

# Rhodium(II)-Catalyzed Strain-Enabled Stereoselective Synthesis of Skipped Dienes

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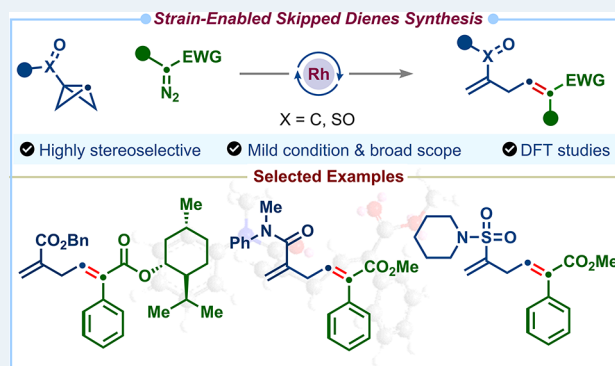
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**ABSTRACT:** Skipped dienes are not only present in fatty acid primary metabolites and natural products but also serve as reactive intermediates in diverse chemical synthesis. Despite this, the regioselective and stereoselective synthesis of skipped dienes remains a challenging goal. Strain release in organic molecules is a powerful tool for creating chemical complexity under mild conditions. The reactivity of strained bicyclo[1.1.0]butane (BCB) systems is mainly dominated by transformations relying on their innate electrophilic reactivity. Herein, we report a rare example of the carbene-type reactivity of the BCB system based on rhodium–carbene chemistry, which enables the highly stereoselective synthesis of skipped dienes through strain release. The reaction is compatible with a diverse range of functional groups on both diazo compounds and BCBs and could be applied successfully to complex structures, providing highly valuable and functionalizable skipped dienes. The functional groups introduced during the reaction served as synthetic handles for downstream manipulations. The high stereoselectivity observed has been rationalized based on DFT calculations, which suggests that the reaction is likely proceeding via a concerted mechanism, and noncovalent interactions between the metalcarbene and BCB mainly control the observed exclusive selectivity.

**KEYWORDS:** strain release, metalcarbene, skipped dienes, bicyclobutanes, diazo compounds



## INTRODUCTION

Skipped dienes are widely present in biologically active natural products such as alkaloids, polyunsaturated fatty acids, polyketides, and terpenoids, which are potent antibiotic, antifungal, and cytotoxic agents (Scheme 1A).<sup>1</sup> They also serve as versatile building blocks in chemical synthesis, with applications in the total synthesis of complex natural products. Consequently, several strategies have been developed for the synthesis of skipped dienes, including allylmetalation of alkynes,<sup>2</sup> allylic vinylations,<sup>3</sup> and cross-coupling reactions.<sup>4</sup> Despite their efficiency, strategies to access structurally diverse skipped dienes in high regioselective and stereoselective fashion remain a significant challenge in organic chemistry.

Ring strain in organic molecules is a powerful driving force promoting myriad transformations that have found several applications in chemical synthesis, materials science, and biorthogonal chemistry.<sup>5</sup> In particular, motifs that have a bridge between opposite carbon atoms, such as bicyclo[1.1.0]butanes (BCBs) (63.9 kcal/mol of strain energy) and [1.1.1]propellane (98 kcal/mol of strain energy), have garnered significant attention since they are often used to install the cyclobutane and bicyclo[1.1.1]pentane derivatives that serve as high-value biososteres in medicinal chemistry and drug discovery.<sup>6</sup> Several groups have explored the reactivity of

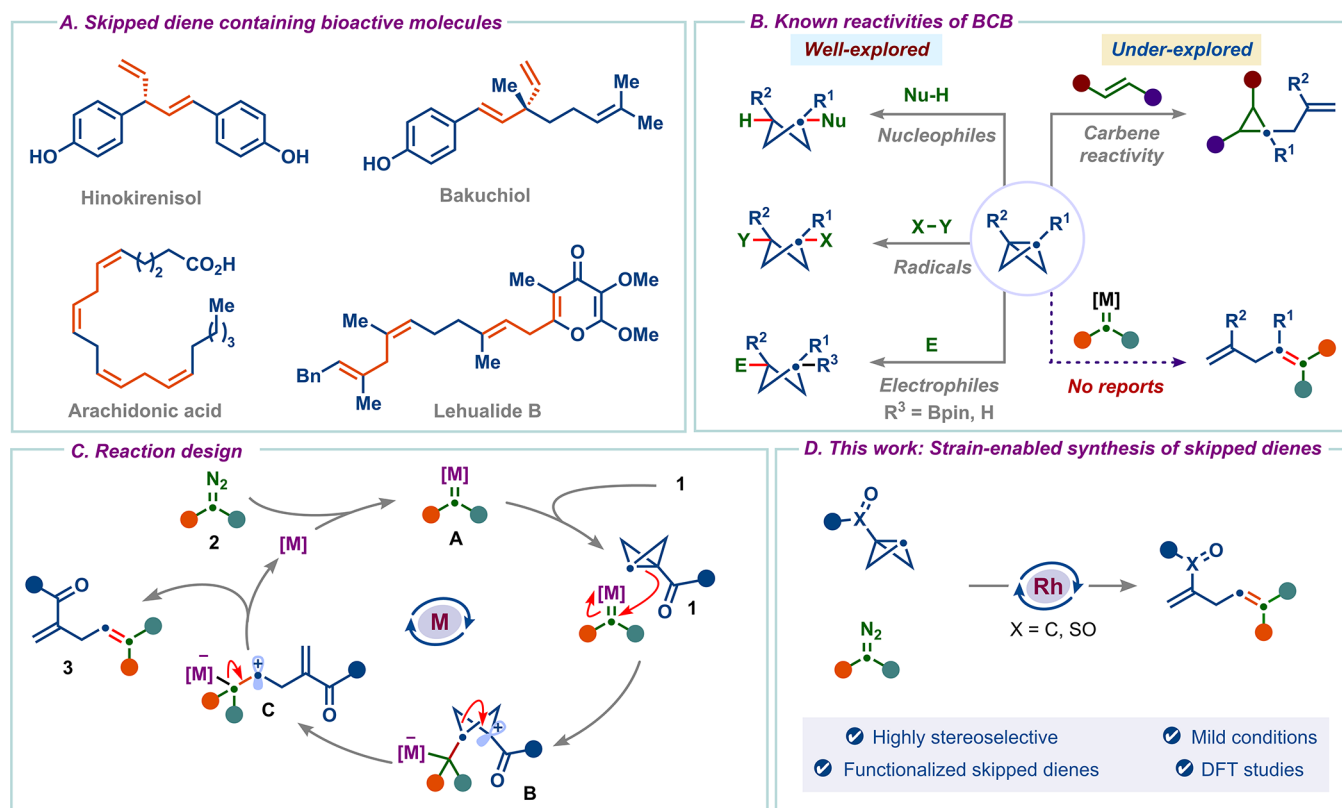
strained carbon–carbon  $\sigma$  bond of BCB derivatives in various difunctionalizations,<sup>7</sup> cycloadditions,<sup>8</sup> carbene insertions,<sup>9</sup> and fragmentations<sup>10</sup> (Scheme 1B). However, the developments in the field of strain-release functionalizations of BCB derivatives rely primarily on the inherent electrophilic reactivity of the strained carbon–carbon  $\sigma$  bond. To reverse this reactivity, Aggarwal and co-workers utilized nucleophilic BCB boronate complexes, which could react with electrophilic palladium(II) intermediates or electrophilic radicals.<sup>11</sup> Along this line, Gryko and co-workers generated nucleophilic radicals from BCBs, via a polarity-reversal cobalt-catalyzed strategy, which are subsequently trapped with Michael acceptors or intercepted in a Ni-catalyzed cross-coupling reaction.<sup>12</sup> On the other hand, a complementary carbene reactivity of BCBs, which would undoubtedly give access to a new chemical space, remains extremely rare.<sup>13</sup> In 1981, Noyori and co-workers reported a nickel-catalyzed reaction of BCBs with electron-deficient

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**Scheme 1.** (A) Skipped Diene Containing Bioactive Molecules; (B) Known Reactivities of BCBs; (C) Reaction Design; (D) This Work: Strain-Enabled Synthesis of Skipped Dienes



olefins to give the corresponding allylcyclopropane derivatives, but poor selectivity and efficiency hampered its application in organic synthesis.<sup>13c</sup> In 2008, Wipf and co-workers reported that heteroatom-tethered BCBs could undergo a Rh(I)-catalyzed cycloisomerization to give a carbene intermediate that could be trapped intramolecularly with an olefin, which resulted in the construction of pyrrolidines and azepines.<sup>5a,13g</sup> Considering these scant literature precedents, we were interested in developing a new, efficient strategy for harnessing a carbene-type reactivity of BCBs under mild conditions and engaging them in further functionalizations.

Metal-mediated carbene transfer reactions using diazo precursors have emerged as powerful tools in organic synthesis since they give fast access to valuable chemicals from structurally simple compounds.<sup>14</sup> A wide range of metal-carbene reactions, including X-H insertions,<sup>15</sup> cyclopropanations,<sup>16</sup> and rearrangement reactions,<sup>17</sup> have been studied extensively. In contrast, coupling reactions between metal-carbenes and carbon nucleophiles are less investigated, and they are mainly limited to electron-rich (hetero)aromatic compounds<sup>18</sup> and cyclopropanol.<sup>19</sup> In a merger of strain-release and metal-carbene chemistry, we questioned whether BCB **1** could act as a nucleophile first to add onto electrophilic metal-carbene **A** generated by the reaction of diazo compound **2** with a metal catalyst that would give intermediate **B**, which can undergo fragmentation to give intermediate **C**, resulting in a carbene-type reactivity for BCB and leading to skipped diene **3** (Scheme 1C). This proposal not only presents novel reactivity between BCB and metal-carbene but also offers a mechanistically distinct method to prepare valuable skipped dienes. Herein, we report our success in realizing this strategy, presenting the design and development of an

unprecedented rhodium-catalyzed strain-enabled strategy for high regioselective and stereoselective synthesis of skipped dienes (Scheme 1D). A broad range of diazo compounds and BCBs are well tolerated. The combination of experimental results and DFT calculations revealed the origins of stereo-control in this transformation.

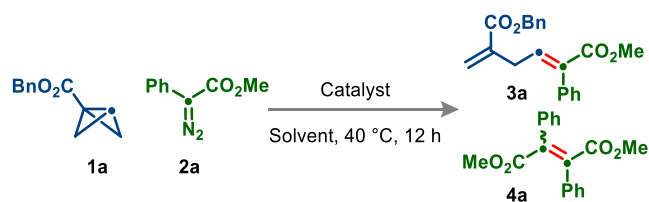
## MATERIALS AND METHODS

**Materials.** Rh<sub>2</sub>(OAc)<sub>4</sub> (209058, Sigma-Aldrich), dichloromethane (dried over CaH<sub>2</sub> and distilled under an argon atmosphere), and borosilicate Schlenk tube (Tensil).

**Catalytic Reactions.** BCB **1** and Rh<sub>2</sub>(OAc)<sub>4</sub> (2 mol %) were taken in a 5 mL borosilicate Schlenk tube. Then, the tube was evacuated and refilled with argon gas (three times). DCM (0.15 M) was added. Next, a solution of diazo compound **2** in DCM (0.45 M) was added via a syringe pump over a period of 30 min and stirred for 12 h at room temperature. Finally, the solvent was evaporated, and the crude product was purified by column chromatography using silica gel.

## RESULTS AND DISCUSSION

We commenced our studies by examining a model reaction between BCB **1a** and diazo compound **2a** using 5 mol % Cu(acac)<sub>2</sub>, a commonly used catalyst for the decomposition of diazo compounds,<sup>20</sup> in DCM at 40 °C. We did not observe the formation of the desired skipped diene **3a**. Instead, we obtained dimerization product **4a** in a 62% yield (Table 1, entry 1). Next, we continued the screening of other copper catalysts, which are used for carbene generation. Cu(OTf)<sub>2</sub> and Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> gave only dimerization product **4a** (Table 1, entries 2 and 3). To our delight, CuCl<sub>2</sub> gave the

Table 1. Optimization of the Reaction Conditions<sup>a</sup>

entry	catalyst	solvent	3a (%) <sup>b</sup>	E/Z	4a (%) <sup>b</sup>
1	Cu(acac) <sub>2</sub>	DCM	ND		62
2	Cu(OTf) <sub>2</sub>	DCM	<5		64
3	[Cu(ACN) <sub>4</sub> ]PF <sub>6</sub>	DCM	<5		38
4	CuCl <sub>2</sub>	DCM	9	>20:1	24
5	Rh <sub>2</sub> (TFA) <sub>4</sub>	DCM	29	>20:1	trace
6	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCM	56	>20:1	trace
7	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>3</sub> CN	ND		ND
8	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCE	13	>20:1	trace
9	Rh <sub>2</sub> (OAc) <sub>4</sub>	CHCl <sub>3</sub>	14	>20:1	trace
10	Rh <sub>2</sub> (OAc) <sub>4</sub>	PhCH <sub>3</sub>	12	>20:1	trace
11 <sup>c</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCM	90	>20:1	ND
12 <sup>c,d</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCM	90	>20:1	ND
13 <sup>c,d,e</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCM	90	>20:1	ND
14 <sup>c,e</sup>	no catalyst	DCM	ND		ND

<sup>a</sup>1a (0.15 mmol), 2a (1 equiv), solvent (0.1 M), catalyst (5 mol %), 40 °C, 12 h. <sup>b</sup>NMR yields using dibromomethane as the internal standard. <sup>c</sup>1.5 equiv of 2a. <sup>d</sup>2 mol % catalyst. <sup>e</sup>Room temperature. ND = not detected.

desired product **3a** as a single geometrical isomer, albeit with a very poor yield (Table 1, entry 4). Although the yield could be improved to 29% using a more reactive Rh<sub>2</sub>(TFA)<sub>4</sub>, large amounts of C–H insertion product and azine were observed (Table 1, entry 5, see Supporting Information for more information). Pleasingly, Rh<sub>2</sub>(OAc)<sub>4</sub> gave the desired product **3a** in a 56% yield (Table 1, entry 6). A solvent screen revealed that DCM was the optimal solvent, with other solvents leading to lower yields or no reactivity (Table 1, entries 7–10). A significant improvement in the yield was observed when we used 1.5 equiv of diazo compound **2a** (Table 1, entry 11). The catalyst loading could be reduced to 2 mol % without affecting the reaction yield (Table 1, entry 12). The reaction also worked at room temperature and gave the desired product in a 90% yield (Table 1, entry 13). Finally, the control experiment demonstrated that Rh<sub>2</sub>(OAc)<sub>4</sub> was essential for this transformation (Table 1, entry 14).

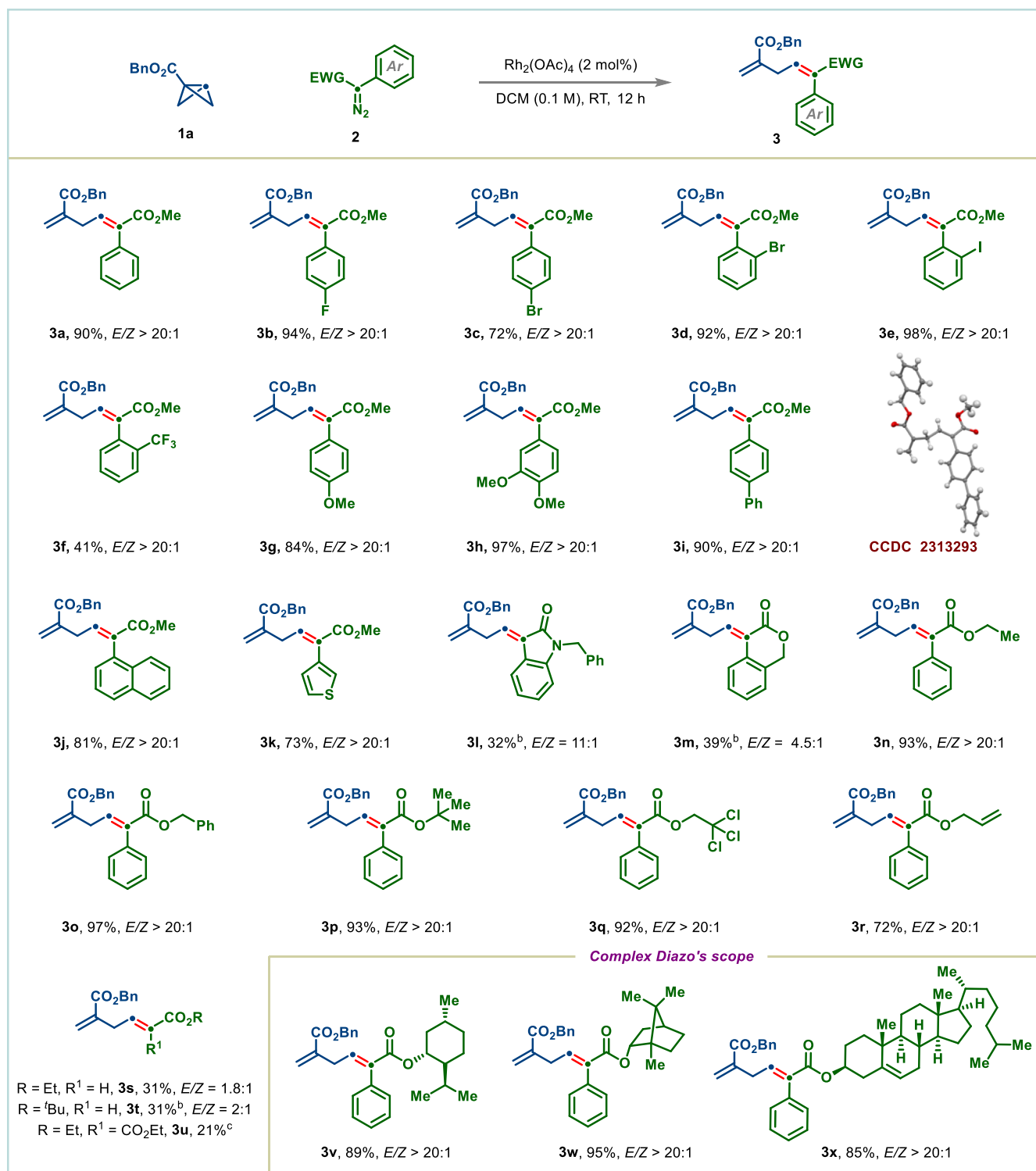
Under the optimized set of conditions, various diazo compounds were examined by using BCB **1a** (Scheme 2). Electron-withdrawing groups on the aryl group of diazo compounds, including fluoro, bromo, iodo, and trifluoromethyl groups, reacted smoothly to give the products **3b–3f** in moderate to excellent yields with excellent stereoselectivities. Electron-donating groups were also well tolerated (products **3g** and **3h**). We continued to investigate biphenyl-, naphthalene-, and thiophene-bearing diazo derivatives and were delighted to obtain the corresponding products in excellent yields and selectivities (products **3i–3k**). The structure of product **3i** was determined by X-ray analysis (CCDC 2313293), which confirmed the *E*-geometry of the olefin. Cyclic  $\alpha$ -diazo compounds are also viable substrates, giving the products **3l** and **3m** in moderate yields and selectivity. A range of alkyl groups on the diazo ester could be accommodated, including ethyl, benzyl, and *tert*-butyl, highlighting that the reaction is

amenable to the full spectrum of steric demand and furnish products **3n–3p** with excellent yields and selectivities. Diazo esters bearing trichloroethyl and allyl groups could also be used and delivered the products **3q** and **3r** in 92 and 72% yields, respectively. Ethyl diazoacetate, *tert*-butyl diazoacetate, and diethyl diazomalonnate also reacted in this reaction (products **3s–3u**). Notably, complex diazo compounds derived from biologically relevant molecules, such as menthol, borneol, and cholesterol, also participated well in this reaction (products **3v–3x**). Unfortunately, pyridine-substituted diazo compound failed to participate in this transformation (see Supporting Information for unsuccessful substrates).<sup>21</sup>

Subsequently, the scope of the reaction with respect to BCBs was investigated with the diazo compound **2a** (Scheme 3). Various BCB esters bearing phenethyl, *iso*-propyl, *tert*-butyl, and vinyl cyclohexyl groups proved compatible in this reaction, providing the skipped dienes **3aa–3ad** in good yields with excellent selectivities. Next, we examined the scope of the reaction with respect to BCB amides. Various substituents on the nitrogen, including simple phenyl, electron-deficient aryls, and benzyl groups, reacted well (products **3ae–3ah**). The reaction also tolerated aryl ketone BCBs. *p*-Methoxyphenyl and *p*-fluorophenyl BCB ketones participated to give the corresponding products **3ai** and **3aj** in synthetically useful yields. Naphthyl BCB ketone also provided skipped diene **3ak** in a low yield but with excellent selectivity. Phenyl sulfone- and piperidinyl sulfonamide-derived BCBs yielded skipped dienes **3al** and **3am** in excellent yield and selectivity. Unfortunately, disubstituted phenyl BCB did not work in this reaction.<sup>21</sup>

To further demonstrate the potential utility of this strategy, we sought to convert the obtained products into valuable building blocks. First, we prepared **3a** on a larger scale. We were delighted that the reaction between **1a** and **2a** on a 2.0 mmol scale proceeded efficiently under our standard reaction conditions, providing the desired product **3a** in an 82% yield (Scheme 4A). Reduction of both ester groups in **3a** was possible using DIBAL-H and afforded bis-allylic alcohol **5** in a 78% yield (Scheme 4B). Bromination using Br<sub>2</sub>/pyridine was found to take place selectively on the less substituted double bond and afforded the dibrominated product **6** in a 41% yield. On treatment with DBU, the skipped diene **3a** isomerized to give 1,3-diene **7** in good yield and selectivity. Finally, the epoxidation of **3a** using *m*-CPBA led to epoxides **8** and **9** in a 54% yield with a 2:1 ratio.

We next focused on the mechanism of this transformation (Scheme 5). Wipf and co-workers proposed that Rh(I) could undergo oxidative addition across the central carbon–carbon  $\sigma$  bond in a tethered BCB, followed by a rearrangement to give Rh–carbene species.<sup>13g,j,22</sup> If this were the case in our reaction, a control experiment without the diazo compound would provide the carbene dimerization product **10**. When we subjected BCB **1a** to the standard conditions without the diazo compound, no conversion of the BCB was observed, indicating that Rh<sub>2</sub>(OAc)<sub>4</sub> is not directly activating BCB (Scheme 5A). Furthermore, the reaction of BCB **1a** with *tert*-butyl acrylate did not furnish the cyclopropane **11**. Similarly, no intramolecular cyclopropanation product **12** was observed when we used BCB-allyl ester **1f**. These results further suggest that, unlike the Rh(I) catalyst, Rh<sub>2</sub>(OAc)<sub>4</sub> is not undergoing oxidative addition across the strained carbon–carbon bond of the BCB. Based on these control experiments and literature reports,<sup>22,23</sup> we propose that first Rh<sub>2</sub>(OAc)<sub>4</sub> reacts with the diazo compound **2a** and furnishes Rh–carbene intermediate I

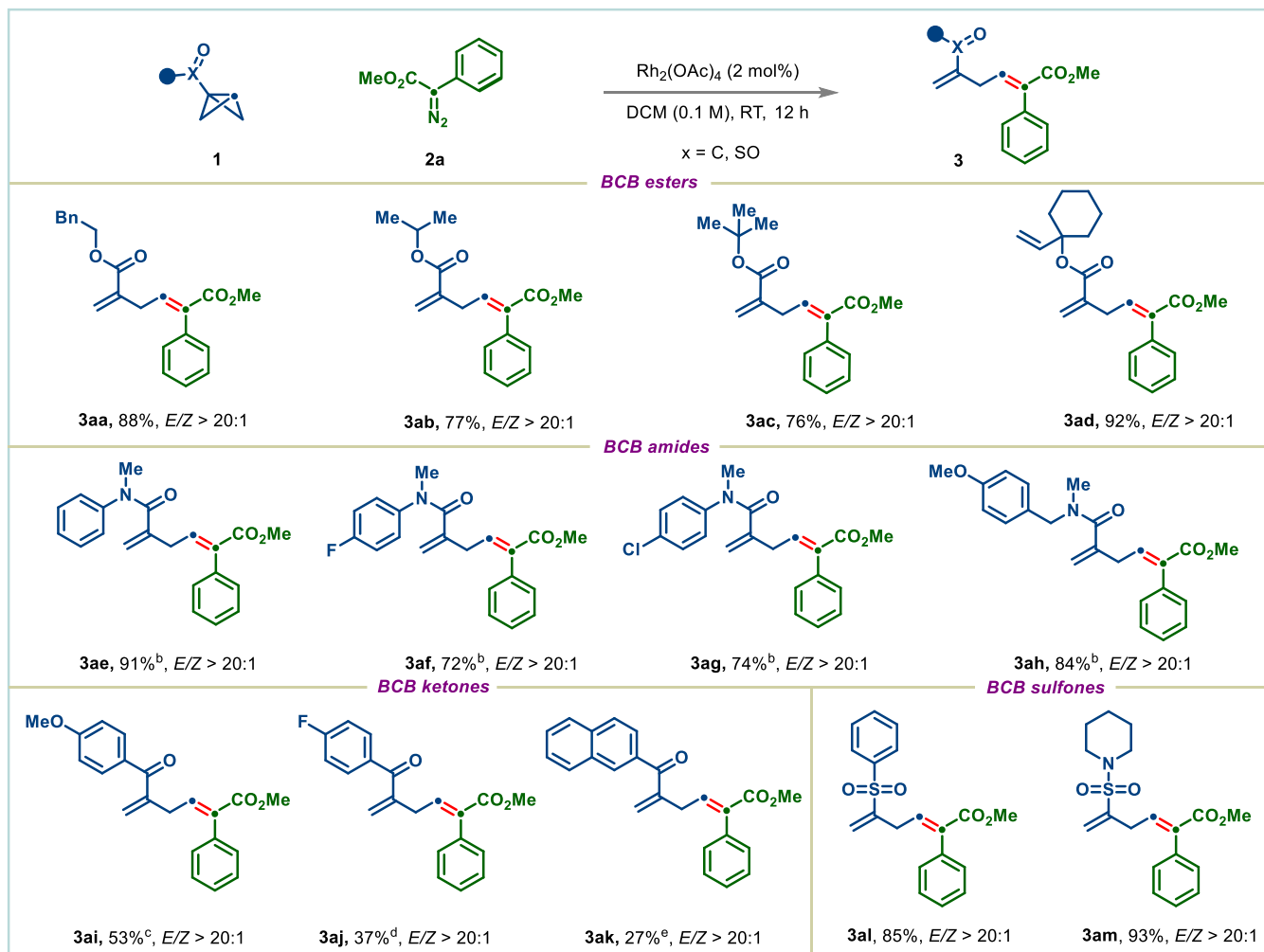
Scheme 2. Scope of Diazo Compounds<sup>a,b,c</sup>

<sup>a</sup>Reaction conditions: 0.3 mmol of **1a**, 0.45 mmol of diazo compound **2**, 3.0 mL of dry DCM, 2 mol % of  $\text{Rh}_2(\text{OAc})_4$ , RT, 12 h. Yields are of isolated products, and *E/Z* ratio was determined by <sup>1</sup>H NMR from the crude reaction mixture. <sup>b</sup>Yields are of major diastereomer only. <sup>c</sup>NMR yield.

that reacts with the BCB **1a** either in a concerted fashion or in a stepwise manner to give the desired skipped diene **3a** and regenerates the Rh-catalyst. To understand the mechanism and stereoselectivity, we conducted a DFT study at the SMD<sub>(DCM)</sub>/B3LYP-D3BJ/6-311++G\*\*, SDD(Rh)//B3LYP-D3BJ/6-31G\*\*, and SDD(Rh) level of theory. In 2022, Houk and

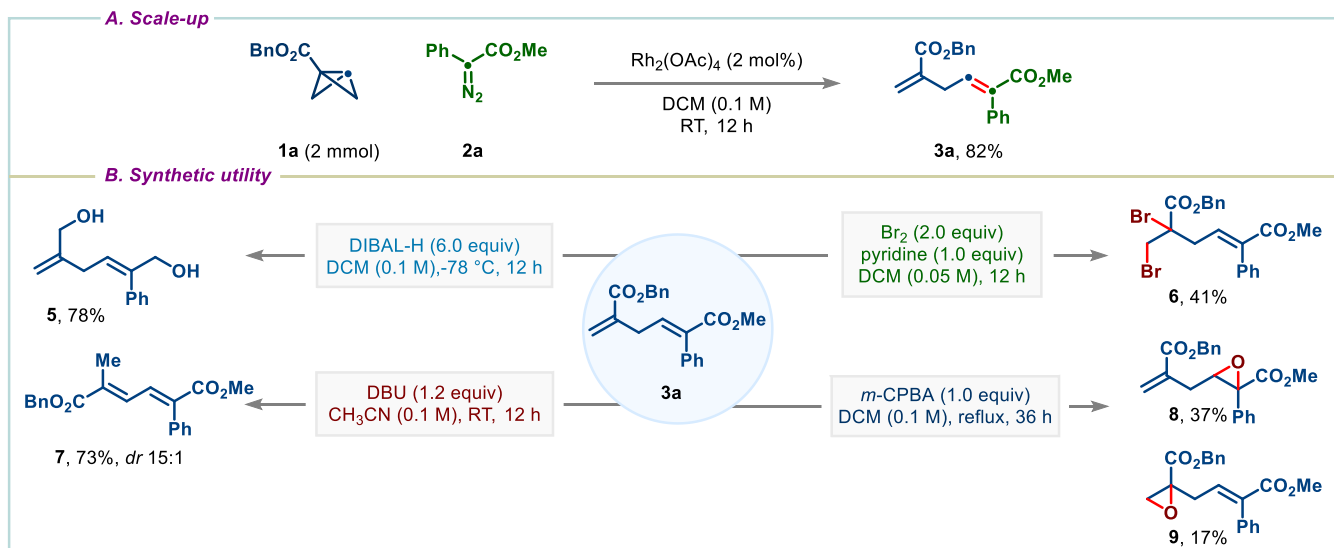
co-workers proposed both neutral and ionic mechanisms for Rh(I)-catalyzed BCB activation reaction.<sup>22</sup> While seeking inspiration, we explored both pathways in our system. However, our DFT studies revealed that it follows a concerted pathway. Since the N<sub>2</sub> expulsion step is well investigated, we began our study with metalcarbene (MC) **I**. Despite several

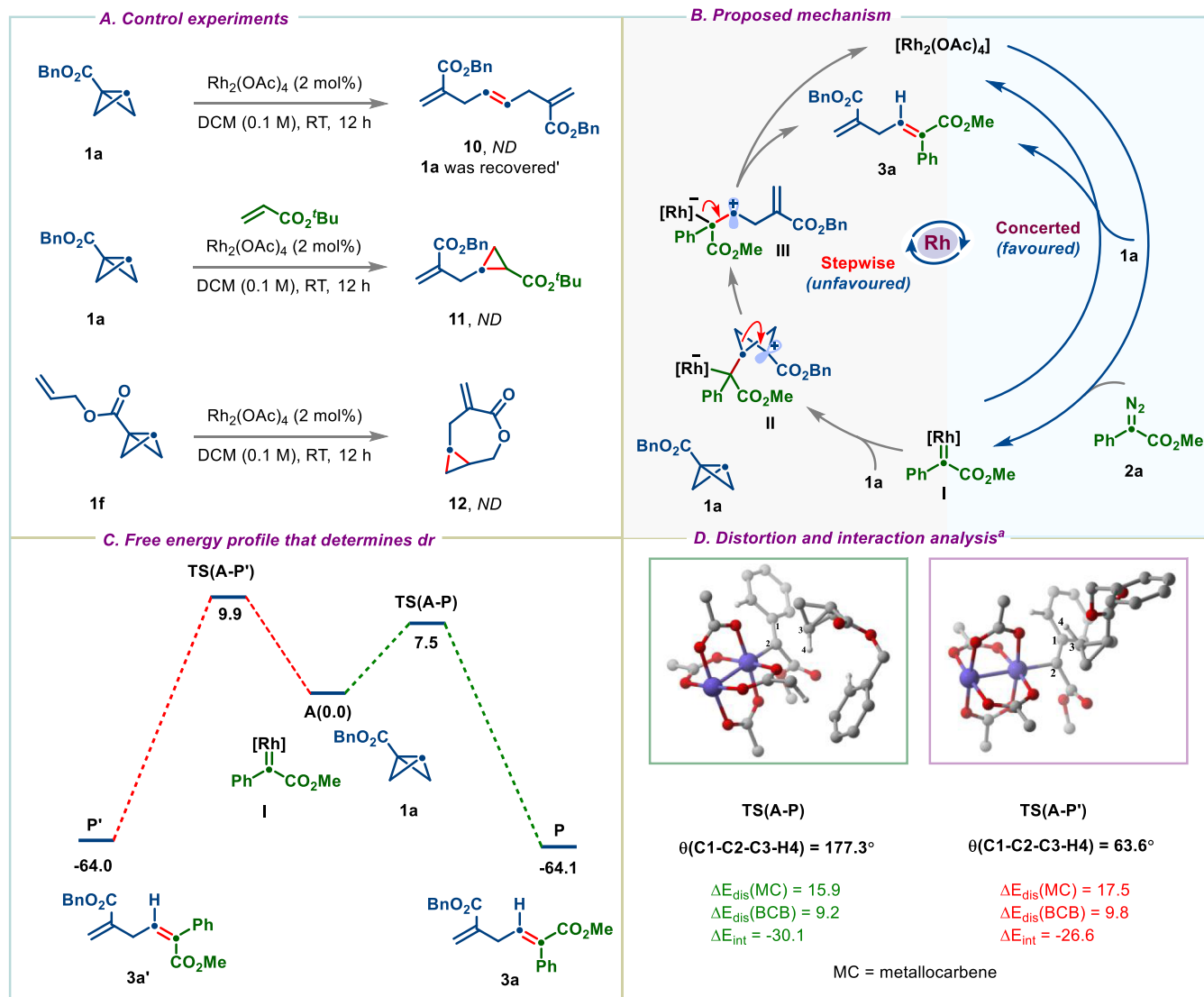


Scheme 3. Scope of Bicyclobutanes (BCBs)<sup>a,b,c,d,e</sup>

<sup>a</sup>Reaction conditions: 0.3 mmol of **1**, 0.45 mmol of diazo compound **2a**, 3.0 mL of dry DCM, 2 mol % of  $\text{Rh}_2(\text{OAc})_4$ , RT, 12 h. Yields are of isolated products, and *E/Z* ratio was determined by <sup>1</sup>H NMR from the crude reaction mixture. Yields are of major diastereomer only. <sup>b</sup>0.15 mmol. <sup>c</sup>0.26 mmol. <sup>d</sup>0.23 mmol. <sup>e</sup>0.20 mmol.

## Scheme 4. (A) Scale Up; (B) Synthetic Utility



Scheme 5. (A) Control Experiments; (B) Proposed Mechanism; (C) Free-Energy Profile (kcal/mol) for the Formation of the Major Diastereomer; (D) Optimized Geometries<sup>a</sup>

<sup>a</sup>Hydrogen atoms that are not involved in any interaction are removed for clarity in CYL images. ND = not detected.

attempts, we could not optimize intermediates II and III, and it always converged to the final product, 3a, thereby indicating the concertedness of the process. The concerted pathway via TS(A-P) is a facile process with an activation free-energy barrier of only 7.5 kcal/mol (Scheme 5C). To explain the observed stereoselectivity, possible conformations of the TSs in the concerted pathway were explored by DFT calculations. It was found that the TS(A-P) ( $\theta = 177.3^\circ$ ) leading to the *trans* product 3a is favored by  $-2.4$  kcal/mol over TS(A-P') ( $\theta = 63.6^\circ$ ) leading to the *cis* product 3a' (Scheme 5C). This is fully consistent with the observed experimental outcome. To explain the exclusive selectivity toward the *trans* isomer, we conducted a distortion–interaction analysis of both diastereomeric TSs. The activation strain analysis revealed that the formation of the major diastereomer is driven by a higher interaction energy between the BCB and the MC fragments in TS(A-P). The interaction energy in TS(A-P) is 3.5 kcal/mol higher compared to TS(A-P') (Scheme 5D). However, the difference in the distortion energy between the MC and BCB fragments in these competing TSs is minimal, suggesting that

the energetic preference arises from various noncovalent interactions (NCIs). We calculated the bond paths and strength of interactions using the AIM formalism to identify the presence of different types of NCIs in both TSs. This analysis revealed a network of NCIs between the MC and BCB, including C–H–O and C–H– $\pi$  interactions. Notably, TS(A-P) exhibits C–H– $\pi$  interactions, which are absent in TS(A-P'), and stronger C–H–O interactions, leading to higher stereoselectivity (see Figure 2 in Supporting Information).

## CONCLUSIONS

We described the development of a highly stereoselective protocol for the construction of functionalized skipped dienes by merging strain-release and rhodium–carbene chemistry. The transformation operates under mild conditions and tolerates a diverse array of functional groups on diazo compounds and BCBs. The synthetic utility of this transformation is further demonstrated by the transformation of the obtained products into valuable building blocks. The high

stereoselectivity observed was rationalized by DFT studies. This work expands the chemical space related to both strain-release functionalization and metal–carbene chemistry, opening access to a new avenue for the merger of these fields. We expect that the strategy delineated here will stimulate researchers to develop further potential for the carbene-type reactivity of strained molecules.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.4c03569>.

General information, experimental procedures, characterization data, NMR spectra for all new compounds, and DFT studies data (PDF)

Crystallographic data for **3i** (CCDC 2313293) (CIF)

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### Author Contributions

G.K., T. S., and D.P.H. conceived and designed the project. G.K. and T. S. carried out optimization studies, substrate scope, and mechanistic studies. S.R. performed the DFT studies. D.P.H. wrote the manuscript with suggestions from G.K., T.S., and S.R.

### Notes

The authors declare no competing financial interest.

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