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Cu(I)-Catalyzed Intramolecular C−C Coupling of Activated Methylene Compounds with Vinyl Halides: Efficient Synthesis of Functionalized Alkylidenecyclobutanes

Liqun Chen,[†] Min Shi,[†,‡] and Chaozhong Li*[,‡]

School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. China, and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

clig@mail.sioc.ac.cn

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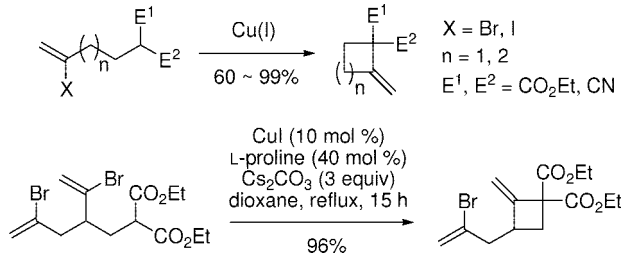
ABSTRACT



With the catalysis of CuI/L-proline, a number of 2-(3-bromobut-3-enyl)malonates underwent efficient intramolecular C-vinylation leading to the synthesis of functionalized alkylidenecyclobutanes. Competition experiments revealed that this four-membered ring closure is fundamentally preferred over the corresponding five-membered ring closure.

Alkylidenecyclobutanes represent a unique class of moderately strained alkenes. They are structural motifs in a number of natural products.[1] In the meantime, they have recently been shown to be versatile intermediates in organic synthesis.[2] However, to our surprise, methods for their synthesis are few. A commonly used method is the Wittig reaction of (4-bromobutyl)triphenylphosphonium bromide with a carbonyl compound,[2a−c] a method similar to that for the synthesis of alkylidenecyclopropanes.[3] However, only simple derivatives of methylenecyclobutane were prepared by this method, and its generality and functional group tolerance have yet to be examined. Other methods include the 4-*exo* cyclization of acetylenic alkyllithiums,[4] the [2 + 2] cycloaddition of allenes to appropriately substituted olefins,[5] and the HX (X = I or OH) elimination reactions.[1d,2d] As a result, the chemistry of alkylidenecyclobutanes is far less explored

[†] East China University of Science and Technology.
[‡] Chinese Academy of Sciences.

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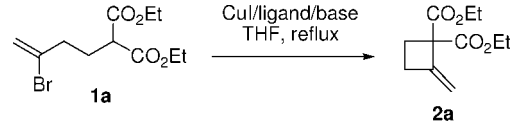
compared to that of alkylidenecyclopropanes.[3] It is therefore highly desirable to develop general and efficient methods for the synthesis of alkylidenecyclobutanes, especially the functionalized ones. We report here that the copper-catalyzed intramolecular C-vinylation of activated methylene compounds with vinyl halides provides an efficient and convenient entry to functionalized alkylidenecyclobutanes.

The past few years have witnessed a rapid progress in the formation of aryl (or vinyl) C−X (X = O, N, S, etc.) bonds via copper-catalyzed Ullmann coupling between aryl (or vinyl) halides and heteroatom-centered nucleophiles.[6] The high stability and low cost of the copper catalysts enable these transformations to be a useful complement to the more extensively investigated Pd(0)-catalyzed processes.[7] This method was then successfully extended to the C−C bond formation via copper-catalyzed C-arylation of active methylene compounds (the Hurtley coupling[8]).[9] However, the analogous C-vinylation is far less explored. Qian and Pei reported the intermolecular cross-coupling of activated methylene compounds with β-bromostyrenes.[10] The only other example was reported by us as the side reaction in the intramolecular O-vinylation of 1,3-dicarbonyl compounds.[11] Driven by our interest in Cu(I)-catalyzed intramolecular O- and N-vinlyation reactions,[11,12] we set out to study the Cu(I)-catalyzed intramolecular C-vinylation.

Thus, diethyl 2-(3-bromobut-3-enyl)malonate (**1a**) was chosen as the model substrate, which was readily available by monoalkylation of diethyl malonates. Compound **1a** was first subjected to the following typical Ullmann coupling conditions: CuI (10 mol %), *N*,*N*′-dimethylethylenediamine (**L-1**, 20 mol %),[13] Cs_2CO_3 (2 equiv) in refluxing THF. After 8 h, the expected cyclization product **2a** was obtained in only 4% yield, while most of the starting material was recovered (entry 1, Table 1). Increasing the amount of ligand **L-1** to 40 mol % resulted in a slightly faster reaction (entry 2, Table 1). We then screened the ligands. 1,10-Phenanthroline (**L-2**)[14] and *N*,*N*-dimethylglycine hydrochloride (**L-3**)[15] showed an effect similar to **L-1**, while 2-hydroxybenzaldehyde oxime (**L-4**)[12a] was inactive (entries 3−5, Table 1). On the other hand, the use of 2-isobutyrylcyclohexanone (**L-5**)[16] or L-proline (**L-6**)[17] as ligand led to a much faster reaction (entries 6 and 7, Table 1). With the use of the more readily available **L-6**, a higher yield (79%) of **2a** could be achieved by simply lengthening the reaction time to 20 h (entry 8, Table 1).

Table 1. Optimization of the Synthesis of **2a** from **1a**



entry[a]	ligand (mol %)[b]	base (equiv)	time (h)	yield (%)[c]
1	**L-1** (20)	Cs_2CO_3 (2)	8	4
2	**L-1** (40)	Cs_2CO_3 (2)	8	11
3	**L-2** (40)	Cs_2CO_3 (2)	8	10
4	**L-3** (40)	Cs_2CO_3 (2)	8	10
5	**L-4** (40)	Cs_2CO_3 (2)	8	0
6	**L-5** (40)	Cs_2CO_3 (2)	8	61
7	**L-6** (40)	Cs_2CO_3 (2)	8	59
8	**L-6** (40)	Cs_2CO_3 (2)	20	79
9	**L-6** (40)	K_2CO_3 (2)	20	trace
10	**L-6** (40)	K_3PO_4 (2)	20	20
11	**L-6 (40)**	**Cs_2CO_3(3)**	**20**	**92**
12	none	Cs_2CO_3 (3)	20	trace

[a] Reaction conditions: **1a** (0.3 mmol), CuI (0.03 mmol), ligand, base, THF (10 mL), reflux. [b] **L-1**: *N*,*N*′-dimethylethylenediamine. **L-2**: 1,10-phenanthroline. **L-3**: $Me_2NCH_2CO_2H$·HCl. **L-4**: 2-hydroxybenzaldehyde oxime. **L-5**: 2-isobutyrylcyclohexanone. **L-6**: L-proline. [c] Isolated yield based on **1a**.

We next examined the effects of different bases. It turned out that Cs_2CO_3 is superior over K_2CO_3 and K_3PO_4 (entries 8−10, Table 1). To speed up the coupling reaction, we increased the amount of Cs_2CO_3 to 3 equiv. To our delight, a clean reaction was observed. The substrate **1a** was all consumed within 20 h, and the product cyclobutane **2a** was achieved in 92% isolated yield.

With the optimized combination (combination A: 10 mol % of CuI, 40 mol % of **L-6**, and 3 equiv of Cs_2CO_3) in hand, we then examined the generality of this method. The results are summarized in Table 2. Substrates **1b**−**1e** bearing different substituents at the C-3 or C-4 position, all afforded the expected cyclization products in excellent yields (entries

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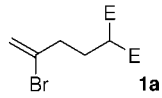
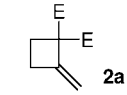
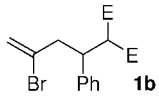
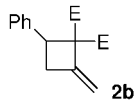
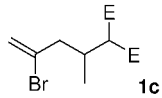
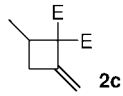
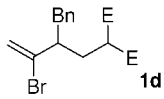
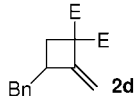
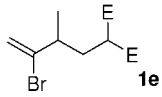
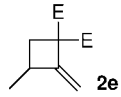
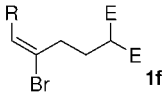
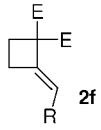
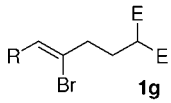
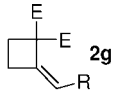
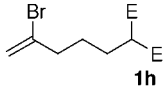
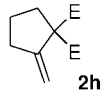
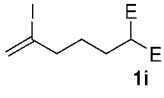
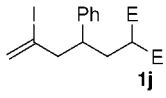
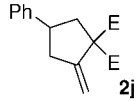
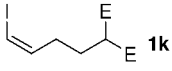
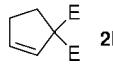
Table 2. Cyclization of Malonates **1**

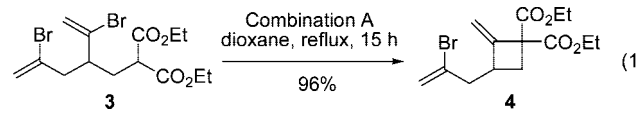
entry	substrate[a]	product	condition[b]	yield[c]
1	 **1a**	 **2a**	THF, 20 h	92%
2	 **1b**	 **2b**	THF, 17 h	99%
3	 **1c**	 **2c**	CH_3CN, 22 h	96%
4	 **1d**	 **2d**	CH_3CN, 16 h	99%
5	 **1e**	 **2e**	dioxane, 15 h	94%
6[d]	 **1f**	 **2f**	CH_3CN, 18 h	91%
7[d]	 **1g**	 **2g**	dioxane, 15 h	50%
8[d]			toluene, 46 h	88%
9	 **1h**	 **2h**	dioxane, 24 h	trace
10			toluene, 72 h	71%
11	 **1i**	**2h**	THF, 30 h	88%
12	 **1j**	 **2j**	THF, 17 h	97%
13	 **1k**	 **2k**	THF, 12 h	99%

[a] E = CO_2Et. [b] Reaction conditions: **1** (0.3 mmol), CuI (0.03 mmol), **L-6** (0.12 mmol), Cs_2CO_3 (0.9 mmol), solvent (10 mL), reflux. [c] Isolated yield based on **1**. [d] R = n-$C_{10}H_{21}$.

2−5, Table 2). The configuration of the C=C double bond was nicely retained as evidenced by the reactions of **1f** and **1g** (entries 6−8, Table 2). It should be noted that the cyclization of some substrates such as **1g** was slow in refluxing THF or CH_3CN presumably because of the steric factors. However, by simply raising the reaction temperature (refluxing dioxane or toluene), the coupling products could be generated in high yields.

We then extended this method to the intramolecular coupling via a five-membered ring closure (entries 9−12, Table 2). The cyclization of 2-(4-bromopent-4-enyl)malonate **1h** in dioxane was very slow. Nevertheless, the prolonged reaction of **1h** in refluxing toluene afforded the desired product **2h** in 71% yield. On the other hand, the iodo-analogue of **1h**, substrate **1i**, underwent efficient cyclization at a much lower temperature (refluxing THF) to produce the same product **2h** in 88% yield. Furthermore, iodide **1j** having a 3-phenyl substituent afforded the cyclization product **2j** in almost quantitative yield within a shorter period of time. The C−C bond formation in a 5-*endo*-like mode was also successful as exemplified by the reaction of (*Z*)-2-(4-iodobut-3-enyl)malonate **1k** in which the expected coupling product **2k** was achieved in quantitative yield under mild conditions (entry 13, Table 2).

The above results clearly demonstrated the high efficiency of copper catalysis in the intramolecualr C-vinylation of malonates. The data in Table 2 also indicated that the uncommon four-membered ring closure is much easier that the corresponding five-membered cyclization. To have a direct comparison, dibromide **3**, which has two possible modes of cyclization, was synthesized and subjected to the above optimized conditions (Combination A). Indeed, the four-membered ring product **4** was isolated in 96% yield, while no five-membered cyclization product could be detected (eq 1). This result unambiguously pointed out that four-membered ring closure is fundamentally preferred in the Cu(I)-catalyzed C-vinylation, a phenomenon also observed in the O- and N-vinylation under the catalysis of copper.[12c,e] Although the reason for such a preference remains unclear, it could be possible that the transition state for four-membered ring closure as a Cu-containing five-membered ring is kinetically and thermodynamically more favorable. Theoretical analyses on this assumption are currently underway in our laboratory and will be reported in due course.

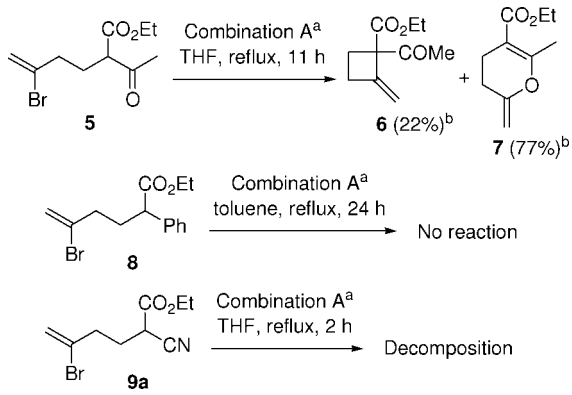


(1)

The above reactions employed malonates as the nucleophiles. We next examined other types of nucleophiles. As can be seen in Scheme 1, the reaction of β-keto ester **5** yielded the mixture of methylenecyclobutane **6** (22%) and cyclic ether **7** (77%), the latter being the O-vinylation product via a six-membered ring closure. Apparently the O-vinylation of the enolate competes well with C-vinylation. Monoesters such as 2-phenylacetate **8** did not undergo the C−C coupling under the optimized conditions. This should be attributed to the lower acidity of the 2-methylene protons. Surprisingly, 2-cyanoacetate **9a** failed to give any cyclized product under the conditions of combination A, while all the starting material decomposed within 2 h in refluxing THF. Lowering the reaction temperature did not help.

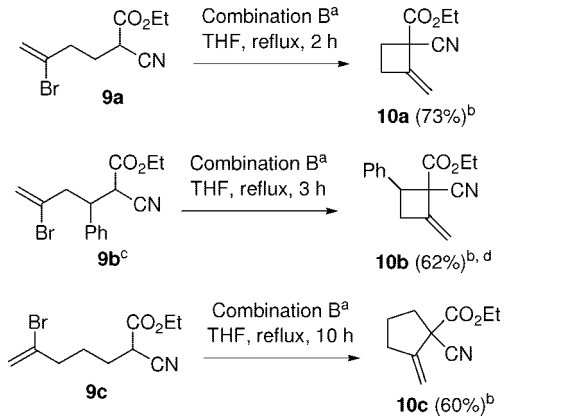
With the assumption that the combination A might not be the right combination for the cyclization of 2-cyanoacetates, we went on to reoptimize the conditions for **9a**. Indeed, switching the ligand back to **L-1** allowed the generation of the expected methylenecyclobutane **10a** in 30% yield. Further changing the base to K_3PO_4 (2 equiv) increased the yield of

Scheme 1. Reactions of Esters **5**, **8**, and **9a**[a,b]



[a] Combination A: CuI (10 mol %), **L-6** (40 mol %), Cs_2CO_3 (3 equiv). [b] Isolated yield based on **5**.

Scheme 2. Reactions of Cyanoacetates **9**[a,b,c,d]



[a] Combination B: CuI (10 mol %), **L-1** (40 mol %), K_3PO_4 (2 equiv). [b] Isolated yield based on **9**. [c] Two stereoisomers in ~ 1.7:1 ratio determined by ^{1}H NMR (300 MHz). [d] Trans:cis = ~10:1 determined by ^{1}H NMR (300 MHz).

10a to 73%. On the other hand, ligands such as **L-2** or **L-5** and the base K_2CO_3 failed to activate the coupling process.

The above reoptimized conditions (combination B: 10 mol % of CuI, 40 mol % of **L-1**, and 2 equiv of K_3PO_4) were then applied to other 2-cyanoacetates (Scheme 2). The reaction of 3-phenyl-substituted 2-cyanoacetate **9b** in THF for 3 h afforded the cyclization product **10b** in 62% yield. Interestingly, a very good stereoselectivity (~10:1) was observed with the major isomer in a *trans*-configuration (determined by 2D NOESY experiments), which might be attributed to the steric control of the phenyl group. The five-membered ring closure was also successful even with the use of vinyl bromide, as evidenced by the reaction of bromide **9c** in which the methylenecyclopentane **10c** was achieved in 60% yield under mild conditions (THF, reflux, 10 h). By comparison with the reaction of malonate **1h**, it seems that 2-cyanoacetates are more reactive toward C-vinylation. The results in Table 1 and Scheme 2 also strongly implied that, by the appropriate choice of ligand and base, other activated methylene compounds could also undergo the corresponding copper-catalyzed intramolecular C-vinylation.

In conclusion, the chemistry detailed above has clearly demonstrated for the first time that with the catalysis of Cu(I) highly efficient intramolecular C-vinylation of activated methylene compounds with vinyl halides via four- or five-membered ring closure can be successfully implemented under mild conditions, leading to the convenient synthesis of alkylidenecyclobutanes and cyclopentanes. Moreover, the uncommon four-membered ring closure is intrinsically preferred over the corresponding five-membered ring closure, illustrating the unique property of Cu(I) catalysis. This finding should be of useful application in organic synthesis.

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Supporting Information Available: Experimental procedures for C−C coupling and the characterizations of **1**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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