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# Another Role of Copper in the Simmons–Smith Reaction: Copper-catalyzed Nucleophilic Michael-type Cyclopropanation of α,β-Unsaturated Ketones

Kanami Fujii, Tomonori Misaki, and Takashi Sugimura*
*Graduate School of Material Science, University of Hyogo, 3-2-1 Kohto, Kamigori, Ako-gun 678-1297*

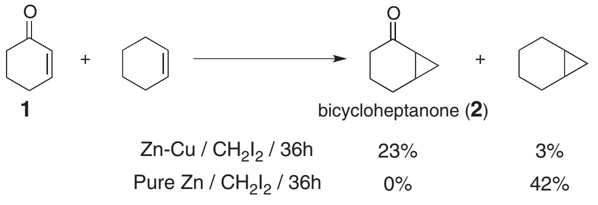
(E-mail: sugimura@sci.u-hyogo.ac.jp)

Cyclopropanation was performed using the Furukawa procedure with $CH_2I_2/Et_2Zn$ and α,β-unsaturated ketones. The reaction was performed in the presence of a copper salt. The reactivity was highly dependent on the substrate structure, and cyclopropanated products were obtained in better yields than those achieved using the original Simmons–Smith conditions with a Zn–Cu couple in some cases. Stereospecificity was observed in a certain case; however, the synthesis of an asymmetric version with a chiral ligand was not successful.

The Simmons–Smith reaction was first reported in 1958,[1] and numerous synthetic approaches use this synthetically valuable cyclopropanation reaction with electron-rich olefins.[2] The sluggish reaction between the zinc metal and $CH_2I_2$ was first performed using a zinc–copper couple (Zn–Cu) at the reflux temperature of ether. In 1966, the Furukawa modification using the organometallic reagent $Et_2Zn$ solved this metal-surface activation problem to allow cyclopropanation to proceed at low temperatures in a desired solvent,[3] although the true generated species, commonly represented by $IZnCH_2I$ or $ICH_2ZnCH_2I$, may not be the same in the two procedures. Two decades ago, the Zn–Cu couple was found to be unnecessary to perform the reaction when zinc was sufficiently pure. A trace lead impurity drastically deactivated the reactivity of the zinc surface toward $CH_2I_2$; however, in the presence of copper (or trimethylsilyl chloride), the reactivity increased.[4] Despite this current common understanding, we found that copper plays a role in surface activation; however, in the case of an electron-deficient olefin, copper plays a second important role. In fact, the general method of using the Furukawa procedure for α,β-unsaturated ketones involves the use of an appropriate copper salt, which may open a new future for zinc carbenoid reactions.

The Simmons–Smith reaction with an electron-deficient substrate is limited to one report by Limasset et al.[5] In that report, 2-cyclohexenone (**1**) with Zn–Cu and $CH_2I_2$ resulted in cyclopropanation to afford **2**. The authors also reported that, in the reaction with a mixture of **1** and cyclohexene (50% each), **1** exhibited greater reactivity toward cyclohexene. Initially, we investigated the role of the copper additive under the Simmons–Smith conditions. The same mixture with pure zinc resulted in bicyclo[4.1.0]heptane in 42% yield, but **2** was not obtained (Scheme 1). Thus, copper in the Zn–Cu couple clearly changed the electrophilic property of zinc carbenoid to nucleophilic.

Cyclopropanation of **1** with an electron-deficient olefin was performed using the Furukawa procedure with $CH_2I_2/Et_2Zn$. In the absence of a copper additive, the reaction did not proceed; however, in the presence of a copper salt, cyclopropanated product **2** was obtained, as shown in Table 1. For this Michael-type Furukawa cyclopropanation, both Cu(I) and Cu(II) were effective.[6]



**Scheme 1.** Simmons–Smith reaction with a mixed substrate of 2-cyclohexenone (**1**) and cyclohexene (50/50).

**Table 1.** Isolated yield of **2** from the reaction of **1** with $Et_2Zn/CH_2I_2$ in the presence of various copper salts[a]

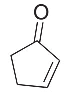
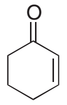
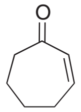
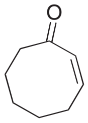
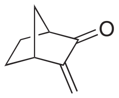
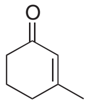
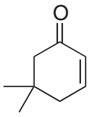
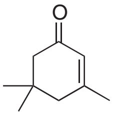
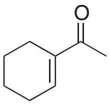
| Entry | Additive | Yield of **2**/% Additive/equiv: 0.1 | 0.2 | 0.5 | 1.0 |
|---|---|---|---|---|---|
| 1 | CuBr | ≤2 | 36 | 14 | 38 |
| 2 | CuCN | ≤2 | 20 | 8 | 34 |
| 3 | CuBr•$SMe_2$ | ≤2 | 37 | <1 | 13 |
| 4 | CuI•$PBu_3$ | <1 | ≤2 | <1 | <1 |
| 5 | CuOTf | — | ≤2 | 33 | — |
| 6 | $Cu(OTf)_2$ | — | 39 | 20 | — |

[a] The reaction of **1** was performed at r.t. for 3 days with $Et_2Zn$ (5 equiv) and $CH_2I_2$ (10 equiv) in diethyl ether in the presence of 0.1, 0.2, 0.5, or 1.0 equivalents of copper salts.

Notably, **1** did not react under the conventional Furukawa cyclopropanation conditions (5 equiv of $Et_2Zn$ and 10 equiv of $CH_2I_2$ in diethyl ether at r.t.), which are applicable for most simple and electron-rich olefins. In the presence of 0.2 or 0.5 equiv of copper salt, **1** was consumed and **2** was obtained in low to moderate yield. The reaction yield was not improved through the use of other solvents: 28% in cyclopentyl methyl ether and 2% in THF (both with 0.2 equiv of CuBr•$SMe_2$). The yield dependency on the copper salt amounts is irregular and the reaction conditions were not completely optimized, but the subsequent reactions were performed in diethyl ether with 0.2 equiv of $Cu(OTf)_2$, which is the best catalyst reported to date.[7]

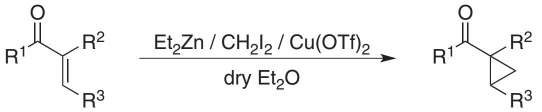
The copper-catalyzed Furukawa cyclopropanation was performed with various unsaturated ketones to demonstrate the synthetic limitations of the reaction and to provide mechanistic information. In Table 2, the isolated product yields with cyclic enones achieved using 5 equiv of $Et_2Zn$, 10 equiv of $CH_2I_2$, and 0.2 equiv of $Cu(OTf)_2$ in diethyl ether are summarized to show a comparison of the classic Simmons–Smith reaction with Zn–Cu/$CH_2I_2$ (5 equiv each) in diethyl ether. The ring size of the *endo*-cyclic substrates was a dominant factor with respect to product yield, which increased with increasing ring size (Entries 1–4). The *exo*-cyclic substrate in a fixed conformation resulted in a

**Table 2.** The product yields[a] with Zn–Cu vs. $Et_2Zn + Cu$ catalyst

| Entry | Substrate | Yield/% | |
|---|---|---|---|
| | | S–S reaction Zn–Cu | Furukawa method $Et_2Zn + Cu(OTf)_2$ |
| 1 |  | 0 | <2 |
| 2[b] |  **1** | 45 | 39 |
| 3 |  | 41 | 50<br>23 (Cu salt 0.4 equiv) |
| 4 |  | 60 | 61 |
| 5 |  | 71 | 41 |
| 6 |  | 0[c] | 3 |
| 7 |  | Decomp.<br>(14) | Decomp.<br>(<21) |
| 8 |  | 0[c] | 0[c] |
| 9 |  | 25 | 0[c] |

[a] The reaction was performed until all of the substrate was consumed unless otherwise noted. Product decompositions and reactant side reactions were difficult to distinguish. [b] The reaction was performed at r.t. for 3 days with $Et_2Zn$ (5 equiv), $CH_2I_2$ (10 equiv), and $Cu(OTf)_2$ (0.2 equiv) in diethyl ether. [c] No reaction.

**Table 3.** Cyclopropanation of acyclic substrates



| Entry | $R^1$ | $R^2$ | $R^3$ | Yield/% (time) |
|---|---|---|---|---|
| 1 | Pent | H | H | 84 (3 h)[a] |
| 2 | Pent | H | Me | 61 (21 h) |
| 3 | Pent | Me | H | 49 (21 h) |
| 4 | Cy | H | H | 82 (1 h)[a] |
| 5 | Cy | H | Me | 54 (24 h) |
| 6 | Bu | Me | Me | 31 (18 h)[b] |
| 7 | Ph | H | H | 54 (3 h)[a] |
| 8 | Ph | H | Me | 51 (20 h)[a] |
| 9 | Ph | Me | H | 75 (7 h) |
| 10 | *p*-Anis | H | H | 48 (4 h) |
| 11 | *p*-$NO_2C_6H_4$ | H | H | 13 (9 h) |
| 12 | *p*-$CF_3C_6H_4$ | H | H | <1 (3 h) |
| 13 | Ph | Ph | H | 20[c] (3 days) |
| 14 | 2-Fulyl | H | H | <1 (4 h) |
| 15 | $OC_{12}H_{25}$ | H | H | <1 (3 days) |
| 16 | H | H | Ph | <1 (3 days) |

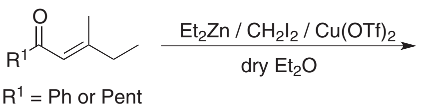
[a] With a longer reaction time, the reaction yields produced by the Simmons–Smith reaction with Zn–Cu were 51% (24 h), 44% (5 h), 21% (4 h), and 44% (23 h) for the substrates shown in Entries 1, 4, 7, and 8, respectively. [b] The product decomposed gradually (<1%, 3 days). [c] Intramolecular *O*-alkylation followed by the second cyclopropanation afforded 2,4-diphenyl-4,5-dihydrofuran, which was an abnormal product, in 19% yield in addition to the 20% yield of the expected product.

moderate yield (Entry 5). The reactivity became negligible with the introduction of a β-methyl substituent (Entry 6). The low product yields achieved with 5,5-disubstituted **1a** (Entry 7) and *exo*-carbonyl (Entry 9) are noteworthy for their implications related to the reaction mechanism. In summary, the product yield depends on the substrate structure; however, in some cases, the yields were better than that of the reported Zn–Cu cyclopropanation.

In contrast to the conformationally regulated cyclic enones, acyclic enones were more reactive, as reported in Table 3. The terminal olefin in aliphatic α,β-unsaturated ketones afforded high yields of 82%–84% (Entries 1 and 4). The aromatic ketone represented by Entry 7 showed poorer reactivity (54%), but the yield increased to 75% with the α-methyl substitution (Entry 9). Low reactivity with the aromatic enone (Entry 7) was likely due to the electron-withdrawing nature of the phenyl substituent; in fact, electron-withdrawing *p*-substitutions further reduced the product yields (Entries 11 and 12). An unsaturated ester (Entry 15) and aldehyde (Entry 16) were inert under the investigated conditions.

One of the advantages of the reaction used in the present study is its ability to provide a motif for an asymmetric reaction that forms two C–C bonds and two chiralities. In the case of the Zn–Cu reaction, the introduction of a chiral ligand or some other chiral source can be difficult. To establish this new asymmetric reaction by further study, we performed two additional series of preliminary experiments.

When a diastereomeric mixture of an aromatic enone ($R^1 = Ph$) in a ratio of $E/Z = 2.4/1$ was reacted under the copper-catalyzed Furukawa procedure, the ratio of the remaining substrate was unchanged, whereas the ratio of the product decreased to 1.2/1 (Scheme 2). In contrast, an aliphatic ketone



**Scheme 2.** Stereospecificity of the present reaction.

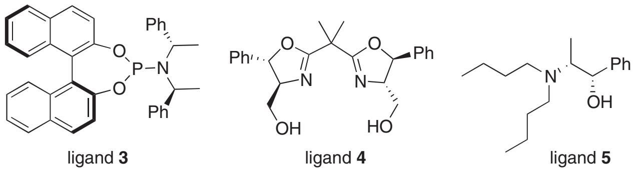


**Figure 1.** Chiral ligands employed for the present reaction with cycloheptenone.

($R^1 = \mathrm{Pent}$, $E/Z = 2.2/1$) afforded a product with an $E/Z$ ratio of 2.0/1, which is identical to the starting ratio within the experimental error range ($^1$H NMR). Hence, the stereospecificity of the new reaction is currently limited to aliphatic enones or cyclic enones.

Finally, some representative chiral ligands of $Cu(OTf)_2$ for the dialkylzinc reagents were tested with cyloheptenone. With the addition of ligand **3**[8] shown in Figure 1 (left, 0.2 equiv), the reaction rate increased, but the product was determined to be racemic by chiral GLC analysis (64% yield). Another representative chiral ligand **4**[9] also failed to yield the optically active product (90% yield). The zinc species itself can be a chiral complex; however, ligand **5**[10] did not lead to a stereoselective reaction (76% yield).

In this investigation, the Simmons–Smith reaction was determined to be not only effective for electron-rich double bonds but also for electron-deficient double bonds through the use of the Furukawa procedure with a copper salt. The developed method would be useful in organometallic chemistry, and our results indicate that more extensive study is necessary to understand all the reaction mechanism.

## References and Notes

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