and their physicochemical properties were evaluated.

Anderson and co-workers developed a practical synthesis of 1-halo-3-alkyl-substituted BCP derivatives **6** under mild reaction conditions through triethylborane-promoted atom-transfer radical addition ring opening of propellane with alkyl halides (Scheme 7).[27] This method shows high functional-group tolerance and a broad substrate scope, and the resultant BCP halides can be transformed into a wide range of functionalized BCP derivatives.



Scheme 7 Synthesis of highly functionalized 1-halo 3-substituted BCP derivatives, and transformations of the products

Heteroatom installation at the BCP bridgehead carbon is still undeveloped. For example, bicyclo[1.1.1]pent-1-ylamine (BCP-amine) has long been expected to be an important building block for pharmaceuticals (Figure 2).[28]

However, few BCP-amine derivatives have been synthesized, despite intensive synthetic studies on BCP-amine since 1970.[29] 3-Substituted BCP-amines would be particularly useful as building blocks, but the synthetic chemistry of 3-substituted BCP-amine derivatives has remained largely unexplored. In 2016, Baran an co-workers established a ring-opening reaction of propellane by turbo-Grignard amido reagents to give BCP-amine derivatives.[30] However, the transformation of BCP-amines into 3-substituted BCP-amines is expected to be difficult.

3-Functionalized BCP-amines have generally been synthesized by multistep transformations of symmetrically disubstituted BCP derivatives, as illustrated in Schemes 5C and 5D.[24,25] However, such methods often suffer from low diversity of products. For example, before we developed the

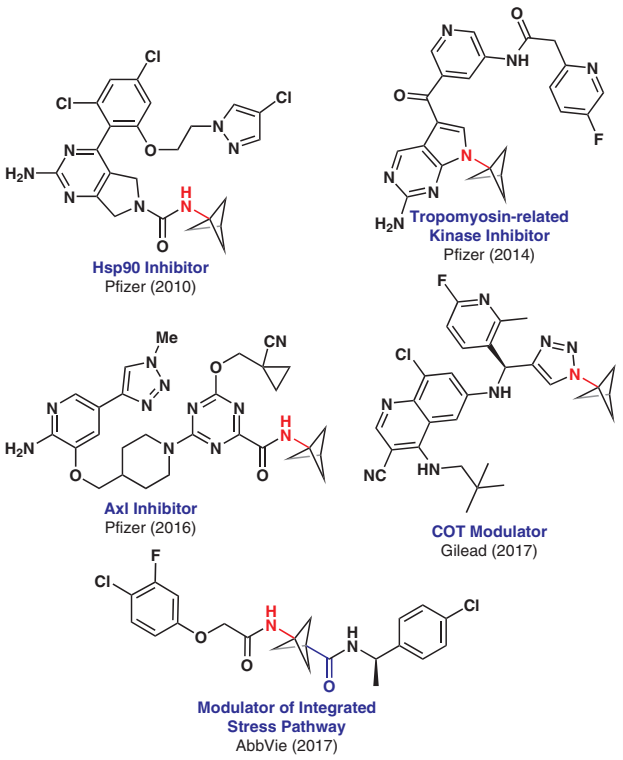
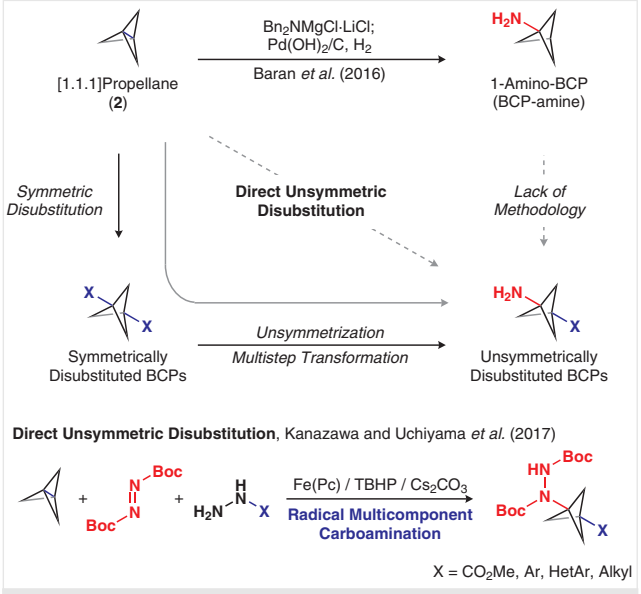


Figure 2 Selected bioactive compounds containing BCP-amine or 3-substituted BCP-amine scaffolds



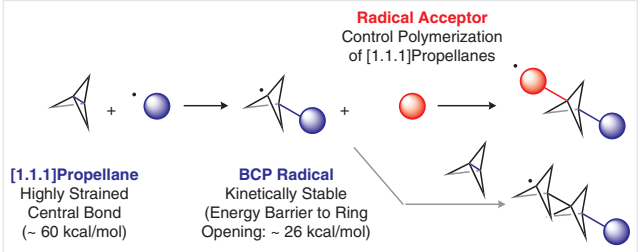
Scheme 8 Direct synthesis of 3-substituted BCP-amines

radical multicomponent carboamination, which we will describe below, there was only one report on the synthesis of 3-phenyl-BCP-amine (Scheme 5D),[25] and there had been no examples of the introduction of substituted aryl groups into BCP-amine.

Our recently developed radical multicomponent carboamination of propellane permits the straightforward synthesis of a variety of unsymmetrically disubstituted BCP derivatives (Scheme 8).[31] In Section 4, we describe this reaction in detail.

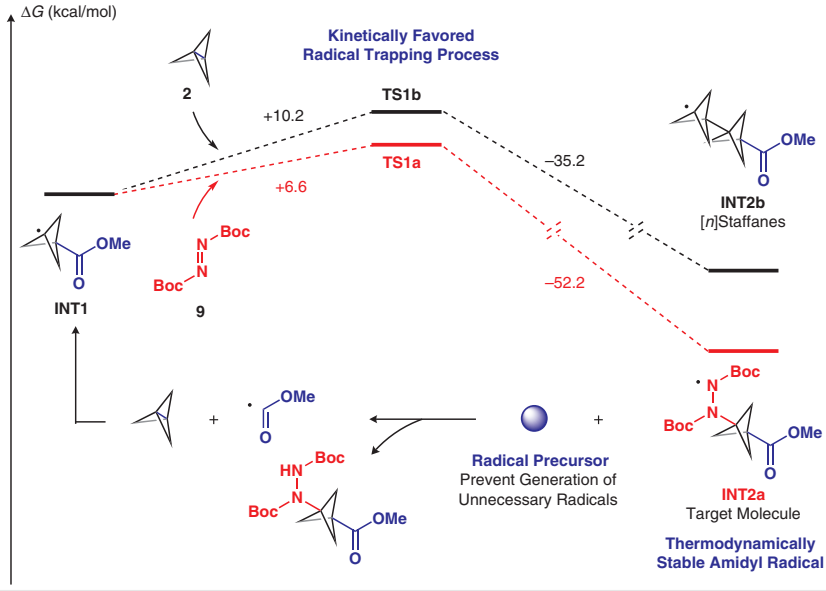
4 Radical Multicomponent Carboamination of [1.1.1]Propellane Permits the Direct Synthesis of 3-Substituted Bicyclo[1.1.1]pent-1-ylamine Derivatives

Propellane has a characteristic fragile central bond,[12] a so-called charge-shift bond with an energy of ~60 kcal/mol,[9] which readily reacts with radical species to give the kinetically stable bicyclo[1.1.1]pent-1-yl radical (the energy barrier to ring opening is ~26 kcal/mol).[32] We hypothesized that a radical multicomponent carboamination (radical addition to propellane/central-bond cleavage/BCP radical trapping) might permit C–C and C–N bonds to be formed simultaneously on a BCP scaffold to generate 3-functionalized BCP-amine derivatives. In a radical reaction involving propellane, as described above, it is generally difficult to control polymerization as a side reaction,[16,17] but we thought that this problem might be overcome by choosing an appropriate radical acceptor (Scheme 9).



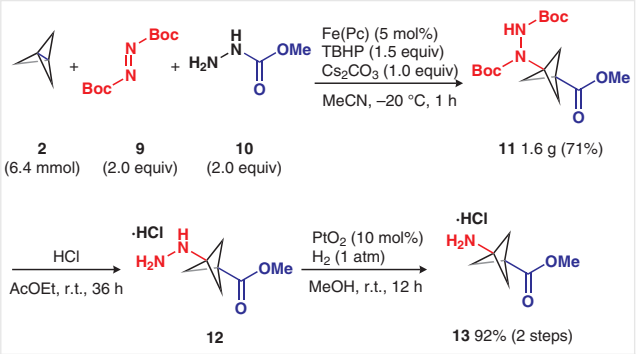
Scheme 9 Working hypothesis for a radical multicomponent reaction

Indeed, model calculations showed that di-*tert*-butyl azodicarboxylate (**9**)[29d,33] might be used as an appropriate acceptor of the 3-substituted BCP radical **INT1** to give a more stable amidyl radical intermediate **INT2a**. The C–N bond formation to give **INT2a** ($\Delta G^{\ddagger}$ = 6.6 kcal/mol) is kinetically preferred by 3.6 kcal/mol over radical oligomerization involving propellane to give [*n*]staffanes **INT2b** ($\Delta G^{\ddagger}$ = 10.2 kcal/mol) (Scheme 10). **INT2a** has a stable amidyl radical, resulting in a highly exothermic process. On the basis of this result, we expected that generation of a carbon radical species through hydrogen abstraction by **INT2a** should occur, resulting in a radical chain reaction that would prevent the generation of undesired radical species and suppress side reactions.



Scheme 10 Model calculation at the UM062X/6-31G* level (ΔG‡ in kcal/mol) and the importance of the radical precursor in preventing the generation of undesired radicals

To test this working hypothesis, we first chose methyl hydrazinecarboxylate (**10**) as a methoxycarbonyl radical precursor.[34] Because the hydrogen-abstraction step from **10** to give a methoxycarbonyl radical proceeds in the presence of oxidant and a transition-metal catalyst, the use of photoirradiation equipment or toxic tin reagents is not necessary.[35] We investigated the radical multicomponent carboamination of propellane in pentane solution with **9** and **10**.[36] The optimized reaction could be carried out on a gram scale to provide **11** in 71% yield (Scheme 11). The protected hydrazine group provides a versatile platform for further chemical transformations. Treatment of **11** with hydrochloric acid in EtOAc gave the hydrazine monohydrochloride **12**. Further transformation under hydrogenation conditions in the presence of platinum(IV) oxide afforded methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate monohydrochloride (**13**) in 92% yield (over the two steps).



Scheme 11 Gram-scale synthesis and transformation into an amine

The structure of **11** was confirmed by single-crystal X-ray diffraction analysis, and as expected, it was found that the hydrazine moiety and the methoxycarbonyl group were located at the bridgehead carbons of the BCP skeleton (Figure 3).

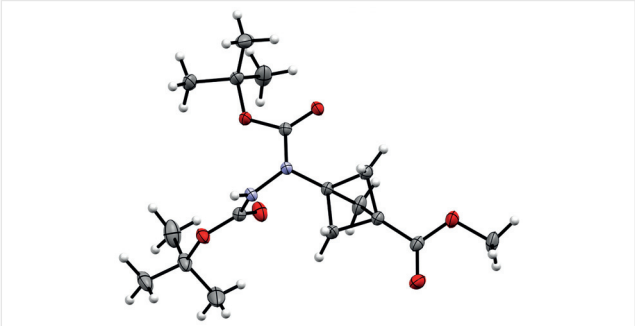
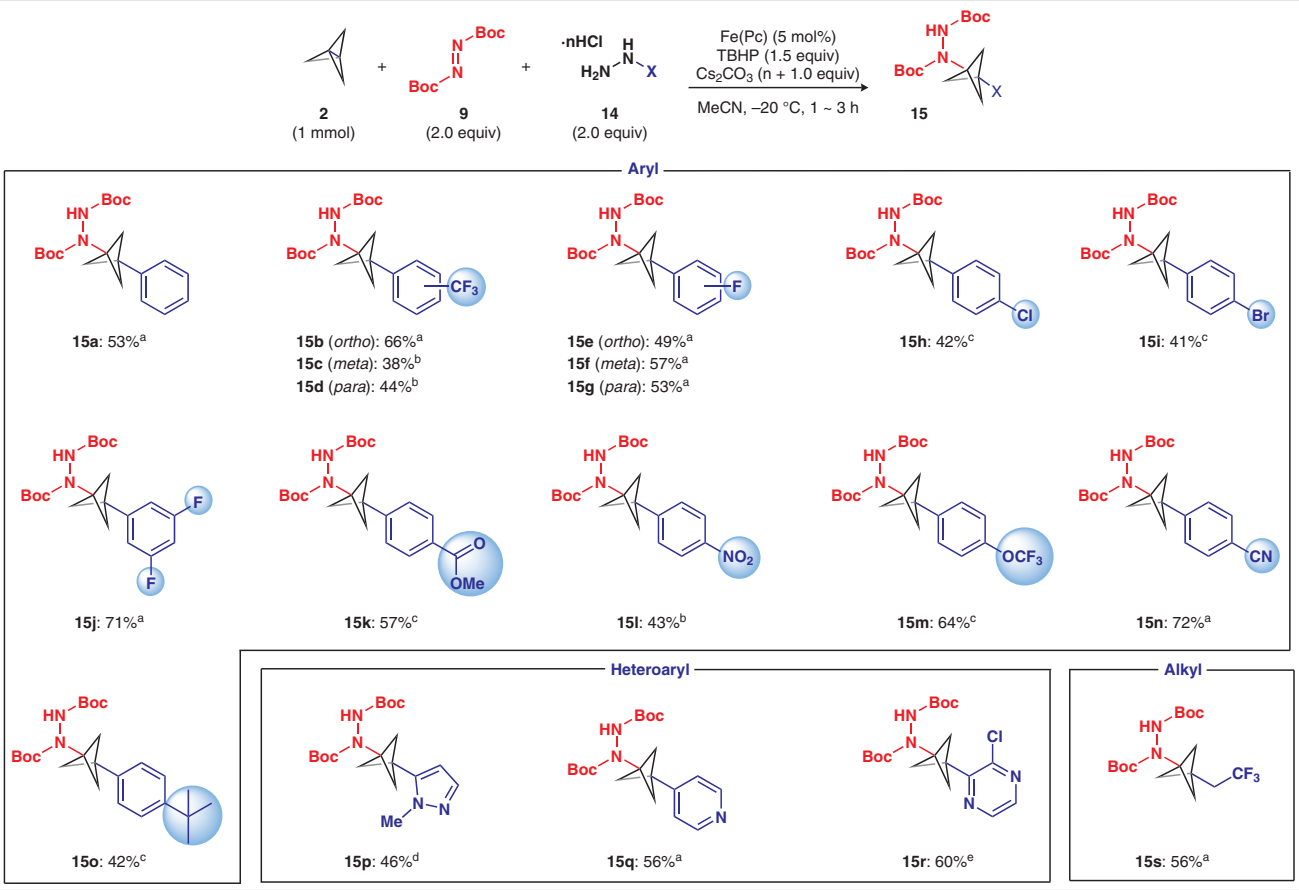


Figure 3 ORTEP diagram of **11** (ellipsoids displayed at 50% probability; gray: carbon, red: oxygen, blue: nitrogen)

The optimized radical multicomponent carboamination has a broad scope for the synthesis of a wide range of 3-aryl-BCP-amine equivalents (Scheme 12). Various arylhydrazines can be employed, and electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-positions of the aryl ring are well tolerated (**15b–g**). Halogens (F, Cl, or Br) on the aryl ring were also tolerated, and the target products **15e–j** were obtained without the occurrence of dehalogenation reactions. A range of functional groups, such as methyl ester (**15k**), nitro (**15l**), trifluoromethyl ether (**15m**), nitrile (**15n**), or *tert*-butyl (**15o**) were also compatible. Notably, this reaction also enabled us to introduce heterocyclic

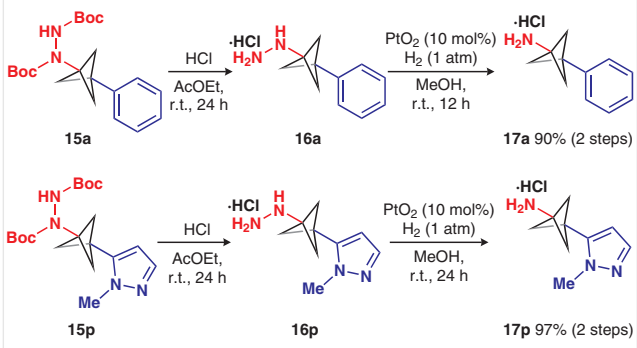


Scheme 12 Radical multicomponent carboamination of propellane with aryl, hetaryl, or alkyl hydrazines *Reaction conditions*: **2** in pentane (1.0 mmol), **9** (2.0 equiv), **14** (2.0 equiv.), TBHP, Fe(Pc), Cs_2CO_3 in MeCN (6.0 mL) at −20 °C. Yields were determined by ^{1}H NMR with benzyl benzoate as an internal standard. [a] Hydrazine monohydrochloride (n = 1), 1 h. [b] Hydrazine (n = 0), 3 h. [c] Hydrazine monohydrochloride (n = 1), 3 h. [d] Hydrazine dihydrochloride (n = 2), 1 h. [e] Hydrazine (n = 0), 1 h.

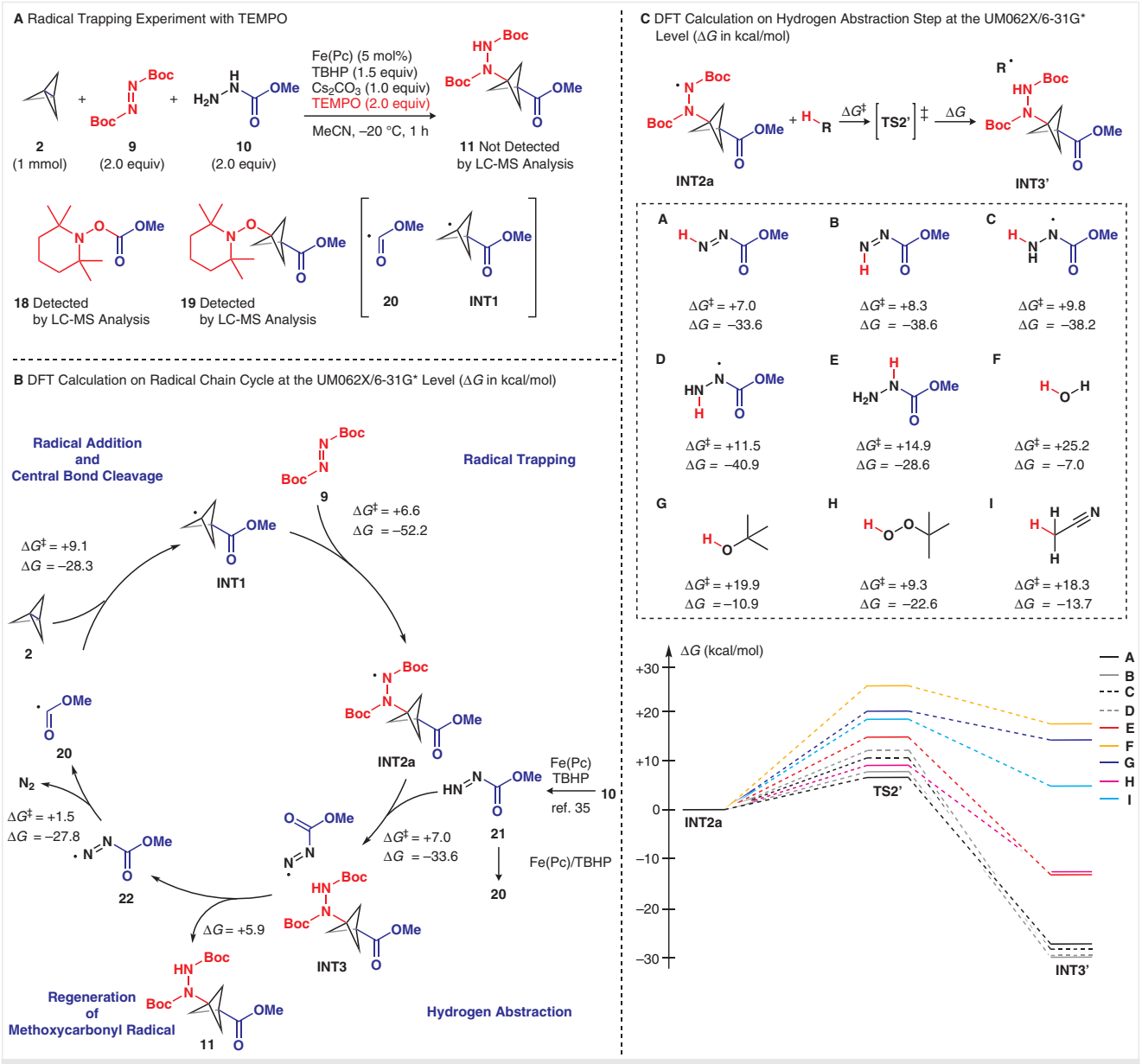
rings, including pyrazolyl (**15p**), pyridinyl (**15q**), or pyrazinyl (**15r**). To synthesize other types of scaffold, we examined alkyl hydrazines as substrates. When (2,2,2-trifluoroethyl)hydrazine was used as an alkyl substrate, **15s** was obtained in moderate yield. This result suggests that our optimized radical multicomponent carboamination can be used to introduce C(sp^3)–functional groups on the BCP scaffold. As far as we know, this is the first example of a one-pot radical multicomponent carboamination of propellane to afford a wide range of highly multifunctionalized BCPs.

We also confirmed that the aryl-substituted products **15a** and **15p** can be transformed into the corresponding amines in good yields (Scheme 13).

Finally, a mechanistic investigation was performed. When TEMPO (2.0 equiv) was used as a radical inhibitor, **11** was not obtained at all, and TEMPO adducts [TEMPO-COOMe (**18**) and TEMPO-BCP-COOMe (**19**)] were detected by LC-MS analysis (Scheme 14A). This result supports the expected free-radical mechanism (via **20**, **INT1**). To elucidate the radical chain cycle, we next conducted density functional theory (DFT) calculations at the UM062X/6-31G* level (Scheme 14B).



Scheme 13 Transformation of aryl-substituted products into amines



Scheme 14 (A) Radical-trapping experiment with TEMPO. (B) DFT calculations for the radical chain cycle at the UM062X/6-31G* level ($\Delta G^{\ddagger}$ in kcal/mol). (C) DFT calculations for the hydrogen-abstraction step at the UM062X/6-31G* level ($\Delta G^{\ddagger}$ in kcal/mol).

First, addition of the methoxycarbonyl radical (**20**) [generated in situ by hydrogen abstraction and denitrogenation of methyl hydrazinecarboxylate (**10**)] to propellane with a small activation energy ($\Delta G^{\ddagger}$ = 9.1 kcal/mol) leads to cleavage of the central charge-shift bond to give the BCP radical species **INT1** with a high stabilization energy (ΔG = 28.3 kcal/mol). Then, di-*tert*-butyl azodicarboxylate (**9**) acts as an appropriate radical acceptor of **INT1** to give a more stable amidyl radical **INT2a** ($\Delta G^{\ddagger}$ = 6.6 kcal/mol) with a very high stabilization energy (ΔG = 52.2 kcal/mol). As intended, **INT2a** abstracts hydrogen from **21** with a small activation energy ($\Delta G^{\ddagger}$ = 7.0 kcal/mol) to give the unsymmetrically disubstituted BCP product **11** and the diazenyl radical **22**, which smoothly gives **20** with the release of molecular nitrogen ($\Delta G^{\ddagger}$ = 1.5 kcal/mol). In this hydrogen-abstraction process, there are many candidates for potential hydrogen sources in the reaction mixture, including H_2O, TBHP, *t*-BuOH, or MeCN. On the basis of a comparison of activation energies, **21A** or **21B** appears to be the most energetically favorable substrate (Scheme 14C). This result means that the hydrazine moiety is an excellent precursor for the carbon-centered radical, preventing the generation of highly

reactive oxygen-centered free radicals.[35,37] The overall DFT-calculated catalytic cycle turned out to be thermodynamically and kinetically favorable, in good accordance with the experimental observations [the reaction proceeds under very mild conditions (−20 °C), and is generally completed within 1 h].

5 Conclusion

In the wake of the discovery that bicyclo[1.1.1]pentane is an effective bioisostere for 1,4-disubstituted aromatics, internal alkynes, and the *tert*-butyl group in medicinal chemistry and drug discovery, a general procedure was required for the introduction of various functional groups at the bridgehead carbons of BCP. Here, we have described some representative recent examples of activation of the characteristic central charge-shift bond of [1.1.1]propellane, which have opened up a new window onto the synthesis of substituted BCP derivatives.

We have focused particularly on our highly efficient and direct method for forming C–C and C–N bonds simultaneously on a BCP scaffold, providing access to unsymmetrically 1,3-disubstituted BCP derivatives. These novel multifunctionalized products can be easily transformed into a variety of synthetically useful 3-substituted BCP-amines. We also describe our comprehensive analysis of the reaction profile of this radical multicomponent carboamination, based on a combination of experimental and computational methods. These results should contribute to further development of the synthetic chemistry of BCP, and thus to encourage its practical applications in pharmaceutical chemistry, agricultural chemistry, and materials sciences.

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