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A Modular Approach to α-Arylated Carbonyl Compounds *via* Indium Tris(bistriflylamide)-Catalyzed Regioselective Addition of β-Ketoesters to 1,3-Diynes

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Abstract: A modular synthesis of α-arylated carbonyl compounds has been achieved by the combination of an indium-catalyzed regioselective addition of β-keto esters to conjugated diynes and a palladium-catalyzed benzannulation reaction. Indium tris(bistriflylamide), $In(NTf_2)_3$, was found to be an efficient catalyst for the first addition reaction of β-keto esters to diynes. The reaction proceeds with perfect regioselectivity to give conjugated enynes in high yield. The second palladium-catalyzed benzannulation proceeds in high to excellent yield and with high regioselectivity for a variety of diynes. This two-step α-arylation of carbonyl compounds thus proceeds in a catalytic manner without loss of elements in the starting materials. The reaction may be performed in a single pot without isolation of the product of the first step.

Keywords: addition reaction; annulation; α-aryl carbonyl compounds; enynes; indium; palladium

Introduction

Unlike α-alkylation of carbonyl compounds that can be achieved effectively by the reaction of an enolate anion with an alkyl halide, α-arylation of carbonyl compounds is an intrinsically more difficult reaction, and hence has attracted the interest of synthetic chemists for a long time.[1] There have been two standard approaches to this problem, one involving transition metal-catalyzed arylation of an enolate with a haloarene, and another coupling of an α-halocarbonyl compound with an arylmetal compound.[2] The previous success of these methods notwithstanding, the structural diversity of the accessible compounds is limited by the availability of the aryl halides and arylmetal compounds. In view of the recent development of new methods for the synthesis of aromatic compounds, we considered a possibility of making α-aryl carbonyl compounds in a modular manner, where a part of the latent aryl group is introduced first to the α-position of the target carbonyl compound and is then converted to the desired aryl group in the second step. Such an approach would make available α-aryl carbonyl compounds that cannot be synthesized by the known approaches.[2] We report herein a new modular synthesis starting with a β-keto ester, a diyne and an acetylene as illustrated in Figure 1. The synthesis relies on our own indium-catalyzed protocol for α-vinylation of an active methylene compound[3] which is combined with Yamamoto's palladium-catalyzed [4+2]benzannulation of an enyne to diyne.[4] To achieve the goal, we developed a new set of catalytic conditions to effect the addition of a β-keto ester to a diyne. The modular synthesis produces a variety of new benzene derivatives as detailed below.

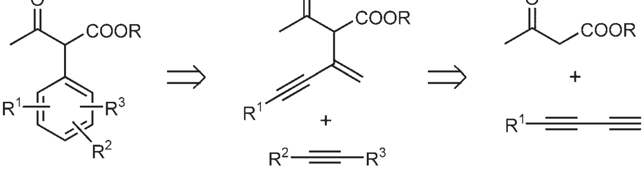


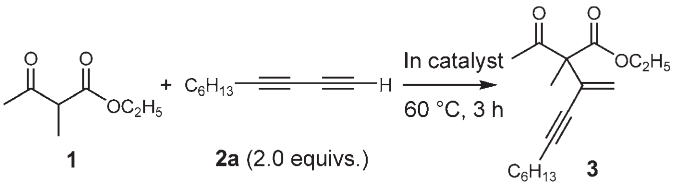
Figure 1. A modular approach to α-arylated carbonyl compounds.

Results and Discussion

Preliminary investigations indicated that our previous conditions for addition of a β-keto ester to a monoyne[3a] failed to effect the desired addition reaction to diynes. We therefore examined several indium catalysts for the reaction between ethyl 2-methyl-3-oxobutanoate (**1**) and 1,3-decadiyne (**2a**; Scheme 1). For these experiments, we used a 1 : 2 mixture of **1** and **2a** that was heated, without solvents, at 60 °C for 3 hours in the presence of 5 mol % of the indium catalyst shown in Table 1. With the In(OTf)$_3$ catalyst that we used for simple monoynes,[3a] the addition of **1** to **2a** was slow, but, to our satisfaction, was completely regioselective to produce the desired α-ynenylated product **3** in 50% yield with 50% recovery of the starting ketoester **1** (entry 1).

It is interesting to note that only the terminal triple bond took part in the addition reaction. We tentatively ascribed the origin of this selectivity to steric effect. The regioselectivity as to the C–C bond formation at this terminal triple bond conforms to the general rule of the carbometalation of alkynes.[5]

A few other more elaborate catalyst systems based on In(OTf)$_3$ were ineffective in terms of reaction rate (entries 2 and 3). Screening of the counteranion of the indium salt (entries 1, 4–6) led us to find that In(NTf$_2$)$_3$ is an excellent catalyst for the desired transformation.[6] The adduct **3** formed instantly in 93% isolated yield under otherwise the same reaction conditions. In(ONf)$_3$[7] was not as effective as In(NTf$_2$)$_3$, and InCl$_3$ was entirely ineffective.



Scheme 1.

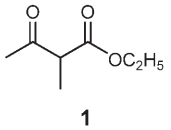
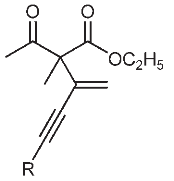
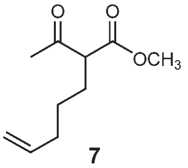
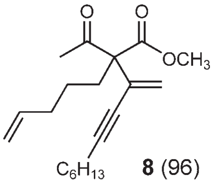
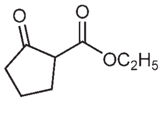
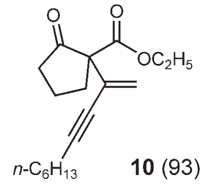
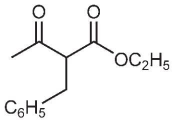
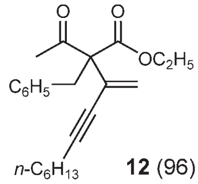
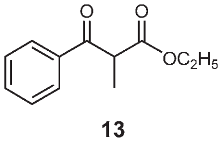
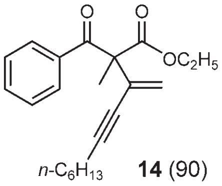
Table 1. In-catalyzed regioselective addition of a β-keto ester to a conjugated diyne.

Entry	In catalyst	Yield [%][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(ONf)$_3$[c] (5 mol %)	59
5	In(NTf$_2$)$_3$[d] (5 mol %)	93[e]
6	InCl$_3$ (5 mol %)	0

[a] NMR yield using dibromomethane as an internal standard.
[b] 1,8-Diazobicyclo[5.4.0]undec-7-ene.
[c] Indium tris(nonafluorobutanesulfonate).
[d] Indium tris[bis(trifluoromethanesulfonyl)amide].
[e] Yield of isolated product.

With the effective indium catalyst in hand, we optimized the reaction conditions and established the standard conditions: an equimolar mixture of a β-keto ester and a diyne (which may be used in excess due to competing decomposition of the diyne) is heated at 60 °C for 48

Table 2. In(NTf$_2$)$_3$-catalyzed regioselective addition to 1,3-diynes.[a].

Entry	Substrate	1,3-Diyne	Product (% yield)[b]
	 **1**		
1[c]		**2a**, R = C$_6$H$_{13}$	**3** (98)
2		**2b**, R = C$_6$H$_5$	**4** (72)
3		**2c**, R = 1-cyclohexene	**5** (76)
4		**2d**, R = Si(C$_2$H$_5$)$_3$	**6** (70)
5	 **7**	**2a**	 **8** (96)
6	 **9**	**2a**	 **10** (93)
7	 **11**	**2a**	 **12** (96)
8	 **13**	**2a**	 **14** (90)

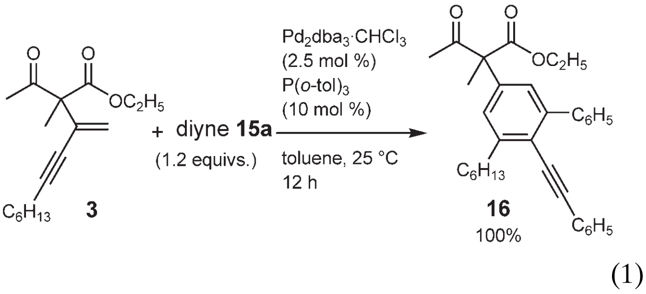
[a] All reactions were conducted by heating a mixture of β-keto ester and 1,3-diyne (1.05 or 2.0 equivs.) in the presence of In(NTf$_2$)$_3$ (5 mol %) at 60 °C under solvent-free conditions unless otherwise noted.
[b] Isolated yield.
[c] The reaction was carried out with 1,3-decadiyne (1.05 equivs.) in the presence of In(NTf$_2$)$_3$ (1 mol %) at 60 °C for 48 hours.

hours in the presence of 1 mol % of $In(NTf_2)_3$. Precautions may be necessary to shield the reaction vessel against ambient light since the diynes and the products may be light sensitive. Representative examples are shown in Table 2. Diynes substituted by an alkyl group such as **2a** are the highest yielding, to give a single adduct in almost quantitative yield with complete regioselectivity (entry 1). While 4-phenyl-1,3-butadiyne (**2b**) and 4-cyclohexen-1-yl-1,3-butadiyne (**2c**) are unstable by their nature, they afforded the desired adducts **4** and **5** in 72% and 76% yield, respectively, also with 100% regioselectively (entries 2 and 3). The addition to silyldiyne **2d** proceeded to give adduct **6** in 70% yield with the same regioselectivity (entry 4). This selectivity stands in contrast to the one observed previously for the addition to silyl-substituted monoynes (rather than to the diyne system), where the C–C bond formation takes place at the carbon center attached by the silyl group.[3a] Not unexpectedly the olefinic double bond in the substrate tolerates the reaction conditions and remains untouched (entry 5). Ethyl 2-oxo-cyclopentylcarboxylate (**9**), which is rather sensitive to the reaction conditions, gave the α,α-disubstituted cycloalkanone **10** in 93% yield (entry 6). Friedel–Crafts-type side reactions of the aromatic substituents[7] in **11** and **13** did not compete at all with the desired addition reaction (entries 7 and 8).

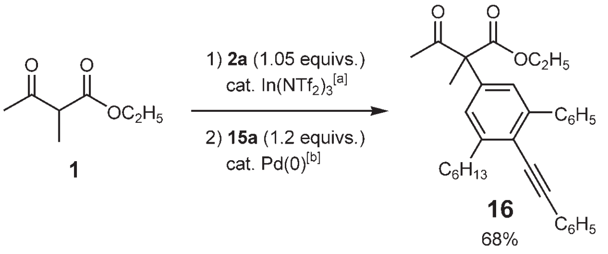
Having found the catalytic system to produce the α-ynenylated keto esters, we examined the construction of the desired benzene ring on the enyne moiety. After some experimentation, we found a set of the conditions developed by Yamamoto for [4+2]-type benzannulation between an enyne and a diyne is suitable for our purpose. The annulation reaction proceeded with internal 1,3-diynes in the presence of a palladium(0) catalyst and a phosphine ligand to give α-arylated β-dicarbonyl compounds in excellent yield. The carbonyl group in the enyne substrate did not interfere with the catalytic benzene ring formation. For instance, the adduct **3** reacted with 1,4-diphenyl-1,3-butadiyne (1.2 equivs.) in the presence of $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol %) and P(*o*-tol)$_3$ (10 mol %) in toluene at 25 °C for 12 hours. The α-arylated product possessing the multiply substituted benzene ring **16** was obtained in quantitative yield as a sole regioisomer [Eq. (1); Table 3, entry 1).

The synthesis of a variety of α-substituted phenyl β-keto esters including the one shown in Eq. (1) is illustrated by the examples listed in Table 3. The benzannulation of the enyne adduct **4**, which was found to be rather unstable, proceeded smoothly to give a symmetrically substituted product **17** in 83% yield (entry 2). Various β-keto esters take part in the benzannulation reaction to give the corresponding product in high to excellent yields (entries 3–6). Several internal diynes were investigated to install a multiply-functionalized benzene ring at the position α to the carbonyl group (entries 7–11). In all cases except entry 11, the reaction took place in a regioselective manner. An aliphatic diyne, 5,7-dodecadiyne (**15b**), reacted with the enynyl adduct **3** to give the α-arylated product **22** in 91% yield (entry 7). The dienediyne **15c** possessing an extended conjugation system gave **23** in high yield as a sole regioisomer (entry 8). The reaction of a disilylbutadiyne **15d** produced a silicon-containing compound (entry 9). Bisferrocenylbutadiyne **15e** afforded an attractive organometallic compound **25** in high yield (entry 10). Unsymmetrical 1-phenyl-4-silyl-1,3-butadiyne (**15f**) afforded the product **26** in quantitative yield with a 9:1 regioselectivity. The bulky substituent is placed at the benzene ring in accordance to the literature precedent (entry 11).[4] The benzannulation with terminal diynes did not occur at all.[8]

The two-step synthesis can be carried out in a single pot without isolation of the enyne intermediate as shown in Eq. (2), although the presence of the indium catalyst appears to interfere slightly with the second annulation reaction. The reaction was conducted by sequential additions of diynes **2a** (1.05 equivs.) and **15a** (1.2 equivs.) to the starting β-keto ester **1**. The first addition reaction of ethyl 2-methyl-3-oxobutanoate (**1**) to 1,3-decadiyne (**2a**) (1.05 equivs.) was performed in the presence of $In(NTf_2)_3$ (1 mol %) at 60 °C for 48 hours. In the same reaction vessel, 1,3-diphenyl-1,4- butadiyne (**15a**; 1.2 equivs.), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol %) and P(*o*-tol)$_3$ (10 mol %) in toluene were added to the reaction mixture. The second benzannulation reaction was completed at 60 °C in 12 hours to give the corresponding arylation product **16** in 68% yield. We have so far found that the present conditions of the enyne synthesis are unsuitable for active methylene compounds other than β-keto esters, and will continue our effort to find better conditions as well as to establish a more operationally simple procedure.



(1)

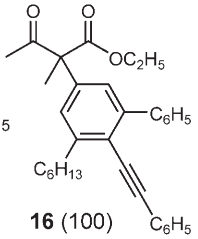
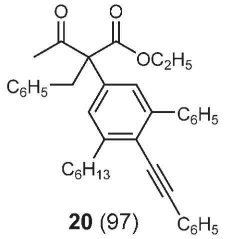
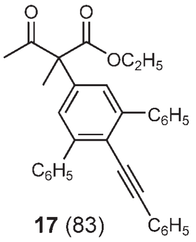
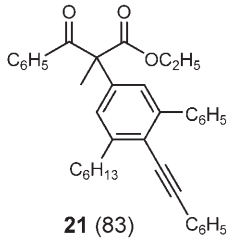
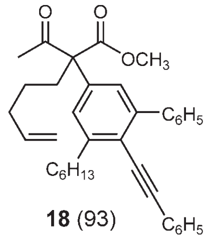
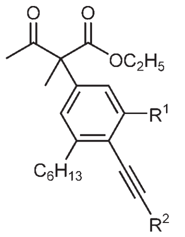
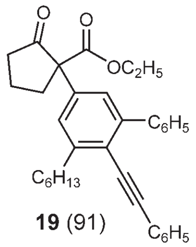


[a] $In(NTf_2)_3$ (1.0 ml %) 60 °C, 48 h

[b] $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol %), P(*o*-tol)$_3$ (10 mol %), toluene, 60 °C, 12 h

(2)

Table 3. Pd(0)-catalyzed [4+2]benzannulation of the enyne adduct with diynes.[a]

Entry	Enyne adduct	1,3-Diyne	Product (% yield)[b]	Entry	Enyne adduct	1,3-Diyne	Product (% yield)[b]
1	**3**	**15a**, $R^1 = R^2 = C_6H_5$	 **16** (100)	5	**12**	**15a**	 **20** (97)
2	**4**	**15a**	 **17** (83)	6	**14**	**15a**	 **21** (83)
3	**8**	**15a**	 **18** (93)		**3**	**15b – f**	
4	**10**	**15a**	 **19** (91)	7	**15b**, $R^1 = R^2 = C_4H_9$		**22** (91)
				8	**15c**, $R^1 = R^2 =$ 1-cyclohexene		**23** (90)
				9	**15d**, $R^1 = R^2 = Si(CH_3)_3$		**24** (92)
				10	**15e**, $R^1 = R^2 =$ Ferrocenyl (Fc)		**25** (86)
				11	**15f**, $R^1 = C_6H_5$, $R^2 = Si(CH_3)_3$		**26** (100)[c]

[a] $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol %) and $P(o\text{-tol})_3$ (10 mol %) in degassed toluene 1 M at 25–80 °C.

[b] Yield of isolated product.

[c] The major regioisomer is shown. The regioselectivity was 9:1.

Conclusion

The present study illustrates the power of the combination of two highly selective and efficient catalytic C–C bond-forming reactions into one for the construction of complex molecules. The modular approach using a combination of the $In(NTf_2)_3$-catalyzed addition of β-keto esters to 1,3-diynes and the Pd(0)-catalyzed [4+2]benzannulation reaction provides an effective synthesis of a wide variety of functionalized α-aryl carbonyl compounds, most of which are difficult to obtain by the conventional reactions. Given the possibility of further transformation of the keto ester moiety (e.g., decarbonylation) and the aryl moiety, we expect that the present modular protocol will be useful as a method of considerable applicability for the synthesis of substituted aromatics.

Experimental Section

General Remarks

All reactions were carried out in dry reaction vessels under an argon or nitrogen atmosphere unless otherwise noted. Flash column chromatography was performed with silica gel 60 (spherical, neutral, 140–325 mesh). All ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were measured on a JEOL ECA-500 for $CDCl_3$ solutions in the presence of tetramethylsilane as an internal standard and data are reported in ppm (δ). IR spectra were recorded on a React IR 1000 Reaction Analysis System equipped with DuraSample IR (ASI Applied System) and are reported in cm^{-1}. Anhydrous toluene was distilled in the presence of CaH_2 and stored over molecular sieves in a storage flask. The water content of the solvent was confirmed with a Karl-Fischer Moisture Titrator (MKC-210, Kyoto Electronics Company) to be less than 10 ppm. The abbreviation rt stands for room temperature ranging from 15–25 °C.

Materials

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification before use. $In(OTf)_3$ was purchased from Aldrich Inc. and dried prior to use. $In(NTf_2)_3$ and $In(ONf)_3$ were prepared as described in the Supporting Information and dried prior to use.

Representative Procedure for Catalytic Addition of Ethyl 2-Methyl-3-oxobutanoate (1) to 1,3-Decadiyne (2a):

***Ethyl 2-acetyl-2-methyl-3-methylene-4-undecynoate* (3):** In a flame-dried reaction vessel, $In(NTf_2)_3$ was dried at 140 °C under reduced pressure (26 Pa) for 10 h. After the In-containing vessel was flushed with argon at rt, a mixture of ethyl 2-methyl-3-oxobutanoate (**1**; 151.4 mg, 1.05 mmol) and 1,3-decadiyne (**2a**; 147.6 mg, 1.10 mmol, 1.05 equivs.), $In(NTf_2)_3$ (10.0 mg, 0.0105 mmol, 1 mol %) was heated at 60 °C in the dark for 48 h. The resulting reaction mixture was filtered through a pad of silica gel with ether eluent to give a crude product. Purification by silica gel column chromatography (2% EtOAc/hexane) gave the title compound **3**; yield: 286.5 mg (1.03 mmol, 98%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.889$ (t, $J = 6.9$ Hz, 3H), 1.24–1.32 (m, 4H), 1.28 (t, $J = 6.9$ Hz, 3H), 1.33–1.40 (m, 2H), 1.50 (quint, $J = 6.9$ Hz, 2H), 1.56 (s, 3H), 2.28 (t, $J = 6.9$ Hz, 2H), 2.32 (s, 3H), 4.23 (dq, $J = 1.7$, 6.9 Hz, 2H), 5.37 (s, 1H), 5.59 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.8$, 13.9, 19.1, 19.9, 22.4, 27.3, 28.3, 28.4, 31.2, 61.4, 64.9, 78.6, 92.8, 122.3, 130.7, 170.8, 203.9; IR: n = 2934 (m), 2860 (m), 2223 (w), 1718 (s), 1606 (w), 1451 (m), 1355 (m), 1239 (s), 1112 (s), 1023 (m), 907 cm^{-1} (m); anal. calcd. for $C_{17}H_{26}O_3$: C 73.34, H 9.41, O 17.25; found: C 73.59, H 9.60.

Representative Procedure for Palladium(0)-Catalyzed [4+2]Benzannulation; Reaction of Enyne (3) and 1,4-Diphenyl-1,3-butadiyne (15a)

***Ethyl 2-acetyl-2-(3′-hexyl-4′-phenylethynyl-5′-biphenyl)-propanoate* (16):** A mixture of enyne (**3**; 139.2 mg, 0.5 mmol), 1,4-diphenyl-1,3-butadiyne (**15a**; 121.4 mg, 0.6 mmol, 1.2 equivs.), $Pd_2dba_3 \cdot CHCl_3$ (13.0 mg, 0.0125 mmol, 2.5 mol %), and P(*o*-tol)$_3$ (15.2 mg, 0.05 mmol, 10 mol %) in degassed toluene (0.5 mL) was stirred at 25 °C for 12 h. The resultant reaction mixture was filtered through a pad of silica gel with ether as eluent to give a crude product. Purification by silica gel column chromatography (2% EtOAc/hexane) gave the title compound **16**; yield: 240.4 mg (0.5 mmol, 100%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3H), 1.30–1.36 (m, 4 H), 1.31 (t, $J = 6.9$ Hz, 3H), 1.37–1.56 (m, 2H), 1.73 (quint, $J = 7.5$ Hz, 2H), 1.79 (s, 3H), 2.17 (s, 3H), 2.93 (m, 2H), 4.28 (q, $J = 6.9$ Hz, 2H), 7.14 (aromatic, s, 1H), 7.18 (aromatic, s, 1H), 7.28 (aromatic, 5H), 7.39–7.41 (aromatic, 1H), 7.44–7.47 (aromatic, 2H), 7.61–7.63 (aromatic, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.0$, 21.2, 22.6, 27.2, 29.3, 30.7, 31.7, 35.5, 61.7, 64.6, 87.4, 96.6, 120.6, 123.5, 125.9, 126.8, 127.5, 127.7 (2C), 128.1, 128.2 (2C), 129.5 (2C), 131.1 (2C), 138.1, 140.8, 144.6, 145.9, 171.6, 204.5; IR: $\nu = 2930$ (m), 2856 (w), 1714 (s), 1598 (w), 1494 (m), 1459 (m), 1355 (m), 1243 (s), 1193 (m), 1092 (s), 1023 (m), 911 (w), 884 (w), 861 (w), 776 (m), 767 cm^{-1} (s); anal. calcd. for $C_{33}H_{36}O_3$: C 82.46, H 7.55, O 9.99; found: C 82.29, H 7.65.

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[8] We could not use monoynes for the benzannulation instead of diynes, which is the limitation of the original Yamamoto reaction.