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Catalytic C−C Cleavage/Alkyne−Carbonyl Metathesis Sequence of Cyclobutanones

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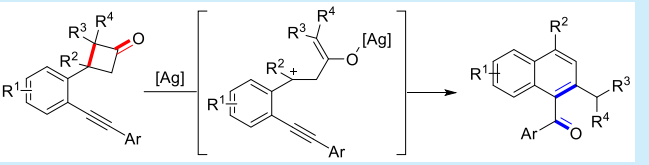
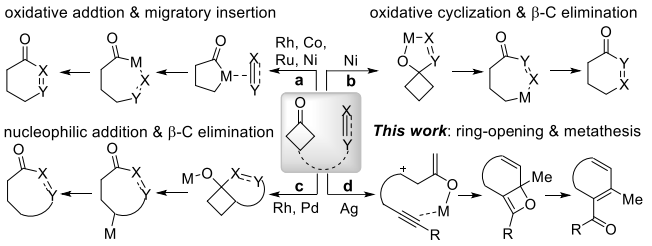
ABSTRACT: A ring-opening/alkyne−carbonyl metathesis sequence of alkyne-tethered cyclobutanones catalyzed by $AgSbF_6$ is realized for the first time to furnish multisubstituted naphthyl ketones under mild conditions. A range of substrates decorated with various substituents at different positions were all well accommodated. Preliminary mechanistic studies show that silver salt acted as a Lewis acid to facilitate both C−C cleavage of the cyclobutanone moiety and the subsequent metathesis between C═O and C≡C bonds.



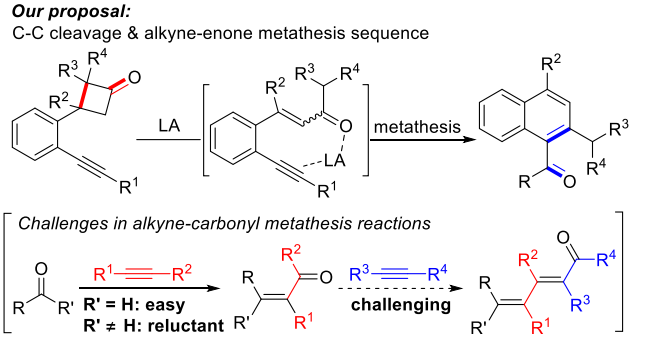
Activation of carbon−carbon bonds by transition-metal catalysts has shown unique potentials in molecule reorganization, providing intriguing transformations and synthetic strategies that are otherwise difficult to achieve by traditional methods.[1] The release of ring strain in small rings provides an extra driving force for such a purpose, making them versatile substrates in a range of molecule reorganizations.[2] In particular, catalytic ring expansion of cyclobutanones with unsaturated motifs such as carbonyl groups, alkenes, allenes, and alkynes provides efficient access to various cyclic scaffolds.[3] In general, these processes can be classified into the following patterns (Scheme 1): (a) oxidative addition of transition metals with cyclobutanones leading to five-membered cyclic acylmetal species,[4a−c] followed by migratory insertion with pendant unsaturated moiety (path a);[4d−k] (b) β-carbon elimination of cyclobutanolates generated by either oxidative cyclization of the two moieties with metals (path b)[5] or addition of in situ generated metallic moiety with the carbonyl of cyclobutanones (path c).[6] Apart from the above advances, other catalytic ring-expansion processes have rarely been disclosed. Based on our interest in ring-opening reactions of small rings,[7] we engaged in developing unprecedented ring expansion of cyclobutanones with unsaturated motifs to extend the reactivity space. Herein we disclose the first Ag-catalyzed ring-opening-metathesis sequence of alkyne-tethered cyclobutanones, wherein both the C−C and C═O bonds of the cyclobutanone moiety were cleaved synergistically (path d).

We envisioned that proper metal salts would function as Lewis acid catalysts to facilitate the selective C−C bond cleavage of cyclobutanones leading to the conjugated enone intermediate. Introduction of a pendant alkyne would provide an opportunity for a further intramolecular alkyne−carbonyl metathesis sequence using the same catalyst (Scheme 2, top). Although Lewis acids such as $TiCl_4$, $EtAlCl_2$, and $BF_3{\cdot}Et_2O$,

Scheme 1. Catalytic Ring-Expansion Reactions of Cyclobutanones with Unsaturated Chemical Motifs



Scheme 2. Proposed Catalytic Ring-Opening/Metathesis Sequence of Alkyne-Tethered Cyclobutanones



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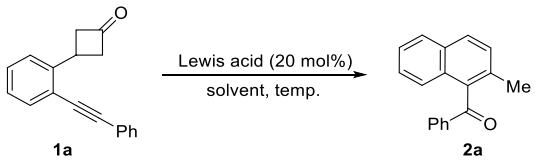
among others, typically in stoichiometric amounts, have been reported to promote ring-opening of 3-donor-substituted cyclobutanones (the "push–pull" structure),[8] such a catalytic ring-opening/alkyne–carbonyl metathesis (ROACM) sequence has never been realized before.[9] Notably, alkyne–carbonyl metathesis (ACM) has emerged as an efficient pathway to α,β-unsaturated compounds.[10] Compared to aldehydes, however, the low reactivity of ketones makes them reluctant to undergo such a transformation with simple alkynes.[11] It is especially challenging for simple conjugated enones, which are normally the final products of ACM reactions, to be applied for further metathesis sequence (Scheme 2, bottom).[12] Herein we present our success in this field, which employs cyclobutanones as synthons of conjugated enones for the ACM reaction, delivering naphthyl ketones as final products, a frequently present scaffold in fine chemicals, pharmaceuticals, agrochemicals, among others.[13]

We initiated our study by evaluating the ROACM reaction of the model substrate **1a** with $AgSbF_6$ as catalyst (Table 1).

Table 1. Optimization of Reaction Conditions[a]



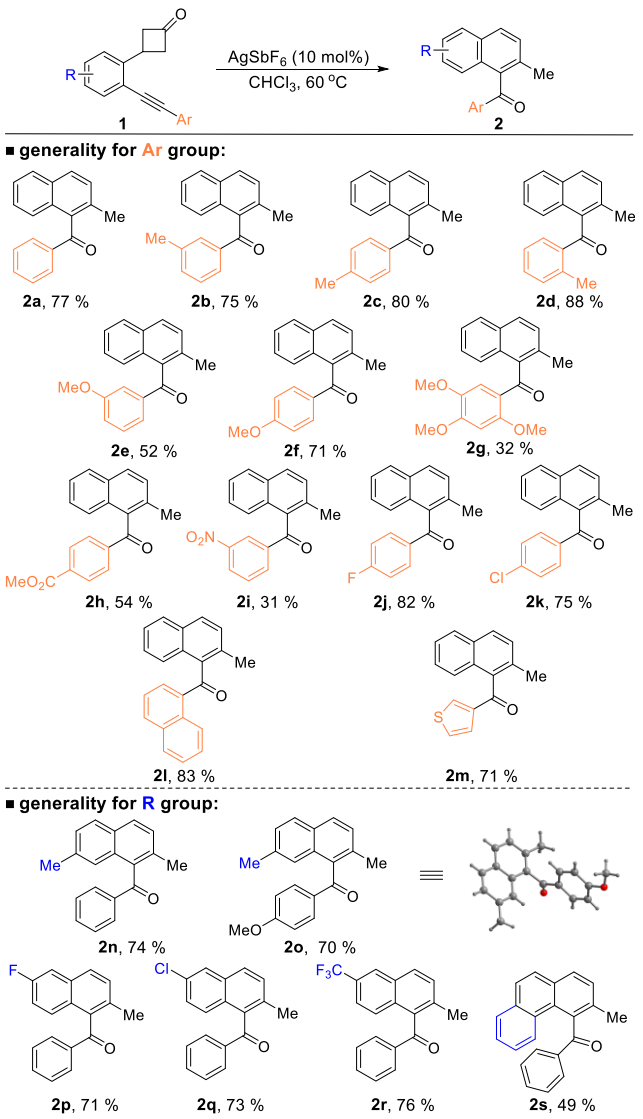
entry	Lewis acid	solvent	temp (°C)	yield[b] (%)
1	$AgSbF_6$	DMF	60	5
2	$AgSbF_6$	1,4-dioxane	60	5
3	$AgSbF_6$	THF	60	0
4	$AgSbF_6$	CH_2Cl_2	60	64
5	$AgSbF_6$	$CHCl_3$	60	82
6	$AgSbF_6$	CCl_4	60	50
7	$AgSbF_6$	DCE	60	70
8	AgOTf	$CHCl_3$	60	23
9	$AgNO_3$	$CHCl_3$	60	0
10	$Sc(OTf)_3$	$CHCl_3$	60	11
11	$Zn(OTf)_2$	$CHCl_3$	60	0
12	$Fe(acac)_3$	$CHCl_3$	60	0
13	$AgSbF_6$	$CHCl_3$	70	79
14	$AgSbF_6$	$CHCl_3$	50	77
15	$AgSbF_6$	$CHCl_3$	40	72
16[c]	$AgSbF_6$	$CHCl_3$	60	80

[a]Reactions were performed with **1a** (0.2 mmol), Lewis acid (20 mol %), solvent (2 mL), 12 h. [b]Determined by crude ^1H NMR. [c]10 mol % of $AgSbF_6$ was added.

Solvents were found to exert a profound influence on the reactivity. Thus, the product **2a** was obtained in 5% yield in DMF or 1,4-dioxane, but not detected in THF (entries 1–3). Strikingly, the yield of **2a** was significantly improved in dichloromethane (entry 4). Other chlorinated solvents could also be employed, with $CHCl_3$ as the best candidate, providing the target compound in 82% yield (entries 5–7). A screening of the Lewis acid catalysts revealed that both the metal source and counterion played a pivotal role. Specifically, markedly inferior results were observed with AgOTf or $AgNO_3$ as catalysts (entries 8 and 9). The reaction was more sluggish using $Sc(OTf)_2$, leading to **2a** in only 11% yield (entry 10). No reaction took place in the presence of other metal salts such as $Zn(OTf)_2$ and $Fe(acac)_3$ (entries 11 and 12). Elevating the reaction temperature resulted in slight erosion of the yield (entry 13), while lower temperatures had a deleterious effect (entries 14 and 15). Finally, the catalyst loading could be reduced to 10 mol %, delivering **2a** in comparative yield (entry 16).

With the optimized conditions in hand, we turned to explore the generality of our protocol (Scheme 3). As shown, besides

Scheme 3. Generality on the Aromatic Moieties[a]



[a]All reactions were performed on a 0.3 mmol scale, with isolated yields.

the model substrates, which provided the naphthyl ketone **2a** in 77% isolated yield, cyclobutanone derivatives decorated with pendant alkynes that possess a diverse set of aromatic groups could be well tolerated. Substrates bearing *o*-, *m*-, or *p*-tolyl substituents all worked smoothly under the standard conditions, offering products **2b–2d** in high yields, suggesting the insensitivity of the system to steric effect. Electron-donating methoxy substituent was also accommodated, and the naphthyl ketones were generated in moderate to good yields (**2e**, **2f**). An acceptable yield could still be achieved with a 2,4,5-trimethoxy substituted phenyl as alkyne terminus (**2g**). Electron-withdrawing ester and nitro groups could be

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Org. Lett. XXXX, XXX, XXX–XXX

tolerated, albeit affording the products **2h** and **2i** in lower yields. Fluoro- and chloro-containing products **2j** and **2k** were obtained in high yields from the corresponding cyclobutanone derivatives. The generality of the system was further showcased by the tolerance of naphthyl and thiophene moiety, as products **2l** and **2m** were uneventfully afforded in comparable yields.

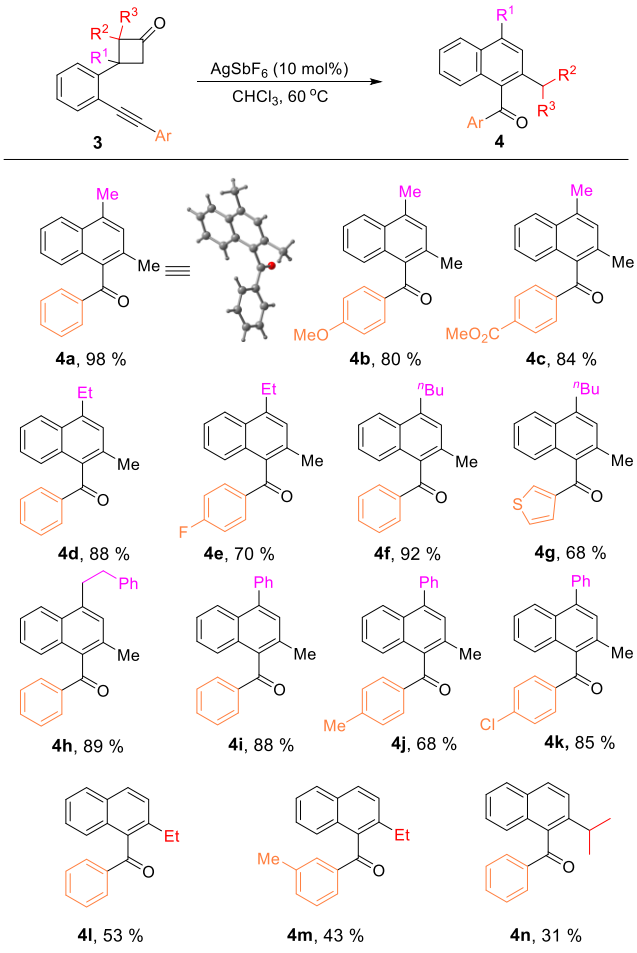
Variation of the arene core was next investigated. Various substituents including methyl-, fluoro-, chloro-, and trifluoromethyl groups were all accommodated, and the final products **2n**−**2r** were invariably prepared in ≥70% yields. The structure of the methoxy product **2o** was unambiguously determined by X-ray diffraction study. Finally, starting from naphthyl substrate, phenanthrenylphenyl methanone **2s** was afforded in moderate yield.

In conjugation with our mechanistic proposal, which features a cation intermediate (Scheme 7, **B**), we postulated that placing a proper substituent on the 3-position of cyclobutanone moiety would be favorable as stabilization of the cation fragment can enhance the reactivity. Indeed, the substrates containing a methyl group reacted exceptionally facilely, affording dialkylnaphthyl ketones **4a**−**4c** in up to quantitative yields (Scheme 4). The X-ray diffraction analysis of **4a** also confirmed its structure. Other alkyl substituents such as ethyl, *n*-butyl, and phenethyl groups showed comparable results, leading to the corresponding naphthyl ketones **4d**−**4h** in high yields. Replacing the alkyl group with a phenyl ring had no deleterious effect on the reaction, providing target compounds **4i**−**4k** smoothly. To our delight, cyclobutanones bearing mono- or *gem*-dimethyl substituents at the α-position of the carbonyl group were compatible, with the more hindered C−C bond being selectively cleaved (**4l**−**4n**). This is especially notable, since cyclobutanones bearing extra substituents at the α-position of the carbonyl group have seldom been applied in transition-metal-catalyzed ring-expansion systems.[14] In a Rh-catalyzed intramolecular allene-involved ring-expansion reaction of α-methyl cyclobutanones, the C−C bond was cleaved selectively at the less bulky C4 position.[14b]

The reaction could be performed on a gram scale, delivering the target compound **2a** in excellent yield (Scheme 5). The potential applicability of the system was further illustrated by transformation of this naphthyl ketone product. Oxidation of the methyl group was easily achieved by SeO_2 to deliver 1-benzoyl-2-naphthoic acid **5**.[15] Conversion to acyl chloride and subsequent intramolecular Friedel−Crafts reaction resulted in benz[*a*]anthracene-7,12-dione **6**, which is the core structure of angucycline antibiotics that exhibit a large spectrum of biological properties including antibacterial, antiviral, and cytostatic activities, among others.[16]

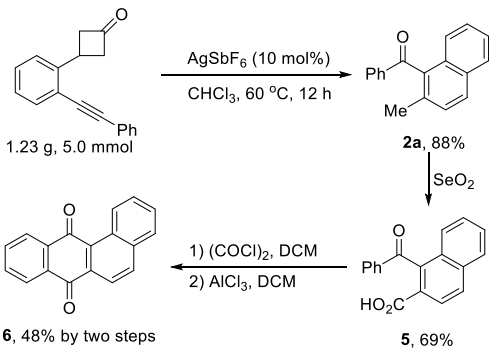
Additional studies were conducted to shed light on the reaction mechanism (Scheme 6). When the alkyne moiety was omitted from the substrate, diphenyl cyclobutanone **7** was transformed to α, β-unsaturated ketone **8** in moderate yield under the standard conditions (eq 1). To explore the stereoselectivity of the ring-opening process, naphthyl cyclobutanone **9** was subjected to the conditions and conjugated enone **10** was obtained as a single *E*-isomer (eq 2). The appreciably lower yield compared with the diphenyl substrate **7** again demonstrates the enhancement of the reactivity by the extra substituent at the 3-position. Moreover, when alkyne-tethered enone (*E*)-**11** was prepared and tested under the standard conditions, naphthyl ketone **2a** was obtained, albeit in a significantly lower yield (eq 3).[11,12] Residual water seems to play an important role in the system, since the reaction was appreciably retarded in the presence of molecular sieves (eq 4). Consistently, when extra D_2O was added into the reaction system, methyl group was partly deuterated. Addition of ^{18}O-water did not lead to labeled product (eq 5). Finally, When α,α-bisdeuterated substrate d_2-**3n** was applied, monodeuterated product *d*-**4n** was obtained exclusively (eq 6). As comparison, trideuterated diaromatic ketone d_3-**2a** was

Scheme 4. Generality on the Cyclobutanone Moieties[a]



[a]All reactions were performed on a 0.3 mmol scale, with isolated yields.

Scheme 5. Application of the Reaction System



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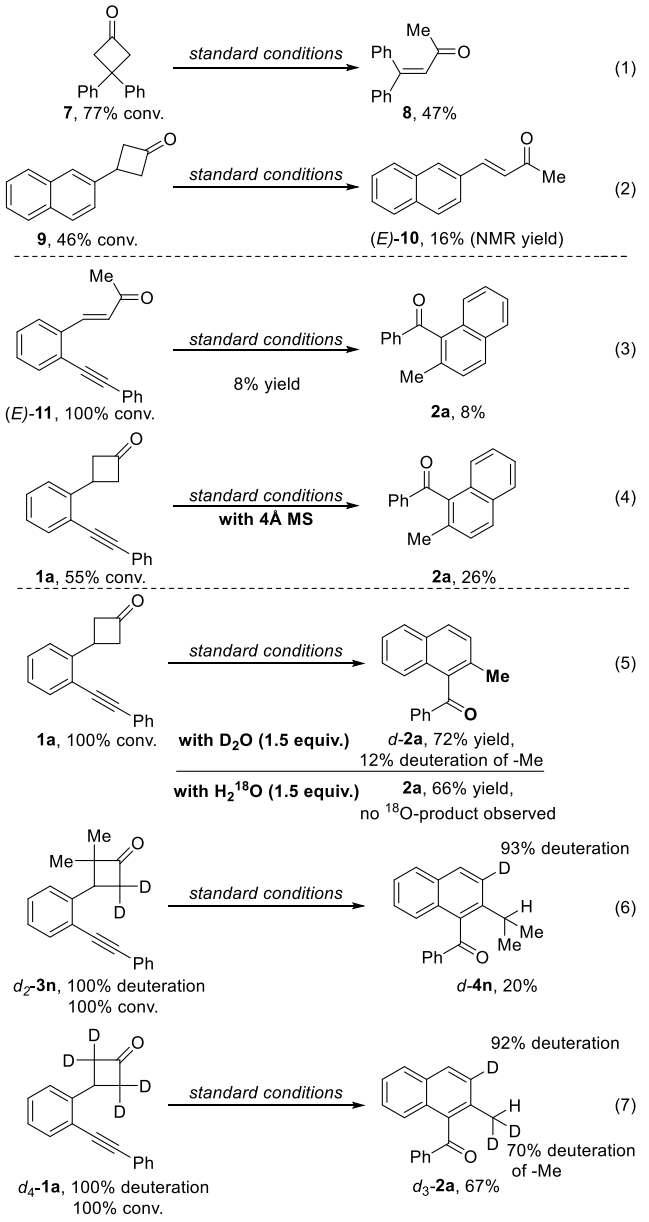
Scheme 6. Preliminary Mechanistic Studies



generated starting from d_4-**1a** with full deuteration on the α-positions (eq 7).

To gain a better understanding of the mechanistic details, density functional theory (DFT) calculations were performed on the Ag-promoted ring-opening process on b3lyp/g-31G(d)/SDD(Ag) level of theory. As shown in Figure 1, coordination between the substrate and $AgSbF_6$ delivers complex **A1** or **A2**, depending on the poise of Ag coordinated to cyclobutanone. C−C bond cleavage of **A1** occurs through **TS1** with an activation barrier of 24.7 kcal/mol, leading to cationic species **B**. Subsequent σ-bond rotation provides **Int1** with a slight uphill. From this intermediate, an interesting concerted protonation/deprotonation process takes place with the aid of two molecules of H_2O. This step requires a 5.5 kcal/mol barrier, leading to a steep downhill to **C** with a large free energy difference of 53.3 kcal/mol. In contrast, conversion of **A2** is accompanied by higher free energies for both the C−C cleavage and generation of enone **E**. The energy profiles of the

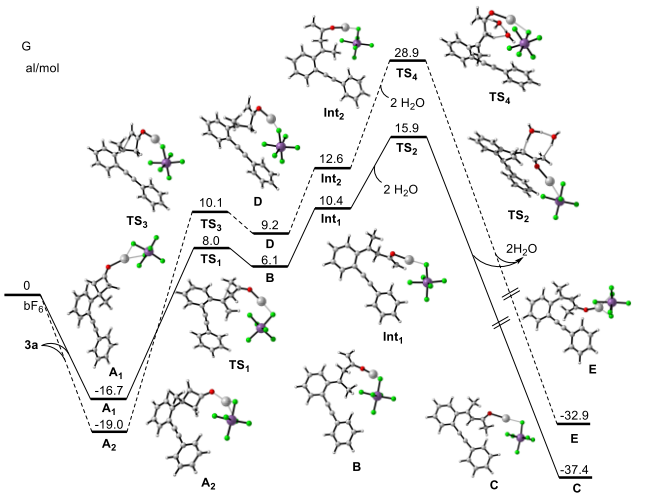
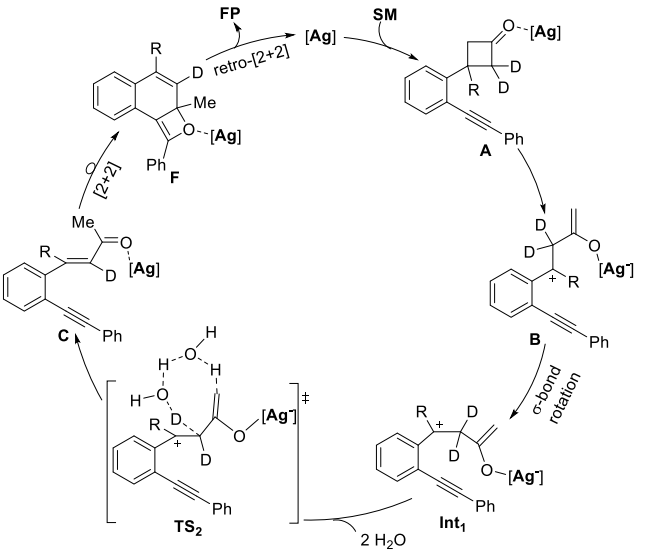


Figure 1. Computed energy profiles for the ring-opening process.

ring-opening indicate that the C−C bond cleavage process may be involved as a rate-determining step.

Based on the above investigations and literature precedents,[8−12] a plausible reaction pathway is proposed in Scheme 7. The reaction proceeds by Lewis acid activation of the

Scheme 7. Proposed Mechanism



cyclobutanone moiety to furnish cationic intermediate **B**,[8] which provides **Int1** via σ-bond rotation, leaving space for two H_2O molecules to participate in the concerted deprotonation/protonation process to deliver enone **C**. Ag(I)-assisted isomerizatioin[17] and subsequent [2 + 2] cycloaddition would give oxacyclobutene **F**, which undergoes retro-[2 + 2] cycloaddition[11,12] to produce the final product and releases the silver catalyst.

In conclusion, we have developed a novel intramolecular alkyne participated ring-expansion reaction of cyclobutanone derivatives. Silver salt was utilized as catalyst for the first time to facilitate the ring-opening metathesis sequence, in which both C−C and C═O bonds are cleaved and reorganized, leading to multisubstituted naphthyl ketones under mild conditions. The study paves an unprecedented pathway for transition-metal-catalyzed structural reorganization of cyclo-

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Org. Lett. XXXX, XXX, XXX−XXX

butanones, leaving space for more types of inter- and intramolecular transformations. Further studies regarding the detailed mechanism and extension of the reaction patterns are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01317.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1967107 and 1967473 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#J.G. and C.L. contributed equally.

Notes

The authors declare no competing financial interest.

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