π–π Chelation controlled chemoselective conjugate addition of lithium dimethylcuprate

Naoki Asao, Sunyoung Lee and Yoshinori Yamamoto*

*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

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Abstract—The conjugate addition of Me_2CuLi to ethyl cinnamate derivatives bearing an alkynyl group at the *ortho*-position, took place preferentially in the presence of the corresponding α,β-unsaturated esters bearing an alkynyl group at the distal position or having no alkynyl groups. The observed chemoselectivity is most probably a reflection of the π–π chelation between π-electrons of the olefinic moiety of the enoates and those of the C-C triple bond located at the proximal position. © 2003 Elsevier Science Ltd. All rights reserved.

It is well accepted that chelation-controlled reactions proceed through the coordination of the lone pair of a heteroatom, such as an oxygen of an aldehyde or a nitrogen atom of an imine, to a Lewis acid, which is recognized as a σ–σ type chelation.[1] Recently, we reported that chemo- and regioselective reactions of certain alkynyl and alkenyl aldehydes were accomplished through a σ–π chelation between a lone pair of the carbonyl moiety and the π-electrons of the C–C multiple bond.[2,3] Now, we report the chemoselective conjugate addition of an organocopper reagent derived from a π–π chelation. The conjugate addition of Me_2CuLi to α,β-unsaturated esters, bearing an alkynyl group at the proximal position, took place preferentially in the presence of the corresponding α,β-unsaturated esters, bearing an alkynyl group at the distal position or having no alkynyl groups (Eq. (1)); this interesting chemoselectivity is most probably a reflection of π–π chelation between the π-electrons of the olefinic moiety of the enoate and those of the C–C triple bond located at the proximal position (Eq. (2)).
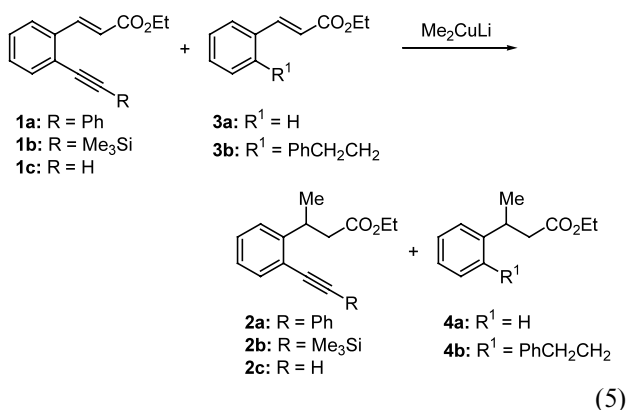

(1)

(2)
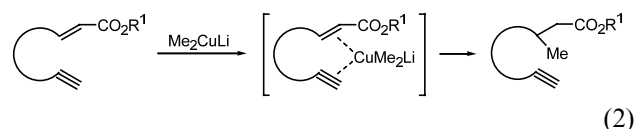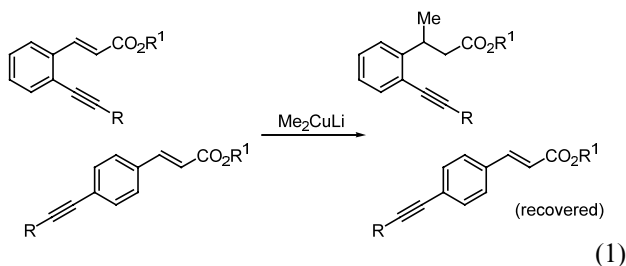
First, we examined the reaction of dimethylcopper lithium with the ethyl cinnamate derivatives **1**, bearing an alkynyl group at the *ortho*-position. Treatment of **1a** with Me_2CuLi at −30°C in CH_2Cl_2 for 1 hour gave **2a** quantitatively. The reaction of **1b** also proceeded smoothly under the same reaction conditions and **2b** was obtained quantitatively (Eq. (3)). On the other hand, when the reaction of ethyl cinnamate **3a** was carried out under the same reaction conditions, the conjugate adduct **4a** was obtained in only 50% yield and some starting material was recovered (Eq. (4)).

1a: R = Ph
1b: R = Me_3Si

2a: R = Ph, quant.
2b: R = Me_3Si, quant.
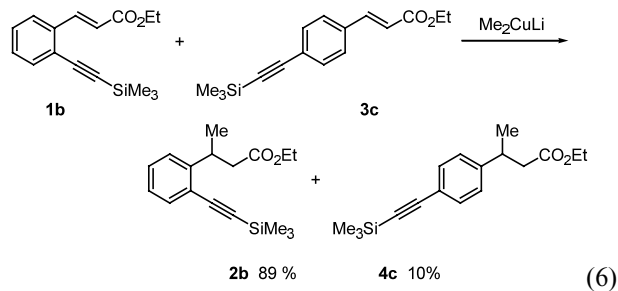
(3)

3a

4a, 50 %

(4)
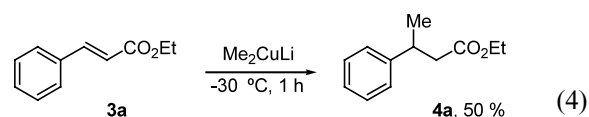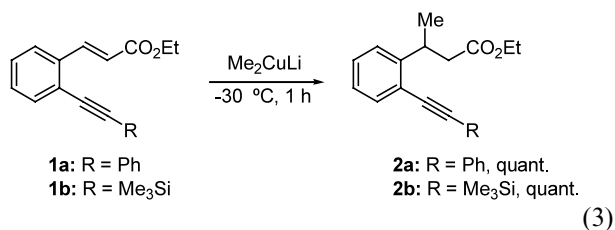
Based on the above results, we next performed a competitive reaction between **1** and **3** (Eq. (5)). The reaction of a 1:1 mixture of **1a** (1 equiv.) and **3a** (1 equiv.) with

* Corresponding author. Tel.: +81-22-217-6581; fax: +81-22-217-6784; e-mail: yoshi@yamamoto1.chem.tohoku.ac.jp
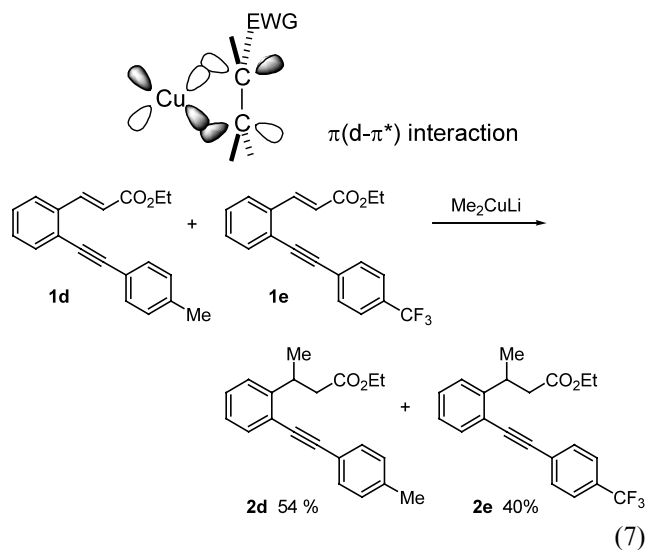
Me₂CuLi (3 equiv.) in CH₂Cl₂ at −30°C for 1 hour gave **2a** in 85% yield along with **4a** in 12% yield (Table 1, entry 1). The remarkable chemoselectivity suggested that bidentate chelation between the alkene and the alkyne of **1a**, as shown in Eq. (2), was operating and enhancing the reactivity of **1a** in comparison with **3a**. Similarly, high chemoselectivities were observed in competitive reactions between **1b** and **3a**, and between **1c** and **3a** (entries 2–3). There may be an argument that due to a certain steric reason the reactivity of **1** is enhanced in comparison with **3a**, in which there is no substituent at the *ortho*-position. Accordingly, the competitive reaction between **1a** and **3b**, in which phenethyl group is substituted at the *ortho*-position was carried out. Again, a high chemoselectivity was observed (entry 4); **2a** was obtained in 85% yield together with **4b** in 13% yield. This result clearly indicates that the chemoselectivity observed in the above competitive reactions cannot be ascribed to steric effects at the *ortho*-position.

The reactions of organocopper reagents with cinnamates, bearing functional groups including heteroatoms at the *ortho*-position, were investigated by Ullenius and Alexakis, independently. From the observed enhancement of the reaction rate and the stereoselectivity, it was suggested that the chelation between substrates and organocopper reagents involved the coordination of the π-electrons of olefinic part of the enoates and the lone pair of the heteroatoms of the functional group at the *ortho*-position.[4] Taking account of these observations, our results may be rationalized by postulating that d–π coordination occurs between Me₂CuLi and the *ortho*-alkynyl group. It is well known that a d–π interaction between Cu atom of R₂CuLi and π-electrons of C–C multiple bond becomes stronger when an electron withdrawing group is located on the multiple bond.[5,6] If this mechanism is operative in producing the present chemoselectivity, it is expected that **1e** would be more reactive than **1d** in the competitive reaction with Me₂CuLi (Eq. (7)), since **1e** has an electron-withdrawing trifluoromethyl group, while **1d** has an electron-donating methyl group. However, **2d** was obtained predominantly over **2e**. Therefore, it is clear that the inductive effect of the *ortho*-alkynyl group is not influential in the present chemoselectivity.

$$(5)$$

The reaction of an equimolar mixture of **1b** and its *para*-isomer **3c** with Me₂CuLi (3 equiv.) was also examined. Again, conjugate addition to **1b** took place preferentially and **2b** was produced predominantly over **4c** in the ratio of 8.9:1 (Eq. (6)).

$$(6)$$

$$(7)$$

Finally, the regioselective conjugate addition of Me₂CuLi to the α,β-unsaturated ester **5**, bearing two enoate units in one molecule, was examined (Eq. (8)). The reaction was carried out by using 3 equiv. of Me₂CuLi at −25°C for 1 hour and the enoate moiety

Table 1. π–π Chelation controlled chemoselective conjugate addition of Me₂CuLi[a]

	Substrate					Yield[b]		Yield[b]		Ratio
Entry	**1**	R	**3**	R¹	Conditions	**2**	%	**4**	%	**2:4**
1	**1a**	Ph	**3a**	H	−30°C, 1 h	**2a**	85	**4a**	12	7.1:1
2	**1b**	Me₃Si	**3a**	H	−25°C, 0.5 h	**2b**	83	**4a**	10	8.3:1
3	**1c**	H	**3a**	H	−25°C, 0.5 h	**2c**	84	**4a**	10	8.4:1
4	**1a**	Ph	**3b**	PhCH₂CH₂	−30°C, 1 h	**2a**	85	**4b**	13	6.5:1

[a] Equimolar mixtures of **1** and **3** were treated with Me₂CuLi (3 equiv.) in CH₂Cl₂.
[b] Isolated yield.

located at the *ortho*-position was attacked by Me$_2$CuLi selectively to give the conjugate adduct **6** predominantly.

(8)
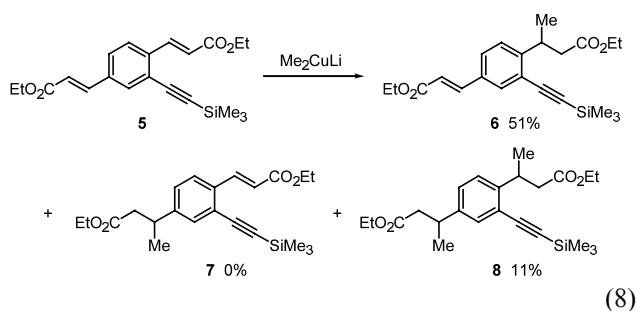
The high chemo- and regioselectivities observed here are most probably due to the effective bidentate chelation of Me$_2$CuLi to alkenyl and alkynyl groups. We believe that the present finding and concept will be useful for controlling the reactions with organocopper reagents.

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