

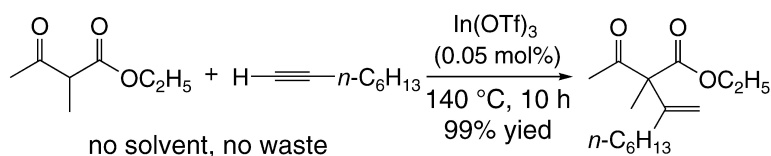
Communication

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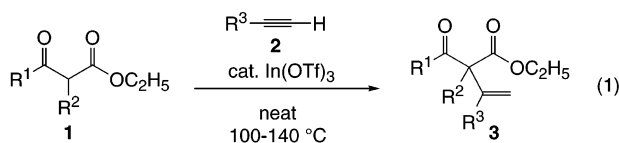
## Indium-Catalyzed Addition of Active Methylene Compounds to 1-Alkynes

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It is generally accepted that an enolate anion does not undergo intermolecular addition to a nonactivated C–C multiple bond,<sup>1</sup> except for certain limited cases.<sup>2</sup> We recently challenged this conventional wisdom and reported that zinc enolate species derived from ester, amide, hydrazone, and imine undergo addition to ethylene and other olefins in high yield.<sup>3</sup> The reaction is useful also for enantioselective synthesis of  $\alpha$ -substituted ketones.<sup>3a</sup> We report herein the result of our second challenge—the addition of enolate species to unactivated alkynes (eq 1).



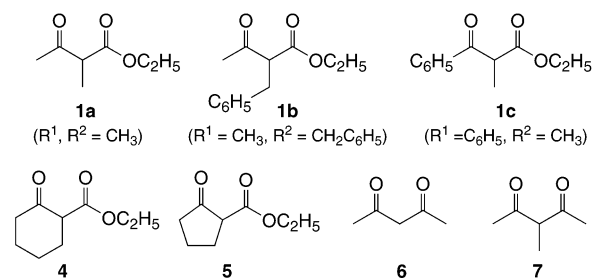
We found that heating of a neat mixture of nearly stoichiometric amounts of an active methylene compound and a terminal alkyne at 100–140 °C in the presence of a catalytic amount of In(OTf)<sub>3</sub> gives the desired  $\alpha$ -alkenylated carbonyl compound in a high to excellent yield. The reaction possesses several synthetically attractive features: (1) simple procedure allowing large-scale preparation, (2) high catalytic efficiency (turnover number up to 2000), (3) high yield, (4) perfect regioselectivity, (5) no requirement of solvent, and (6) the ability to create densely functionalized molecules in a single step without loss of any atoms in the starting materials. These features make the new reaction particularly attractive among a few other related reactions of similar nature reported in the literature.<sup>4</sup>

The following example illustrates the effectiveness of the process. A mixture of ethyl 3-oxo-2-methylbutanoate **1a** (14.5 g, 0.10 mol), phenylacetylene **2a** (R<sup>3</sup> = C<sub>6</sub>H<sub>5</sub>) (12.3 g, 0.12 mol), and In(OTf)<sub>3</sub> (28.1 mg, 0.05 mol %) was heated under nitrogen at 140 °C for 10 h. Distillation at 120 °C (6.7 Pa) gave the desired product, ethyl 2-acetyl-2-methyl-3-phenyl-3-butenolate **3** (R<sup>1</sup>, R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = C<sub>6</sub>H<sub>5</sub>) as a single product (21.7 g, 92% yield; 99% yield on a 4-mmol scale with a chromatographic purification, Table 1, entry 1). In(OTf)<sub>3</sub> was found to be the best catalyst after screening of a number of metal triflates.<sup>5</sup> While the reaction is best carried out in the absence of solvent, the mixture may be diluted with a solvent such as toluene at the expense of the reaction rate.

The generality of the reaction is illustrated with the results in Table 1. The yield is essentially quantitative both for the active methylene compound and for the alkyne, and the regioselectivity was always 100% favoring the introduction of the carbonyl compound to the internal alkynic carbon atom. The use of excess alkyne is beneficial when it is volatile, unreactive, or unstable under the reaction conditions. Internal alkynes are inert for the coupling reactions under the present reaction conditions. Despite the high reaction temperature, no side products were formed due to decarbonylation or self-condensation of the active methylene compounds.

<sup>†</sup> PRESTO, Japan Science and Technology Corporation (JST).

### Chart 1. Active Methylene Compounds Examined

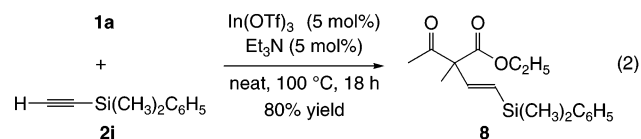


Comparison among phenyl acetylene derivatives for the reaction with 3-oxo-2-methylbutanoate (entries 1–4) indicated that phenylacetylene **2a** is less reactive than **2b** (R<sup>3</sup> = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>), and more reactive than **2c** (R<sup>3</sup> = 4-CH<sub>3</sub>OCOC<sub>6</sub>H<sub>4</sub>) and **2d** (R<sup>3</sup> = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>): The reaction becomes faster, but the yield becomes lower (entries 2–4) as the alkyne becomes more electron-rich. The lower yield with the more reactive alkyne is due to the formation of high-molecular weight side product. The reaction is, however, entirely free of such side products for the less reactive substrates.

The reaction with aliphatic alkynes also proceeded in high yield (entries 5–7). As shown in entries 6 and 7, 1-alkynes bearing a nearby oxygen functionality (i.e., **2e** and **2f**) also take part in the reaction, while the propargyl ether substrate in entry 7 was rather unstable under the reaction conditions. The addition to a conjugated enyne compound **2h** took place exclusively at the triple bond in 1,2-fashion to give the corresponding diene product in 94% yield (entry 8).

The reaction tolerates a wide range of structural variations of the active methylene compound. The  $\beta$ -ketoester can bear a benzoyl group or can be a part of a ring structure (entries 9–13). We can also use  $\beta$ -diketones, while they are slightly less reactive than  $\beta$ -ketoester and need a small modification of the reaction conditions. Thus, acetylacetone and 3-methyl-2,4-pentanedione react with an excess alkyne to give the desired compounds in high yield in the presence of an equimolar mixture of 2.5 mol % In(OTf)<sub>3</sub>, Et<sub>3</sub>N, and *n*-BuLi.<sup>6</sup> In contrast, acetylacetone reacts with an alkyne to give cleanly the  $\alpha$ -alkenylation product and give the product 100% in its enol form (entry 13).<sup>7</sup>

All reactions shown above proceeded with perfect regioselectivity to form the new C–C bond at the C<sup>2</sup> position of the 1-alkyne. On the other hand, a silyl acetylene **2i** [R<sup>3</sup> = Si(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>5</sub>] undergoes the coupling reaction with completely reversed regioselectivity (eq 2). The adduct **8** has a trans olefinic double bond, indicating that the *cis* addition took place.

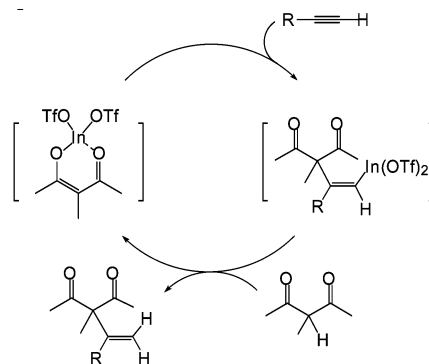


**Table 1.** In(OTf)<sub>3</sub>-Catalyzed Alkenylation of Active Methylene Compounds with 1-Alkynes<sup>a,b</sup>

entry	carbonyl compd	1-alkyne: R <sup>3</sup> CCH (equiv)	yield (%)	product
1	<b>1a</b>	C <sub>6</sub> H <sub>5</sub> CCH: <b>2a</b> (1.2)	99	
2	<b>1a</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CCH: <b>2b</b> (1.2)	76	
3	<b>1a</b>	4-(CH <sub>3</sub> OCO)C <sub>6</sub> H <sub>4</sub> CCH: <b>2c</b> (1.2)	97	
4	<b>1a</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CCH: <b>2d</b> (1.2)	92	
5	<b>1a</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub> CCH: <b>2e</b> (2.0)	99	
6	<b>1a</b>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>4</sub> CCH: <b>2f</b> (2.0)	94	
7	<b>1a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OCH <sub>2</sub> CCH: <b>2g</b> (3.0)	80	
8	<b>1a</b>	-CCH: <b>2h</b> (5.0)	94	
9	<b>1b</b>	<b>2f</b> (2.0)	95	
10	<b>1c</b>	<b>2f</b> (2.0)	88	
11	<b>4</b>	<b>2a</b> (1.2)	92	
12	<b>5</b>	<b>2a</b> (1.2)	94	
13	<b>6</b>	<b>2a</b> (5.0)	97	
14	<b>7</b>	<b>2a</b> (5.0)	88	

<sup>a</sup> The reaction was carried out with 0.05–5 mol % of In(OTf)<sub>3</sub> at 60–140 °C for 4–18 h. See Supporting Information for details. <sup>b</sup> The alkenylation reaction can also be performed at 40–50 °C by use of 10 mol % catalyst.

On the basis of the regio- and stereoselectivity of the reaction, we propose the following catalytic mechanism (see also Figure 1): An indium enolate, generated by the reaction between In(OTf)<sub>3</sub> and  $\beta$ -dicarbonyl compound<sup>8</sup> adds across the triple bond of 1-alkyne, and the resulting alkenyl indium is protonated by the  $\beta$ -dicarbonyl compound to regenerate the indium enolate. The higher reactivity of electron-rich alkynes suggests that coordination of the indium atom to the alkyne is important in this carbometalation process. The observed regioselectivity of the addition follows the general rule of carbometalation of alkynes and alkenes, the origin

**Figure 1.** A mechanistic rationale for the catalytic alkenylation.

of which we elucidated some time ago.<sup>9</sup> We expect that the new reaction described above will further expand the utilities of active methylene compounds that have already been amply demonstrated by numerous previous reports.

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**Supporting Information Available:** Details of the experimental procedure, characterization, and physical data of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- Reviews: (a) Fallis, A. G.; Forgiione, P. *Tetrahedron* **2001**, *57*, 5899–5913. (b) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071–1087. (c) Marek, I.; Normant, J. F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Ed; WILEY-VCH: Weinheim, 1998; pp 271–337.
- To alkenes: (a) Rodriguez, A.-L.; Bunlaksananusorn, T.; Knochel, P. *Org. Lett.* **2000**, *2*, 3285–3287. To alkynes: (b) Koradin, C.; Rodriguez, A.-L.; Knochel, P. *Synlett* **2000**, 1452–1454. (c) Bertrand, M. T.; Courtois, G.; Miginiac, L. *Tetrahedron Lett.* **1975**, *36*, 3147–3150. (d) Bertrand, M. T.; Courtois, G.; Miginiac, L. *Tetrahedron Lett.* **1974**, *23*, 1945–1948. (e) Schulte, K. E.; Rucker, G.; Feldkamp, J. *Chem. Ber.* **1972**, *105*, 24–33.
- (a) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362–6363. (b) Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505–1507. (c) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457–5458. (d) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491–2493. (e) Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099–7102.
- (a) Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970–973. (b) Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789–790. (c) Badanyan, Sh. O.; Chobanyan, Zh. A.; Tirakyan, M. R.; Danielyan, A. O. *Russ. J. Org. Chem.* **1997**, *33*, 17–20 and references therein.
- Zinc, copper, and lanthanoid triflate did not promote the coupling reaction under the same reaction conditions.
- The role of Et<sub>3</sub>N and *n*-BuLi is unknown at this time. A large amount of uncharacterized side products formed without the bases.
- The In-catalyzed coupling reaction between ethyl 3-oxobutanoate **1** (R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H) and an alkyne gave the corresponding  $\alpha$ -alkylidene compound due to transposition of the double bond after the C–C bond formation.
- The alkyne substrates act as the trapping agent for TfOH and gives, upon hydrolysis, a corresponding ketone, such as acetophenone.
- (a) Nakamura, E.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686–6692. (b) Nakamura, M.; Inoue, T.; Sato, A.; Nakamura, E. *Org. Lett.* **2000**, *2*, 2193–2196.

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