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Indium-Catalyzed 2-Alkenylation of 1,3-Dicarbonyl Compounds with Unactivated Alkynes

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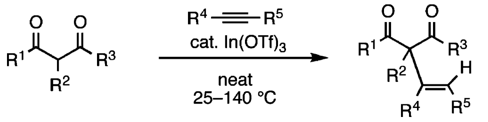
Abstract: 1,3-Dicarbonyl compounds add to unactivated alkynes in the presence of a catalytic amount of indium(III) trifluoromethanesulfonate in high to excellent yield to give 2-alkenylated 1,3-dicarbonyl compounds with exclusive regioselectivity as to the position of C−C bond formation on the acetylene moiety. In most of the cases, the reaction requires less than 1-mol % loading of the catalyst and does not require solvent. The reaction tolerates a wide variety of functional groups including ester, ether, allylic halide, furan, thiophene, and protected amine. Experimental and theoretical studies suggested that the reaction proceeds via a concerted carbometalation reaction of an indium(III) enolate with the acetylene, where indium−acetylene interaction is important.

Introduction

Aldol addition to a carbonyl compound, Michael addition to an unsaturated carbonyl compound, and alkylation with an alkyl halide are the three major categories of C−C bond formation reactions of metal enolates. What has remained unexplored[1] is the addition of a metal enolate to an unactivated olefin and acetylene.[2] It has been widely considered that an enolate anion is entirely unreactive to an unactivated alkene, because of well established thermodynamic and kinetic reasons: Among those issues, major concerns are the unfavorable thermodynamics of the formation of a carbanion from a stable enolate anion and the high-lying LUMO of an unactivated alkene. We reported sometime ago that zinc(II) enolates or enamides add to unactivated olefins in high yield with remarkable facility.[3] The use of the soft zinc countercation expedites the addition through favorable interaction between the π-orbital of the olefin and the aza-allyic π-orbital of the enolate and also stabilizes the carbanionic product through formation of a chelate organozinc compound.[3c] While our effort to utilize the zinc chemistry for catalytic addition to alkenes has so far met with little success, we found that zinc and indium enolates do add to an unactivated alkyne in a catalytic manner.[4] We report herein an indium catalyzed addition of a 1,3-dicarbonyl compound to a terminal alkyne that provides us with an efficient synthetic route to 2-alkenyl-1,3-dicarbonyl compounds (eq 1).[5,6] The reaction possesses several synthetically attractive features: (1) simple procedure allowing large scale reactions, (2) high catalytic efficiency, (3) high yield, (4) high regioselectivity, (5) no requirement of solvent, (6) good chemoselectivity, and (7) high atom economy. These features make the new reaction particularly attractive among a few other related reactions of similar nature reported recently (e.g., catalysis using rhenium,[5a] palladium,[7] gold,[8] and potassium[9]).



(1)

[†] Present address: International Research Center for Elements Science, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan.

[‡] ERATO, Japan Science and Technology Agency.

(1) 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.

(2) Reviews: (a) Fallis, A. G.; Forgione, 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., Eds.; WILEY-VCH: Weinheim, 1998; pp 271−337.

(3) (a) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 14344−14345. (b) Nakamura, M.; Hatakeyama, T.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 11820−11825. (c) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362−6363. (d) Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org, Lett.* **1999**, *1*, 1505−1507. (e) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157−2158. (f) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5458. (g) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493. (h) Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099−7102.

(4) Preliminary report: Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002−13003.

(5) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823−4825. (b) Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970−973. (c) Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789−790. (d) Badanyan, Sh. O.; Chobanyan, Zh. A.; Tirakyan, M. R.; Danielyan, A. O. *Russ. J. Org. Chem.* **1997**, *33*, 17−20 and references cited therein.

(6) The alkenyl halide reagents are generally inert to an S_N2 substitution reaction. For the coupling reaction of alkenyl halide reagents and metal enolates, see: (a) Pei, L.; Qian, W. *Synlett* **2006**, *11*, 1719−1723. (b) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897−1900. Recently, vinylic substitution reaction via 1,4-addition was reported; see: (c) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensene, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551−6554.

(7) Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2004**, 660−661.

(8) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884−6885.

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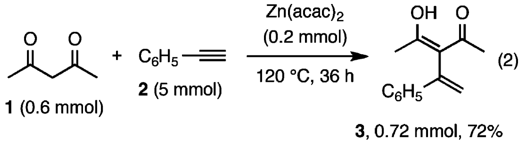
Table 1. Counteranion Effect on Catalytic Activity of Zinc Catalysts[a]

entry	catalyst (20 mol %)	% yield[b,c]
1	Et_2Zn	27
2	$ZnCl_2/Et_3N$	3
3	ZnI_2/Et_3N	10
4	$Zn(OTf)_2/Et_3N$	76[d]

[a] The reaction of acetylacetone **1** and phenylacetylene **2** (5.0 equiv) in the presence of catalyst was carried out at 100 °C for 16 h in a sealed tube. [b]The yield was determined by ^{1}H NMR using bromoform as an internal standard. [c]The regioselectivity was >99:1. [d]Isolated yield.

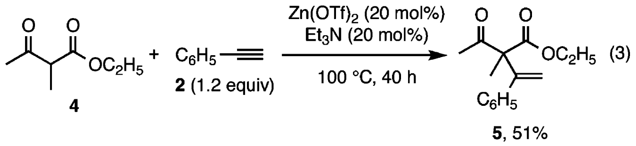
Results and Discussion

In analogy with the stoichiometric reaction of zinc enamides with alkenes, we initially examined a zinc(II)-catalyzed reaction of acetylacetone **1** and phenylacetylene **2**. For instance, the reaction starting from 0.6 mmol of acetylacetone **1** was catalyzed by 20 mol % of $Zn(acac)_2$ to give 0.72 mmol of **3** (eq 2). The product stoichiometry indicated that the zinc acetylacetonate catalyst took part in the addition reaction. Optimization of the reaction was carried out briefly as summarized in Table 1. The reaction in the presence of 20 mol % of diethylzinc gave the desired product **3** in 27% yield (entry 1). Among several zinc(II) salts, zinc(II) trifluoromethanesulfonate, $Zn(OTf)_2$, combined with triethylamine (Et_3N)[10] showed the highest catalytic activity to furnish **3** in 76% yield (entry 4). $Zn(OTf)_2$ was manipulated quickly under air atmosphere and dried in the reaction vessel.



1 (0.6 mmol) + **2** (5 mmol) → **3**, 0.72 mmol, 72% (2)

The $Zn(OTf)_2/Et_3N$-catalyzed reaction was found to be powerful enough to create a quaternary carbon center by the reaction with less reactive β-ketoesters. Thus, the reaction of ethyl 2-methyl-3-oxobutanoate **4** catalyzed by 20 mol % $Zn(OTf)_2/Et_3N$ at 100 °C proceeded smoothly to generate an α-alkenylated diketone **5** (eq 3).[11]



4 + **2** (1.2 equiv) → **5**, 51% (3)

After further experimentation, however, we felt it necessary to find metal countercations more powerful than zinc and examined the reaction of ethyl 2-methyl-3-oxobutanoate **4** and phenylacetylene **2** (1.2 equiv), which was carried out in the presence of 0.5 mol % of a metal triflate at 100 °C for 3 h. Among triflates of Cu(I), Cu(II), Mg(II), Zn(II), Hg(II), Sc(III), La(III), Nd(III), Dy(III), Ho(III), Yb(III), Lu(III), Al(III), Ga(III), In(III), and others, only $Hg(OTf)_2$, $Ga(OTf)_3$, and $In(OTf)_3$ gave the desired product **3** in 3%, 14%, and 100% yields, respectively. The reaction in the presence of $Hg(OTf)_2$ gave a small amount of **5** accompanied by rapid decomposition of phenylacetylene.[12] Many of the corresponding metal chlorides were entirely ineffective. It is interesting to note that $In(OTf)_3$ did not require any base while $Zn(OTf)_2$ was ineffective in the absence of amine such as Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[13] TfOH (0.5 mol %) did not catalyze the addition at all.

Table 2. Counteranion Effect of Indium(III) Salt in the Reaction between **4** and **2**[a]

entry	InX_3 (5 mol %)	additive	time (h)	% yield[b]
1	$InCl_3$			no reaction
2	$InCl_3$	AgOTf	12	80
3		AgOTf	12	6
4	$InCl_3$	$AgSbF_6$	12	38
5	$In(OTf)_3$		12	100
6	$In(NTf_2)_3$		6	100

[a] The reaction (1.2 equiv of **2**) was carried out in the presence of 5 mol % InX_3 and 15 mol % additive in a sealed tube at 40 °C for the time indicated. [b]The yield was determined by ^{1}H NMR using bromoform as an internal standard.

Counterion effect of the indium catalysis was examined in some details (Table 2). The reaction between **4** and **2** in the presence of an indium salt and an additive at 40 °C showed an interesting trend. $InCl_3$ (5 mol %) was entirely ineffective (entry 1)[14] but could be activated by addition of 15 mol % of AgOTf (entry 2). The mixture of $InCl_3$ and AgOTf produced a precipitate of AgCl and probably produced an indium triflate. AgOTf itself was far less active (entry 3). A mixture of 5 mol % of $InCl_3$ and 15 mol % of $AgSbF_6$ that may produce an indium hexafluoroantimonate showed moderate catalytic activity (entry 4). $In(OTf)_3$ was a very good catalyst (entry 5), and indium(III) tris[bis(trifluoromethanesulfonyl)amide], $In(NTf_2)_3$, was even better (entry 6). The latter reagent however is more costly than the former and is not a preferred catalyst in the cases where the former is effective.

The $In(OTf)_3$-catalyzed reaction was found to be facile and versatile, taking place with as little as 0.05 mol % of the catalyst with no necessity of solvent. Table 3 summarizes the results of the first set of experiments carried out on a combination of ethyl 2-methyl-3-oxobutanoate **4** and functionalized phenylacetylene derivatives (carried out on a 0.2−4.0-mmol scale). The regioselectivity of the reaction was always such that C−C bond formation takes place next to the benzene ring. The product **5** was obtained in 99% isolated yield upon simple heating of near stoichiometric amounts of **4** and **2** in the presence of 0.05 mol % $In(OTf)_3$ at 140 °C for 90 min (entry 1). The reaction was

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(9) Rodriguez, A. L.; Bunlallsananusorn, T.; Knochel, P. *Org. Lett.* **2000**, *2*, 3285−3287.

(10) (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245−11246. (b) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381. (c) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (d) Anad, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (e) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606.

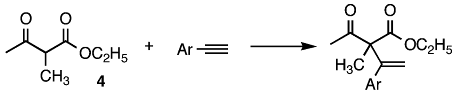
(11) The reaction of ethyl 3-oxobutanoate and phenylacetylene in the presence of catalytic or stoichiometric amounts of $Zn(OTf)_2$ and Et_3N gave a mixture of products as an α,β-unsaturated form and a β,γ-unsaturated form; see; Nakamura, M.; Fujimoto, T.; Endo, K.; Nakamura, E. *Org. Lett.* **2004**, *6*, 4837−4840.

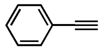
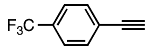
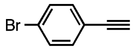
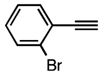
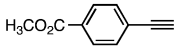
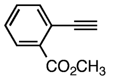
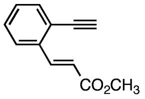
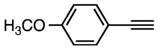
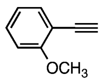
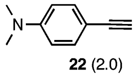
(12) (a) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611. (b) Nishizawa, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563−4565. (c) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681. (d) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453.

(13) $Zn(OTf)_2$ and $Al(OTf)_3$ showed the catalytic activity in the presence of 1 equiv of amine base, such as DBU, to metal triflate to give the corresponding product in 7% and 5%, respectively. This is due to the assistance of the deprotonation reaction to generate the metal enolate intermediate.

(14) The high reaction temperature is required for the reaction in the presence of $InCl_3$; see: Zhang, J.; Blazecka, P. G.; Angell, P.; Lovdahl, M.; Curran, T. T. *Tetrahedron 61*, 7807−7813.

Table 3. Indium-Catalyzed Addition of **4** to Aromatic Alkynes[a]



entry	alkyne (equiv)	$In(OTf)_3$ (mol%) conditions	product (%)[b, c]
1	 **2** (1.2)	0.05 140 °C, 90 min	**5** (99, 95)
2	 **6** (1.2)	0.05 140 °C, 24 h	**7** (92)
3	 **8** (1.2)	0.05 140 °C, 20 h	**9** (97)
4	 **10** (2.0)	0.5 140 °C, 60 h	**11** (96)
5	 **12** (1.2)	0.05 140 °C, 18 h	**13** (97)
6	 **14** (3.0)	20 60 °C, 50 h	**15** (82)
7	 **16** (1.05)	0.5 160 °C, 12 h	**17** (85)
8	 **18** (2.0)	1.0 toluene, 100 °C, 2 h	**19** (98)
9	 **20** (2.0)	1.0 100 °C, 2 h	**21** (96)
10	 **22** (2.0)	1.0 100 °C	(–)

[a] The reaction was carried out in the presence of $In(OTf)_3$ in a sealed tube. No solvent was used except in entry 8, where toluene was used. [b]Isolated yield. [c]The regioselectivity was >99:1.

scaled up with equal ease to a 0.1-mol scale and afforded the product in 95% yield after vacuum distillation of the reaction mixture.

An electron-deficient acetylene, 1-ethynyl-4-trifluoromethylbenzene **6**, reacted more slowly and required 24 h for completion but still gave the desired product **7** in 92% yield (entry 2). 1-Bromo-4-ethynylbenzene **8** and 1-bromo-2-ethynylbenzene **10** participated in the reaction to give the corresponding product, and they are also slow reacting substrates: The reaction of the alkyne **8** required 20 h for completion in the presence of 0.05 mol % catalyst to give the product **9** in 97% yield (entry 3). The alkyne **10** was even less reactive requiring 0.5 mol % catalyst and 60 h to afford the product **11** in 96% yield (entry 4). We assume that the steric effect of the *o*-bromo group in **11** retarded the reaction.

Likewise, ester-bearing compounds **12** and **14** are not very reactive but still high-yielding. The reaction of 1-ethynyl-4-methoxycarbonylbenzene **12** provided the product **13** in 97% yield in the presence of 0.05 mol % catalyst at 140 °C (entry 5). Because of the thermal instability of 1-ethynyl-2-methoxycarbonylbenzene **14**, the reaction of **14** needed to be finished quickly under higher catalyst loading and at a lower reaction temperature (entry 6).

Intramolecular competition between the acetylene and the acrylic ester moiety in **16** resulted in an exclusive reaction on the acetylene to give the corresponding alkenylated product **17** in 85% yield (entry 7). This lack of reactivity toward the Michael accepter moiety indicates that the present addition reaction is not a simple nucleophilic addition reaction but rather an electrophilic reaction involving coordination of the indium metal to the acetylene π-bond.

The addition to 1-ethynyl-4-methoxybenzene **18** in toluene afforded the product **19** in 98% yield (entry 8). The reaction required a solvent (toluene), without which the reaction afforded a large amount of what appears to be the products of an intermolecular Friedel−Crafts reaction including the aromatic ring and the acetylene moiety.[15] The reaction of 1-ethynyl-2-methoxybenzene **20** was not complicated by this side reaction and afforded, without the use of the solvent, the product **21** in 97% yield (entry 9). A dimethylamino group entirely inhibited the reaction (entry 10), probably because of the coordination of the amino moiety to the In(III) atom.

Table 4 illustrates further examples of alkynes other than phenylacetylene derivatives, including functionalized alkynes, an enyne and a diyne. 1-Octyne **23** was less reactive than phenylacetylene but still gave the desired alkenylated product **24** in 99% isolated yield with the regioselectivity being the same as the one observed for phenylacetylenes (entry 1). An ether moiety can be tolerated as shown by the synthesis of **26** in 94% yield (entry 2). The reaction of a conjugated enyne **27** took place exclusively on the acetylene moiety in the presence of 2 mol % $In(OTf)_3$ at 60 °C to afford the diene **28** in 90% yield (entry 3). An amino group can be tolerated if it is protected for instance as a phthalimide as illustrated by the reaction of **29** that gave the desired product **30** in 90% yield (entry 4). Benzyl propargyl ether **31** was so labile under the reaction conditions that the product was not obtained at all (entry 5). However, the addition of 5 mol % Et_3N furnished the desired product **32** in 80% yield (entry 6).

Furan and thiophene are also acid sensitive and caused a problem as illustrated for ethynylfuran **33** (entry 7). The use of 1 mol % of DBU, however, improved the addition to give the desired product **34** in 79% yield (entry 8). Ethynylthiophene **35** gave the corresponding product **36** in 85% yield in the presence of $In(OTf)_3$ (entry 9), but the yield improved to 99% by the use of DBU (entry 10). 1,3-Decadiyne **37** was a rather sensitive substrate and gave the product **38** in 50% yield (entry 11), and the yield could not be improved by DBU (13% yield as in entry 12). In both reactions, the C−C bond formation took place with perfect selectivity on the internal carbon atom of the terminal acetylene moiety.

The vinylation reaction of ketoester **39** under an atmospheric pressure of acetylene gas **40** was not an easy reaction at first. Commercially available purified acetylene gas in the presence

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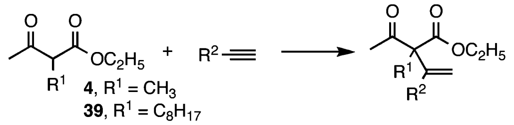
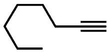
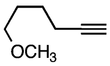
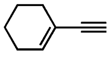
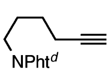
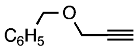
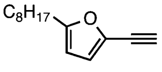
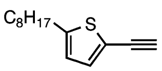
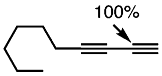
(15) (a) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573−1574. (b) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336−1340.

Table 4. Indium-Catalyzed Addition of Ketoesters **4** and **39** to a Variety of Alkynes[a]

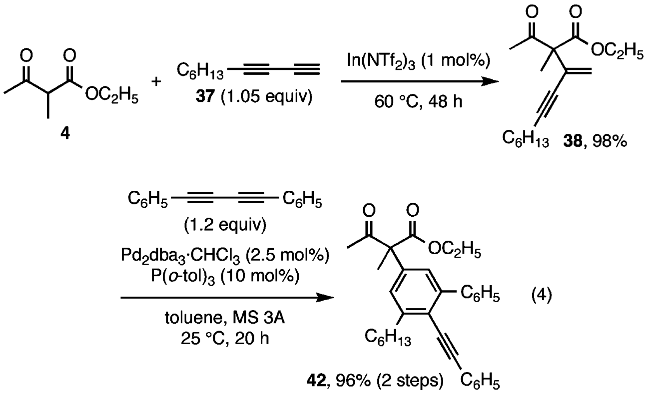


entry	alkyne (equiv)	catalyst (mol%) conditions	product (%)[b,c]
1	 **23** (2.0)	In(OTf)$_3$ (0.05) 140 °C, 10 h	**24** (99)
2	 **25** (2.0)	In(OTf)$_3$ (0.05) 140 °C, 16 h	**26** (94)
3	 **27** (5.0)	In(OTf)$_3$ (2.0) 60 °C, 4 h	**28** (94)
4	 **29** (1.05)	In(OTf)$_3$ (1.0) toluene, reflux, 20 h	**30** 90
5	 **31** (3.0)	In(OTf)$_3$ (5.0) 80 °C	**32** (–)
6		In(OTf)$_3$, Et$_3$N (5.0) 80 °C, 22 h	**32** (80)[e]
7	 **33** (2.0)	In(OTf)$_3$ (1.0) 60 °C, 1 h	**34** (10)
8		In(OTf)$_3$ DBU (1.0) 60 °C, 1 h	**34** (79)
9	 **35** (2.0)	In(OTf)$_3$ (1.0) 60 °C, 1 h	**36** (85)
10		In(OTf)$_3$, DBU (1.0) 60 °C, 1 h	**36** (99)
11[f]	 **37** (2.0)	In(OTf)$_3$ (5.0) 60 °C, 3 h	**38** (50)
12[f]		In(OTf)$_3$, DBU (5.0) 60 °C, 3 h	**38** (13)
13	$\mathrm{H{\equiv}H}$ (purified)[g]	In(OTf)$_3$ (20.0) 100 °C, 8 h	**41** (25)
14	**40** (1 atm)[i]	In(OTf)$_3$, DBU (20.0) 100 °C, 8 h	**41** (94)
15	$\mathrm{H{\equiv}H}$ (welding grade)[h]	In(OTf)$_3$, DBU (20.0) 100 °C, 8 h	**41** (15)
16	**40** (1 atm)[i]	In(OTf)$_3$ (20, 5), MS 3A[j] 100 °C, 8 (36) h	**41** (95)

[a] The reaction was carried out in the presence of In(OTf)$_3$ and additives in a sealed tube. Ketoester **4** was used in entries 1−12. Ketoester **39** was used in entries 13−16. [b]Isolated yield. [c]The regioselectivity was >99:1. [d]NPht = phthalamide. [e]A trace amount of a regioisomeric addition product was detected by ^{1}H NMR analysis. [f]The reaction that took place exclusively at the position indicated by an arrow was conducted in the dark because of the sensitivity of the product to light. [g]The commercially available dry acetylene gas was used. [h]The commercially available wet acetylene gas for welding use was used. [i]The reaction vessel was connected to a balloon filled with acetylene gas. [j]MS 3A was activated at 200 °C under 5 Pa for 4 h prior to use.

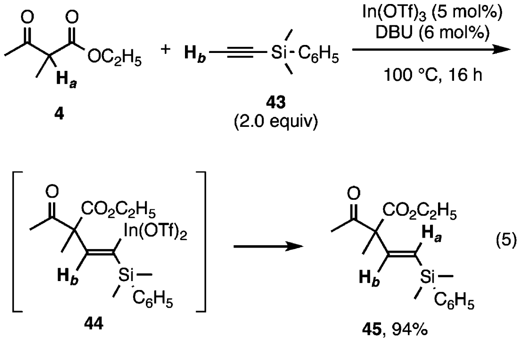
of 20 mol % In(OTf)$_3$ provided the desired product **41** in 25% yield and uncharacterized oligomeric products (entry 13). The combined catalyst system, 20 mol % In(OTf)$_3$/DBU, was effective when the purified acetylene gas **40** was used and gave the desired vinylated product **41** in 94% (entry 14). On the contrary, the welding grade acetylene gas **40**, which is much cheaper and safer than the purified one but contains water, acetone, etc., did not afford the product **41** even in the presence of DBU additive. Ester hydrolysis and decarboxylation posed problems (entry 15). We found molecular sieves much improved the reaction that then gave the desired product **41** in 95% yield (entry 16). The catalyst loading can be reduced to 5 mol % at the expense of the reaction rate. The details of the investigation have been described elsewhere.[16]

The In(OTf)$_3$/DBU catalytic system was inefficient for the reaction of 1,3-diynes, but In(NTf$_2$)$_3$ was found to be effective. The reaction of ethyl 2-methyl-3-oxobutanoate **4** and 1,3-decadiyne **37** (1.05 equiv) in the presence of 1 mol % In(NTf$_2$)$_3$ at 60 °C for 48 h furnished the corresponding product **38** in 98% yield with perfect regioselectivity (eq 4). The resultant conjugated enyne **38** can be used for the Pd(0)-catalyzed [4 + 2] benzannulation[17] to obtain the densely functionalized 2-arylketone **42** in 96% yield regioselectively in a single reaction vessel without purification. The details of this tandem reaction have been described elsewhere.[18]



(4)

The addition to a silylacetylene gave us information on the stereochemistry of the reaction. The addition of **1** to ethynyldimethylphenylsilane **43** in the presence of In(OTf)$_3$ (5 mol %) and DBU (6 mol %) gave the product **45** in 94% yield that bears a *trans*-olefinic double bond (eq 5).[19] The *trans* stereochemistry was deduced from the ^{1}H NMR coupling constant of $^3J_{ab}$ 19.6 Hz.[20] Assuming that the *geminal*-indium/silane bimetallic intermediate such as **44** is configurationally stable, we



(5)

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(16) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279−3281.

(17) (a) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391−6402. (b) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313−11314.

(18) Nakamura, M.; Endo, K.; Nakamura, E. *Adv. Synth. Catal.* **2005**, *347*, 1681−1686.

(19) DBU is essential. The reaction without DBU promotes the desilylation reaction to give a vinylated product.

could conclude that the addition took place in a *cis* manner. The observed regioselectivity of addition is then typical of a carbometalation reaction.[21]

Table 5 illustrates the diversity of 1,3-dicarbonyl compounds to be used for the reaction. The allyl ester **46** gave the desired vinylated compound (entries 1, 2, and 3), which can be used then for a decarboxylative α-allylation reaction.[22] The reaction of 2-benzyl substituted substrate **50** gave the product in good yield (entries 4, 5, and 6). The product from the 2-allyl substituted substrate **54** was too labile under the $In(OTf)_3$ conditions, but the presence of added Et_3N afforded the desired products **55** and **56** in high yield (entries 7, 8, and 9). The reaction of ethyl cyclopentanone-2-carboxylate **57** and phenylacetylene **2** in the presence of 1 mol % catalyst at 100 °C afforded the corresponding product **58** in 94% yield, but lower catalyst loading (0.05 mol %) and higher temperature (140 °C) lowered the yield to 72% (entries 10 and 11). 1-Octyne **23** gave a comparable result (entry 12). Ethyl cyclohexanone-2-carboxylate **60** and phenylacetylene **2** reacted in the presence of 2 mol % catalyst at 100 °C to give the corresponding adduct **61** in 83% yield (entry 13). The more stable enolate of benzoylacetate **62** and a tetralone derivative **66** gave the products **63**−**67** in excellent yields at the expense of reaction rate (entries 14−17). Overall, cyclic dicarbonyl compounds are less reactive than open chain compounds such as **4**.

Ethyl 2-fluoro-3-oxobutanoate **68** and ethyl 2-chloro-3-oxobutanoate **71** also took part in the addition reaction to phenylacetylene **2** and 1-octyne **23** in moderate to high yield under the $In(OTf)_3$ or $In(OTf)_3/Et_3N$ conditions (entries 18−23). We consider it noteworthy that the products bear a fluorine or a chlorine atom on a quaternary carbon center flanked by two carbonyl groups and one alkenyl group. These compounds are interesting for their chemical reactivities[23] and their potential biological activity.[24]

Diethyl methylmalonate **74** also added to alkynes in excellent yield (entries 24 and 25), although β-nitroketone, cyanoketone, cyanoester, phosphonylester, and sulfonylester were rather unreactive. 1,3-Diketones participate in the addition reaction as a pronucleophile. The reaction of 2,4-pentanedione **1** and phenylacetylene **2** proceeded in the presence of 5 mol % *n*-BuLi and Et_3N as additives to give the product **3** in excellent yield in its enol form. The use of *n*-BuLi and Et_3N suppressed byproduct formation.[25] The reaction of 3-methyl-2,4-pentanedione **77** gave the corresponding products **78** and **79** under the same reaction conditions in 88% and 77% yields, respectively (entries 28 and 29). The reaction without *n*-BuLi produced more byproducts and afforded the product only in 65% yield (entry 27). Similarly, 2-acetylcyclopentanone **80** and 2-acetylcyclohexanone **82** reacted with phenylacetylene **2** in the presence of *n*-BuLi to give the products **81** and **83** in high to excellent yields (entries 30 and 31). Although the exact roles of *n*-BuLi and Et_3N are unclear, the results indicate the necessity of an added base in the 1,3-diketone reactions. We might speculate that indium-catalyzed addition of the terminal alkyne to the carbonyl group has caused the byproduct formation.[26]

The experimental observations described above gave us some insights into the mechanism of the reaction, and we suggest the catalytic cycle shown in Figure 1. Thus, the reaction begins with the generation of an indium enolate by the reaction of the dicarbonyl compound with $In(OTf)_3$. This process produces TfOH, which is trapped by an alkyne to give a neutral alkenyl triflate. The addition reaction of the indium(III) enolate to the alkyne takes place via a concerted carbometalation pathway to afford an alkenyl indium(III) intermediate. Protonation of the alkenyl indium(III) intermediate by the starting dicarbonyl compound completes the catalytic cycle.

The first piece of mechanistic evidence is the following: The reaction requires a base that removes the acidic methylene or methyne proton in the starting 1,3-dicarbonyl compound. In some cases, Et_3N and *n*-BuLi deprotonate the substrate, and we found, in the phenylacetylene reaction, that the alkyne can accept the proton through formation of an acetylene−TfOH adduct, styryl triflate **85**, (Scheme 1). Thus, the reaction between **4** and **2** in the presence of $In(OTf)_3$ (20 mol %) at ambient temperature gave the adduct **5** in 98% yield and acetophenone **86** in 17% yield (85% based on one indium atom). It is known that trifluoromethanesulfonic acid reacts with phenylacetylene **2** to give styryl triflate **85** and that the latter hydrolytically decomposes to give acetophenone.[27] The ^{19}F NMR spectrum of the reaction mixture showed signals at 88.5, 87.3, and 85.3 ppm ($C_6F_6 = 0$ ppm as an internal standard in C_6D_6, 1:trace:9 integration ratio of signals), of which the 88.5 ppm signal is the one expected for **85** as compared with an authentic sample. The remaining two signals may well be due to some indium(III) enolate intermediates. We therefore surmise that an $In(OTf)_2$ enolate is a reactive species.

The second important observation is that alkyne is more reactive than an acrylic ester as revealed by the competitive experiment in entry 7, Table 3. This is a clear indication that the reaction is not a simple nucleophilic 1,2-addition but the reaction involves a metal−alkyne interaction as an important step. The

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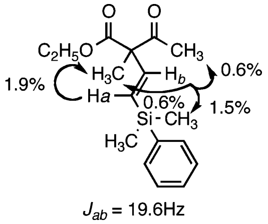
(20) The geometry of olefinic double bond was confirmed as *trans* by NOE experiments and the value of the coupling constant between H_a and H_b.



(21) The theoretical study of the regioselectivity of carbometalation reaction was reported: Nakamura, E.; Miyachi, Y.; Koga N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686−6692.

(22) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248−7251.

(23) For the cross coupling reaction of an α-chloroketone and an organozinc reagent, see: (a) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240−10241. For the Nozaki−Hiyama allylation using an allylhalide reagent, see: (b) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554−2555.

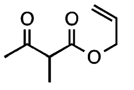
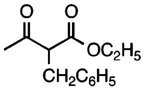
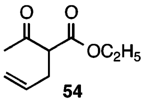
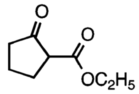
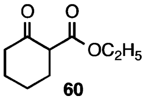
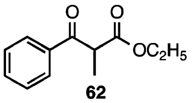
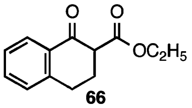
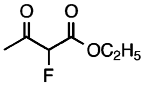
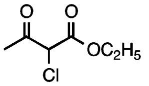
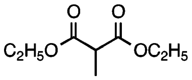
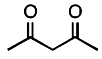
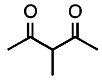
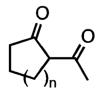
(24) (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) *Asymmmetric Fluoroorganic Chemistry; Synthesis, Application and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. For synthetic chemistry of α-fluorocarbonyl compounds, see: (c) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111−1153.

(25) The addition of *n*-BuLi decreased the generation of the major byproduct, 3,3-diphenylethynyl-2,4-pentandione. The addition of Et_3N decreased the generation of uncharacterized complex byproducts.

(26) (a) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760−13761. (b) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363−1366.

(27) (a) Stang, P. J.; Summerville, R. H. *J. Am. Chem. Soc.* **1969**, *91*, 4600−4601. (b) Summerville, R. H.; Senkler, C. A.; Schleyer, P. v. R.; Dueber, T. E.; Stang, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 1100−1110.

Table 5. Indium-Catalyzed Addition of Various 1,3-Dicarbonyl Compounds to Alkynes[a]

entry	dicarbonyl compound	R-C≡CH (eqiuiv)	$In(OTf)_3$ (mol%)	additives (mol%)	conditions	product (%)[b,c]
1	 **46**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 10 h	**47** (93)
2		**23,** R = C_6H_{13} (2.0)	0.1	–	140 °C, 20 h	**48** (86)
3		**25**, R = $(CH_2)_4OCH_3$ (2.0)	0.05	–	140 °C, 20 h	**49** (82)
4	 **50**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 60 h	**51** (93)
5		**23,** R = C_6H_{13} (2.0)	0.05	–	140 °C, 60 h	**52** (96)
6		**25**, R = $(CH_2)_4OCH_3$ (2.0)	0.1	–	140 °C, 60 h	**53** (95)
7	 **54**	**2**, R = C_6H_5 (3.0)	2.5	–	100 °C	**55** (–)
8		**2**, R = C_6H_5 (3.0)	2,5	Et_3N (2.5)	100 °C, 6 h	**55** (90)
9		**23**, R = C_6H_{13} (3.0)	5	Et_3N (5.0)	100 °C, 6 h	**56** (84)
10	 **57**	**2**, R = C_6H_5 (1.2)	1.0	–	100 °C, 5 h	**58** (94)
11		**2,** R = C_6H_5 (1.2)	0.05	–	140 °C, 10 h	**58** (72)
12		**23,** R = C_6H_{13} (1.2)	2.0	–	140 °C, 10 h	**59** (88)
13	 **60**	**23,** R = C_6H_5 (1.2)	2.0	–	100 °C, 8 h	**61** (83)
14	 **62**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C,64 h	**63** (91)
15		**23,** R = C_6H_{13} (2.0)	0.05	–	140 °C, 64 h	**64** (93)
16		**25**, R = $(CH_2)_4OCH_3$ (2.0)	0.1	–	140 °C, 36 h	**65** (88)
17	 **66**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 30 h	**67** (97)
18	 **68**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 4 h	**69** (89)
19		**23,** R = C_6H_{13} (1.2)	0.05	–	140 °C, 16 h	**70** (90)
20	 **71**	**2**, R = C_6H_5 (1.2)	1.0	–	100 °C, 4 h	**72** (93)
21		**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 2 h	**72** (61)
22		**23,** R = C_6H_{13} (1.2)	1.0	–	100 °C	**73** (–)
23		**23,** R = C_6H_{13} (1.2)	5.0	Et_3N (5.0)	100 °C, 2 h	**73** (77)
24	 **74**	**2**, R = C_6H_5 (1.2)	0.05	–	140 °C, 16 h	**75** (99)
25		**23,** R = C_6H_{13} (2.0)	0.05	–	140 °C, 16 h	**76** (98)
26	 **1**	**2**, R = C_6H_5 (5.0)	2.5	Et_3N (2.5) *n*-BuLi (2.5)	100 °C, 24 h	**3** (97)
27	 **77**	**2**, R = C_6H_5 (5.0)	5.0	Et_3N (5.0)	100 °C, 24 h	**78** (65)
28		**2**, R = C_6H_5 (5.0)	5.0	Et_3N (5.0) *n*-BuLi (5.0)	100 °C, 32 h	**78** (88)
29		**23**, R = C_6H_{13} (5.0)	5.0	Et_3N (5.0) *n*-BuLi (5.0)	100 °C, 32 h	**79** (77)
30	 **80**, **82**	**2**, R = C_6H_5 (5.0)	5.0	Et_3N (5.0) *n*-BuLi (5.0)	100 °C, 34 h	n = 1, **81** (99)
31		**2**, R = C_6H_5 (5.0)	5.0	Et_3N (5.0) *n*-BuLi (5.0)	100 °C, 17 h	n = 2, **83** (88)

[a] The reaction was carried out in the presence of $In(OTf)_3$ and additives in a sealed tube. [b]Isolated yield. [c]The regioselectivity was >99:1.

effectiveness of soft Lewis acids, indium(III) and zinc(II), supports this conjecture. Third, the addition reaction to a silylacetylene exhibits stereo- and regioselectivities typical for 1,2-carbometalation reactions (eq 5). The *cis*-selectivity was also proved through deuterium labeling experiments as described in the next paragraph.

The deuterium-labeled experiment was examined first as shown in eq 6. The reaction of ethyl 2-methyl-3-oxobutanoate

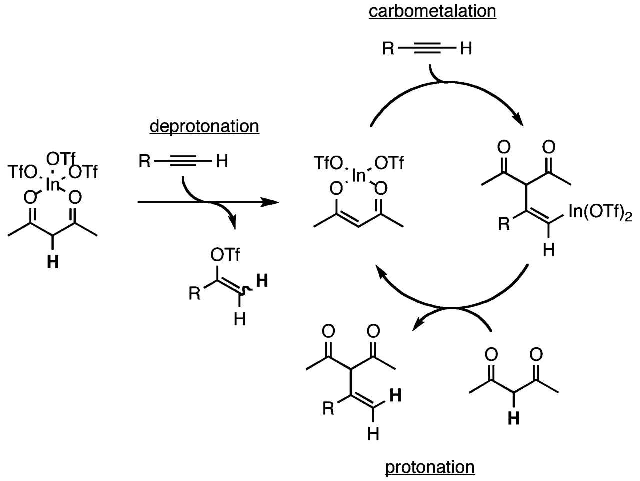
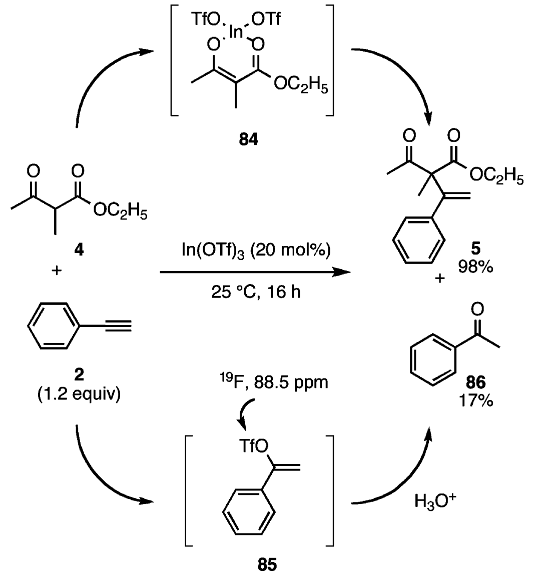
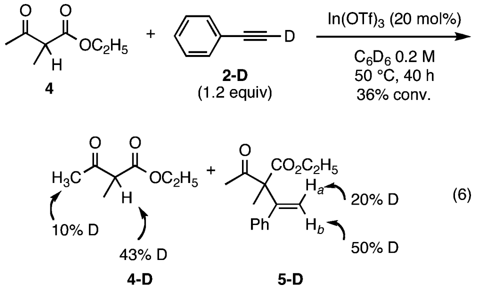


Figure 1. A plausible mechanism of indium-catalyzed addition reaction.

Scheme 1. Generation of acetophenone **86** via deprotonation reaction of ethyl 2-methyl-3-oxobutanoate **4**



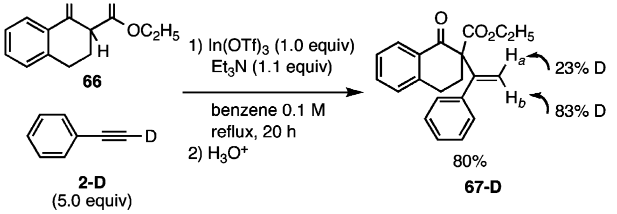
4 and 1-deuterio-2-phenylethyne **2-D** (1.2 equiv) was carried out in the presence of In(OTf)$_3$ (20 mol %) in C_6D_6 at 50 °C.



(6)

The reaction was monitored *in situ* by ^{1}H NMR. The product **5-D** was obtained with 20% deuterium incorporation at *cis*-position (H$_a$) and 50% deuterium incorporation at *trans*-position (H$_b$) in the product **5-D**. A considerable degree of H−D exchange between ethyl 2-methyl-3-oxobutanoate **4** and 1-deuterio-2-phenylethyne **2-D** also took place.

The reaction of the tetralone derivative **66** and **2-D** was also examined (eq 7). To speed up the reaction and suppress the H−D exchange between **66** and **2-D** as much as possible, we used a stoichiometric amount of In(OTf)$_3$ and Et$_3$N and obtained the product **67-D** with 83% deuterium incorporation at *trans*-position (H$_b$) together with 23% deuterium at the *cis*-position (H$_a$). We therefore conclude that the *cis*-carbometalation is likely the key step of the reaction.



(7)

The final evidence has come from theoretical analysis. We carried out density functional calculations to examine if it is indeed possible to add an indium enolate to acetylene. Thus, we obtained some transition state (TS) structures for a few simple model systems. These calculations afforded a consensus structure (Figure 3A) that lies on a reaction coordinate between the starting π-complex and the vinyl indium product (as shown in Figure 2). The forming C−In bond and the forming C−C bond in TS are almost the same (2.356 Å and 2.373 Å, respectively). Judging by the final lengths of the corresponding bonds in the vinyl indium product (2.144 Å and 1.555 Å, respectively, Figure 3), the formation of the C−In bond is apparently much more advanced than that of the C−C bond. Different courses of the rehybridization of two acetylene carbons also demonstrate the advanced nature of the C−In bond formation over that of the C−C bond (the H−C_γ−C_β and C_γ−C_β−H angles are 134.2° and 163.3°, respectively). Such structural characteristics strongly suggest the importance of the interaction between acetylene and the indium metal center in the earlier stage of the carboindation step. One interesting feature of this structure is that the acetylene is located just above the center of the pseudo-C_2 symmetry plane of the indium enolate of a 1,3-dicarbonyl compound and that the two asterisked C*−H* bonds are parallel to each other. This special geometry can maximize the orbital interaction between the indium enolate and acetylene and may be a part of the reasons why certain substrates such as cyclic ketone substrates (entries 10−17, Table 5) are less reactive than acyclic substrates.

Conclusion

We reported in this paper the discovery and development of the indium-catalyzed addition reaction of active methylene compounds to alkynes. A number of examples provided in this article illustrate the versatility of this new synthetic reaction. The key to success is the choice of the indium metal and its counteranion. The reaction may require a base but quite often does not require any apparent base because the acetylene substrate acts as a latent base by scavenging TfOH, generating a π-Lewis acidic indium enolate, which is suitable for the carboindation reaction. The resulting 2-alkenyl 1,3-dicarbonyl compounds are useful synthetic intermediates that can be used for further synthetic transformations and for the synthesis of pharmaceutically important compounds.

Experimental Section

A Representative Procedure of the Alkenylation of 1,3-Ketoesters (4.0-mmol Scale): Ethyl 2-Methyl-2-(1-oxoethyl)-3-phenyl-3-butenoate

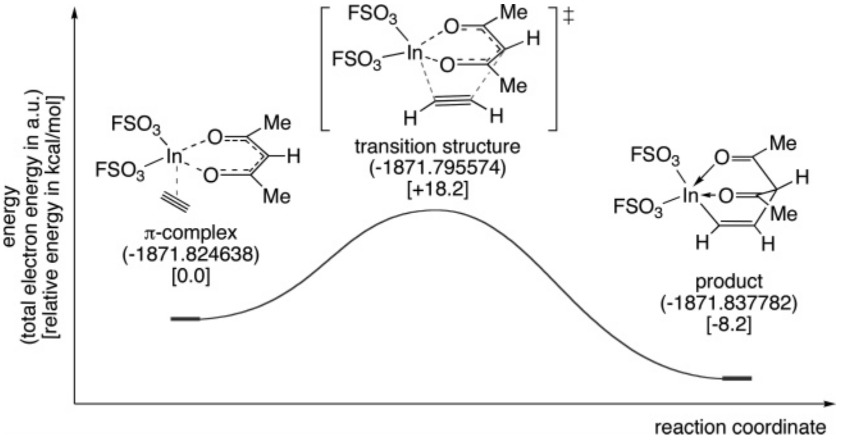


Figure 2. Potential surface of the addition of indium enolate to acetylene.

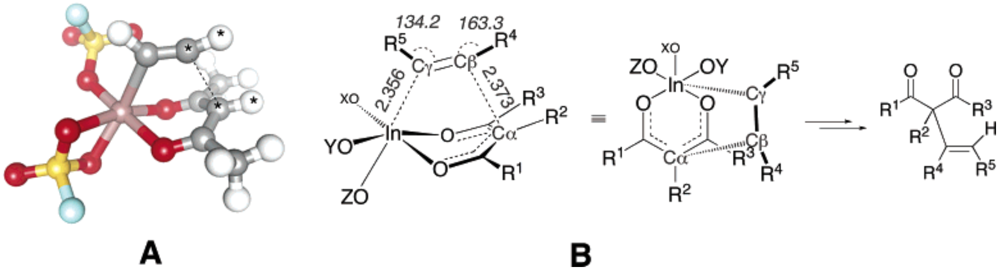


Figure 3. TS models of addition of indium enolate to acetylene. (A) A theoretical TS model of addition of $In(FSO_3)_2$ enolate of acetylacetone to acetylene (B3LYP/6-31G* and LANL2DZ for In). Carbon, gray; hydrogen, white; oxygen, red; fluorine, blue; sulfur, yellow; indium, purple. (B) The pseudo three-dimensional representations of structure A. The substituent numbering follows the one in eq 1. Bond lengths and angles are in angstrom and degree, respectively.

(5). A CH_3CN solution of $In(OTf)_3$ (0.1 M, 20 μL, 0.05 mol %) was introduced into a dried reaction vessel under an argon atmosphere. Then CH_3CN was removed under reduced pressure (130 Pa) at room temperature for 1 h. Ethyl 2-methyl-3-oxobutanoate (4.0 mmol, 576 mL, 576 mg) and phenylacetylene (4.8 mmol, 527 μL, 490 mg, 1.2 equiv) were introduced into the reaction vessel. The reaction mixture was stirred at 140 °C for 90 min and then cooled to room temperature. Flash column chromatography (silica gel 10 g, eluent; hexane/Et_2O = 95/5) of the reaction mixture gave the title compound in 99% yield (973 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.52 (s, 3H), 2.29 (s, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.28 (s, 1H), 5.44 (s, 1H) 7.18−7.31 (m, 5H, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.8, 27.2, 61.5, 65.8, 118.7, 127.5, 127.7 (2C), 128.0 (2C), 140.3, 147.9, 171.7, 205.2; IR (cm^{-1}) 2987, 1710, 1239, 1092, 1021, 915. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.32; H, 7.46.

A Representative Procedure of the Alkenylation of 1,3-Diketones (1.0-mmol scale): 4-Hydroxy-3-(1-phenylethenyl)-3-penten-2-one (3).[1e,28] To phenylacetylene (5.0 mmol, 549 μL, 511 mg, 5.0 equiv) *n*-BuLi (0.025 mmol, 1.51 M in hexane, 17 μL, 2.5 mol %) was added at 0 °C. After 30 min, $In(OTf)_3$ (0.025 mmol, 14.0 mg, 2.5 mol %) and Et_3N (0.025 mmol, 3.5 μL, 2.5 mg, 2.5 mol %) were added. Then 2,4-pentanedione (1.0 mmol, 103 μL, 100 mg) was added at room temperature. The reaction mixture was stirred at 100 °C for 24 h and then quenched with a pH 6.88 phosphate buffer solution. The aqueous layer was extracted with ether (3 times, 10 mL). The combined organic layers were dried over Na_2SO_4. Removal of solvent and the following flash column chromatography (silica gel 10 g, eluent; hexane/ethyl acetate = 95/5) gave the alkenylated compound in 97% yield (197 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 6H), 5.23 (d, $J = 1.2$ Hz, 1H), 5.90 (d, $J = 1.6$ Hz, 1H), 7.29−7.44 (m, 5H, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (2C), 113.8, 118.3, 125.8 (2C), 128.3, 128.7 (2C), 139.6, 143.5, 191.2 (2C); IR (cm^{-1}) 3083, 1598, 1574, 1493, 1391, 1243, 910.

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Supporting Information Available: Experimental procedure and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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