

Indium-catalyzed addition of carbon units to acetylenes: Development of a new C–C bond formation toward exploitation of chemical resources*

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Abstract: This account deals with an overview of the development of catalytic addition reactions of carbonyl compounds to alkynes catalyzed by a variety of indium salts. The new C–C bond formation reactions provide a powerful tool for α -functionalization of carbonyl compounds, including direct α -vinylation with acetylene, regioselective α -alkenylation, and α -ynylenylation that can be applied to a modular synthesis of α -arylated β -keto esters.

Keywords: carbon–carbon bond formation; indium catalyst; carbonyl compounds; alkenylation; carbometallation.

INTRODUCTION

Controlled C–C bond-forming reactions exploiting simple unsaturated hydrocarbons, such as ethylene and acetylene, have been emerging as versatile tools in synthetic chemistry [1]. Taking advantage of the ample supply of these unsaturated hydrocarbons has growing importance in terms of exploitation of chemical resources, and may serve as a basis of organic synthesis for future production of functional organic molecules (drugs, liquid crystals, LEDs, etc.). Although catalytic addition of heteroatom nucleophiles (oxygen, nitrogen, etc.) to acetylenes has been extensively developed recently, the corresponding addition of a carbon unit, especially a neutral pronucleophile [2], is rather rare and remains as a challenge in organometallic-mediated synthetic chemistry. Herein, we will present an overview on catalytic addition of various 1,3-dicarbonyl compounds to acetylenes, which has been achieved by metal catalysts consisting of In^{III} and noncoordinating anions, such as trifluoromethane sulfonate (triflate, TfO[−]) and bis(trifluoromethanesulfonyl)amide (bistriflylamide, Tf₂N[−]).

CATALYTIC ADDITION OF 1,3-DICARBONYL COMPOUNDS TO TERMINAL ALKYNES

Certain d^{10} transition metals, such as Cu^I, Zn^{II}, and Hg^{II}, can promote the addition reaction of anionic carbon nucleophiles across the carbon–carbon multiple bonds of unactivated alkenes and alkynes [3]. In particular, zinc-mediated addition of an enolate anion to simple alkenes has provided synthetically valuable C–C bond formations [4]. It is also known that catalytic addition of carbonyl compounds or alkyl cyanides to styrene derivatives takes place in the presence of potassium cation under strongly

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basic conditions [5]. Such bond reorganization processes between a carbon nucleophile and an unsaturated compound proceed with or without participation of the *d*-orbitals (electrons) of the metal promoters [6]. The known precedents have led us to screen various transition and main group metal triflates to find zinc-catalyzed α -alkyldienation reactions of β -ketoamides [7] and indium-catalyzed α -alkenylation reactions for a variety of 1,3-dicarbonyl compounds (eq. 1) [8].

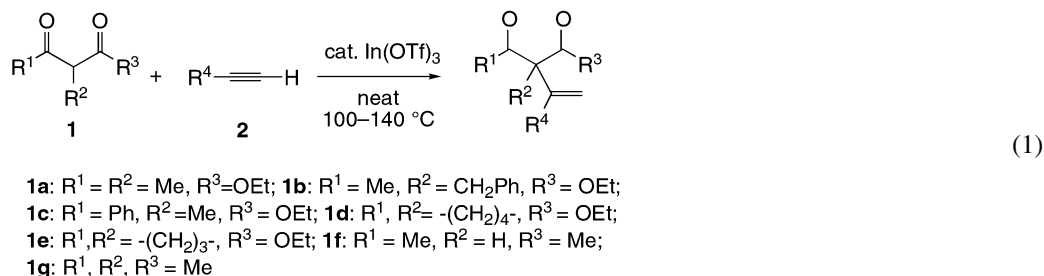


Figure 1 shows the screening of various metal triflates for a catalyst of the α -alkenylation reaction between ethyl 2-methyl-3-oxobutanoate **1a** and phenylethyne. The reaction in the presence of 0.5 mol % of $\text{In}(\text{OTf})_3$ proceeds smoothly at 100°C to give quantitatively the desired adduct **3** within 3 h, while other metal triflates result in much lower or entirely no conversion of **1a**. Zinc, gallium, and mercury triflates catalyze the alkenylation reaction in the presence of an organic base, such as triethylamine or DBU, whereas the other metals examined here do not show any catalytic activity for the addition reaction regardless of the use of the base.

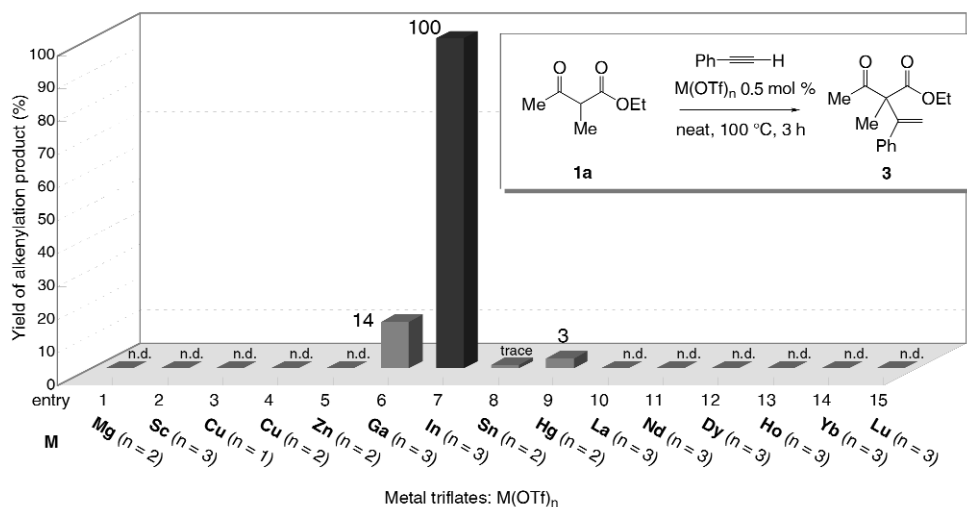
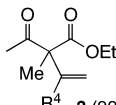
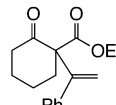
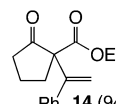
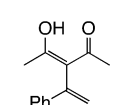
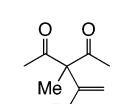
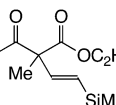
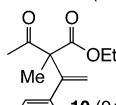
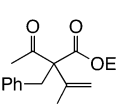
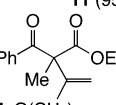


Fig. 1 Screening of metal triflates as a catalyst for the α -alkenylation reaction.

A synthetic advantage of the reaction is its operational simplicity and scalability: A mixture of **1a** (14.5 g, 0.10 mol), phenylethyne (12.3 g, 0.12 mol), and 0.05 mol % of $\text{In}(\text{OTf})_3$ (0.028 g) was heated at 140°C for 10 h without solvent to give **3** as a single product (21.7 g, 92 % yield; 99 % yield on a 4 mmol scale with chromatographic purification, Table 1, entry 1). The reaction is best carried out in the absence of solvent. Whereas highly coordinating solvents, such as THF, stop the reaction, the mixture may be diluted with a solvent such as toluene, resulting in a slower conversion rate.

Table 1 In(OTf)₃-catalyzed alkenylation of active methylene compounds with 1-alkynes^a.

Entry	Carbonyl	Alkyne	Product (% yield)	Entry	Carbonyl	Alkyne	Product (% yield)
1	1a	R ⁴ = Ph	 3 (99)	11	1d	R ⁴ = Ph	 13 (92)
2	1a	R ⁴ = 4-MeOC ₆ H ₄	4 (98)	12	1e	R ⁴ = Ph	 14 (94)
3	1a	R ⁴ = 4-(MeOCO)C ₆ H ₄	5 (97)	13	1f	R ⁴ = Ph	 15 (97)
4	1a	R ⁴ = 4-CF ₃ C ₆ H ₄	6 (92)	14	1g	R ⁴ = Ph	 16 (88)
5	1a	R ⁴ = C ₆ H ₁₃	7 (99)	15	1a	R ⁴ = PhMe ₂ Si	 17 (80)
6	1a	R ⁴ = MeO(CH ₂) ₄	8 (94)				
7	1a	R ⁴ = PhCH ₂ OCH ₂	9 (80)				
8	1a	R ⁴ = 1-cyclohexenyl	 10 (94)				
9	1b	R ⁴ = MeO(CH ₂) ₄	 11 (95)				
10	1c	R ⁴ = MeO(CH ₂) ₄	 12 (88)				

^aThe reaction was carried out with 0.05–5 mol % of In(OTf)₃ at 60–140 °C for 4–18 h.

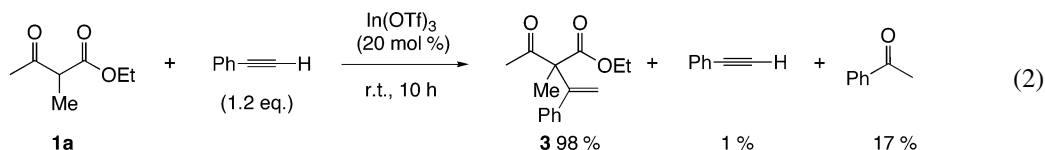
Table 1 illustrates the scope and limitations of the α -alkenylation reaction. The yield is essentially quantitative both for the active methylene compound and for the alkyne, and the regioselectivity exclusively favored the new C–C bond formation at the internal *sp* carbon. The use of excess alkyne is recommended, when it is volatile, unreactive, or unstable under the reaction conditions. Internal alkynes are inert for the coupling reactions under the present reaction conditions. Comparison among phenylethyne derivatives for the reaction with **1a** indicated that phenylethyne (R⁴ = Ph) is less reactive than **2** (R⁴ = 4-MeOC₆H₄), and more reactive than **2** (R⁴ = 4-MeOCOC₆H₄) and **2** (R⁴ = 4-CF₃C₆H₄): The reaction becomes faster, but the yield becomes lower (entries 2–4) as the alkyne becomes more electron-rich. The reaction with aliphatic alkynes also proceeded in high yield (entries 5–7). The addition to a conjugated enyne compound proceeds exclusively at the triple bond in 1,2-fashion (entry 8).

The reaction tolerates a wide range of structural variations of the active methylene compound. The β -keto ester can bear a benzoyl group or can be a part of a ring structure (entries 9–12). β -Diketones also take part in the alkenylation with slight modification of reaction conditions, because they are slightly less reactive than β -keto esters and rather unstable under the original conditions. Thus, 3-methyl-2,4-pentandione **1g** reacts with excess phenylethyne to give the desired compounds in 88 % yield in the presence of an equimolar mixture of 2.5 mol % In(OTf)₃, Et₃N and *n*-BuLi [9] (entry 14). Acetylacetone **1f** gives the α -alkenylation product **15** in 97 % yield as its enol tautomer (entry 13).

All reactions shown above proceeded regioselectively to form the new C–C bond at the more substituted carbon atom of the 1-alkyne. In contrast, an ethynylsilane undergoes the addition with completely reversed regioselectivity (Table 1, entry 15) to give the product that bears a trans olefinic double bond. Thus, the reaction between **1a** and ethynyldimethylphenylsilane gave the corresponding

α -alkenylation product (**17**) in 80 % yield. The geometry of the alkenyl substituent indicates *cis* addition of the metal enolate across the C–C triple bond (see below).

The reaction shown in eq. 2 provides further mechanistic information. Addition of **1a** to phenylethyne proceeds at room temperature in the presence of 20 mol % of $\text{In}(\text{OTf})_3$ to give adduct **3** in quantitative yield along with the formation of acetophenone in ca. 20 % yield.



On the basis of this observation, as well as the regio- and stereoselectivity of the addition reaction, the following catalytic mechanism is proposed as plausible (Fig. 2). An indium enolate, generated by the reaction between $\text{In}(\text{OTf})_3$ and a β -dicarbonyl compound, adds to the 1-alkyne. It is known that the alkyne substrates act as trapping agents for TfOH and give acetophenone upon hydrolysis. The β -dicarbonyl substrate protonates the alkenyl indium intermediate and regenerates the indium enolate. The higher reactivity of electron-rich alkynes suggests that coordination of the indium atom to the alkyne is a key step in this carbometallation process. The observed regioselectivity of the addition can be explained by the general tendency toward carbometallation for the alkynes bearing a carbon substituent [10], and by the stability of *gem*-organodimetallic species toward ethynylsilane [11]. The formation of acetophenone is ascribable to hydrolysis of the alkenyl triflate during the work-up process.

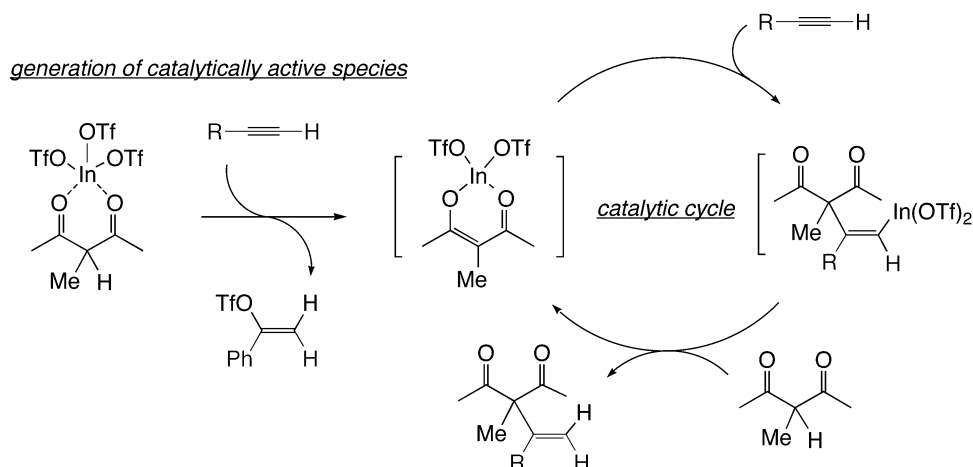
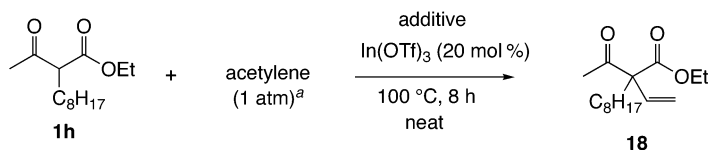


Fig. 2 A mechanistic rationale for the catalytic alkenylation.

DIRECT α -VINYLTION WITH ACETYLENE GAS [12]

Because acetylene gas is a primary and useful carbon resource in industry and laboratory synthesis [13], direct α -vinylation reaction of carbonyl compounds with the simplest alkyne would be an attractive synthetic method [6a,7,14,15]. Unfortunately, the conditions for the addition of 1,3-dicarbonyl compounds to unactivated monoynes described above failed for the reaction with acetylene gas. A considerable amount of oligomeric by-products forms, reducing the yield of desired adduct. This may be due to the base and acid sensitivity of acetylene. Some acid scavengers were examined in the reaction of **1h** with acetylene and found to modify the reactivity profile of the $\text{In}(\text{OTf})_3$ catalyst (eq. 3). Thus, the combi-

nation of $\text{In}(\text{OTf})_3$ and an equal weight of molecular sieves (MS) works very well to catalyze the direct α -vinylation to give the adduct **18**.



additive: none, 15 % yield

additive: MS 4A (100 wt %/ $\text{In}(\text{OTf})_3$), 95 % yield

additive: DBU (20 mol %), 28 % yield (95 % yield)^b

(3)

^aA welding-grade acetylene is used without purification unless otherwise noted.

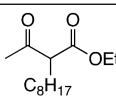
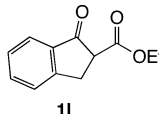
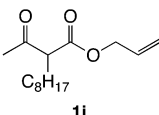
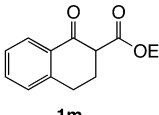
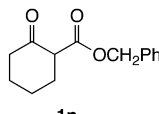
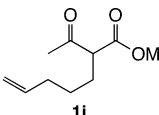
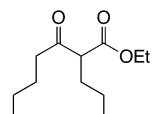
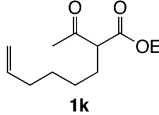
^bThe yield of **18** by using purified acetylene is shown in parentheses.

Table 2 tabulates the results of the direct vinylation of various β -keto esters with the optimal catalyst system by using unpurified acetylene gas (welding grade). The vinylation reaction is scalable, being carried out on a 100-mmol scale without any experimental difficulty: The reaction of **1h** and acetylene proceeds without solvent to give ca. 25 g of **18** (90 % yield) (entry 1). An acid-sensitive allyl acetoacetate **1i** (entry 2) undergoes α -vinylation to give the corresponding product **19** in 74 % yield by using toluene as solvent (condition B). The products bearing allylic esters undergo an enantioselective decarboxylative allylation catalyzed by palladium in the presence of an optically active phosphinyl oxazoline [16].

Similarly, ω -alkenyl- β -keto esters, **1j** and **1k**, reacted with acetylene either with or without solvent to give the vinyl products **21** and **22**, respectively. No intramolecular cyclization reaction is observed (entries 4 and 5). Aromatic substrates can also participate in the vinylation reaction (entries 3, 6, and 7). 2-Benzoylpropionate **1c** reacted with acetylene in toluene to give adduct **20** in 82 % yield. Cyclic β -keto esters fused with a benzene rings **1l** and **1m** are also readily vinylated in 75 and 100 % yield, respectively. No Friedel–Crafts reaction took place on the aromatic moiety under the reaction conditions [17]. A cyclic keto ester, benzyl 2-oxocyclohexanecarboxylate **1n** was found to be relatively unstable under the reaction conditions. Slight modification of the conditions (DBU added; condition C) gives the product **25** in 89 % yield (entry 8). Similarly, a 12-membered cycloalkanone **1o** afforded adduct **26** in 98 % yield (entry 9).

The $\text{In}(\text{OTf})_3$ /MS/DBU conditions effect the addition of β -keto esters to acetylene in good to excellent yields, which almost fails under previous additive-free $\text{In}(\text{OTf})_3$ conditions developed for substituted acetylenes [8]. The new conditions that tolerate acid-sensitive groups may be applicable to the synthesis of more elaborate molecules, such as an advanced synthetic intermediate of bioactive molecules.

Table 2 In(OTf)₃/MS-catalyzed vinylation of β -keto esters.

Entry	β -Keto ester	Condition ^{a,b}	Product (% yield) ^c	Entry	β -Keto ester	Condition ^{a,b}	Product (% yield) ^c
1		A	18 (90 %) ^d	6		C	23 (75 %)
2		B	19 (74 %)	7		C	24 (100 %)
3	1c	B	20 (82 %)	8		C	25 (89 %)
4		B	21 (82 %)	9		A	26 (98 %)
5		A	22 (93 %)				

^aCondition A; In(OTf)₃ (20 mol %) and MS 3A (100 wt %/In(OTf)₃) at 100 °C. Condition B; In(OTf)₃ (20 mol %) and MS 3A (100 wt %/In(OTf)₃) in toluene at 100 °C. Condition C; In(OTf)₃ (20 mol %), MS 3A (100 wt %/In(OTf)₃), and DBU (20 mol %) in toluene at 100 °C.

^bUnder an atmosphere of welding-grade acetylene (balloon).

^cIsolated yield. The yield in parentheses was determined by ¹H NMR with dibromomethane as an internal standard.

^dA 25-g scale experiment is described in the text. Purity was determined using a noncalibrated GC area ratio.

ADDITION OF β -KETO ESTERS TO DIYNES

There is a challenge in controlling the regioselectivity of the addition when an unsymmetrical conjugated diyne is the substrate. It is noteworthy that addition of a β -keto ester to a conjugated diyne, such as 1,3-decadiyne, proceeds at the terminal triple bond in an exclusively regioselective manner to form α -ynenylated β -keto ester **27** (eq. 4). [18] While In(OTf)₃ and more elaborate systems (with MS or DBU) did not show adequate catalytic activity, the more Lewis acidic In(NTf₂)₃ has been found to be an effective catalyst for the regioselective C–C bond-forming reaction (Table 3). For these experiments, a 1:2 mixture of **1a** and the diyne was heated, without solvents, at 60 °C for 3 h in the presence of 5 mol % of the indium catalyst. By using 5 mol % of In(NTf₂)₃, the adduct **27** formed instantly in 93 % isolated yield under reaction conditions that were otherwise the same.

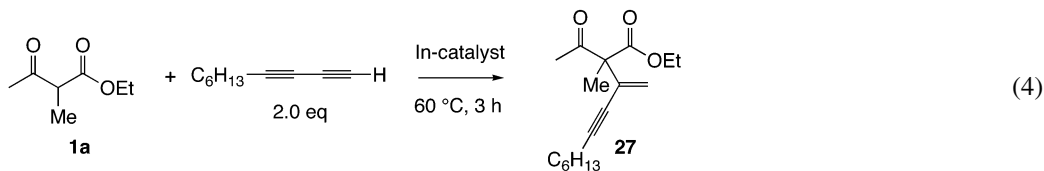


Table 3 In-catalyzed regioselective addition of β -keto esters **1a** to 4-phenyl-1,3-butadiyne.

Entry	In(III) catalyst	% Yield of 27 ^a
1	In(OTf) ₃ (5 mol %)	50
2	In(OTf) ₃ (5 mol %), DBU ^b (5 mol %)	13
3	In(OTf) ₃ (5 mol %), MS 3A (200 wt %/cat.)	63
4	In(NTf ₂) ₃ ^c (5 mol %)	93 ^d

^a¹H NMR yield using dibromomethane as an internal standard.^b1,8-Diazobicyclo [5.4.0] undec-7-ene.^cIndium tris[bis(trifluoromethane sulfonyl)amide].^dIsolated yield.

The optimized reaction conditions are as follows: an equimolar mixture of a β -keto ester and a diyne (which may be used in excess in the case that decomposition of the diyne competes with the addition) [19] is heated at 60 °C for 48 h in the presence of 1 mol % of In(NTf₂)₃. Table 4 summarizes the scope and limitations of the addition reaction under the optimum conditions. A terminal diyne substituted by an alkyl group such as 1,3-decadiyne is high yielding, to give a single adduct in almost quantitative yield with complete regioselectivity (entries 1, 5–8). While 4-phenyl-1,3-butadiyne and 4-cyclohexen-1-yl-1,3-butadiyne are inherently unstable, they afforded the desired adducts **28** and **29** in 72 and 76 % yield, respectively, with complete regioselectivity (entries 2 and 3). The addition to 4-triethylsilyl-1,3-butadiyne proceeded to give adduct **30** in 70 % yield with the same regioselectivity (entry 4). The silyl substituent does not work as a directing group in this case, whereas the C–C bond formation takes place at the carbon center attached by the silyl group with the simple ethynylsilane (vide supra). Olefinic double bonds in the substrates are not touched under the reaction conditions (entries 3 and 8). Benzene rings in the diyne substrate or the 1,3-dicarbonyl substrate also remain untouched, and no Friedel–Crafts-type reaction on the aromatic ring was observed (entries 2, 5, and 6). Ethyl 2-oxo-cyclopentylcarboxylate **1e**, which is rather sensitive to the reaction conditions, gave the α,α -disubstituted cycloalkanone **33** in 93 % yield (entry 7).

Table 4 In(NTf₂)₃-catalyzed regioselective addition of β -keto esters to 1,3-diynes.^a

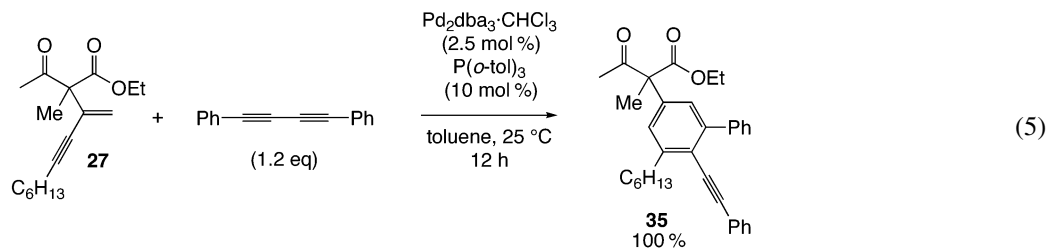
Entry	Substrate	1,3-Diyne	Product (% yield) ^b	Entry	Substrate	1,3-Diyne	Product (% yield) ^b
1 ^c	1a	R ⁵ = C ₆ H ₁₃	27 (98)	6	1c	R ⁵ = C ₆ H ₁₃	32 (90)
2	1a	R ⁵ = Ph	28 (72)				
3	1a	R ⁵ = 1-cyclohexenyl	29 (76)	7	1e	R ⁵ = C ₆ H ₁₃	33 (93)
4	1a	R ⁵ = SiEt ₃	30 (70)				
				8	1j	R ⁵ = C ₆ H ₁₃	34 (96)
5	1b	R ⁵ = C ₆ H ₁₃	31 (96)				

^aAll reactions were conducted by heating a mixture of β -keto ester and 1,3-diyne (1.05 or 2.0 equiv) in the presence of In(NTf₂)₃ (5 mol %) at 60 °C without solvents unless otherwise noted.

^bIsolated yield.

^cThe reaction was carried out with 1,3-decadiyne (1.05 equiv) in the presence of In(NTf₂)₃ (1 mol %) at 60 °C for 48 h.

The products, conjugated enynes, are amenable to a stepwise synthesis of α -arylated carbonyl compounds. Yamamoto's benzannulation conditions between an enyne and a diyne can be applied to this new synthetic strategy [20]. Thus, catalytic [4 + 2]-type benzannulation between **27** and 1,4-diphenyl butadiyne proceeded at room temperature in the presence of Pd₂dba₃·CHCl₃ (2.5 mol %) and P(*o*-tol)₃ (10 mol %) to give α -arylated product **35** possessing the multiply substituted benzene ring in quantitative yield as the sole regioisomer (eq. 5). This α -arylation protocol demonstrates well the power of the combination of two highly selective catalytic C–C bond formations in the synthesis of complex molecules.



SUMMARY

A new catalytic C–C bond-forming reaction has been developed: In(OTf)₃, as well as In(NTf₂)₃, effects the addition reaction of 1,3-dicarbonyl compounds to a variety of terminal alkynes, including acetylene and conjugated diynes. The reaction proceeds with excellent regioselectivity to give the corresponding α -alkenylated carbonyl compounds in good to high yield. The present method embodies several practical advantages; no by-product formation, high yield, low catalyst loading, and no need for solvent in most cases. Thus, the formal insertion of acetylenes to an α C–H bond of carbonyl compounds may provide a simple and viable route to a variety of functionalized 1,3-dicarbonyl synthetic intermediates. The

In(NTf₂)₃-catalyzed regiocontrolled additions to conjugated diynes gives α -enylated β -keto esters, which are amenable to modular-type synthesis of α -arylated carbonyls, showing the potential of the new C–C bond formation for the synthesis of complex molecules. We hope that development of an efficient C–C bond formation utilizing simple unsaturated hydrocarbons, such as the ones described in this account, would contribute as a first step for achieving concise chemical synthesis in the next generation.

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