## One-pot $\beta$ -substitution of enones with alkyl groups to $\beta$ -alkyl enones<sup>†</sup>

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Vinylic hydrogens at the  $\beta$ -position of enones were effectively substituted with alkyl groups in a one-pot procedure to afford  $\beta$ -alkyl enones in good to high isolated yields by conjugate addition of higher-order dialkyl cyanocuprates to enones, followed by a reaction with *N*-tert-butylbenzenesulfinimidoyl chloride at -78 °C.

Substitution of the vinylic hydrogen of a carbon–carbon double bond with aryl, heterocyclic, benzyl, or vinyl halides in the presence of a palladium catalyst, known as the Heck reaction, is a useful method for the synthesis of various olefinic compounds having a new carbon–carbon bond.<sup>1</sup> The Heck reaction has been effectively utilized in the total synthesis of complex natural products because of its unique carbon–carbon bond formation and its mild reaction conditions.<sup>2</sup>

In the Heck reaction, however, alkyl halides are not employed for substitution with alkyl groups, due to the very facile β-elimination of the alkyl palladiums formed by oxidative addition of palladium to those alkyl halides.<sup>2,3</sup> Several other methods for substitution of the vinylic hydrogen of olefins with alkyl groups have been reported. For example, the vinylic hydrogen of styrene can be replaced by alkyl groups to afford β-alkylstyrenes by using alkyl bromide and a catalytic amount of (PPh<sub>3</sub>)<sub>2</sub>NiCl<sub>2</sub>.<sup>4</sup> Similar vinylic hydrogen substitution has been achieved by using cobalt catalysts under alkyl radial-olefin coupling conditions.<sup>5</sup> Still, the remaining problem regarding the substitution of vinylic hydrogens with alkyl groups, is that the above-mentioned coupling reactions using nickel or cobalt catalysts are limited to styrene derivatives. Considering the synthetic utility of  $\beta$ -alkyl  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds for the Michael reaction, the Diels-Alder reaction, etc., substitution of the β-vinylic hydrogen of an  $\alpha,\beta$ -unsaturated carbonyl compound with an alkyl group is also an important synthetic reaction. Although β-alkyl enones are known to be prepared by the reaction of  $\beta$ -bromo enones and alkyl cuprates,<sup>6</sup> or the reaction of  $\beta$ -alkoxy enones and alkyllithium or Grignard reagents,7 the mild introduction of leaving groups at the  $\beta$ -position of enones is not easy. Therefore, a method for the efficient preparation of  $\beta$ -alkyl enones from simple enones is strongly needed.

Several methods for substitution of the  $\beta$ -vinylic hydrogen of enones with an alkyl group, by longer than single-step procedures have been reported:<sup>8</sup> for example, Reich *et al.* have reported<sup>9</sup> substitution by (i) conjugate addition of alkyl cuprates to enones, followed by reaction of the formed enolates with phenylselenyl bromide, and (ii) oxidation of the isolated  $\alpha$ -phenylselenyl ketones

and successive elimination of PhSeOH. Recently, Nicolaou *et al.* have reported<sup>10</sup> a new method by (i) conjugate addition of an alkyl cuprate, followed by the trapping of the enolate with chloro-trimethylsilane, and (ii) the reaction of the formed trimethylsilyl enol ether with IBX (*o*-iodoxybenzoic acid). Snider *et al.* have reported a direct method whereby the  $\beta$ -vinylic hydrogens of enones were substituted with alkyl groups by using alkenes and EtAlCl<sub>2</sub>, but applicable alkenes were limited to trisubstituted ones.<sup>11</sup>

In 2000, we introduced N-tert-butylbenzenesulfinimidoyl chloride (1) as a new and variable oxidation (dehydrogenation) reagent for organic synthesis,12 and various oxidation reactions such as oxidation of alcohols,13 amines,14 and hydroxylamines15 were investigated. Among the 1-mediated oxidations, dehydrogenation of carbonyl compounds to the corresponding  $\alpha,\beta$ -unsaturated compounds is notable because it proceeds under rather mild conditions (-78 °C) and in a one-pot manner:<sup>16</sup> that is, it is carried out by the reaction of 1 and lithium enolates generated from carbonyl compounds with LDA. This unique dehydrogenation has recently been utilized by other research groups for the steps that are difficult to accomplish by conventional methods in the total synthesis of natural products.<sup>17</sup> Because lithium enolates have been found to react with 1, and elimination takes place under very mild conditions, we have hypothesized that enolate species formed by conjugate addition of alkyl cuprates to enones would also react with 1 to afford  $\beta$ -alkyl enones in a one-pot manner (Scheme 1). We would like to describe here a new method for direct  $\beta$ -substitution of enones with alkyl groups based on the above-mentioned concept.

We first tried to substitute the  $\beta$ -vinylic hydrogen of 2-cyclohexen-1-one (2) with a methyl group as a model reaction (Table 1). When 1.1 equivalents of Me<sub>2</sub>CuCNLi<sub>2</sub> were added to 2 at -78 °C in diethyl ether, and then 1.1 equivalents of 1 were added at the same temperature, the desired product,



Scheme 1 A concept for one-pot substitution of the  $\beta$ -vinylic hydrogen of enones with an alkyl group by using alkyl cuprate and 1.

<sup>†</sup> Electronic supplementary information (ESI) available: experimental procedures and characterization data for all new compounds. See http:// www.rsc.org/suppdata/cc/b5/b502134k/ \*matuo@lisci.kitasato-u.ac.jp

Table 1 One-pot  $\beta$ -substitution of 2-cyclohexen-1-one (2) with a methyl group to give 3-methyl-2-cyclohexen-1-one (3a)



Entry	"Me–Cu"	1 (equiv.)	Yield $(\%)^a$
1	Me <sub>2</sub> CuCNLi <sub>2</sub>	1.1	32
2	Me <sub>2</sub> CuCNLi <sub>2</sub>	2.2	62
3	Me <sub>2</sub> CuCNLi <sub>2</sub>	3.0	88
4	Me <sub>2</sub> CuLi	3.0	27
5	Me(2-Th)CuCNLi <sub>2</sub>	1.5	31
6	Me(2-Th)CuCNLi <sub>2</sub>	3.0	55
7	Me(Imid)CuCNLi <sub>2</sub>	1.5	7
8	Me(Imid)CuCNLi <sub>2</sub>	3.0	1
<sup>a</sup> Determ	ined by GC-analysis using	an internal stan	dard.

3-methyl-2-cyclohexen-1-one (**3a**), was obtained in 32% yield (Entry 1). After screening various reaction conditions, it was found that the yield of **3a** was greatly improved by increasing the amount of **1** employed: the use of 2.2 and 3.0 equivalents of **1** gave the desired product **3a** in 62 and 88% yields, respectively (Entries 2 and 3). In contrast, the use of a Gilman reagent (Me<sub>2</sub>CuLi), which was prepared from 2 equivalents of MeLi and CuI, gave **3a** in a low yield, even when 3 equivalents of **1** were used (Entry 4). It was thought that the lithium iodide generated in the preparation of the Gilman reagent would influence the reaction of **1** (*vide infra*). Also, higher-order cyanocuprates having dummy ligands such as 2-lithiothiophene<sup>18</sup> or *N*-lithioimidazole<sup>19</sup> gave insufficient yields of **3a** (Entries 5–8).

Next, the scope and limitations of 1-mediated  $\beta$ -substitution of enones with alkyl groups were investigated by using 1.1 equivalents of higher-order dialkyl cyanocuprates and 3 equivalents of 1 in diethyl ether (Table 2). In addition to a methyl group, *n*-butyl, sec-butyl, and even tert-butyl groups were smoothly introduced to the  $\beta$ -position of **2** or 4-phenyl-2-cyclohexen-1-one (4), and the corresponding enones were obtained in high yields (Entries 1-3, 7-10). When 4 was used as a substrate, the cuprate addition was carried out at -23 °C, but an elimination step after the addition of 1 proceeded at -78 °C within a few minutes to afford  $\beta$ -alkyl enones in high yields after isolation by silica gel column chromatography (Entries 7-10). A phenyl and a trimethylsilylmethyl group were also introduced in 80 and 46-41% isolated yields, respectively (Entries 6, 4, and 11), by preparing a cyanocuprate using commercially available phenyllithium or trimethylsilylmethyllithium.

In order to introduce various alkyl groups, we tried to use alkyl halides as a source of alkyl groups. When higher-order cyanocuprate was prepared from CuCN and 2-phenylethyllithium, which was formed from 2-phenylethyl iodide and 2 equivalents of *tert*-butyllithium, the desired enone having a phenylethyl group at the  $\beta$ -position was isolated in only 34% yield (Entry 5). It was assumed that lithium iodide, formed in the lithiation of the alkyl iodide with *tert*-butyllithium, produced an unfavorable effect in the reaction of the enolate with 1. Then, cyclopropyllithium generated

Table 2 One-pot  $\beta\mbox{-substitution}$  of enones with alkyl and phenyl groups





<sup>*a*</sup> Isolated yield unless noted otherwise. <sup>*b*</sup> Determined by GC-analysis using an internal standard. <sup>*c*</sup> The cuprate addition was carried out at  $-78 \sim -50$  °C. <sup>*d*</sup> The cuprate addition was carried out at -23 °C. <sup>*e*</sup> 2.2 equiv. of cuprate were employed. <sup>*f*</sup> THF was used as solvent. <sup>*g*</sup> Two diastereomers were formed (dr = 41:59). <sup>*h*</sup> E/Z = 1:1.

from cyclopropyl bromide<sup>20</sup> was employed for the preparation of a cyanocuprate, and it was found that the desired reaction proceeded smoothly to give  $\beta$ -cyclopropyl enone in 84% isolated yield (Entry 12). These results suggested that cyanocuprates for the present  $\beta$ -substitution of enones should be prepared from alkyl chlorides or bromides.

In addition to six-membered enones (2 and 4), cyclopentenone (6), cycloheptenone (8), and non-cyclic enones were effectively employed in the 1-mediated  $\beta$ -substitution with alkyl groups (Entries 13–17). In the case of vinyl ketone 10 (Entries 16 and 17), many by-products were detected that were primarily formed in the conjugate addition step.  $\beta$ -Substitution of *N*-crotonoyl-2-oxazolidinone (12) with the butyl group also gave the desired product 13 [as separable (*E*),(*Z*)-isomers, *E*/*Z* = 1:1] in 67% combined yield (Entry 18). It was noted that the regioselectivity of the reaction of 1 was controlled, and the elimination step proceeded at -78 °C in all cases.

Thus, a new method for the one-pot substitution of vinylic hydrogen of enones was established<sup>‡</sup> by using higher-order dialkyl cyanocuprates and **1**. The present method can be regarded as an alternative to Heck-type alkylation,<sup>4,5</sup> and can be employed for synthesizing a variety of  $\beta$ -alkyl enones under mild conditions.§

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## Notes and references

‡ Typical experimental procedure (Table 2, Entry 10) is as follows: to a stirred solution of CuCN (29.9 mg, 0.33 mmol) in dry ether (2 mL) was added a solution of methyllithium in diethyl ether (0.98 N, 0.63 mL, 0.62 mmol) at -78 °C, and the mixture was stirred for 10 min at 0 °C. Then, a solution of 4 (49.6 mg, 0.28 mmol) in ether (1.5 mL) was added at -78 °C, and the reaction mixture was stirred for 20 min at -23 °C. During this period, the bright yellow color of the mixture faded out. Next, a solution of 1 (183 mg, 0.85 mmol) in ether (1 mL) was added at -78 °C, and the mixture was stirred for 30 min. The reaction was quenched by adding 10% NH<sub>4</sub>OH in saturated NH<sub>4</sub>Cl (5 mL) at -78 °C, and the resulting mixture was extracted with ether three times. The combined extracts were washed with water and brine, dried over anhydrous Na2SO4, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes-ether) to afford 3-methyl-4-phenyl-2cyclohexen-1-one (5d) (48.8 mg, 0.26 mmol, 94%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.35–7.15 (m, 5H), 6.09 (s, 1H), 3.57 (t, J = 4.6 Hz, 1H), 2.40–2.25 (m 3H), 2.10–2.00 (m, 1H), 1.81 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): & 199.4, 162.5, 140.5, 128.7, 128.4, 128.0, 127.0, 46.4, 33.9, 31.4, 23.4.

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