Homogeneous Catalysis

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Site-Selective C–C Cleavage of Benzocyclobutenones Enabled by a Blocking Strategy Using Nickel Catalysis

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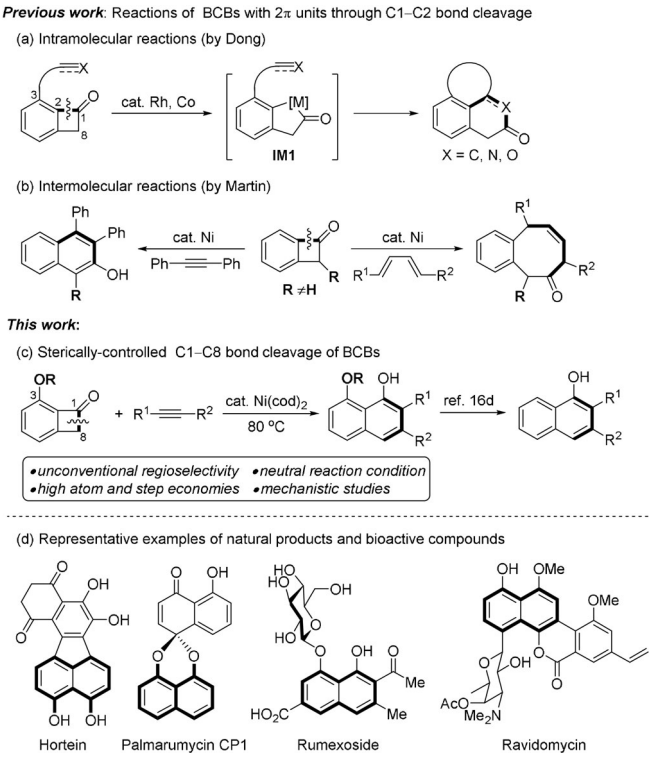
Abstract: *Controlling the chemo- and regioselectivity of transition-metal-catalyzed C–C activation remains a great challenge. The transformations of benzocyclobutenones (BCBs) usually involve the cleavage of C1–C2 bond. In this work, an unprecedented highly selective cleavage of C1–C8 bond with the insertion of alkynes is achieved by using blocking strategy via Ni catalysis, providing an efficient method for synthesis of 1,8-disubstituted naphthalenes. Notably, the blocking group could be readily removed after the transformation.*

Not only can C–C single bond cleavage and functionalization streamline the synthetic route to complex compounds, but also provide unique opportunities to prepare traditionally inaccessible organic compounds through the tailoring of molecular skeletons.[1] In this context, pioneering studies of Murakami, Aïssa, Liebeskind, and others have demonstrated that the ring expansion of four-membered rings such as cyclobutanones,[2] cyclobutenones,[3] 3-azetidinones[4] and 3-oxetanones[5] driven by releasing strain is particularly useful in constructing polycyclic compounds. Recently, structurally related benzocyclobutenones (BCBs) have shown great potential in the synthesis of aromatic systems.[6] Dong and co-workers developed a series of elegant transition-metal-catalyzed intramolecular reactions of BCBs with 2π components to produce various complex benzo-fused rings (Scheme 1 a).[7] In contrast, the intermolecular reaction of BCBs is lagged. Recently, several beautiful examples have been described to tear the hole in the field. In 2015, Martin and co-workers realized the first Ni-catalyzed intermolecular reaction of BCBs with 1,3-dienes to afford eight-membered rings with excellent chemo- and regioselectivities (Scheme 1 b).[8] In this development, a few examples of the reaction of BCBs with diphenylacetylene were also reported. Other representative intermolecular transformations of BCBs included the Pd-catalyzed intermolecular cross-metathesis reaction of BCBs with silacyclobutanes,[9] the Ru-catalyzed cycloaddition of BCBs with diols and ketols,[10] and the cross coupling of BCBs with indoles.[11] In most cases, the activation of C(sp^2)–C(CO) (C1–C2) bond was observed, which was distinct from the reaction of cyclobutenones that usually cleaved the C(sp^3)–C(CO) bond via a vinylketene intermediate.[3] Among the sporadic examples that involved the C1–C8 bond cleavage of BCBs,[10–12] factors that controlled the site selectivity were not investigated. Undoubtedly, it is highly valuable to develop novel strategy to realize the functionalization of BCBs based on C1–C8 bond activation and to get more information about the reaction mechanism.

DFT calculations suggested that the Rh-catalyzed selective C1–C2 bond activation of BCBs was realized through oxidative addition of the kinetically reactive C1–C8 bond, decarbonylation of the resulting rhodacycle and re-insertion of CO, which was driven by the formation of the thermodynamically more stable C(aryl)-M intermediate **IM1** (Scheme 1 a).[13] It was also found that the substituent at C8 position



Scheme 1. The catalytic reactions of BCBs with 2π components via C–C bond activation and the bioactive representatives of 1,8-naphthalenediol derivatives.

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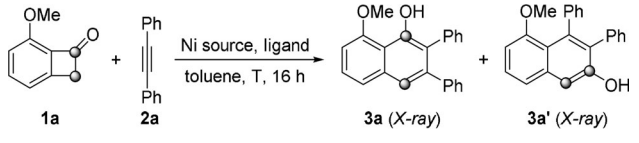
may increase the C1–C2 selectivity.[14] These results indicated that, besides thermodynamic reasons, the steric effect may also play an important role in controlling the regioselectivity. Following our continuous interests in the selective functionalizations of inert C–C σ-bonds,[15] we envisioned that the introduction of a substituent at C3 position of BCBs may block the adjacent C1–C2 bond and enforce the cleavage of the distal, less hindered C1–C8 bond (Scheme 1c). To prove our concept, the intermolecular reaction of BCBs bearing a 3-alkoxy group with alkynes was investigated for the following reasons: 1) the alkoxy group may be readily removed and functionalized after the transformation;[16] 2) the reaction would lead to the formation of 1,8-naphthalenediol derivatives, making the designed chemistry more valuable. As shown in Scheme 1d, 1,8-naphthalenediol is a key structural motif found in various natural products,[17] bioactive compounds,[18] ligands,[19] and organic functional materials.[20] The thermally induced or base-promoted [4+2]-type ring expansions of benzocyclobutenols with the cleavage of C1–C8 bond has been well developed by Murakami and others.[21] The methodology described herein represents an alternative approach with the advantages of pH-neutral conditions, lower reaction temperature, and high step economy that avoids the preactivation of carbonyl group to alcohols.

First of all, the reaction of 3-MeO substituted BCB **1a** with diphenylacetylene **2a** was tested. As illustrated in Table 1, the use of Ni^{II} complexes as precatalysts either delivered no product or afforded a mixture of naphthalenes **3a** and **3a′**, resulting from the C1–C8 and C1–C2 bond cleavage, respectively (Table 1, entries 2 and 3). The structures of **3a** and **3a′** were unambiguously confirmed by single crystal X-ray analysis.[22] Pleasantly, the yield of the desired naphthalene **3a** was improved by using $Ni(cod)_2$ as a catalyst and phosphines as ligands (Table 1, entries 5–10). After extensive screening of various parameters (see Table S1 in the supporting information), the optimal conditions were found to be 5 mol% $Ni(cod)_2$ as the catalyst, 5 mol% (p-$MeOC_6H_4)_3P$ as the ligand, and toluene as the solvent at 80 °C for 16 h (Table 1, entry 10). Under these conditions, **3a** was obtained in 94% NMR yield and only 3% of **3a′** was detected in the crude reaction mixture. Although a few examples of the C1–C8 bond cleavage of BCBs has been reported by heating at high temperature through retro-4π cyclization,[23] the [4+2] cycloaddition of BCBs with unactivated alkynes has not been realized. Indeed, control experiments showed that no desired reaction occurred in the absence of nickel catalyst, precluding the possibility of thermal cycloaddition pathway (Table 1, entry 1).

With the optimized conditions in hand, the scope of BCBs was further investigated (Table 2). A variety of protecting groups on hydroxyl group of BCBs, including alkyl, benzyl, silyl, and methoxymethyl groups, were well compatible under current conditions (Table 2, **3a**–**3e**). BCBs bearing electron-donating or withdrawing groups on the 4, 5, or 6 positions smoothly underwent the annulation reaction (Table 2, **3f**–**3i**). It was worth noting that the 6-chloro group was also tolerated for further orthogonal transformations (Table 2, **3i**). To our delight, BCB bearing a 3-amino group was also engaged in the reaction and useful 8-hydroxy-1-naphthylamines **3j** was produced in 78% yield.[22] Unfortunately, BCBs with free hydroxy or chloro group at the 3-position failed to participate in the reaction.

Next, we explored the scope of alkynes (Table 3). Symmetric diaryl alkynes with electron-withdrawing substitu-

Table 1: Selected optimization of BCB **1a** with diphenylacetylene **2a**.[a]

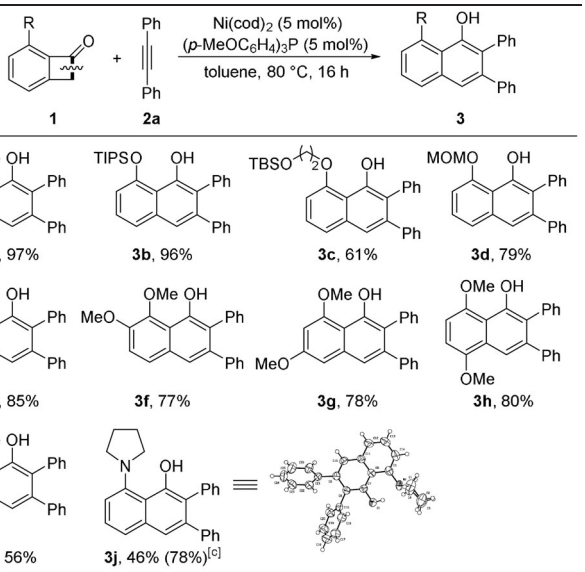


1a **2a** **3a** (*X-ray*) **3a'** (*X-ray*)

Entry	Ni source	Ligand	T [°C]	Yield of **3a**[b]	Yield of **3a′**[b]
1	none	PPh_3	100	–	–
2[c]	$Ni(acac)_2$	PPh_3	100	–	–
3[c]	$Ni(dppp)Cl_2$	PPh_3	100	10%	8%
4	$Ni(cod)_2$	none	50	–	–
5	$Ni(cod)_2$	PCy_3	50	68%	5%
6	$Ni(cod)_2$	PPh_3	50	57%	2%
7	$Ni(cod)_2$	(p-$CF_3C_6H_4)_3P$	50	40%	6%
8	$Ni(cod)_2$	(p-$MeOC_6H_4)_3P$	50	76%	5%
9	$Ni(cod)_2$	(p-$MeOC_6H_4)_3P$	80	95%	3%
10[d]	**$Ni(cod)_2$**	**(p-$MeOC_6H_4)_3P$**	**80**	**94% (97%)**[e]	**3%**

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (1.5 equiv), Ni catalyst (10 mol%), ligand (10 mol%) at the indicated temperature for 16 h. [b] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] 50 mol% Zn was added. [d] 5 mol% $Ni(cod)_2$ and 5 mol% (p-$MeOC_6H_4)_3P$ were used. [e] Isolated yield is given in the parenthesis. acac = acetylacetonate; dppp = 1,1-bis(diphenylphosphino)propane; cod = 1,5-cyclooctadiene.

Table 2: Scope with respect to BCBs.[a,b]



1 **2a** **3**

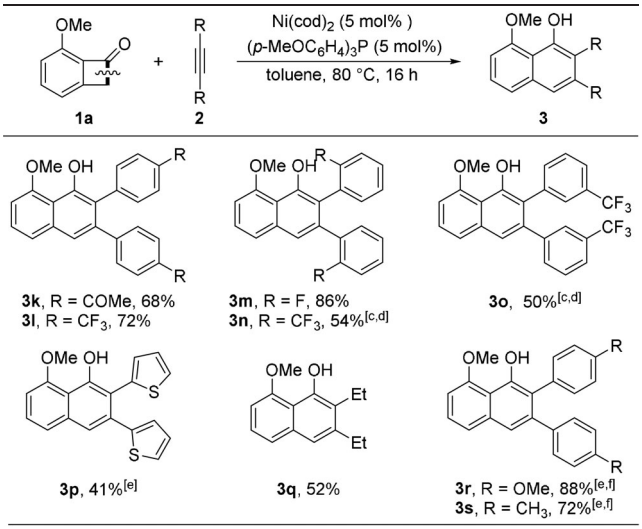
3a, 97% **3b**, 96% **3c**, 61% **3d**, 79%

3e, 85% **3f**, 77% **3g**, 78% **3h**, 80%

3i, 56% **3j**, 46% (78%)[c]

[a] The reaction was run on a 0.2 mmol scale. [b] Isolated yields. [c] 20 mol% $Ni(cod)_2$ and 20 mol% (p-$MeOC_6H_4)_3P$ were used. TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl; MOM = methoxymethyl.

Table 3: Scope with symmetric alkynes.[a,b]

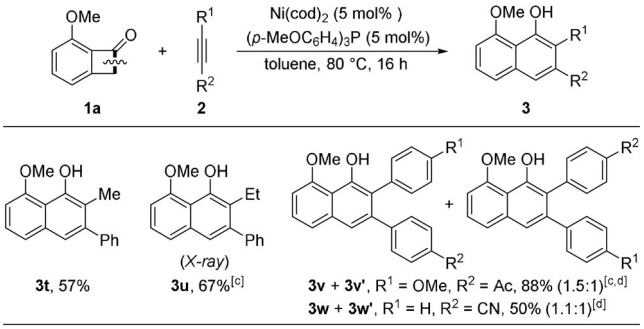


[a] The reaction was run on a 0.2 mmol scale. [b] Isolated yields. [c] 10 mol% $Ni(cod)_2$ and 10 mol% $(p\text{-}MeOC_6H_4)_3P$ were used. [d] At 120°C. [e] 20 mol% $Ni(cod)_2$ and 20 mol% $(p\text{-}MeOC_6H_4)_3P$ were used. [f] 20 mol% $Mg(OTf)_2$ was added.

ents, such as acetyl, fluoro, and trifluoromethyl groups, at *ortho*, *meta*, or *para* positions all smoothly underwent the annulation reaction (Table 3, **3k**–**3o**). Diheteroaryl and dialkyl alkynes also successfully delivered the products in acceptable yields (Table 3, **3p** and **3q**). To our interest, only a trace amount of **3r** was obtained when 1,2-bis(4-methoxyphenyl)ethyne was subjected to the standard conditions. Considering that coordination of Lewis acid with alkynes or BCBs might increase the reactivity,[7a,c] we then screened a variety of Lewis acids (see Table S2 in the Supporting Information) and found that 20 mol% $Mg(OTf)_2$ substantially enhanced the efficiency to afford naphthalene **3r** in excellent yield (Table 3). Similar results were obtained with other electron-rich diarylalkynes. For example, the reaction of 1,2-bis(4-methylphenyl)acetylene was unsuccessful under the standard conditions. However, the desired **3s** was obtained in 72% yield by using 20 mol% $Mg(OTf)_2$ as additive (Table 3).

As shown in Table 4, distinct results were obtained with respect to unsymmetric alkynes. The reaction of 1-aryl

Table 4: Scope with respect to unsymmetric alkynes.[a,b]

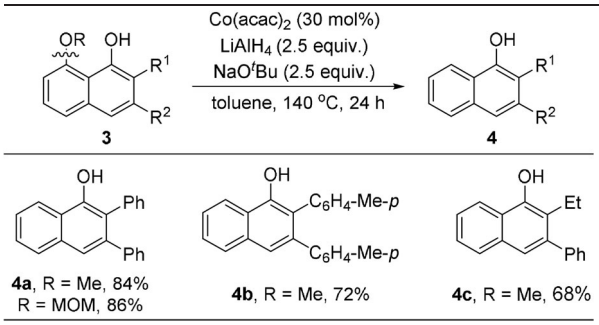


[a] The reaction was run on a 0.2 mmol scale. [b] Isolated yields. [c] 10 mol% $Ni(cod)_2$ and 10 mol% $(p\text{-}MeOC_6H_4)_3P$ were used. [d] Isolated yields of the two inseparable isomers.

alkynes delivered the corresponding products **3t** and **3u**[22] with excellent regioselectivities. In these cases, only naphthalenes with the alkyl group next to the hydroxy group were separated. This regioselectivity was consistent with those observed in the Ni-catalyzed annulation reaction of cyclobutanones,[2i] cyclobutenones,[3g] and 3-azetidinones[4] with alkynes. The reaction of unsymmetric diaryl alkynes with acetyl, methoxy, or nitrile groups afforded two inseparable regioisomers (Table 4, **3v** and **3w**). In these cases, the structure of the major isomer was not confirmed. Other unsymmetric alkynes such as phenylacetylene, 1-phenyl-2-(trimethylsilyl)acetylene and 1-phenyl-1-hexyne were not suitable partners that were either unreactive or polymerized under standard conditions.

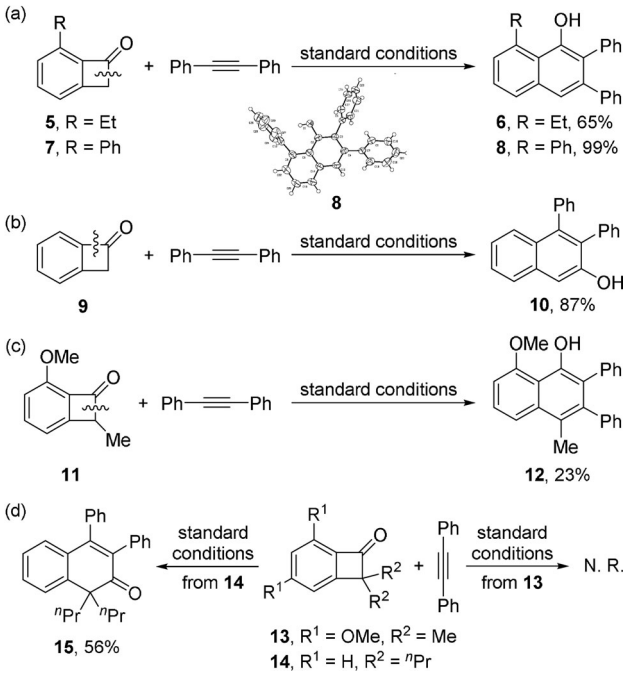
Next, the removal of the blocking group was attempted (Table 5). It was found that the methoxy group could be conveniently removed by $Co(acac)_2$ and LAH.[16d] Aryl, heteroaryl, and alkyl-substituted naphthalenes **3** were all converted to the corresponding demethoxylated products **4** in good to excellent yields. Notably, other ether group such as methoxymethoxy group was also removable (Table 5, **4a**). Consequently, this methodology realized a formal switch of selectivity compared with Martin's work by using a removable blocking group.[8]

Table 5: Removal of the ether groups.[a,b]



[a] The reaction was run on a 0.2 mmol scale. [b] Isolated yields.

To understand the origination of the regioselectivity, BCBs with different substituents at 3-position were studied. Replacement of 3-methoxy group with aliphatic (Et) or aryl (Ph) group did not affect regioselectivity (Scheme 2a),[22] suggesting that the oxygen-containing group was not necessary in controlling site selectivity. C3-unsubstituted BCB **9** underwent the [4+2] annulation via selective C1−C2 bond cleavage (Scheme 2b). These results clearly demonstrated that the C1−C8 selectivity of BCBs resulted from the steric hindrance by blocking 3-position rather than the coordination of nickel catalyst with alkoxy and carbonyl groups. Moreover, the reaction of BCB **11** bearing a methyl group at 8-position afforded the desired product **12** in a much lower yield (Scheme 2c). Sterically more demanding BCB **13** bearing two methyl groups at 8-position failed to participate in the reaction (Scheme 2d). In contrast, the corresponding C3-unsubstituted BCB **14**, which was investigated in Martin's work, smoothly underwent the annulation reaction under our standard conditions with the same regioselectivity as reported



Scheme 2. Mechanistic studies.

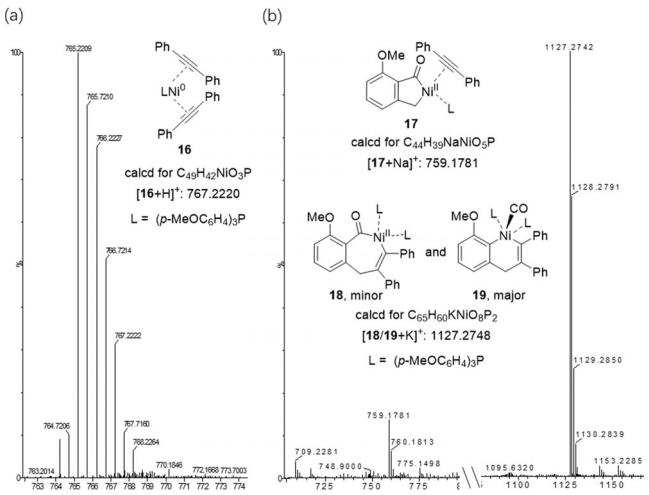


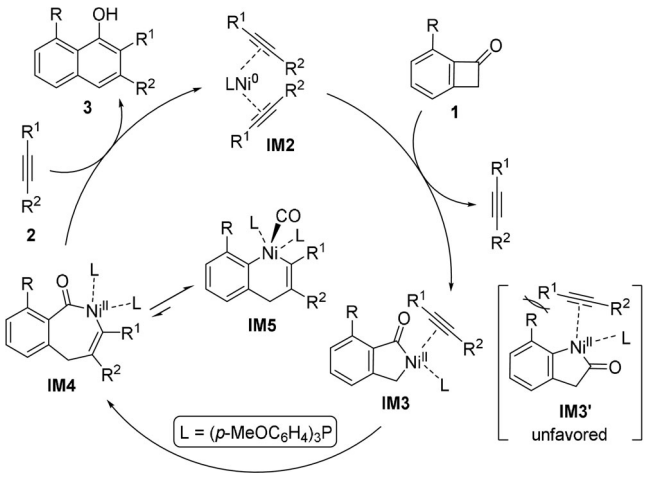
Figure 1. HRMS analysis of the reaction systems. a) diphenylacetylene **2a** (0.1 mmol, 1.0 equiv), $Ni(cod)_2$ (1.0 equiv) and $(p\text{-}MeOC_6H_4)_3P$ (1.0 equiv) at r.t. for 3 h. b) BCB **1a** (0.1 mmol, 1.0 equiv), diphenylacetylene **2a** (1.0 equiv), $Ni(cod)_2$ (1.0 equiv) and $(p\text{-}MeOC_6H_4)_3P$ (1.0 equiv) at 50 °C for 2 h.

by Martin's group.[8] The product resulting from C1–C8 bond cleavage was not observed. These results clearly demonstrated the steric sensitivity of the reaction.

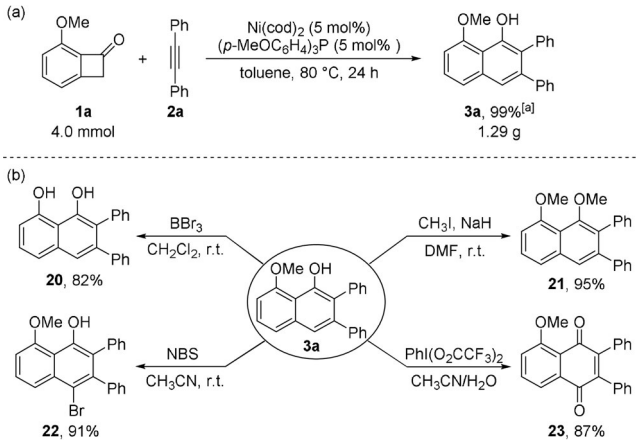
To get more insights into the mechanism, several stoichiometric reactions were conducted. TLC, and in situ ^1H and ^{13}C NMR analysis indicated that BCB **1a** quickly (within 20 min) decomposed to some unidentified compounds in the presence of 1.0 equiv of $Ni(cod)_2$ and 1.0 equiv of $(p\text{-}MeOC_6H_4)_3P$ at room temperature. Further addition of 1.0 equiv of diphenylacetylene to this decomposed mixture could not deliver any desired product **3a**. These data implied that the reaction may not start from direct oxidative addition of Ni^0 with BCBs. HRMS analysis of the reaction systems containing **2a**/$Ni(cod)_2$/$(p\text{-}MeOC_6H_4)_3P$ and **1a**/**2a**/$Ni(cod)_2$/$(p\text{-}MeOC_6H_4)_3P$ gave some useful information. In the former system, a peak at $m/z = 767.2222$ (ESI) was observed, which was assigned to the protonated form of the Ni^0 species **16** (Figure 1a). Addition of 1.0 equiv of BCB **1a** to this system resulted in the formation of naphthalene **3a**, which gave additional support for the formation of intermediate **16**. In the latter system, two signals at $m/z = 759.1781$ and 1127.2742 were detected, which were assigned to the five-membered nickelacycle **17** ($[M+Na]^+$) and the seven-membered nickelacycle **18** ($[M+K]^+$) at first, respectively (Figure 1b). The latter system was also monitored by ReactIR. As shown in Figures S1 and S2, the peak of **1a** at 1774 cm^{-1} was gradually consumed within 2 h. At the same time, a peak at 1918 cm^{-1} was accumulated, suggesting the formation of a species with CO bonded to nickel.[24] Consequently, we speculated that the peak at $m/z = 1127.2742$ on HRMS spectrum might mainly be assigned to intermediate **19** rather than the originally proposed **18**. Small amounts of **17** and **18** were also formed in the reaction system because two signals at 1624 and 1629 cm^{-1}, which were the characteristic ν(CO) bands of acylnickel complexes,[25] were slightly enriched.

Based on these results and previous reports,[26] a tentative mechanism was proposed in Scheme 3. The reaction initiates from the coordination of alkynes with Ni^0. Oxidative addition of the resulting species **IM2** with BCBs **1** affords the five-membered complex **IM3**. In this step, the steric demanding at 3-position favors the activation of the less hindered C1–C8 bond rather than the C1–C2 bond. Subsequent migratory insertion of alkynes to the C(CO)–Ni bond of **IM3** delivers the seven-membered nickelacycle **IM4**, which is in equilibrium with the more stable six-membered complex **IM5**. Complex **IM4** then undergoes reductive elimination to deliver the final product **3** and regenerate Ni^0.

Owing to the synthetic importance of 1,8-naphthalenediols, the synthetic applications of this methodology were further explored. First, naphthalene **3a** could be prepared in



Scheme 3. The tentative mechanism.



Scheme 4. Potential synthetic applications of the methodology. [a] The regioisomer **3a′** was formed in around 3% NMR yield.

a gram scale (Scheme 4a). Subsequently, **3a** underwent a variety of transformations, including bromination, methylation, demethylation, and oxidation to afford many synthetically useful intermediates (Scheme 4b). The formation of compound **23** is especially attractive due to the occurrence of highly oxygenated polycycles in various natural products.[27]

In conclusion, a highly selective C1−C8 bond cleavage of BCBs with the insertion of alkynes was achieved by using a blocking strategy via Ni catalysis, which provided a straightforward method for the synthesis of structurally important 1,8-disubstituted naphthalenes, including 1,8-naphthalenediols. Importantly, the blocking group was conveniently removed after the transformation. Further studies to extend potential application in materials science and to prepare other valuable compounds based on the C1−C8 bond activation are currently underway in our lab.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: benzocyclobutenones · blocking strategy · C–C cleavage · nickel catalysis · regioselectivity

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Communications

Homogeneous Catalysis

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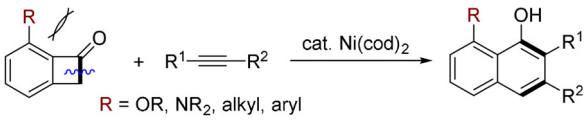
Site-Selective C–C Cleavage of Benzocyclobutenones Enabled by a Blocking Strategy Using Nickel Catalysis



A Ni-catalyzed highly selective C1—C8 bond cleavage of BCBs with the insertion of alkynes was achieved by the assistance of a removable blocking group. This method provided an atom- and step-economical approach to structurally important 1,8-naphthalenediols under pH-neutral conditions.