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NHC-Boryl Radical Catalysis for Cycloisomerization With C–C Triple Bond Reorganization

Ai-Qing Xu[1‡], Feng-Lian Zhang[1‡], Tian Ye[1], Zhi-Xiang Yu[2]* & Yi-Feng Wang[1,3]*

[1]*Hefei National Laboratory for Physical Sciences at the Microscale, Center for Excellence in Molecular Synthesis of CAS, Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026 (China),* [2]*Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871 (China),* [3]*State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071 (China)*

**Corresponding authors: yuzx@pku.edu.cn; yfwangzj@ustc.edu.cn;* [‡]A.-Q. Xu and F.-L. Zhang contributed equally to this work.

Dedicated to the 100th anniversary of Nankai University.
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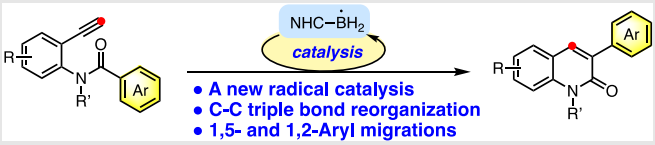
Our present study unveils a new and efficient *N*-heterocyclic carbene (NHC)-boryl radical-catalyzed cycloisomerization of *N*-(2-ethynylaryl)arylamides. This catalytic process is triggered by the addition of an NHC-boryl radical to the alkynyl moiety, followed by a radical cascade comprising of an intramolecular cyclization, successive 1,5- and 1,2-aryl migrations, and the reorganization of a C–C triple bond. Eventually, the catalytic cycle is achieved through a radical β-fragmentation reaction, from which the starting NHC-boryl radical is regenerated, and a structurally important quinolinone framework is assembled. A ^{13}C-labeling experiment was carried out to verify the C–C triple bond reorganization, and the proposed catalytic pathway was supported further by density functional theory calculations. Our identification of NHC-boryl radical as a catalyst, as well as its mode of operation via radical addition/elimination mechanism, would stimulate the advancement of design of radical catalysis and the discovery of novel enantioselective radical-catalyzed processes.



Keywords: radical catalysis, NHC-boryl radical, cycloisomerization, C–C triple bond reorganization, aryl migration, DFT calculation

Introduction

Catalytic reactions have been substantially applied in modern chemical synthesis.[1] Over the past decades, numerous transition metal-catalyzed[2] and organocatalyzed[3] methods have been developed. In sharp contrast, the processes, using a free radical as the catalyst have received much less attention.[4–6] Arguably, by taking advantage of the unique chemical reactivity of radical species, the realization of reliable radical catalysis is expected to trigger incredible molecular transformations that are inaccessible using other methods.

Although some radical-catalyzed reactions have been achieved based on metalloradical catalysis[7–9] and polarity reversal catalysis,[10,11] free radical-catalyzed addition/elimination processes (Scheme 1a) have remained a formidable challenge, as free radical species are generally reactive, it is difficult to identify a reaction system that maintains efficient catalytic turnovers. Due to this challenge, to date, successful examples have been limited

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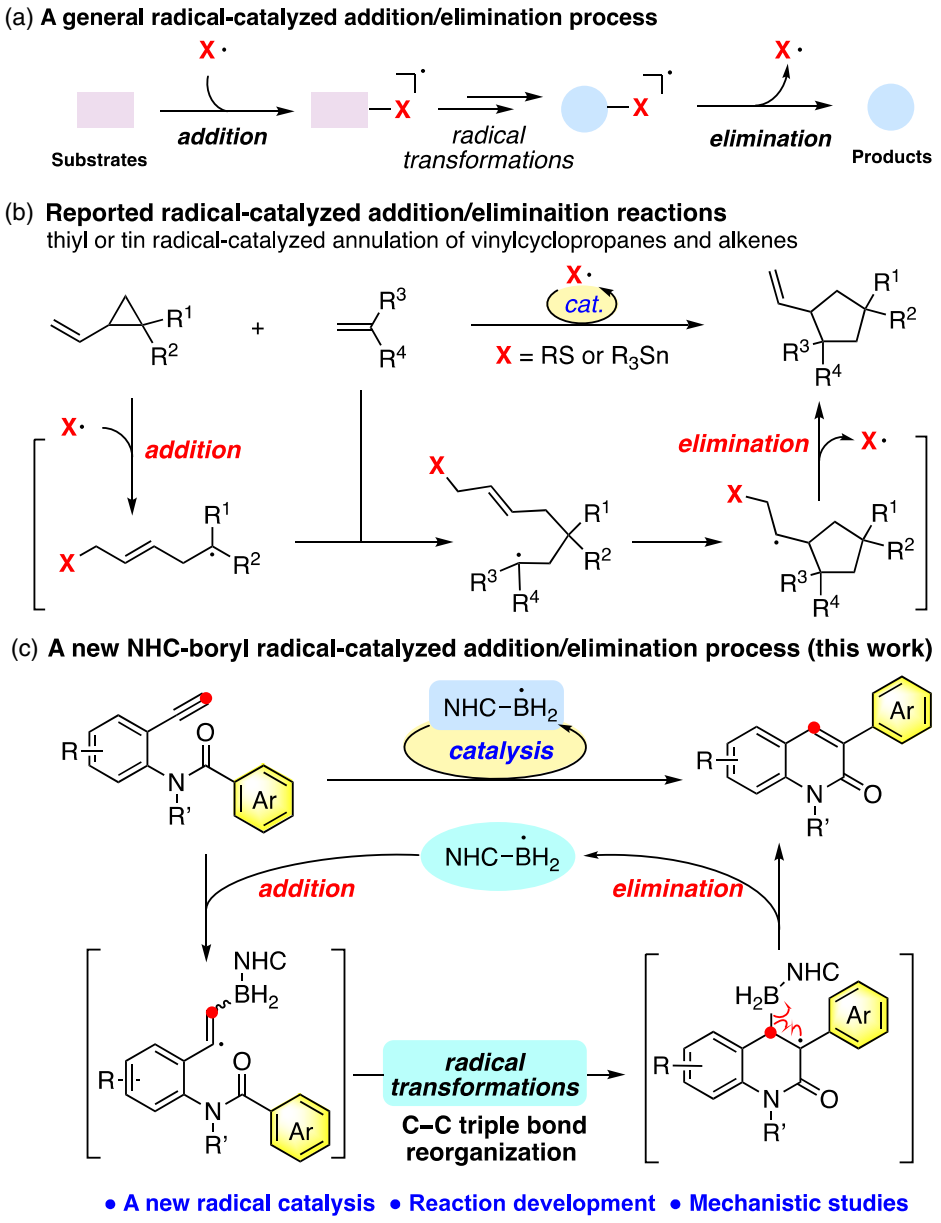
only to thiyl- or tin-radical-catalyzed annulation of vinylcyclopropanes and alkenes (Scheme 1b), based on the pioneering work of Feldman[12,13] and Oshima[14] in 1988. The catalytic cycle starts with a radical addition to vinylcyclopropanes, followed by a radical cascade process, and finally completes by a radical elimination reaction. This catalysis has shown significant applications in the synthesis of five-membered ring molecules[15-19] and related natural products.[20-21] Recently, Maruoka[22] disclosed an elegant enantioselective synthesis using a chiral thiol as the precatalyst. Despite these advances, the exploitation of other new radical catalysts and reaction modes for remarkable molecular transformations has rarely been achieved. Herein, we describe an *N*-heterocyclic carbene (NHC)-boryl radical-catalytic system, in which an unprecedented cycloisomerization reaction of *N*-(2-ethynylaryl)arylamides is achieved (Scheme 1c). This radical-catalyzed reaction proceeds through an intriguing NHC-boryl radical addition/elimination pathway. Remarkably, in this transformation, two alkynyl carbon atoms switched their positions to create a new bond connection pattern. Such C–C triple bond reorganization has scarcely been reported in alkyne transformations.[23-31] The resultant quinolinone skeleton is prevalent in a large number of bioactive molecules and natural products.[32-34] Although various synthetic methods have been developed for their synthesis,[35-39] the present catalytic rearrangement offers a new step- and atom-economical route to access this framework from simple starting materials.



Scheme 1 | *Radical-catalyzed addition/elimination processes.*

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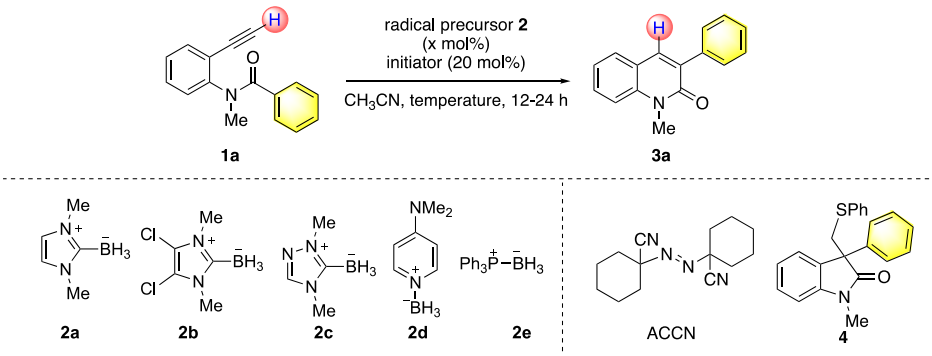
Results

Reaction discovery and development

NHC-boryl radicals have shown versatile chemical reactivity in various organic transformations,[40–47] since the pioneering work of Fensterbank, Lacôte, Malacria, and Curran.[48] Recently, our group has developed a series of radical borylation reactions of alkenes and alkynes to make versatile organoboron compounds.[49–52] When we attempted radical borylation of *N*-(2-ethynylphenyl) benzamide **1a** with NHC–BH_3 (**2a**) in the presence of di-*tert*-butyl peroxide (DTBP) as the radical initiator (Table 1, entry 1), the desired hydroboration product was not formed. Instead, an unexpected product **3a** was isolated in 87% yield (CCDC1887424 contains the supporting crystallographic data of **3a**. These data can also be obtained free of charge from The Cambridge Crystallographic Data Center, using the link: https://www.ccdc.cam.ac.uk/structures/). The formation of **3a** should go through a fantastic skeletal rearrangement, consisting of a cleavage and reorganization of multiple chemical bonds.[28] Notably, a comparable yield was also obtained using as low as 20 mol% of **2a** (entry 2). This suggests that unprecedented radical catalysis might be involved in the reaction process.

To further confirm the nature of radical catalysis, control experiments have been conducted. First, a radical initiator was omitted from the reaction setup and no reaction occurred (entry 3). This supported a radical reaction mechanism. Moreover, the reaction of **1a** with DTBP in the absence of **2a** led to a complex mixture with 81% recovery of **1a** (entry 4). This implied that an NHC-boryl radical species is essential for the catalysis of this transformation. Other radical initiators were also screened (entries 5–7), and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) proved to be the most efficient one (entry 7), affording **3a** in 87% isolated yield. However, lowering the loading of **2a** to 10 mol% resulted in a dramatic decrease in product yield (entry 8), providing

Table 1 | *Optimization of NHC-Boryl Radical-Catalyzed Cycloisomerization of* ***1a***[a]



Entry	**2** (x mol%)	Initiator	Temperature (°C)	**3a** Yield (%)[b]
1	**2a** (100)	DTBP	120	87
2	**2a** (20)	DTBP	120	86
3	**2a** (100)	–	120	ND (94)[c]
4[d]	–	DTBP	120	Complex (81)[c]
5	**2a** (20)	AIBN	80	72 (27)[c]
6	**2a** (20)	di-*tert*-butyl hyponitrite (TBHN)	50	7 (91)[c]
7	**2a** (20)	ACCN	95	87[e]
8	**2a** (10)	ACCN	95	10 (73)[c]
9	**2b** (20)	ACCN	95	43 (47)[c]
10	**2c** (20)	ACCN	95	87
11	**2d** (20)	ACCN	95	21 (71)[c]
12	**2e** (20)	ACCN	95	8 (75)[c]
13	Bu_3SnH (20)	ACCN	95	54 (19)[c]
14	PhSH (20)	ACCN	95	12 (**4**, 13)[f]
15	PhSH (100)	ACCN	95	ND (**4**, 39)

[a]Reaction conditions: **1a** (0.2–0.3 mmol), **2** (x mol%), initiator (20 mol%), CH_3CN (2 mL), under nitrogen. [b]Yield based on ^1H NMR analysis of the crude product with tetrachloroethane as an internal standard. [c]Recovery yield of **1a** based on ^1H NMR analysis of the crude product is shown in parentheses. [d]DTBP (100 mol%) was used. [e]Isolated yield. [f]**1a** was recovered in 43% yield.

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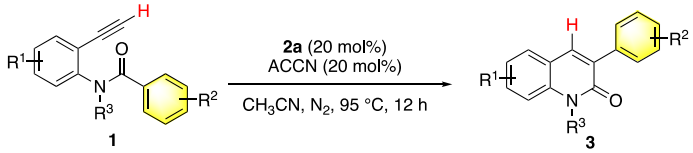
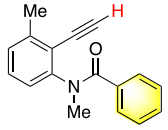
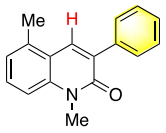
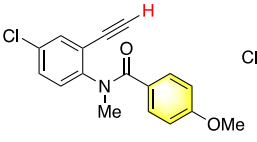
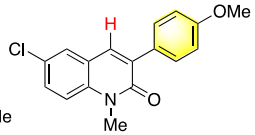
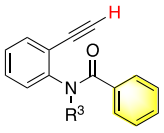
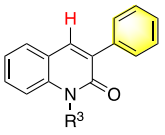
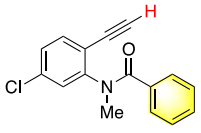
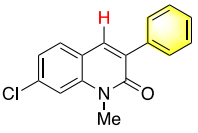
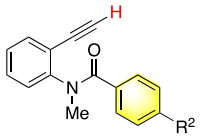
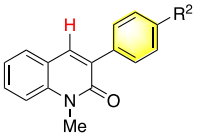
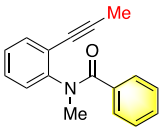
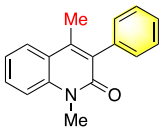
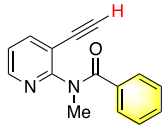
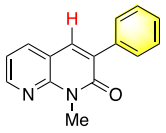
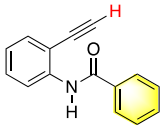
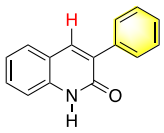
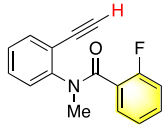
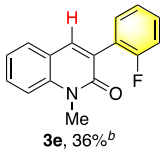
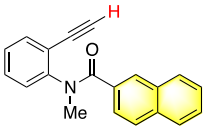
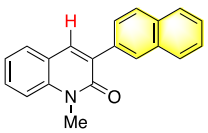
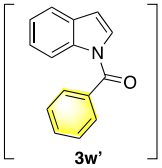
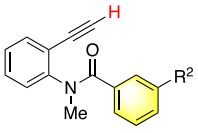
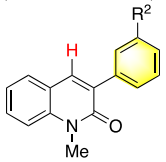
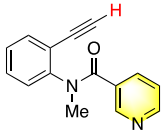
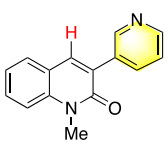
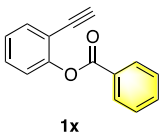
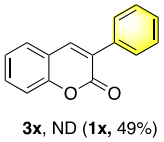
further support for claiming NHC-boryl radical catalysis. In addition, various Lewis-base-boryl radical precursors were examined. It was found that the employment of **2b** resulted in a sluggish reaction (entry 9), while **2c** was found to be as efficient as **2a** (entry 10). DMAP-BH_3 (**2d**) and Ph_3P-BH_3 (**2e**) could also promote this transformation, but with low efficiency (entries 11 and 12). In place of Lewis base-boryl radicals, tin radical was also able to catalyze this transformation, but in a low yield (entry 13). When 20 mol% of thiophenol (PhSH) was used as the precatalyst, beside **3a** (which was generated in 12% yield), thioether-handled oxindole **4** was formed in 13% yield (entry 14). Moreover, increasing the loading of PhSH to 100 mol% led to an exclusive formation of **4**, albeit in 39% yield (entry 15).

Using the optimized reaction conditions (Table 1, entry 7), the scope and limitation of this catalytic radical cycloisomerization was examined. A variety of *N*-(2-ethynyl) arylamides bearing different functional groups worked well, giving the desired quinolinone **3** in moderate to good yields (21–97%) (Table 2). The present method was also applied for the construction of 1,8-naphthyridin-2-one framework (for **3d**). The cycloisomerization proceeded smoothly when the migrating benzene ring had a substituent (R^2) at *para*- and *meta*-positions (**3f**–**3o**), whereas the reaction became sluggish for an *ortho*-substituted site (**3e**), probably due to the slow migration of a sterically demanding aryl ring. Unexpectedly, the reaction could not go to completion, even with the use of 100 mol% of **2a**. The bromine substituent

Table 2 | *The Scope of NHC-Boryl Radical-Catalyzed Cycloisomerization*[a]



1 3

Substrates 1	Products 3	Substrates 1	Products 3	Substrates 1	Products 3
 **1b**	 **3b**, 91%	 **1h**	 **3h**, 89%[d] (**2a**: 53%[c])	 **1r**, R^3 = Bn **1s**, R^3 = cyclopropylmethyl **1t**, R^3 = allyl **1u**, R^3 = propargyl	 **3r**, 65%[d] (**2a**: 53%[c]) **3s**, 77%[d] (**2a**: 45%[c]) **3t**, 32%[b] (**2a**: 67%[c]) **3u**, 21%[b] (**2a**: 62%[c])
 **1c**	 **3c**, 86%	 **1i**, R^2 = OMe **1j**, R^2 = Me **1k**, R^2 = cyclopropyl **1l**, R^2 = Ph **1m**, R^2 = Br **1n**, R^2 = Cl **1o**, R^2 = F	 **3i**, 91% **3j**, 97%[d] (**2a**: 50%[c]) **3k**, 87%[d] (**2a**: 60%[c]) **3l**, 71%[d] (**2a**: 68%[c]) **3m**, 70%[e] (**2a**: 23%[c]) **3n**, 82%[d] (**2a**: 46%[c]) **3o**, 81%	 **1v**	 **3v**, 12%[b] (**1v**: 76%, **2a**: 69%[c])
 **1d**	 **3d**, 81%			 **1w**	 **3w**, ND (**3w'**: 8%, **1w**: 12%)
 **1e**	 **3e**, 36%[b] (**1e**: 55%; **2a**: 53%[c])	 **1p**	 **3p**, 62%[b] (**2a**: 52%[c])		 **3w'**
 **1f**, R^2 = Me **1g**, R^2 = F	 **3f**, 74%[d] (**2a**: 49%[c]) **3g**, 79%	 **1q**	 **3q**, 79%[b] (**2a**: 55%[c])	 **1x**	 **3x**, ND (**1x**, 49%)

[a]Reaction conditions: **1** (0.2–0.3 mmol), **2a** (20 mol%), and ACCN (20 mol%) in CH_3CN (2 mL) under N_2. [b]**2a** (100 mol%) was used. [c]Recovery yield of **2a** based on its amount added. [d]**2a** (40 mol%) was used. [e]**2a** (60 mol%) was used. ND: not detected.

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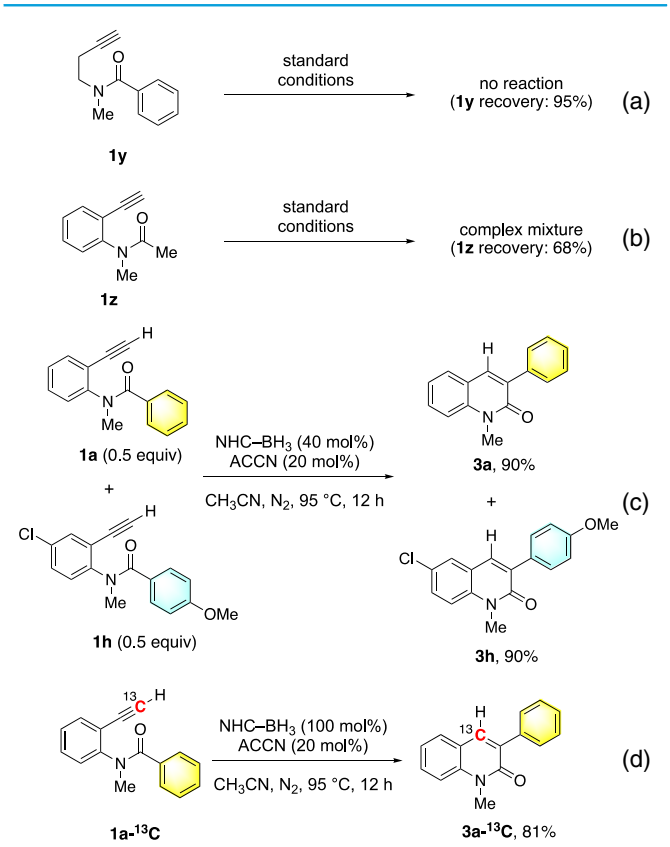
(for **3m**) was also compatible, although it could be reduced potentially by NHC-boryl radicals.[53] Both naphthyl (for **3p**) and pyridyl (**3q**) motifs could participate in the migration. We observed no detectable detrimental effect when benzyl (for **1r**) and cyclopropylmethyl (for **1s**) groups were used as the substituent R^3 on the amide nitrogen. However, the rearrangement was somewhat hampered when an alkenyl (for **1t**) or alkynyl (for **1u**) group was present, whereas no appreciable side products were detected even upon using one equivalent of **2a**, which, presumably, resulted from side reactions between radical intermediates and these C–C unsaturated bonds. Moreover, when *N*-(2-ethynyl)benzamide **1v**, tethering an internal alkynyl moiety was subjected to the same reaction conditions, the cycloisomerization proceeded, albeit with inferior efficiency. It should be noted that in some cases, the starting material **1** could not be consumed with the use of 20 mol% of **2a** as the catalyst. To improve the product yield, substoichiometric to stoichiometric amounts of **2a** (40–100 mol%) were used. However, after the completion of the reaction, some amount of **2a** (23–68% of the total amount added) was recovered, as shown in Table 2. This suggests that only catalytic amounts of **2a** could complete these reactions. Surprisingly, repeating the reaction of *N*-H amide **1w** afforded indole **3w'** in 8% yield without the detection of any desired **3w** (The possible mechanism for the formation of **3w'** is described in the Supporting Information Figure 1). Moreover, our present radical catalysis approach was ineffective for 2-ethynylphenyl benzoate (**1x**).

Mechanistic studies of NHC-boryl radical catalysis

To gain more insights into the reaction mechanism, several mechanistic studies were performed (Scheme 2). First, two control experiments using **1y** and **1z** as substrates with NHC-boryl radicals were conducted (Schemes 2a and b). The experimental results revealed no observable cycloisomerization products, implying that the presence of two aryl rings is essential in promoting the reaction. Furthermore, considering multiple chemical bonds were cleaved and reorganized, we wondered if intermolecular conversions occurred during the reaction sequences. An experiment using **1a** and **1h** did not yield any crossover products (Scheme 2c), thereby, excluding a pathway involving intermolecular reaction mode. To further probe the change of connectivity of the alkynyl moiety, a reaction using ^{13}C-labeled substrate (**1a-^{13}C**) was examined. We found that the terminal alkynyl ^{13}C atom shifted its position, and a new connection with the aryl carbon was created (Scheme 2d). Collectively, our findings prompt us to propose a mechanism for the NHC-boryl radical catalysis below.



Scheme 2 | *Mechanistic studies of NHC-boryl radical catalysis.*

A proposed mechanism and DFT calculations

Based on these findings, a plausible catalytic cycle was proposed for this cycloisomerization (Figure 1). The NHC-boryl radical is first generated through the radical initiation of ACCN.[48,54] Then, it adds to the terminal alkynyl carbon to generate vinyl radical **I**,[41,49] which cyclizes with the benzamide, followed by C–C bond scission to realize the first aryl migration.[55–58] The resulting acyl radical **III** undergoes 5-*exo*-*trig* cyclization with the intramolecular alkene part, giving α-boryl alkyl radical intermediate **IV**. After that, a second aryl migration occurs to give a stabilized radical intermediate **VI**. At this stage, the original two alkynyl carbon atoms exchange their positions and a new chemical bond connection is established. Eventually, product **3a** is formed through a radical β-fragmentation, together with the regeneration of the starting NHC-boryl radical.

To gain more support of this suggested mechanism, density functional theory (DFT) calculations were conducted at the (U)B3LYP-D3/6-311+G(d,p)//(U)B3LYP-D3/6-31+G(d) level in CH_3CN solvent using SMD solvation model. The details of the computational studies are shown in Figure 2 and also provided in the Supporting Information. The results showed that addition of the

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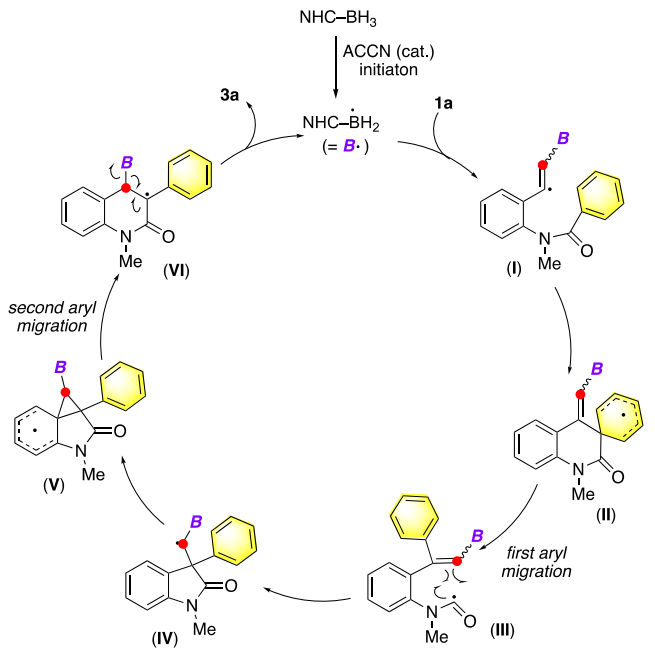

Figure 1 | *A proposed catalytic cycle of NHC-boryl radical.*

NHC-boryl radical to the alkyne moiety of **1a** via **TS-1** has an activation free energy of 8.0 kcal/mol, affording radical intermediate **I** by exergonic 13.6 kcal/mol. From intermediate **I**, intramolecular radical addition to the aryl ring requires an activation free energy of 15.5 kcal/mol to generate intermediate **II**, which undergoes C–C bond cleavage easily, to deliver an acyl radical **III**. The subsequent intramolecular 5-*exo*-*trig* cyclization is a facile process with activation free energy of 2.1 kcal/mol and is exergonic by 16.6 kcal/mol (from **III** to **IV**). From alkyl radical **IV**, the second aryl migration occurs stepwise with an overall activation free energy of 12.0 kcal/mol (from **IV** to **TS-6**) and releases 16.8 kcal/mol of Gibbs free energy (from **IV** to **VI**). Finally, β-elimination of the NHC-boryl radical from **VI** is easy, occurring with an activation free energy of 8.4 kcal/mol.

The above calculation results suggest that the radical-catalyzed cycloisomerization is a downhill cascade reaction, and all steps in the catalytic cycle are irreversible, except for the conversion of **IV** to **V**. The conversion of **VI** to **3a** and NHC-boryl radical is irreversible, because the generated NHC-boryl radical prefers to add to **1a** to enter the next catalytic cycle compared with add to **3a** (8.0 kcal/mol versus 11.4 kcal/mol). Moreover, the radical addition of **I** to form **II** is the rate-determining step in this catalytic cycle ($\Delta G^{\neq}$ = + 15.5 kcal/mol). It should be noted that, from intermediate **III**, a 6-*endo*-*trig* cyclization is also possible to occur, followed by β-fragmentation to give product **5**. However, this product was not observed experimentally. The computational studies reveal that the 6-*endo* cyclization requires an energy barrier of

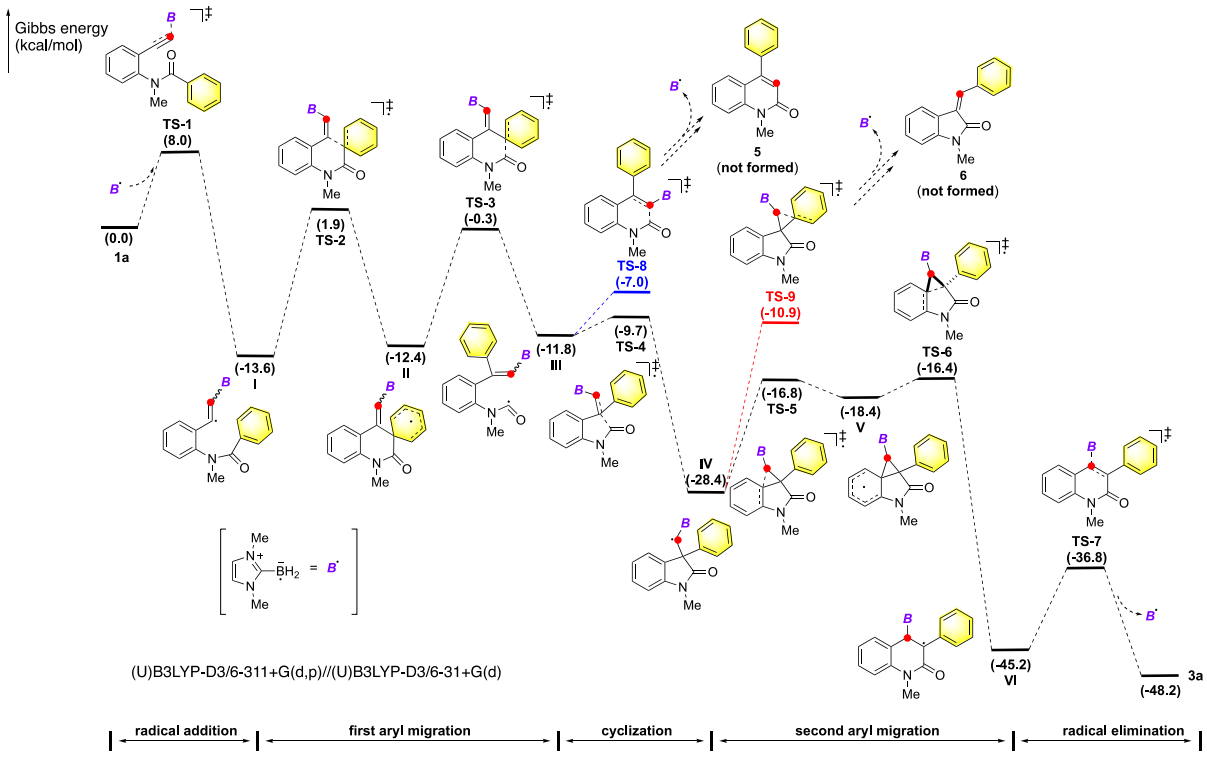

Figure 2 | *DFT calculations supporting the role of NHC-boryl radicals as catalyst.*

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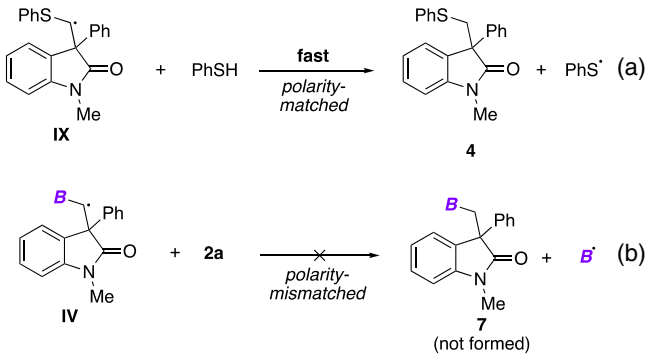
4.8 kcal/mol, which is higher than the irreversible 5-*exo* cyclization by 2.7 kcal/mol, thereby, rendering the formation of **IV** more favorable. Furthermore, as an alternative, 1,2-aryl migration from intermediate **IV** to form **6** could be envisioned. However, our DFT calculations indicate that the corresponding activation energy (17.5 kcal/mol) is much higher than the energy required forming **V** (11.6 kcal/mol). This difference in energy is presumably because the acetamide group may play a role in stabilizing **TS-5**. As such, the possibility to form **6** is excluded.

For some substrates, substoichiometric to stoichiometric amounts of **2a** were required to make the reactions complete. Nonetheless, some amounts were recovered at the end of the reaction, indicating a catalytic reaction nature of these processes. We speculate that in case the aryl group is not easy to migrate due to electronic or steric reasons, the first NHC-boryl radical addition step may be a reversible process, thereby, giving back the NHC-boryl radical through β-fragmentation. However, this radical has a short lifetime, and thus, it decays when it cannot be trapped by other species.[59,60] When the concentration of **2a** increases, the decay of NHC-boryl radical is possible to be somehow decelerated, as the high concentration of **2a** was beneficial to promote the inter-conversions of NHC-boryl radical and **2a** through a fast hydrogen atom transfer. Therefore, the role of the excess **2a** is to keep a sufficient concentration of active NHC-boryl radical in the reaction mixture in order to maintain efficient catalytic turnovers.

Comparison of PhSH and NHC-BH_3 serving as precatalysts

As mentioned in the optimization study (Table 1, entry 14), the use of PhSH as the precatalyst led to the formation of both **3a** and **4**. The formation of **4** is derived from the hydrogen atom transfer from PhSH to intermediate **IX** (Scheme 3a), generated through an analogous radical addition/aryl migration/cyclization sequence. It is known that PhSH is a good hydrogen atom donor with a low bond-dissociation energy (~ 79 kcal/mol),[11] and more importantly, the hydrogen atom transfer to nucleophilic alkyl radicals is extremely fast (> 1×10^8 M^{-1} s^{-1}),[11] owing to the matched polarity. Therefore, product **4** was formed predominately when 100 mol% of PhSH was used (Table 1, entry 15). On the other hand, it has been reported that **2a** also has comparable bond dissociation energy as B–H bond (~ 80 kcal/mol).[61] However, the reduction of **IV** was undetectable (Scheme 3b), due to the mismatched polarity between **IV** and **2a**.[53,62] This finding implied that the relatively inert hydrogen-donating ability of NHC-BH_3 to alkyl radicals makes it profitable for a variety of radical-catalytic reactions, in which it is feasible to avoid the reduction of radical intermediates.



Scheme 3 | *The difference between PhSH and NHC-BH_3 serving as precatalysts.*

Conclusion

We have developed an NHC-boryl radical catalysis for the cycloisomerization of *N*-(2-ethynylaryl)arylamides. This catalytic process includes the migration of two aryl rings and reorganization of C–C triple bond. Moreover, the catalytic reaction features broad functional group tolerance and mild reaction conditions, suggesting that NHC-boryl radical catalysis would have more impact on synthetic potentials. The identification of NHC-boryl radical as the catalyst, as well as the radical addition/elimination mode established in this work would inspire the design of new radical catalysis. In particular, many chiral NHC-BH_3 are readily accessible. Thus, it is plausible to explore enantioselective radical catalysis, which is currently ongoing in our lab.

Supporting Information

Supporting Information is available.

Conflicts of Interest

The authors declare no competing interest.

Acknowledgments

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