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Synthesis of multisubstituted cyclobutenones via copper-catalyzed intramolecular C-vinylation of ketones

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ABSTRACT

With the catalysis of CuI/3,4,7,8-tetramethyl-1,10-phenanthroline, various ketones smoothly underwent the intramolecular C-vinylation with vinyl bromides in refluxing THF leading to the efficient synthesis of the corresponding multisubstituted cyclobutenones.

Cyclobutenones are a class of small ring compounds that have found widespread applications in organic synthesis.[1] For example, they are important building blocks for the synthesis of 1,3-dienes, cyclopentanones, α,β-butenolides, etc.[2] They serve as activated dienophiles in Diels–Alder reactions.[3] They offer a variety of ring-expansion products under thermolytic or transition metal-catalyzed conditions.[4] However, these strained four-membered rings are not readily available. They are typically prepared by the [2+2] cycloaddition of alkynes with ketenes or keteniminium salts generated in situ.[5–7] Other methods include the HBr elimination of β-bromocyclobutanone[8,3a] and nucleophilic addition/cyclization reactions of 2,3-allenoates with organozinc reagents.[9] It is therefore highly desirable to develop general and efficient methods for the synthesis of cyclobutenones. Herein we report that the copper-catalyzed intramolecular C-vinylation of ketones provides a novel and efficient entry to multisubstituted cyclobutenones.

Copper-catalyzed Ullmann coupling reactions leading to the formations of C–X (N, O, S, etc.) and C–C bonds have been demonstrated to be a versatile tool in synthetic organic chemistry.[10] The high stability and low costs of the copper catalysts make these transformations attractive for industrial applications. By the appropriate choice of copper source, ligand, base, and solvent, these reactions have been developed to include a wide range of substrates under mild conditions. In particular, the intramolecular vinylation reactions offer a diverse range of functionalized carbo- or heterocycles of various sizes.[10j] Furthermore, this strategy has proven to be uniquely advantageous in the synthesis of four-membered rings.[11] For example, we have shown that the copper-catalyzed intramolecular C–C coupling of activated methylene compounds with vinyl halides provides an efficient synthesis of functionalized alkylidenecyclobutanes (Scheme 1, part A).[11b] We envisioned that this methodology might be extended to the intramolecular vinylation of ordinary ketone enolates, thus providing a novel route to cyclobutenones (Scheme 1, part B). However, it should be emphasized that the C-alkenylation of enolates is typically catalyzed by palladium or nickel complexes.[12] The copper-catalyzed C-vinylation reactions generally require active methylene compounds as nucleophiles[13] while the use of ordinary enolates is rare.[14] Driven by our interest in intramolecular vinylation reactions,[11,15] we set out to explore this possibility.

Thus, 4-bromopent-4-en-2-one **1a** was chosen as the model substrate for the optimization of reaction conditions (Table 1). Our initial attempt with CuI as the catalyst, 2-hydroxybenzaldehyde oxime (**L-1**) as the ligand, and Cs_2CO_3 as the base in refluxing THF for 24 h failed to give any desired product while the starting material **1a** remained unchanged (entry 1, Table 1). When the reaction was carried out at a higher temperature (in refluxing dioxane), we were delighted to find that the expected product cyclobutenone **2a** was observed in 63% yield (entry 2, Table 1). Since ligands play a vital role in Ullmann coupling reactions, the commonly used ligands[10] were screened, including *N*,*N*-dimethylglycine hydrochloride (**L-2**), L-proline (**L-3**), 3,4,7,8-tetramethyl-1,10-phenanthroline (**L-4**), and *N*,*N*′-dimethylethylenediamine (**L-5**). The highest yield (89%) of **2a** was obtained when **L-4** was used

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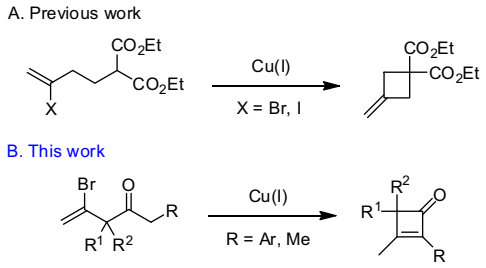
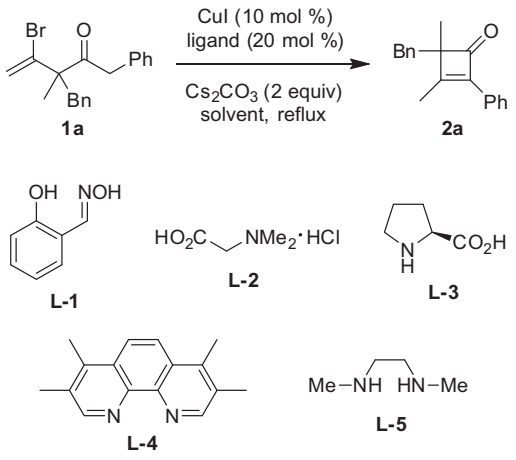


Scheme 1. Intramolecular C-vinylation in 4-*exo* mode.

as the ligand (entries 3–6, Table 1). Furthermore, when the amounts of CuI and **L-4** were increased to 20 mol % and 40 mol %, respectively, the reaction was complete within 12 h leading to the formation of **2a** in almost quantitative yield (entry 7, Table 1). Switching Cs_2CO_3 to other bases such as Na_2CO_3, K_3PO_4, or K_2CO_3 resulted in the decreased yield of **2a** (not shown in Table 1). The control experiments indicated that both Cu(I) and the ligand **L-4** were required for the cyclization (entries 8 and 9, Table 1).

With the optimized conditions in hand, we set out to explore the scope of this method. The results are summarized in Table 2. The reactions of 1-arylpent-4-en-2-ones **1b** and **1c** bearing either an electron-donating group or an electron-withdrawing one proceeded smoothly (entries 2 and 3, Table 2). Substrates **1d–1f** having *ortho*-, *meta*-, or *para*-substitution all led to the corresponding coupling products in excellent yields (entries 4–6, Table 2). Ketone **1g** with *gem*-dimethyl substitution afforded the product cyclobutenone **2g** quantitatively (entry 7, Table 2). The above reactions used arylmethyl ketones as substrates. We then extended the

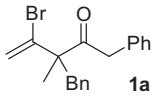
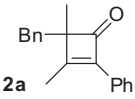
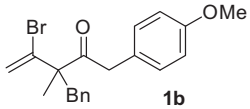
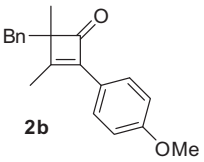
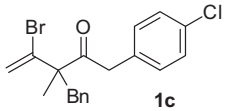
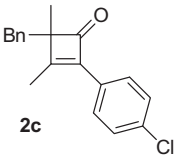
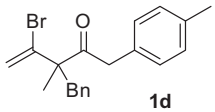
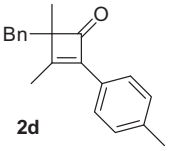
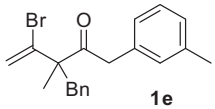
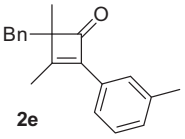
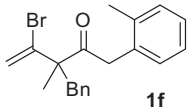
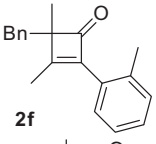
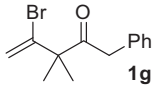
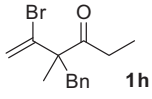
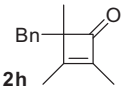
Table 1
Optimization of reaction conditions



Entry[a]	Ligand	Solvent	Time (h)	Yield (%)[b]
1	**L-1**	THF	24	0
2	**L-1**	Dioxane	12	63
3	**L-2**	THF	24	40
4	**L-3**	THF	24	20
5	**L-4**	THF	24	89
6	**L-5**	THF	24	0
7[c]	**L-4**	THF	12	95
8	None	THF or dioxane	24	0
9[d]	**L-4**	THF or dioxane	24	0

[a] Reaction conditions: **1a** (0.2 mmol), CuI (0.02 mmol), ligand (0.04 mmol), Cs_2CO_3 (0.4 mmol), solvent (2 mL), reflux.
[b] Isolated yield based on **1a**.
[c] CuI (20 mol %) and **L-4** (40 mol %) were used.
[d] The reaction was carried out without CuI.

Table 2
Copper-catalyzed C-vinylation of ketones in refluxing THF

Entry[a]	Substrate	Product	Yield[b] (%)
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	86
3	 **1c**	 **2c**	97
4	 **1d**	 **2d**	92
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	86
7	 **1g**	 **2g**	99
8[c]	 **1h**	 **2h**	41

[a] Reaction conditions: **1** (0.3 mmol), CuI (11.6 mg, 0.06 mmol), **L-4** (28.4 mg, 0.12 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), THF (3 mL), reflux, 12 h.
[b] Isolated yield based on the corresponding vinyl bromide **1**.
[c] The reaction was carried in dioxane at reflux for 24 h.

intramolecular vinylation to substrates other than arylmethyl ketones, such as ethyl ketone **1h**. The reaction of **1h** under the above optimized conditions gave no desired product. However, when the reaction was carried out in refluxing dioxane, the cyclization product **2h** was achieved in 41% yield (entry 8, Table 2). The lower reactivity of ethyl ketone **1h** than arylmethyl ketones in vinylation might be attributed to the more difficult enolization of the former.

β-Keto esters or 1,3-diketones that are more prone to enolization than ketones **1** could be anticipated to participate in the above type of intramolecular vinylation more readily. Indeed, the cyclization of β-keto ester **3** proceeded at a much faster rate, leading to the formation of cyclobutenone **4** in a 78% yield within 20 min (Eq. 1). However, the C-vinylation of 1,3-diketone 5 failed. Instead, the intramolecular O-vinylation took place to give 4*H*-pyran-4-one **6** (Eq. 2). It is also interesting to note that the cyclization of ketone **7** as the analog of **1a** also proceeded via O-vinylation rather than C-vinylation, presumably because of the increased steric hindrance associated with C-vinylation (Eq. 3):

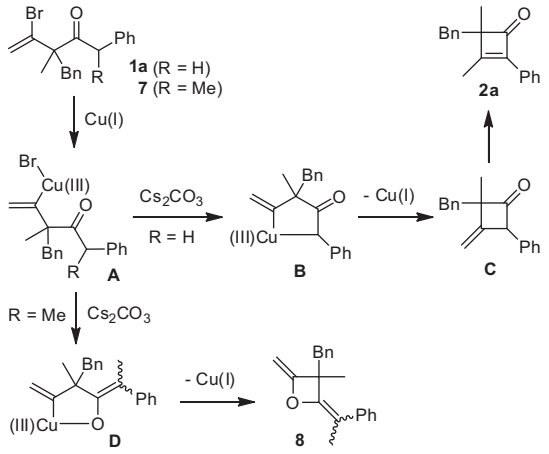
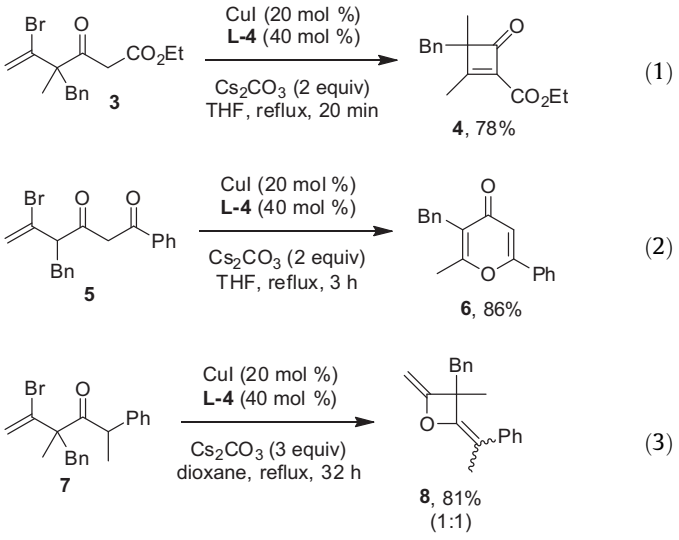


Figure 1. Proposed mechanism.



A plausible mechanism can thus be drawn based on the above results, as depicted in Figure 1. The oxidative addition of Cu(I) with vinyl bromide **1a** generates the vinylic Cu(III) intermediate **A** (R = H), which then undergoes intramolecular ligand exchange with the enolate to give the five-membered metallocycle **B**. The subsequent reductive elimination of **B** (to give **C**) followed by C=C bond migration furnishes cyclobutenone **2a**. It is interesting to note that the intermediate **C** could not be observed in our experiments, indicating the fast conversion of **C** to **2a**. Presumably the conjugation of the C=C bond with the carbonyl and the phenyl ring serves as the driving force for the olefin isomerization. When R is a methyl group, the intramolecular ligand exchange of **A** (R = Me) to produce the metallocycle similar to **B** becomes difficult due to the increased steric hindrance at the α-carbonyl carbon. As a result, the intermediate **D** is now generated, which then affords oxetane **8** as the final product via reduction elimination.

In summary, we have developed a novel method for the efficient synthesis of multisubstituted cyclobutenones via copper-catalyzed intramolecular C-vinylation of ketones. The reactions are easy to operate[16] and enjoy a relatively broad substrate scope, and thus should find important applications in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, characterizations of new compounds and ^{1}H and ^{13}C NMR spectra of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.068.

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16. *Typical procedure for the copper-catalyzed synthesis of multisubstituted cyclobutenones*: 3-Benzyl-4-bromo-3-methyl-1-phenylpent-4-en-2-one (**1a**, 68.7 mg, 0.2 mmol), CuI (7.7 mg, 0.04 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (18.9 mg, 0.08 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) in THF (2 mL) were refluxed for 12 h under nitrogen atmosphere. The resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography on silica gel with petroleum ether/EtOAc (10:1, v:v) as the eluent to give the pure product **2a** as a colorless oil. Yield: 50 mg (95%). For details, see the Supplementary material.