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Copper-catalyzed strain-enabled reaction of bicyclobutanes with diazo compounds to synthesize penta-1,4-dienes†

Peng Yang,‡^a Till Brockmann,‡^a and Xiao-Feng Wu  ^{*,ab}

Herein we report an interesting copper-catalyzed transformation of BCBs with diazo compounds. This reaction leads to the synthesis of substituted skipped penta-1,4-dienes in good to excellent yields with only one diastomer obtained, and the reaction can also be performed on a gram scale. The transformation is compatible with many different functional groups attached to the BCBs and the diazo compounds.

Bicyclo[1.1.0]butane (BCB), the smallest fused-ring carbocycle with the highest strain energy (64 kcal mol^{−1}), caused by the unstable central C–C bond,¹ was first synthesized by Wiberg and Ciula in 1959.² Since then, BCBs have been indispensable synthetic building blocks because of their unusual bonding and the chemistry enabled by strain release, including carbene insertion,³ alkene⁴ and imine⁵ insertion, rearrangement reactions,⁶ functionalization⁷ and ring opening reactions with nucleophiles and electrophiles, to generate diverse molecular frameworks.⁸ Primarily utilizing *p*-character, the ring-opening of this high-energy bond has been accomplished with nucleophiles (including their use as bioconjugation agents), radicals, electrophiles, and transition metal catalysts.⁹ Beyond these reactions, the ring expansion of BCBs to bicyclo[*n*.1.1]alkanes has been achieved through formal addition of one, two, or three atoms.¹⁰ With the help of rearrangement reactions, Wipf and co-workers have even succeeded in producing cyclohexane derivatives from BCBs.¹¹ This also shows that BCB compounds open up completely new possibilities.

The discovery of the chemistry of aliphatic diazo compounds was made a century ago. Theodor Curtius synthesized ethyl diazoacetate in 1883 for the first time, opening the wide field of diazo chemistry, which even still inspires new developments.¹² The solution of the long controversial problem of constitution,

the development of general and facile syntheses, and the application of diazo compounds in organic synthesis, facilitated by their high reactivity, have made this field a truly exciting one. Diazo compounds can be dediazonized to highly reactive free carbene intermediates under thermolytic or photolytic conditions.¹³ Transition metal-catalyzed reactions of diazo compounds generate metal carbene species that can undergo diverse conversions, such as X–H (X = C, Si, N, O, *etc.*) insertions, cyclopropanations, ylide formations and 1,2-migrations.¹⁴ Dirhodium catalysts usually exhibit superior catalytic activity for most reactions of diazo compounds.¹⁵ However, copper catalyzed reactions of diazo compounds have a longer history, which has dominated the literature before the advent of the dirhodium catalysis reactions.¹⁶ Copper catalysts have obvious advantages due to their lower cost, low toxicity and abundance. Recently, copper catalyzed reactions of diazo compounds have been further developed with diazo compounds as versatile cross-coupling partners in various transformations.

As early as in 1981, Mock and Jones reported a reaction on react free carbene with BCB to create penta-1,4-diene.¹⁷ They used C₂N₂ to synthesize skipped dienes, but with no stereoselectivity. Besides the main compound, they also obtained three side products. More recently, Hari and co-workers reported a new Rh₂(OAc)₄-catalyzed procedure for synthesizing pentadienes from bicyclobutanes and diazo compounds (Fig. 1).¹⁸ In their procedure, they used rhodium to produce a metal carbene from a diazo compound which then reacts with BCB to create a skipped diene. Under their conditions, the desired products were formed stereoselectively under mild conditions. It has been clearly noted that replacing rhodium with copper salt did not lead to the desired product under their conditions. Considering the advantages of copper catalysts and the attractiveness of the above discussed chemistry, herein we report our study on copper-catalyzed synthesis of penta-1,4-dienes from BCBs and diazo compounds. Many different diazo compounds and BCBs were tested and transformed successfully.

Initially, by using BCB **1a** and diazo compound **2a** in DCE, we checked different copper pre-catalysts. It was found that copper(i) salts yielded much better results than copper(ii) salts (Table 1, entries 1–3). CuCN emerged as the best catalyst with

^a Leibnitz-Institut für Katalyse e.V., Albert-Einstein-Straße 29a, 18059 Rostock, Germany. E-mail: xiao-feng.wu@catalysis.de

^b Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, China

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‡ These authors contributed equally to this work.



First report by Mock and Jones 1981

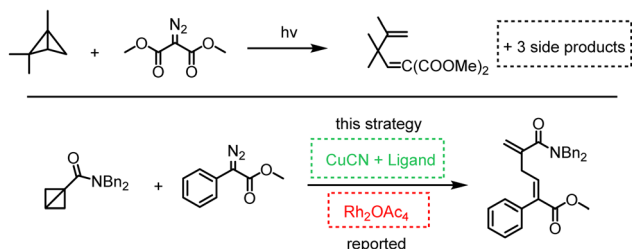


Fig. 1 Synthesis strategies for pentadienes through BCBs and diazo compounds.

60% yield for this transformation, with the desired pentadiene **3a** as the reaction product. Decreasing the loading of copper catalyst to 5% led to a decreased yield of **3a** (Table 1, entry 4). Subsequently, we tested various nitrogen containing and phosphorus containing ligands (Table 1, entries 5–9). The tested nitrogen-based ligands exhibited no reaction while improved yields were obtained with phosphorus-based ligands. Ligands were proven to be crucial for the targeted reactions which may stabilize the copper intermediate (Table 1, entry 10). On the other hand, it was discovered that increasing the reaction time to 36 hours resulted in an increase in the yield. Solvents were screened without exception and DCE was found still the best solvent for this reaction (Table 1, entries 11–13). Afterwards we examined the influence of temperature on the reaction, and increasing the temperature proved to be ineffective (Table 1,

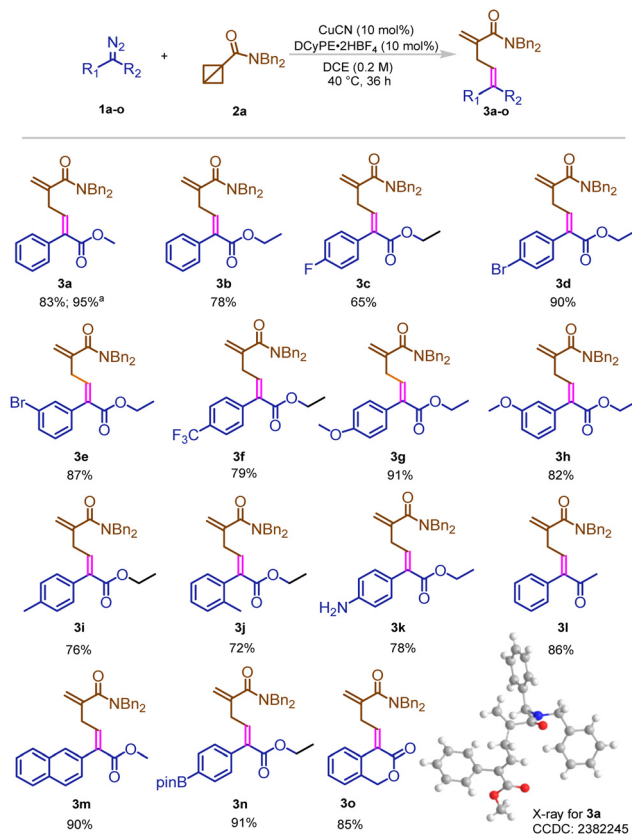
Table 1 Optimization of the reaction conditions^a

| Entry | Catalyst | Ligand | Solvent | T (h) | Yield ^b (%) |
|-----------------|-----------------------|-------------------------|--------------------|-------|------------------------|
| 1 | CuCN | DPPP | DCE | 14 | 60 |
| 2 | CuCl ₂ | DPPP | DCE | 14 | 18 |
| 3 | Cu(acac) ₂ | DPPP | DCE | 14 | 43 |
| 4 ^c | CuCN | DPPP | DCE | 14 | 50 |
| 5 | CuCN | bpy | DCE | 14 | ND |
| 6 | CuCN | dtbpy | DCE | 14 | ND |
| 7 | CuCN | PPh ₃ | DCE | 14 | 62 |
| 8 | CuCN | DPPE | DCE | 14 | 55 |
| 9 | CuCN | DcyPE·2HBF ₄ | DCE | 14 | 77 |
| 10 | CuCN | — | DCE | 14 | ND |
| 11 | CuCN | DCyPE·2HBF ₄ | THF | 14 | 21 |
| 12 | CuCN | DCyPE·2HBF ₄ | Toluene | 14 | 15 |
| 13 | CuCN | DCyPE·2HBF ₄ | CH ₃ CN | 14 | Trace |
| 14 ^d | CuCN | DCyPE·2HBF ₄ | DCE | 14 | 74 |
| 15 | CuCN | DCyPE·2HBF ₄ | DCE | 24 | 88 |
| 16 | CuCN | DCyPE·2HBF ₄ | DCE | 36 | 90 |
| 17 ^e | CuCN | DCyPE·2HBF ₄ | DCE | 36 | 30 |
| 18 ^f | CuCN | DCyPE·2HBF ₄ | DCE | 36 | 95 |
| 19 ^g | CuCN | DCyPE·2HBF ₄ | DCE | 136 | 95 |

^a Reaction Conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), CuCN (10 mol%), DCyPE·HBF₄ (10 mol%), DCE (0.2 M), 40 °C, and 36 h. ^b Isolated yield. ^c CuCN (5 mol%). ^d The reaction was carried out at 50 °C. ^e **1a** (1.0 equiv.). ^f **1a** (2.5 equiv.). ^g **1a** (3.0 equiv.). DPPP: 1,3-bis-(diphenylphosphino)propane. DPPE: ethylene-bis(diphenylphosphine). bpy: 2,2'-bipyridine. dtbpy: 4,4'-di-*tert*-butyl-2,2'-dipyridyl. DCyPE·2HBF₄: 1,2-bis(dicyclohexylphosphino)ethane bis(tetrafluoroborate).

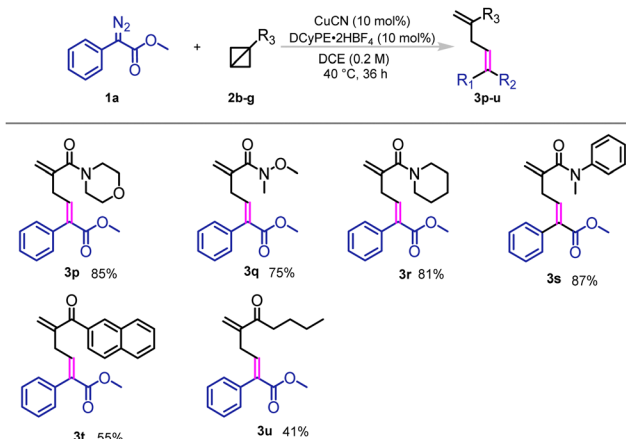
entry 14), as it did further drive the conversion of substrates. Hence, we prolonged the reaction and the yield of **3a** can be improved to 90% (Table 1, entries 15–16). Finally, we have been able to further improve the yield of the desired **3a** by changing the ratio of the reactants (Table 1, entries 17–19).

Under the optimized reaction conditions, diverse diazo compounds and BCBs were tested (Scheme 1). A variety of diazo esters and diazo ketones were able to react smoothly and gave the desired products in good to excellent yields (**3a–3o**). Different electron-withdrawing groups, such as bromo, fluoro and trifluoromethyl groups (**3c–3f**), were tested and gave good to excellent yields of the corresponding products under the standard conditions. Electron donating groups also gave outstanding yields of the desired compounds. Substrates with a methyl group, methoxy group and amino group (**3g–3k**) were successfully converted to their predetermined products. Among these compounds, ketone was also successfully transformed and yielded good results (**3l**). Additionally, structurally interesting compounds were tested, a BPin group, which demonstrated a very good yield, as did a naphthalene group attached to the ester (**3m–3o**). The reaction was also performed on a large scale and 95% yield of **3a** was produced without any problem and the structure was further confirmed by X-ray analysis (CCDC: 2382245[†]). However, it is also worth mentioning that the reactions failed when benzyl bicyclo[1.1.0]butane-1-carboxylate



Scheme 1 Substrate scope of diazo esters. Reaction conditions: **1a–o** (0.5 mmol), **2a** (0.2 mmol), CuCN (10 mol%), DCyPE·2HBF₄ (10 mol%), DCE (0.2 M), 40 °C, 36 h, yields of isolated products are shown. ^a Reaction in 5 mmol scale.





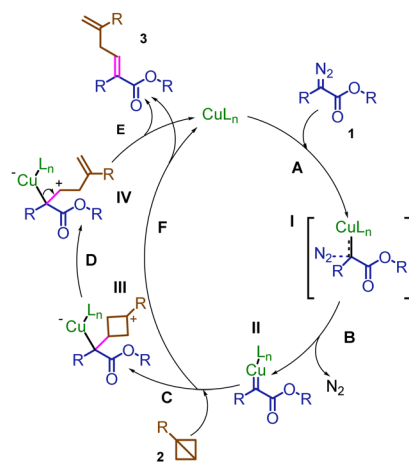
Scheme 2 Substrate scope of BCBs. Reaction conditions: **1a** (0.5 mmol), **2b–g** (0.2 mmol), CuCN (10 mol%), DCyPE·2HBF₄ (10 mol%), DCE (0.2 M), 40 °C, 36 h, yields of isolated products are shown.

or (1-diazo-2,2,2-trifluoroethyl)benzene was tested in our model system.

Furthermore, the influence of different BCBs was also investigated (Scheme 2). Amides, with different substituents at the nitrogen atom, such as Bn groups and non-aromatic substituents were well tolerated in this transformation and excellent yields were obtained. In addition, BCBs with aromatic and aliphatic ketone moieties gave excellent yields in this reaction as well.

Based on our results and literature,^{13–18} a possible reaction pathway is proposed (Scheme 3). Initially, a copper carbene intermediate **II** was formed from the copper catalyst and diazo compound with the release of nitrogen. Then the BCB reacted with the copper carbene intermediate to give the final diene products.

In conclusion, we developed a new copper-catalyzed reaction between bicyclobutanes and diazo compounds to create penta-1,4-dienes (skipped dienes). Under mild conditions, we were able to achieve good to excellent yields of the desired products from a broad scope of diazo compounds and BCBs.



Scheme 3 Proposed reaction pathway.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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