Transition-Metal-Like Catalysis with Tetraalkoxydiboron(4) /Isonicotinate Enabled an Efficient Broad-Scope [3+2] Cycloaddition of Cyclopropanes and Alkenes

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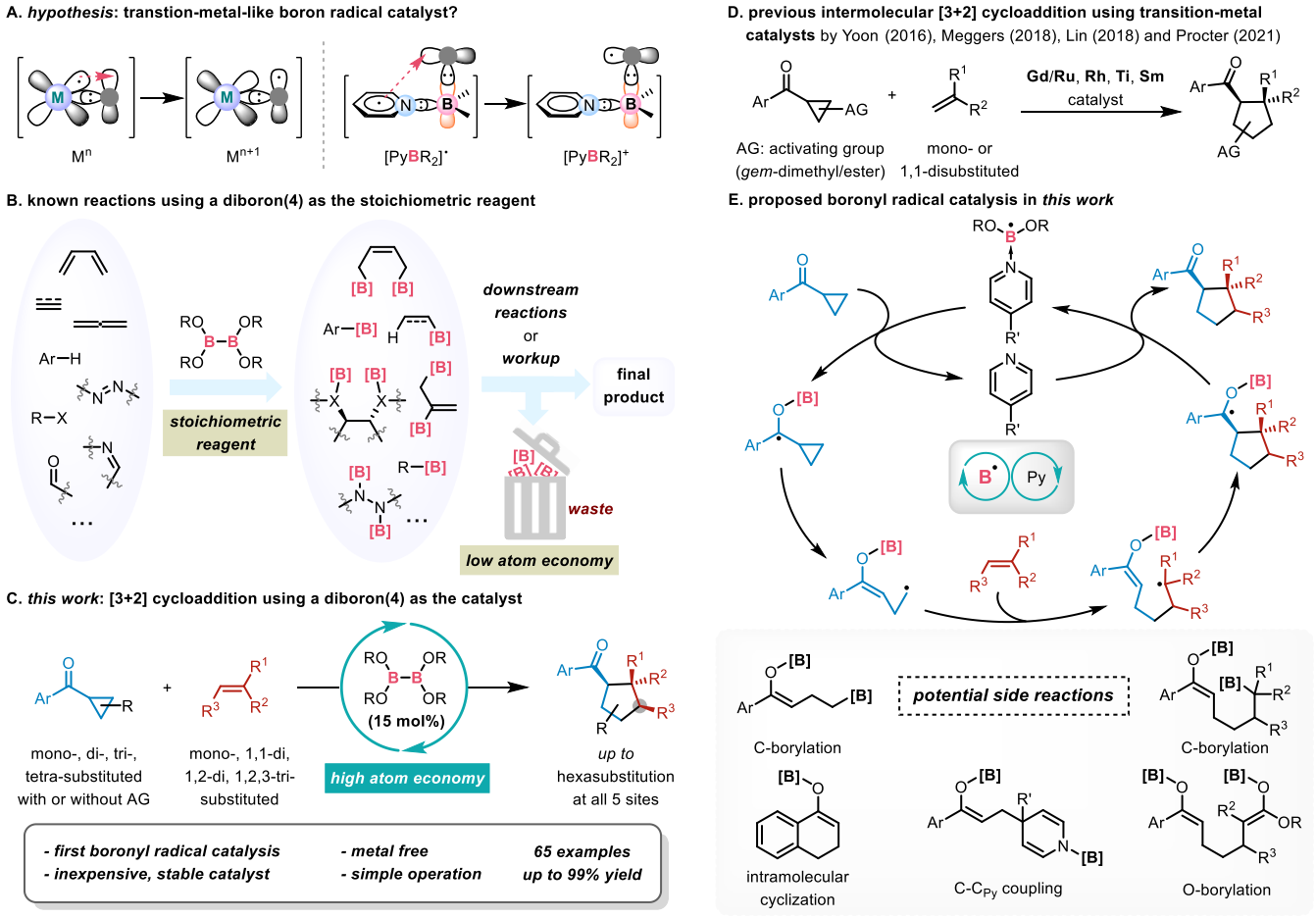
ABSTRACT: In contrast to the extensive but non-recyclable use of tetraalkoxydiboron(4) compounds as stoichiometric reagents in diverse reactions, this article reports an atom-economical reaction using a commercial diboron(4) as the catalyst. The key to success was designing a catalytic cycle for radical [3+2] cycloaddition involving a pyridine cocatalyst to generate from the diboron(4) catalyst and reversibly mediate the transfer of boronyl radicals. In comparison with known [3+2] cycloaddition with transition metal-based catalysts, the current reaction features not only metal-free conditions, inexpensive and stable catalysts, and simple operation, but also remarkably broadened substrate scope. In particular, previously unusable cyclopropyl ketones without an activating group and/or alkenes with 1,2-disubstitution and 1,1,2-trisubstitution pattern were successfully used for the first time. Consequently, challenging cyclopentane compounds with various levels of substitution (65 examples, 57 new products, up to six substituents at all five ring atoms) were readily prepared in generally high to excellent yield and diastereoselectivity. The reaction was also successfully applied in concise formal synthesis of an anti-obesity drug and building natural product-like complex bridged or spiralcyclic compounds. Mechanistic experiments and computational investigation support the proposed radical relay catalysis featuring a pyridine-assisted boronyl radical catalyst. Overall, this work demonstrates the first approach to use tetraalkoxydiboron(4) compounds as catalysts and may lead to the development of new, green and efficient transition metal-like boron-catalyzed organic reactions.

INTRODUCTION

In general, transition metals can change their oxidation states back and forth when engaging an organic substrate as a catalyst.[1] The initiating process of a catalytic cycle is usually where a transition-metal atom accepts an electron pair as a Lewis acid, and donate one or two electron(s) back to activate the substrate (Scheme 1a). In order for better sustainability and economic impact, the searching for main-group catalysts has gained significant attention in the last decade as they might favorably substitute or complement the conventional transition-metal catalysts.[2] Recently, a few heavier elements with intervening *d* orbitals such as bismuth[3] or phosphorus[4] have been elegantly demonstrated as mimics of transition-metals taking advantage of their changeable oxidation states. Conversely, using the lighter main group elements, usually with only fixed oxidation states, for similar goals have been intriguing and challenging.[5] In this context, we hypothesized that a formal 4c-7e boron-centered radical with extensive Lewis base-delocalization[6] might engage a substrate in analogous manner to a single-electron donating transition metal. In such a process, the formally SOMO but essentially vacant p_z orbital can accept an electron pair from the substrate to form a σ-bond. Meanwhile, the delocalized single electron may be intramolecularly transferred to the substrate, thus initiating the following steps. In order to close a boron radical-based catalytic cycle, however, several challenges must be addressed that include but not limited to the following. First of all, a convenient and reliable method is needed to generate the catalyst. In addition, the stability, reducing capability, reversibility of inter-species transfer of the key active species must be well balanced for a specific reaction.

In the last decade, boron-centered radicals have become a type of synthetically relevant active intermediates.[7,8] In particular, the discoveries that Lewis bases such as N-heterocyclic carbenes and pyridines were able to stabilize the otherwise too reactive boron radicals have facilitated their synthetic utility.[9] As a breakthrough, Li and Zhu reported an effective generation of boronyl radicals by 4-cyanopyridine-assisted homolytic cleavage of the B–B bond in tetraalkoxydiboron(4).[10] Subsequently, several transformations using stoichiometric diboron(4) compounds based on radical processes have been developed, such as C–C

Scheme 1. Conceptual Design of a Diboron(4) Catalysis



coupling and radical borylation.[11,12] In fact, although sp^2 hybridized boranes have been widely used as Lewis acid catalysts, the less acidic, more air- and moisture-stable tetraalkoxydiboron(4) compounds have only been used as stoichiometric reagents (Scheme 1A).[13] In recent years, an exponentially increasing number of reports using them have appeared for diverse transformations (Scheme 1B), such as borylation of C-H,[14] C-X[15] or unsaturated bonds,[16] C-C coupling[11] and or simply using them as reductants.[17] In these reactions, the boronyl moiety was firstly incorporated into the intermediates.[18] Their downstream transformations or simple aqueous workup would then deliver the final products.[19] However, the boronate moiety, often accounting for significant mass fraction (e.g., the molecular weight of Bpin group is 126.97), was usually disposed as the waste. Consequently, in order for a more atom-economical strategy, it would be highly desirable to use the diboron(4) as a catalyst. In this article, as a proof of principle, we report the first example that a tetraalkoxydiboron(4) can be used as efficient precursor for a boron radical-catalyzed atom-economical synthesis of poly-substituted cyclopentanes (Scheme 1C).

Substituted cyclopentanes are core motifs in many bioactive natural products and pharmaceuticals, such as pactamycin,[20] peramivir[21] and members of prostaglandins[22] or carbocyclic nucleosides.[23] In sharp contrast to the well-established approaches to substituted cyclohexanes such as the venerable [4+2] Diels-Alder reaction, however, robust methods for highly substituted cyclopentanes are much less developed and intractable. In this context, intermolecular modular assembly of the cyclopentane ring by cycloaddition reactions represents a versatile strategy.[24] Among different types, catalytic ring opening/[3+2] cycloaddition of a cyclopropane with an alkene constitutes an atom-economical approach.[25] In this regard, heterolytic opening of the cyclopropane for [3+2] cycloaddition has been successfully developed by using Lewis acids.[26] However, the substrates were usually restricted to push-pull type cyclopropanes and electron-rich alkenes. Alternatively, radical [3+2] cycloaddition reactions have also been reported.[27] In particular, [3+2] reactions of aryl cyclopropyl ketones with alkenes have emerged as an attractive approach (Scheme 1D).[28-31] Thus, using Gd/Ru photoredox co-catalysis, Yoon first realized the desired [3+2] cycloaddition via a metalated cyclopropyl ketyl radical intermediate.[28] Late on, Meggers,[29] Lin[30] and Procter[31] have independently developed elegant catalysts based on transition-metals Rh, Ti or Sm respectively for various substrates including intramolecular versions. Despite of these exciting advances, the reaction was usually successful only with activated substrates such as monosubstituted or 1,1-disubstituted alkenes, and cyclopropanes with radical-stabilizing substituents. For example, the typical cyclopropane often involved *gem*-dimethyl substituents while the parent cyclopropyl ketone was poorly reactive. Consequently, it was desirable to develop a more general, flexible

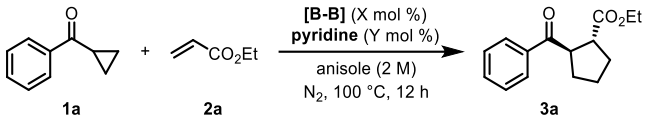
and predictable method for rapid and selective construction of cyclopentanes with various degree of substitution.

In this context, we proposed that a boronyl radical might be employed as the active catalyst for the aimed [3+2] cycloaddition as shown in Scheme 1E. Remarkably, the modular nature of the binary catalyst should allow its properties being readily tuned by changing their substituents, therefore providing opportunity for expanding the scope of radical catalysis. However, several competitive pitfalls must be avoided for a successful catalytic cycle. First, a diboron(4) or its derivatives might trap the involved alkyl radicals to form C- or O- borylation products to terminate the cycle. Second, the 4-substituted pyridine might also react with alkyl radical intermediates to form C-C_{Py} coupling products. Third, as the general challenges for radical reactions, side reactions such as radical dimerization, rearrangement, radical/polar crossover must be overcome, particularly for alkenes of low reactivity. For example, the radical generated from ring-opening might attack the arene by an intramolecular fashion.[31a] With these challenges in mind, we conducted the aimed investigation and the results are disclosed herein. We show that indeed a commercially available, stable and inexpensive diboron(4) compound as the catalyst, together with a simple pyridine, enables an efficient [3+2] cycloaddition reaction with unprecedented broad substrate scope for synthesis of highly substituted cyclopentanes.

RESULTS AND DISCUSSION

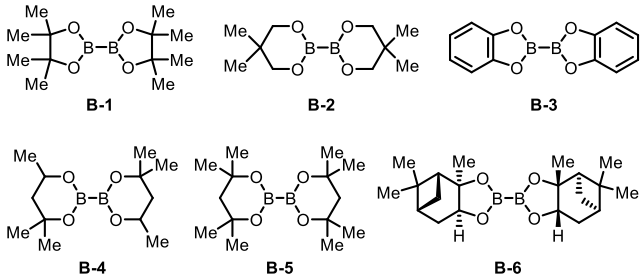
Reaction Discovery and Optimization. Our initial investigation used the commercially available cyclopropyl phenyl ketone (**1a**) and ethyl acrylate (**2a**) as the substrates (Table 1). These substrates were deemed challenging because the opening of **1a** necessitated formation of a non-stabilized primary alkyl radical and **2a** was typically prone to polymerization. Pleasingly, after some experimentation, we found that a diboron(4)/pyridine combination could indeed promote the desired [3+2] cycloaddition. Thus, heating a solution of **1a** and **2a** together with 15 mol% of B_2pin_2 (**B-1**) and ethyl isonicotinate (**P-1**) in anisole at 100 °C for 12 hours cleanly formed the product **3** albeit with low yield (28%, Table 1, entry 1). Several other commercially available diboron(4) compounds were then compared with B_2pin_2. While B_2neop_2 (**B-2**) and B_2cat_2 (**B-3**) were less effective, the multiply methylated diboron **B-4** and **B-5** gave somehow higher yields (Table 1, entries 2-5). Interestingly, the pinene-derived diboron **B-6** afforded clean reaction and high yield (86%, Table 1, entry 6). We then investigated the effect of the pyridine component. While the previously used 4-cyanopyridine (**P-2**) by Li et al. was moderately active (65%, Table 1, entry 7), 4-trifluoromethylpyridine (**P-3**) and 4-phenylpyridine (**P-4**) led to only trace conversion. The electron-rich pyridines **P-5** and **P-6** were completely inactive. These results were consistent with the notion that an electron-poor pyridine can effectively stabilize a boron radical. The alkyl of isonicotinate **P-1** was then changed to tune the reactivity. In comparison with methyl, ethyl and *tert*-butyl isonicotinates, 3-pentyl isonicotinate **P-9** gave the best conversion (92%) and yield (90%) which was deemed to be satisfactory (Table 1, entries 12-14). Next, the loading of **B-6** was assessed. Using 10 mol% of **B-6** led to notably lower yield (80%, Table 1, entry 15) and 5 mol% gave only trace

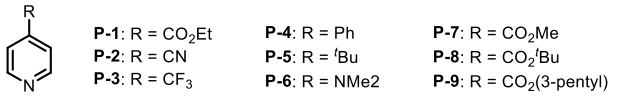
Table 1. Optimization of the diboron(4)/pyridine co-catalyzed [3+2] cycloaddition reaction[a]



entry	[B-B] (X mol%)	pyridine (Y mol%)	conversion (%)	yield (%)
1	**B-1** (15)	**P-1** (25)	32	28
2	**B-2** (15)	**P-1** (25)	7	< 5
3	**B-3** (15)	**P-1** (25)	12	< 5
4	**B-4** (15)	**P-1** (25)	38	37
5	**B-5** (15)	**P-1** (25)	50	48
6	**B-6** (15)	**P-1** (25)	87	86
7	**B-6** (15)	**P-2** (25)	66	65
8	**B-6** (15)	**P-3** (25)	5	< 5
9	**B-6** (15)	**P-4** (25)	7	< 5
10	**B-6** (15)	**P-5** (25)	0	0
11	**B-6** (15)	**P-6** (25)	0	0
12	**B-6** (15)	**P-7** (25)	86	83
13	**B-6** (15)	**P-8** (25)	79	76
14	**B-6** (15)	**P-9** (25)	92	90
15	**B-6** (10)	**P-9** (25)	83	80
16	**B-6** (5)	**P-9** (25)	< 5	< 5
17	**B-6** (15)	**P-9** (50)	70	68
18	**B-6** (15)	**P-9** (10)	67	65
19	-	**P-9** (25)	0	0
20	**B-6** (15)	-	0	0

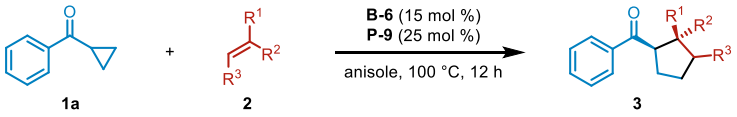
[a] Reactions were run on 0.3 mmol scale in 0.15 mL of anisole at 100 °C for 12 h. Conversion and yield were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.





product (Table 1, entry 16). Remarkably, the loading of **P-9** was also important. Using more or less amount of **P-9** than 25% all resulted in lower conversion (Table 1, entry 17 and

Table 2. Substrate variations of the alkene in diboron(4)-catalyzed [3+2] cycloaddition[a]



1a + 2 → 3

***with* monosubstituted alkenes**	**3a** 87%, d.r > 20:1	**3b** 87%, d.r. > 20:1	**3c** 97%, d.r. > 20:1	**3d**[b] 77%, d.r. = 12:1	**3e** 70%, d.r. > 20:1	**3f** 90%, d.r. > 20:1
	3g 86%, d.r. > 20:1	**3h** 54%, d.r. = 12:1	**3i** 81%, d.r. > 20:1	**3j** 87%, d.r. > 20:1	**3k** 84%, d.r. > 20:1	**3l** 87%, d.r. > 20:1
	3m[c] 93%, d.r. > 20:1	**3n** 84%, d.r. > 20:1	**3o**[c] 58%, d.r. > 20:1	**3p** 99%, 98%[d], 72%[e]	**3q**[f] 94%, d.r. = 4:1	**3r**[f] 77%, d.r. = 12:1
***with* 1,1-disubstituted alkenes**	**3s** 78%, d.r. = 9:1	**3t** 75%, d.r. > 20:1	**3u**[f] 88%, d.r. = 3:1	**3v**[f] 84%, d.r. = 5:1	**3w**[f] 64%, d.r. > 20:1	**3x**[g] 69%, d.r. = 15:1
***with* 1,2-disubstituted and trisubstituted alkenes**	**3y**[g] 74%, d.r. = 15:1	**3z**[g] 70%, d.r. = 13:1	**3aa**[g] 54%, d.r. > 20:1	**3ab**[g] 60%, d.r. > 20:1	**3ac**[g] 91%, d.r. = 15:1	**3ad**[f,g] 74%, d.r. > 20:1
	3ae[g] 72%, d.r. = 8:1	**3af**[g] 70%, d.r. > 20:1	**3ag**[g] 67%, d.r. > 20:1	**3ah** 93%[h], d.r. = 15:1 62%[i], d.r. = 6:1	**3ai**[f,g] 80%, d.r. > 20:1	**3aj**[f,g] 65%*, d.r. > 20:1

[a] Unless indicated otherwise, reactions of **1a** (0.50 mmol), **2** (1.0 mmol), **B-6** (0.075 mmol) and **P-9** (0.125 mmol) were carried out in anisole (0.25 mL) at 100 °C for 12 h, then to the reaction tube was added DBU (0.25 mmol) and EtOH (2.5 mL) and heated at 80 °C for another 3 h. Isolated yield. The d.r. value were determined by ^{1}H NMR analysis of the crude reaction mixture. [b] **2** (2.0 mmol). [c] **B-6** (0.125 mmol), **P-9** (0.25 mmol). [d] **B-6** (0.05 mmol), **P-9** (0.10 mmol). [e] **B-6** (0.025 mmol), **P-9** (0.05 mmol). [f] Without workup by DBU and EtOH. [g] THF (0.25 mL) as solvent, 110 °C, 18 h. [h] using diethyl fumarate. [i] using diethyl maleate.

18). This observation was in accord with our proposed catalytic cycle wherein the pyridine should reversibly transfer a boronyl radical to both the reactant and the product. In addition, control experiments in the absence of either the diboron or the pyridine all led to no reaction, indicating the requirement of both catalysts (Table 1, entry 19 and 20).

Substrate Scope. With the reaction conditions established for the unactivated cyclopropane **1a**, we next investigated

the scope of the alkene partner. The results are summarized in Table 2. In general, the desired cyclopentane products were cleanly formed and no significant side reactions observed. In cases where diastereomers were initially formed, workup with DBU usually afford high diastereoselectivity favoring the thermodynamically more stable *trans* products.[32] As shown in Table 2, various monosubstituted alkenes including alkyl acrylates (for **3a**, **3b**, **3e**), acrylamide (for **3c**), acrylonitrile (for **3d**), styrenes (for **3f**-**3m**) successfully reacted with **1a** to afford the 1,2-disubsti tuted cyclopentanes in mostly high yields and diastereoselectivity. The formation of **3e** containing a styryl side chain suggested the desired cyclization was faster than the potential intramolecular radical attacking to the styryl moiety. Within the styrene series, strongly electron-donating (for **3g**) or withdrawing (for **3k**-**3m**) substituents did not significantly affect the reactivity and the yields were all no less than 84%. Furthermore, vinyl ferrocene (for **3n**) and N-vinyl carbazole (for **3o**) reacted with **1a** to yield the desired products as single diastereomer. In the latter case a heteroatom-substituted cyclopentane could be prepared.

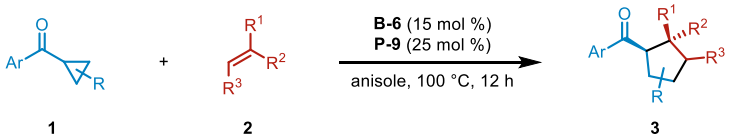
Next we briefly surveyed 1,1-disubstituted alkenes for the [3+2] cycloaddition. 1,1-Diphenylethylene showed great reactivity, quantitatively affording the trisubstituted cyclopentane product **3p** under the above "standard conditions". Notably, when less **B-6** catalyst (10 mol%) was used, the product was still isolated in 98% yield. Further reducing the catalyst loading to 5 mol% led to **3p** in 72% yield. 1,1-Differentially substituted alkenes were also smoothly incorporated into the products by this reaction, generating cyclopentanes with a quaternary stereocenter (**3q**-**3w**). The diastereoselectivity was usually good to excellent, largely depending on the size difference of the two substituents. Functional groups such as alkynyl (**3r**), boronyl (**3t**) were well tolerated, providing handles for further synthetic manipulations. In addition, spirocyclic compounds (**3u**-**3w**) could be readily synthesized using simple starting materials.

To the best of our knowledge, alkenes with 1,2-disubstitution or higher substitution have never been used in previous reports of radical [3+2] cycloaddition, largely due to their low reactivity. In our catalytic system, we were pleased to find that various readily available cinnamates were viable substrates. Thus, under slightly modified conditions, the desired 1,2,3-trisubstituted cyclopentane products (**3x**-**3af**) were successfully isolated in generally good to excellent yield and diastereoselectivity. In all cases, the *trans*,*trans* isomer was predominant. Notably, exclusive regioselectivity was observed that seemed involving a benzylic instead of α-carbonyl radical intermediate before cyclization, and supported by computational studies (see SI). In addition, substituents with different electronic properties and at *para*, *meta*, *ortho* positions were all compatible. Particularly, products with unmasked basic and coordinating N-heterocyclic moieties like imidazole (**3af**) was successfully synthesized, demonstrating the excellent group tolerance of this reaction. Similarly, cinnamonitrile reacted with **1a** to form **3ag** in synthetically useful yield (67%) as a single isomer (d.r. > 20:1). In addition, using diethyl fumarate (*E*-configuration) or maleate (*Z*-configuration) as the alkene reactant, the same product **3ah** was obtained albeit in varied yield (93% or 62%) and diastereoselectivity (d.r. 15:1 or 6:1). The stereo-convergent results were in line with the proposed radical nature of the intermediates. Furthermore, trisubstituted alkenes such as *β*-phenyl cinnamate (for **3ai**) or *β*-phenyl cinnamonitrile (for **3aj**) were also successfully used for this boronyl radical-catalyzed [3+2] cycloaddition, affording tetrasubstituted cyclopentanes in high efficiency.

With the above success in exploring the scope of the 2C alkene reactant, we further investigated the substrate scope with structural variations mainly on the 3C cyclopropane reactant. The obtained products are summarized in Table 3. The arene unit of the monosubstituted cyclopropane was firstly varied. Electron donating or withdrawing groups on different positions of the benzene ring led to similarly high yields (**3ak**-**3aq**). Halogen substituents were compatible under this radical reaction conditions (**3an**, **3ao**, **3aq**). *Ortho* substituents did not show particular steric effect since excellent yield and diastereoselectivity were still remained (**3ak** and **3an**). 2-Naphthoyl cyclopropane also provided the product **3ar** in high yield as a single isomer. Further, a thiophene moiety was also viable in the reaction, although the yield was moderate (**3as**, 53%).

We then probed the effect of substituents within the cyclopropane ring on this [3+2] cycloaddition. *Gem*-dimethylcyclopropanes were the typical active substrates in previous reports likely because of the tertiary radical's ready generation, high nucleophilicity and facile cyclization due to Thorpe-Ingold effect.[18b,19,20,21b] Under our conditions, we used 1-benzoyl-2,2-dimethyl cyclopropane and briefly checked its performance. We found that not only simple styrenes (for **3au**-**3aw**) but also cinnamate (**3ax**) and cinnamonitrile (**3ay**) were able to react and successfully deliver the multiply substituted cyclopentane products in good yield and high diastereoselectivity. Previously Procter and coworkers had observed that when non-*ortho*-substituted benzoyl cyclopropanes were used in SmI_2 catalysis, a side reaction could occur, i.e., intramolecular cyclization of the initially formed radical after ring opening.[21a] Interestingly, in our conditions, such a side reaction was not observed. When the two methyl groups were changed to two ethoxycarbonyl groups, styrenes, enol ester, vinyl silane and cinnamate were again successfully used and the desired cyclopentanes were isolated in good yields and high stereoselectivity (**3az**-**3bd**). The introduction of functional groups such as ester, oxygen and silicon on the five-membered ring could serve as handles for further transformations. In addition, a phenyl group on the cyclopropane ring was compatible and the product was isolated in good yield as a mixture of two isomers (**3be**, 75%, d.r. 1.3:1). When 1,1-dibenzoyl-2-phenyl cyclopropane reacted with ethyl acrylate, the desired product **3bf** could be obtained in 38% yield as a single isomer (d.r. > 20:1). The low efficiency might be attributed to difficulty in the cyclization step owing to steric hindrance or disrupting the conjugation between the second carbonyl and the intermediary enolate. Finally, in order for synthesis of more highly substituted cyclopentane products, a tetrasubstituted cyclopropane, i.e., *tert*-butyl 3-benzoyl-2,2-dimethylcyclopropane-1-carboxylate, was prepared in three steps according to a known route.[18a] Pleasingly, under the standard conditions, we were able to obtain the desired cycloaddition products in high to reasonable yield and excellent diastereoselectivity, not only with monosubstituted

Table 3. Substrate variations of the cyclopropane in diboron(4)-catalyzed [3+2] cycloaddition[a]



1 + 2 → 3

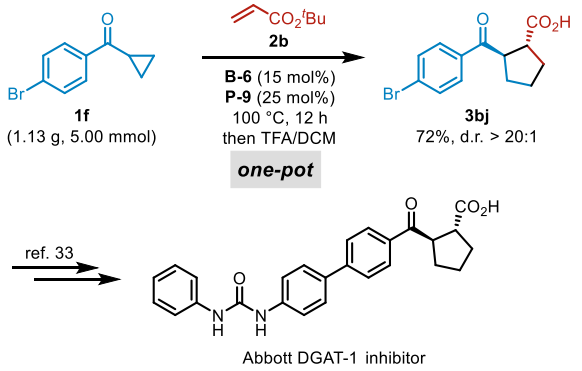
monosubstituted cyclopropanes	**3ak** 93%, d.r. > 20:1	**3al** 92%, d.r. = 12:1	**3am** 87%, d.r. = 13:1	**3an** 90%, d.r. > 20:1	**3ao** 75%, d.r. > 20:1
	3ap 83%, d.r. > 20:1	**3aq** 78%, d.r. > 20:1	**3ar**[b] 85%, d.r. > 20:1	**3as**[c] 53%, d.r. = 10:1	**3at** 83%, d.r. = 10:1
1,2,2-trisubstituted cyclopropanes	**3au** 78%, d.r. = 15:1	**3av** 78%, d.r. = 10:1	**3aw** 66%, d.r. > 20:1	**3ax**[b,c] 65% d.r. > 20:1	**3ay**[b] 60%, d.r. = 7:1
	3az 84%, d.r. > 20:1	**3ba** 79%, d.r. > 20:1	**3bb**[b,d] 68%, d.r. = 2.5:1	**3bc**[d] 63%, d.r. > 20:1	**3bd**[b] 55%, d.r. > 20:1
1,2-disubstituted, 1,1,2-trisubstituted and 1,2,3,3-tetrasubstituted cyclopropanes	**3be** 75%, d.r. = 1.3 :1	**3bf** 38%, d.r. > 20:1	**3bg**[b] 72%, d.r. > 20:1	**3bh**[b] 64%, d.r. > 20:1	**3bi**[b] 35%, d.r. > 20:1

[a] Unless indicated otherwise, reactions of **1** (0.50 mmol), **2** (1.0 mmol), **B-6** (0.075 mmol) and **P-9** (0.125 mmol) were carried out in anisole (0.25 mL) at 100 °C for 12 h, then to the reaction tube was added DBU (0.25 mmol) and EtOH (2.5 mL) and heated at 80 °C for another 3 h. The d.r. value were determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield. [b] Without workup by DBU and EtOH. [c] **B-6** (0.125 mmol), **P-9** (0.25 mmol). [d] **2** (2.0 mmol).

(for **3bg**) and 1,1-disubstituted alkenes (for **3bh**) but also with 1,2-disubstituted alkene such as ethyl cinnamate (for **3bi**). Remarkably, the cyclopentane compound **3bi** contains six substituents on all five ring atoms and four contiguous stereocenters, and is of considerable structural complexity and synthetic challenge for traditional chemistry. With the current method, however, it could be conveniently prepared in just four steps as a single isomer out of eight possible diastereomers.

Furthermore, to demonstrate the utility and scalability of the current boronyl radical-catalyzed cycloaddition reaction, we designed and conducted a new and concise synthetic route of the key intermediate (**3bj**) for a glycerolacyltransferase (DGAT-1) inhibitor which had been developed as a potent and selective anti-obesity agent by Abbott (Scheme 2).[33] The *trans*-cyclopentane carboxylic acid **3bj** had been synthesized by the Abbott team using a highly optimized route in three steps with overall 66% yield from commercial chemicals. In this work, under the standard conditions without optimization, the reaction of commercial *para*-bromobenzoyl cyclopropane (**1f**, 5.00 mmol, 1.13 g), a

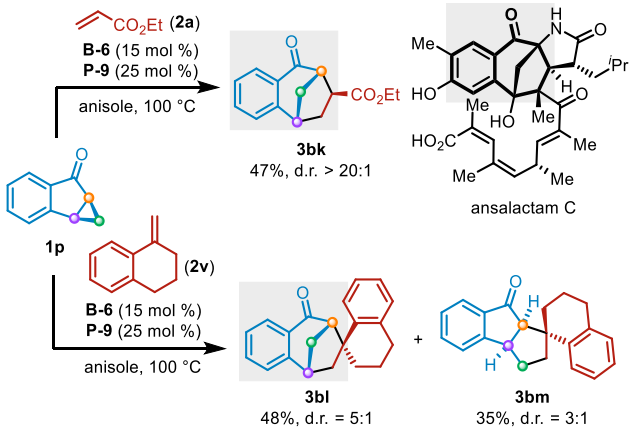
Scheme 2. Gram-scale application of the [3+2] cycloaddition *en route* to an anti-obesity agent



cyclopropyl ketone without further activating groups, and *tert*-butyl acrylate (**2b**) followed by removal of *tert*-butyl ester using trifluoroacetic acid, directly produced the desired cyclopentane **3bj** in 72% yield as a single isomer in a one-pot fashion.

Because many natural products involve bridged ring or spirocyclic skeleton, we wished to apply the current cycloaddition reaction as a method for rapidly building these types of complex natural product-like molecules. A [6/5/3] tricyclic ketone **1p** was readily synthesized following a known route[34] and used as the cyclopropane substrate (Scheme 4). When a mixture of **1p** and ethyl acrylate was heated just under the standard conditions, we observed the facile formation of the bridged ring product **3bk** containing bicyclic [3.2.1] octane in 47% yield as a single isomer. Apparently, the cyclopropane ring-opening preferentially generated a benzylic radical which then underwent cycloaddition with the acrylate. Remarkably, the product **3bk** represented exactly the same core skeleton with correct relative configuration of ansalactam C,[35] an ansamycin natural product of polyketide origin. Interestingly, when the 2C reactant was changed to exocyclic alkene **2v**, two separable polycyclic products **3bl** (48%) and **3bm** (35%) contained the expected spirocyclic substructure could be isolated. Interestingly, while **3bl** still contained the bicyclic [3.2.1] octane core, **3bm** incorporated a bicyclic [3.3.0] octane system. The different reactivity of **1p** with **2a** and **2v** suggested that under

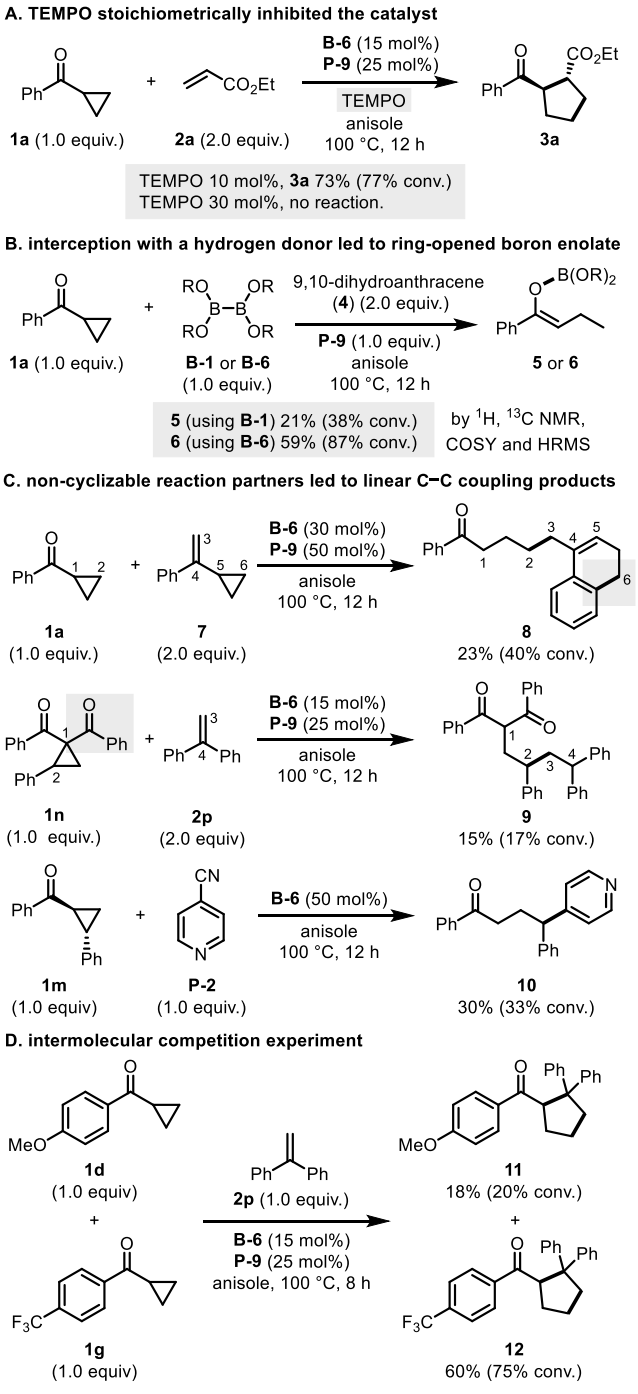
Scheme 3. Synthesis of bridged and spirocyclic cyclopentanes by the diboron(4)-catalyzed [3+2] cycloaddition



the cocatalysis of diboron(4) **B-6** and pyridine **P-9**, the generation of a benzylic radical and a primary radical were both possible and likely interconvertible. The selection of product type might depend on the rate of the first C-C bond formation.

Mechanistic study. Control experiments already showed the indispensable roles of the diboron(4) and the isonicotinate as catalysts (Table 1, entries 19 and 20). To get more mechanistic insights, particularly about the nature of the intermediates, we conducted further mechanistic experiments (Scheme 4). When 10 mol% of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the reaction of **1a**

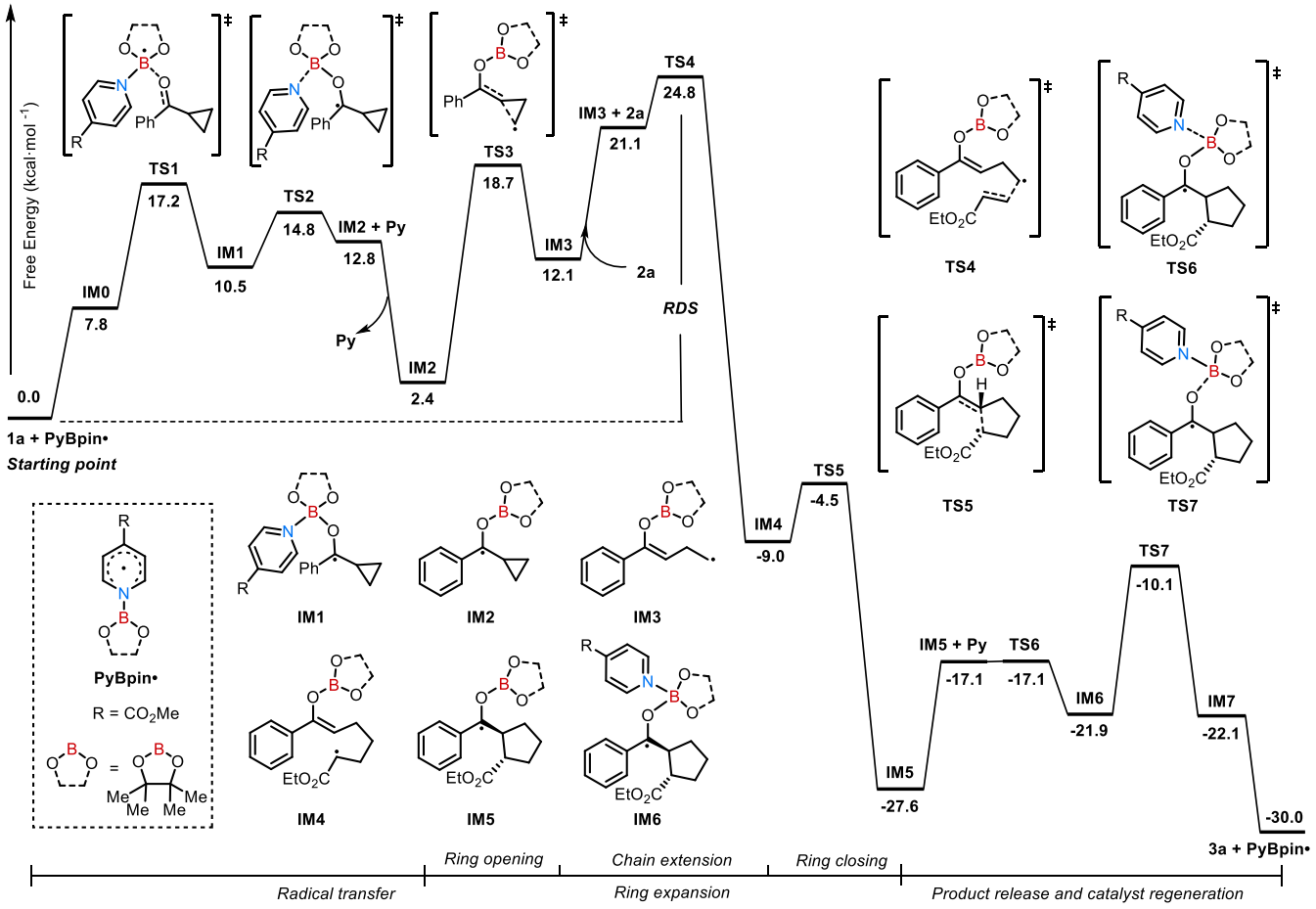
Scheme 4. Mechanistic experiments



and **2a** under the standard conditions, the yield of product **3a** was reduced to 73%. However, further increasing the amount of TEMPO to 30 mol% completely shut down the reaction, probably because the generation of boronyl radicals were stoichiometrically prohibited (Scheme 4A). Next, we asked a question if the reaction is *covalently* catalyzed by a boron species as proposed or just promoted by an electron, i.e., *via* a single electron transfer process. Therefore, we hoped to intercept the ring opening intermediate of **1a**. After a mixture of **1a** and 1.0 equiv. of diboron **B-1** or **B-6** was heated in the presence of 2.0 equiv. of 1,10-dihydroanthracene (**4**) as a hydrogen donor, a compound was observed and determined as the dialkoxyboron enolate **5** or **6** respectively using extensive NMR and high-resolution mass spectrometry analyses (Scheme 4B). These results supported the intermediacy of boron enolates in our proposed catalytic cycle (see Scheme 1E). Furthermore, we wished to probe the species after formation of the first C–C bond by using reaction partners that are difficult or unlikely to undergo cyclization. Thus, under standard conditions, the reaction of **1a** with an vinyl cyclopropane **7** afforded benzocyclohexene **8** in 23% yield that should be formed by an intramolecular radical arene substitution reaction (Scheme 4C). In addition, when the *gem*-dibenzoylcyclopropane **1n** was reacted with 1,1-diphenylethene (**2p**), we observed low conversion and formation of a linear compound **9**, probably because the sterically super-encumbered cyclization step was interrupted by hydrogen transfer from the solvent. Alternatively, 4-cyanopyridine (**P-2**) was reported to react with an alkyl radical to form 4-alkylated pyridine.[5a,5e] Therefore, we attempted to trap the possible radical intermediate using **P-2**. We found that in the presence of 50 mol% of diboron **B-6**, the reaction of phenyl-substituted cyclopropane **1m** with **P-2** indeed gave alkylated pyridine **4** in 30% yield. Finally, in order to probe the electronic feature of the transient interaction between the catalytically active species and the ketone substrate, we conducted an intermolecular competition experiment. When 4-methoxyphenyl ketone **1d**, 4-trifluoromethylphenyl ketone **1g** and alkene **2p** in 1.0 equiv. each were reacted under otherwise standard conditions for 8 hours, the expected product **11** with methoxy group was formed in 18% yield while **12** with trifluoromethyl group in 60% yield. The product ratio (0.3:1) favoring the more electron-withdrawing group was clearly against an cationic intermediacy while consistent with a radical species. Taken together, all above results supported a radical relay catalysis as proposed in Scheme 1E.

In order to get a full picture of the mechanism, we performed detailed computational studies of possible catalytic cycle using density functional theory methods (M06-2X at 6-311G** level). The generation of pyridine-stabilized boronyl radical by B-B homolytic cleavage was firstly addressed and the results were in accord with those reported by Li et al.

Scheme 5. Computed energetic profiles of the diboron(4)/pyridine-cocatalyzed [3+2] cycloaddition



before (see SI).[25] The structures of key intermediates, transition states and related energy profiles, starting from methyl isonicotinate-complexed pinacolato boryl radical (**PyBpin•**) and ketone **1a**, are shown in Scheme 5. As a Lewis base, the carbonyl group of ketone **1a** firstly forms a dative bond with the vacant p_z orbital of **PyBpin•** resulting a tetracoordinated boron intermediate **IM1**, which then release the pyridine to generate borate intermediate **IM2**, a benzylic ketyl radical. The two steps of similarly moderate barriers constitute a boron-centered ligand exchange process. From the other angle, they constitute a pyridine-to-ketone radical transfer process. Though strained, the opening of cyclopropane in **IM2** is uphill (ΔG = +9.7 kcal/mol) and via a relatively high transition state **TS3** (+18.7 kcal/mol). The ring opening/closing process is thus reversible and favoring much to the backward. The resulting primary radical **IM3** then undergoes the rate-determining barrier (**TS4**, +24.8 kcal/mol) for intermolecular radical C-C bond formation with ethyl acrylate. The following 5-*exo*-trig ring-closing step of **IM4** is facile and exergonic, leading to a new benzylic ketyl radical **IM5** (-27.6 kcal/mol). The following process, much like a reversed process of **IM0** to **IM2**, is a pyridine-mediated step-wise release of the product cyclopentyl ketone **3a** and catalyst (the boronyl radical) turn-over with highest energy barrier being 17.5 kcal/mol from **IM5**. Consequently, a formally diboron/pyridine co-catalytic cycle is closed in which the boronyl radical serves as the true catalyst that intimately takes part in the ring-opening and closing processes while pyridine serves as an assisting catalyst that mediates the boronyl generation and transfer processes.

CONCLUSIONS

In summary, we have demonstrated that a simple and stable diboron(4) compound can be successfully employed as the catalyst in an organic reaction that previously needed transition-metal catalysts. Particularly, together with a pyridine cocatalyst, a diboron can effectively catalyze the radical [3+2] cycloaddition of a cyclopropyl ketone with an alkene under operationally simple conditions and with theoretical 100% atom economy. Using this new catalytic system, several potential side pathways can be avoided and the reaction scope has been significantly broadened to covering many previously unusable substrates, and the desired cyclopentanes with various degree of substitution pattern can be readily accessed in generally high to excellent yield and diastereoselectivity. The facile preparation of 57 new compounds together with the successful application of this reaction in concise formal synthesis of an anti-obesity drug and rapid building complex natural product-like bridged or spiralcyclic compounds showed the high potency and robustness of this new method. The mechanistic experiments and computational investigation supported a radical relay catalysis featuring a pyridine-assisted boronyl radical catalyst. Overall, this work has opened new avenues in both boron chemistry and non-metallic main group catalysis. In specific, because many diboron(4) compounds are readily available, structurally tunable and easy-to-handle solids, and their stoichiometric chemistry have been increasingly established, their future applications as catalysts should represent an expectable and attractive approach for greener and novel transformations.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.xxxxxxx.
Detailed procedures, and full characterization data (PDF)
Crystallographic data for **3x** (CIF)
Crystallographic data for **3bf** (CIF)

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Notes

The authors declare no competing financial interest.

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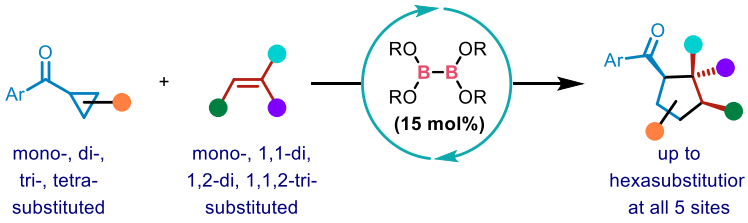

mono-, di-, tri-, tetra-substituted

mono-, 1,1-di, 1,2-di, 1,1,2-tri-substituted

up to hexasubstitutior at all 5 sites

- first diboronate catalysis
- inexpensive, stable catalyst
- atom economical

- metal free
- broad scope
- stereoselective

65 examples
up to 99% yield