Pyridine-Boryl Radical-Catalyzed [2π + 2σ] Cycloaddition of Bicyclo[1.1.0]butanes with Alkenes

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Abstract

Bicyclo[2.1.1]hexanes (BCHs) represent an intriguing class of structurally rigid hydrocarbons that can serve as the bioisosteres of benzenoids in medicinal chemistry. Methods for the synthesis of BCHs are, however, limiting. Reported herein is a facile synthesis of BCHs via a strain-release-driven [2π + 2σ] cycloaddition of bicyclo[1.1.0]butanes (BCBs) with alkenes facilitated by a pyridine-boryl radical catalyst. The mild reaction conditions, broad substrate scope, and decent functional group tolerance of this protocol render it appealing in relevant fields of drug design and synthesis. Theoretical mechanistic studies reveal a radical relay mechanism involved. Synthetic applications of the products are conducted.

Keywords: bicyclo[2.1.1]hexane; cycloaddition; pyridine-boryl radical; redox-neutral; strain-release

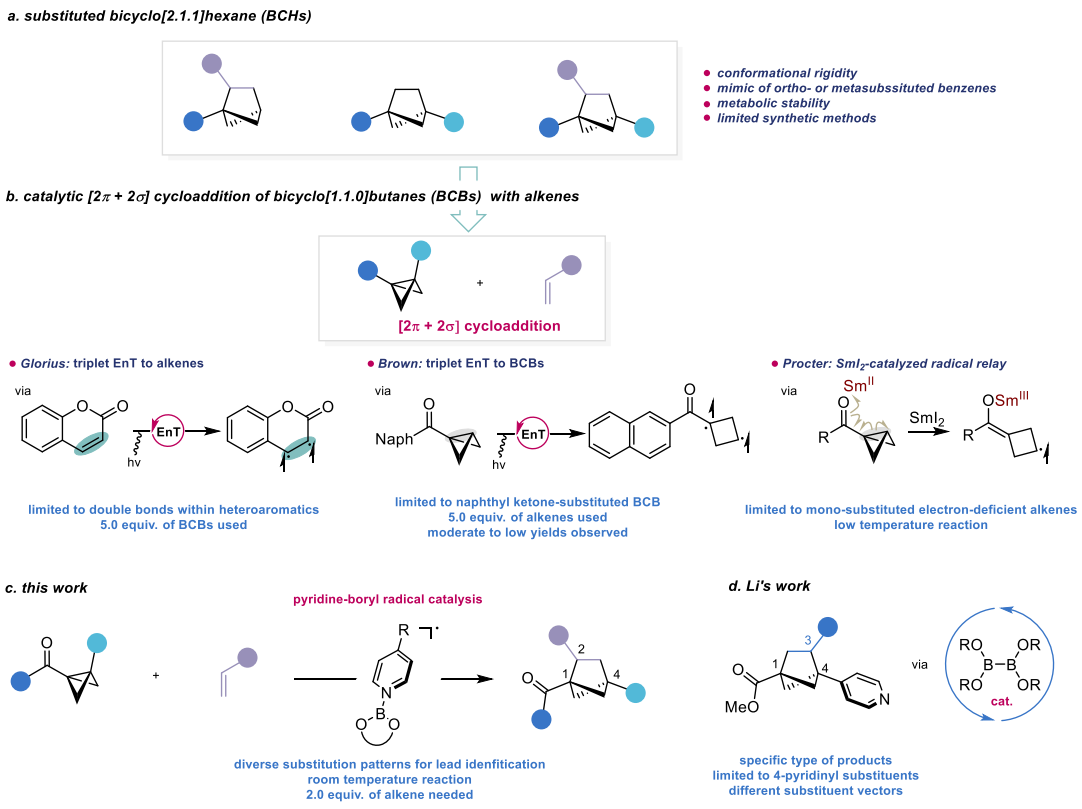
Introduction

The function of a molecule is closely related to its three-dimensional architecture.[1] This is especially true in medicinal chemistry, wherein the precise orientation of each pharmacophore is key for determining the strength and selectivity of protein–ligand interaction.[2] In this regard, the benzene ring, due to its easy accessibility, rich substitutional patterns and structural rigidity, has been ubiquitously used as the core scaffold in therapeutics and other bioactive molecules.[3] Nevertheless, to avoid the potential undesirable metabolic instability under physiological conditions, the search for stable alternatives to replace the benzene ring is of great interest for improved lead identification and therapeutic success. Recently, several C(sp^3)-rich bicyclic hydrocarbons, due to their rigid conformation and metabolic stability, have shown great potential in replacing the benzene rings.[4] Among them, bicyclo[2.1.1]hexanes (BCHs) are of particular interest (Scheme 1a).[5] Depending on the substitution pattern, they can mimic both ortho- and meta-substituted benzenoids, and have therefor received increasing attention in drug design. Nevertheless, their flexible synthesis, especially the catalytic version, still poses a formidable challenge.

Previously, the intramolecular [2 + 2] cycloaddition of 1,5-dienes under UV light irradiation provides an efficient route for BCHs synthesis.[6] Alternatively, the strain-release-driven [2π + 2σ] cycloaddition of bicyclo[1.1.0]butanes (BCBs)[7] with alkenes represents another useful strategy. In this regard, the thermo-driven reactions at high temperature (up to 150 ^{o}C) were known.[8] Wipf later demonstrated that the

intramolecular version of this process could be conducted at ambient temperature, leading to the assembly of an interesting tricyclononane scaffold.[9] With the rapid evolvement of catalytic photochemical reactions, very recently, two inspiring [2π + 2σ] cycloadditions of BCBs with alkenes induced by visible-light-mediated triplet energy transfer were disclosed. Glorius showed that the sensitization of the double bond within several heteroaromatics could initiate an efficient reaction with diverse BCBs (Scheme 1b).[10] On the other hand, Brown found that the sensitization of a naphthyl ketone-substituted BCB is another alternative for efficient reaction (Scheme 1b).[11] The activation mode of these two processes requires the use of photo sensitizable substrates, thereby limiting the generality. In addition, due to the high reactivity of the participating diradicals, the unsensitizable coupling partners were used in large excess (typically 5.0 equiv.) to ensure high efficiency. By using SmI_2 as catalyst, Procter recently disclosed a mechanistically distinct radical relay synthesis of BCHs at low temperature, but the scope was still limited to mono-substituted electron-deficient alkenes (Scheme 1b).[12]

Scheme 1. Bicyclo[2.1.1]hexanes (BCHs) and their synthesis.



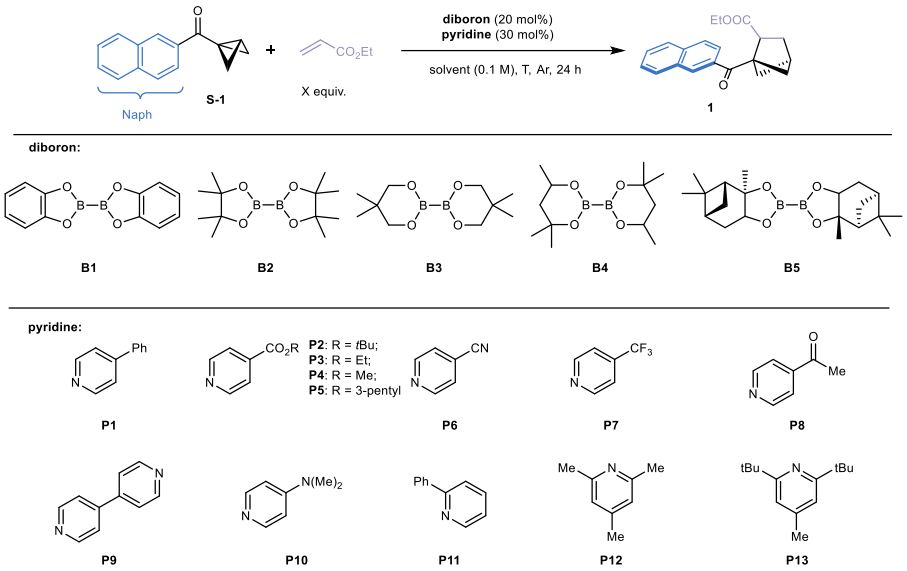
Recently, pyridine-boryl radicals generated from the pyridine induced homolytic cleavage of diboron B–B bond have demonstrated intriguing reactivities.[13] They have been engaged in several radical-type pyridine-functionalization,[14] C–C[15] and C–B[16] coupling reactions. In addition, pyridine-boryl radical have been regarded as super electron donors.[17] We are intrigued by the "electron catalysis" concept[18] and wondered the profound electron-donor ability of pyridine-boryl radicals may induce a new mode of

a redox neutral radical coupling of [2π + 2σ] cycloaddition of BCBs with alkenes. Herein, we report that the combination of 4-Ph-pyrine/B_2cat_2 as catalyst could enable a smooth reaction of BCBs with alkenes at ambient temperature (Scheme 1c). The mildness of the reaction allows the use of 2.0 of alkenes for high efficiency. Importantly, broad substrate scope is achieved on both coupling partners. During the preparation of this manuscript, Li reported a diboron-catalyzed coupling reaction of pyridinyl-substituted BCBs with alkenes at relatively high temperature. The formation of specific type of products and therefore the low generality may limit its application (Scheme 1d).[19] In addition, the reaction generally gave 1,3,4-trisubstituted BCHs, a substitution pattern that is distinct from this study.

Method optimization

Optimization studies began with the cycloaddition of naphthyl ketone-substituted BCB **S-1** with ethyl acrylate (5.0 equiv.). A diverse array of diborons and substituted pyridines were firstly screened (Table 1). Interestingly, with 4-Ph-pyridine (**P1**) as pyridine catalyst, B_2cat_2 (**B1**) showed encouraging reactivity, giving the desired products in 60% yield in dioxane (0.1 M) at room temperature (entry 1). Other alkoxyl-derived diboron such as B_2pin_2 (**B2**), B_2neop_2 (**B3**), **B4** and **B5** gave no products at all, implying the Lewis acidity of diboron may play an important role (entry 2). Previously, the electron-poor pyridine with ester (**P2-5**) or cyano (**P6**) substituent were more often used in boryl radical formation. However, these pyridines showed much inferior catalytic reactivities as compared to 4-Ph-pyridine (entries 3-7). Further tuning the electronic (**P7-10**) and steric (**P11-13**) prosperities on pyridine turned out to be unfruitful (entries 8 and 9). The reaction was not quite sensitive to the polarity of the solvent (entries 10-15), but non-polar aprotic solvent such as *n*-hexane (entry 12) and toluene (entry 14) provided higher yields of 90% and 84% respectively. Interestingly, raising the temperature resulted in low yield probably due to the unproductive decomposition of BCB (entries 16 and 17). Pleasingly, lowering the loading of ethyl acrylate to 2.0 equivalents did not attenuate the yield (entries 18 and 19). The combination of **B5** and **P5** as catalyst in anisole turned out to be ineffective at room temperature (entry 20).[17a, 19] Control experiments showed that both the diboron (entry 21) and pyridine (entry 22) were indispensable for the reaction.

Table 1. Optimization of pyridine-boryl radical-catalyzed cycloaddition of naphthyl ketone-substituted BCB S-1 with ethyl acrylate



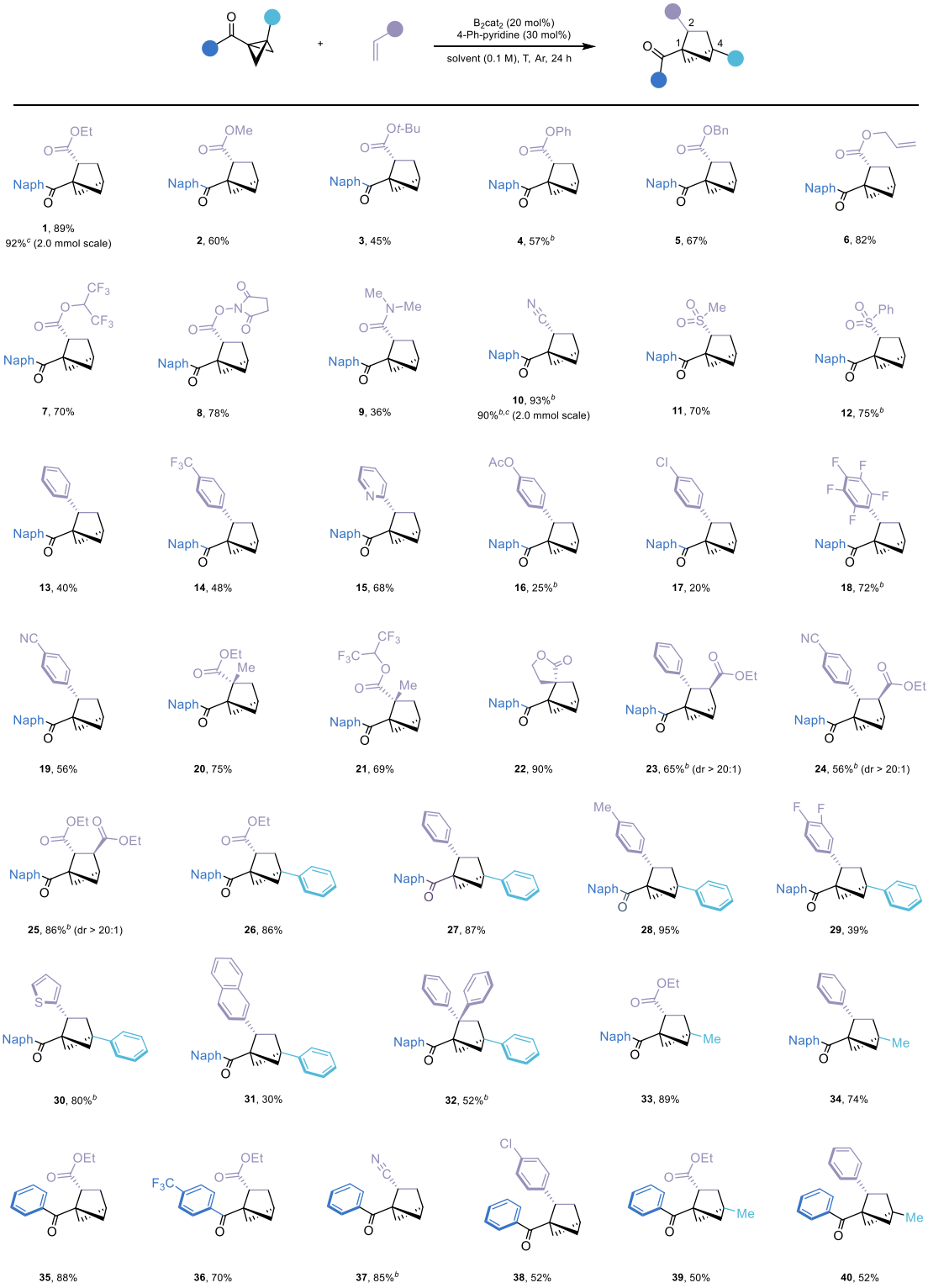
Entry	Solvent	X (equiv.)	Boron	T	Pyridine	Yield
1	dioxane	5.0	**B1**	25 °C	**P1**	60%
2	dioxane	5.0	**B2-5**	25 °C	**P1**	NR
3	dioxane	5.0	**B1**	25 °C	**P2**	17%
4	dioxane	5.0	**B1**	25 °C	**P3**	Trace
5	dioxane	5.0	**B1**	25 °C	**P4**	NR
6	dioxane	5.0	**B1**	25 °C	**P5**	23%
7	dioxane	5.0	**B1**	25 °C	**P6**	Trace
8	dioxane	5.0	**B1**	25 °C	**P7**	44%
9	dioxane	5.0	**B1**	25 °C	**P8-13**	NR
10	anisole	5.0	**B1**	25 °C	**P1**	31%
11	DMF	5.0	**B1**	25 °C	**P1**	70%
12	*n*-hexane	5.0	**B1**	25 °C	**P1**	90%
13	DCE	5.0	**B1**	25 °C	**P1**	41%
14	toluene	5.0	**B1**	25 °C	**P1**	84%
15	DME	5.0	**B1**	25 °C	**P1**	50%
16	*n*-hexane	5.0	**B1**	40 °C	**P1**	81%
17	*n*-hexane	5.0	**B1**	50 °C	**P1**	75%
18	***n*-hexane**	**2.0**	**B1**	**25 °C**	**P1**	**89%**
19	*n*-hexane	1.5	**B1**	25 °C	**P1**	61%
20	anisole	5.0	**B5**	25 °C	**P5**	Trace
21	*n*-hexane	1.0	**-**	25 °C	**P1**	NR
22	*n*-hexane	1.0	**B1**	25 °C	**-**	NR

[a]Reaction conditions: **S-1** (0.1 mmol), B_2cat_2 (20 mol%), 4-Ph-pyridine (30 mol%), solvent (1.0 mL), Ar atmosphere, 24 h.

Substrate scope

With the optimized set of conditions established (entry 18), we first evaluated the compatibility of different alkenes on this pyridine-boryl radical-catalyzed [2π + 2σ] cycloaddition reaction (Scheme 2). A broad range of acrylates bearing varying alkoxy group were generally tolerated (**1-7**), offering ample opportunities for the deprotection of the ester when necessary. *N*-Acryloxysuccinimide, with a labile N-O bond under reductive conditions, gave the corresponding product without difficulty (**8**). In addition, acrylamide (**9**), acrylonitrile (**10**) and vinyl sulfones (**11** and **12**) proved to be competent partners. The remaining amide, nitrile and sulfonyl group in the products were useful pharmacophores in drug design for efficient protein–ligand interaction. Styrenes were identified to be suitable coupling partners as well, bringing about more structure complexities to the final products (**13-19**). In these cases, however, the electron-deficient ones usually provided higher yields as expected (**14**, **15**, **18, 19**). Heteroaromatics were well tolerated (**15, 30**). Gratifyingly, the reaction was not limited to mono-substituted alkenes. Several 1,1- (**20-22, 32**) and 1,2-disubstituted alkenes (**23-25**) also underwent reaction smoothly. For the later cases, a generally high distereoselectivity (> 20:1) was observed. BCB ketones substituted with an additional alkyl or aryl group at the second bridgehead were excellent substrates as well, providing valuable product with another defined exit vector (**26-34, 39, 40**). And aside from naphthyl ketones, other aromatic ketones were generally compatible (**35-40**). Finally, the robustness of the protocol was further demonstrated by the 2 mmol-scale reactions of **S-1** with both ethyl acrylate and acrylonitrile with half catalyst loadings, providing the corresponding products in excellent yields (**1, 10**).

Scheme 2. Substrate Scope[a]

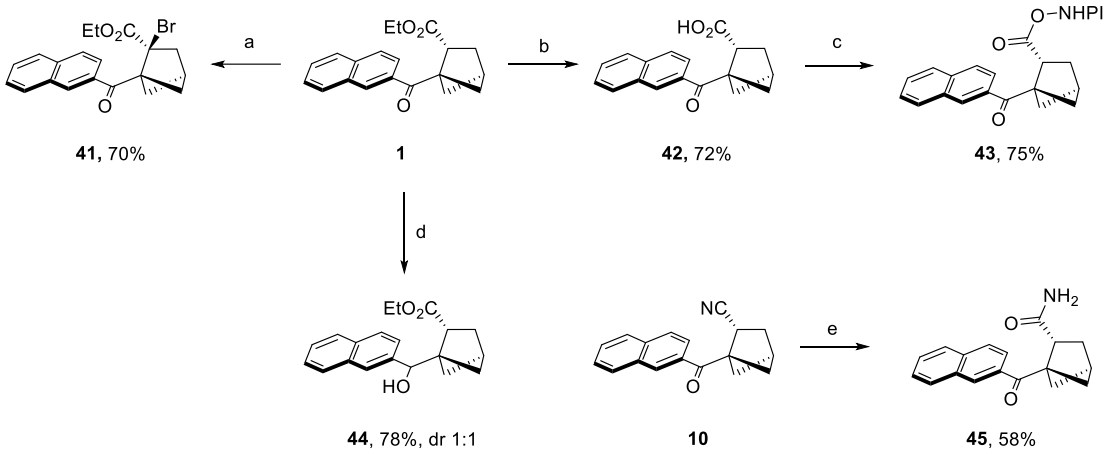


[a]All values indicate the yield of the isolated product. Unless otherwise noted: BCB (0.1 mmol), B_2cat_2 (20 mol%), 4-Ph-pyridine (30 mol%), alkene (2.0 equiv.), *n*-hexane (1.0 mL), 25 °C, Ar atmosphere, 24 h. [b]toluene as solvent. [c]conditions: **S-1** (2.0 mmol), B_2cat_2 (10 mol%), 4-Ph-pyridine (15 mol%), alkene (2.0 equiv.), solvent (20.0 mL), 25 °C, Ar atmosphere, 36 h.

Applications

By simple functional group manipulations, the products obtained from this strategy served as versatile building blocks for the synthesis of other decorated BCHs (Scheme 3). For example, the base-promoted α-bromination of the ester in **1** with CBr_4 gave bromide **41**, wherein the C-Br bond was potentially useful handle for further transformations. Selective reduction of the ketone with $NaBH_4$ furnished a secondary alcohol **44** in good yield. Upon basic hydrolysis, **1** was firstly converted to carboxylic acid **42**. The conversion of the carboxylic acid to a redox-active ester (NHPI = *N*-hydroxyphthalimide) offers another valuable handle for structural diversification. On the other hand, the hydrolysis of the nitrile moiety in **10** provided a primary amide **45**.

Scheme 3. Synthetic utilities



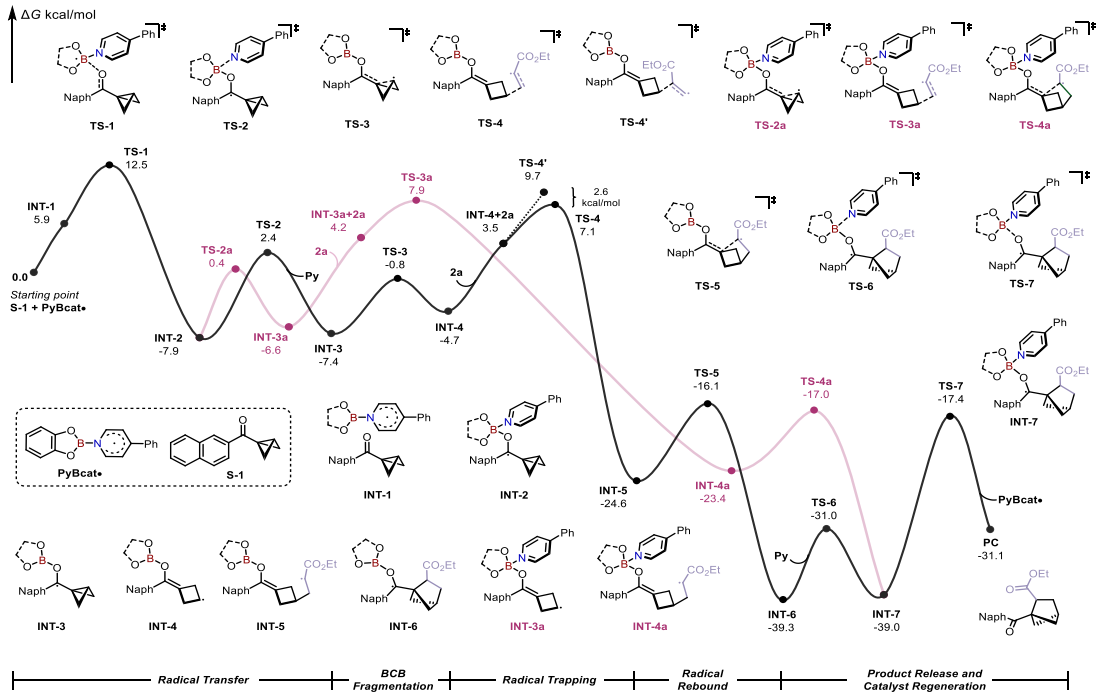
Reaction conditions: [a] LDA (1.1 equiv.), CBr_4 (1.1 equiv.), THF, 0 °C to -78 °C to rt, Ar; [b] LiOH (10.0 equiv.), THF–MeOH–H_2O, rt, 24 h; [c] NHPI (1.1 equiv.), DCC (1.2 equiv.), DMAP (20 mol%), DCM, rt; [d] $NaBH_4$ (1.2 equiv.), MeOH, 0 °C; [e] KOH, EtOH–H_2O, 90 °C. For more details, see the Supporting Information.

Mechanistic investigation

To further elucidate the reaction mechanism for the developed [2π + 2σ] cycloaddition, we performed detailed computational studies with M06-2X functional.[20] The B–B homolytic cleavage of B_2cat_2 facilitated by the coordination of 4-Ph-pyridine generates the pyridine-boryl radical (**PyBcat•**) (see the Supporting Information), which was selected with ketone **S-1** as the starting point of the potential energy surface shown in Scheme 4. Initially, a dative bond formation between the carbonyl group of **S-1** and vacant p_z orbital of **PyBcat•** occurred via **TS-1** ($\Delta G^{\neq}$ = 12.5 kcal/mol), which is followed by pyridine dissociation via **TS-2** with a 10.3 kcal/mol energy barrier to afford a ketyl radical **INT-3**. The following fragment of the BCB ring was relatively facile, leading to the planar cyclobutyl radical **INT-4** via **TS-3** ($\Delta\Delta G^{\neq}$ = 7.1 kcal/mol). This radical is trapped regioselectively by ethyl acrylate **2a** via **TS-4** ($\Delta\Delta G^{\neq}$ = 15.0 kcal/mol) to give a stabilized

radical **INT-5**. Another radical addition orientation was found to be associated with a 2.6 kcal/mol higher activation barrier. A radical rebound on to enolate moiety of the **INT-5** via **TS-5** ($\Delta\Delta G^{\neq}$ = 8.5 kcal/mol) results in a ring-closure to give BCH intermediate **INT-6**. And finally, the coordination of pyridine catalyst to the boryl center would trigger the release of the BCH product and regeneration of the **PyBcat•** catalyst (via **TS-7**). This step is found to be the turn-over limiting step with highest energy barrier of 21.9 kcal/mol. Another reaction pathway involving the pyridine coordinative BCB fragmentation (violet line, from **INT-2** to **INT-3a**) and pyridine coordinative radical addition (from **INT-3a** to **INT-4a**) was also considered. A slightly higher barrier (7.9 kcal/mol for **TS-3a** vs 7.1 kcal/mol for **TS-4**) was found, indicating it could be a competitive reaction pathway. Taken together, these results provide reasonable evidence to support a radical transfer/BCB fragmentation/radical trapping/radical rebound/product release and catalyst regeneration sequence for the developed transformation.

Scheme 4. Computational studies



Conclusion

A new strategy based on the pyridine-boryl radical catalysis towards the atom-economic synthesis of bicyclo[2.1.1]hexanes (BCHs) has been presented. The unique reaction model allows an exceptionally broad substrate scope, and the mildness of this protocol also enables a good functional group tolerance, both of which are important for the application of BCH scaffold as bioisosteres of benzenoids in medicinal chemistry. DFT calculation

supported a radical relay mechanism that is initiated by a pyridine-boryl radical. Further decoration of the BCH products was demonstrated.

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Notes

The authors declare no competing financial interest

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