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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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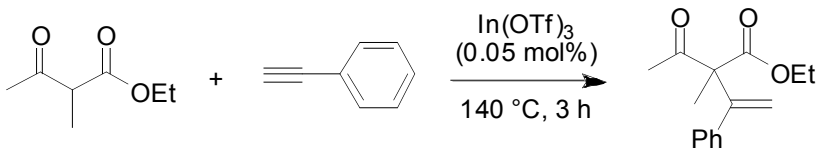
SYNTHESIS OF ETHYL 2-ETHANOYL-2-METHYL-3-PHENYLBUT-3-ENOATE



Submitted by Taisuke Fujimoto,[1] Kohei Endo,[2] Masaharu Nakamura,[3] and Eiichi Nakamura.[1]
Checked by Mark Webster and John A. Ragan.

1. Procedure

Ethyl 2-ethanoyl-2-methyl-3-phenylbut-3-enoate. A flame-dried, 10-mL Schlenk tube (Notes 1 and 2) connected to a vacuum/argon manifold through a glass stopcock and fitted with a glass stopper is equipped with a 1-cm Teflon-coated magnetic stirring bar. $In(OTf)_3$ (64.0 mg, 0.11 mmol) (Notes 3 and 4) is placed in the Schlenk tube and connected to the vacuum line (1.0–1.5 mmHg). The Schlenk tube is immersed in an oil bath. The oil-bath temperature is gradually increased to 180 °C over 1 h and then kept for 30 min at that temperature (Note 5). The Schlenk tube is cooled to ambient temperature and charged with argon. The glass stopper is replaced with a rubber septum, and acetonitrile (4 mL) (Note 6) is introduced into the Schlenk tube via a syringe under argon to obtain a 0.025-M acetonitrile solution of $In(OTf)_3$.

A 50-mL, 3-necked, round-bottomed flask (Note 1), connected to a vacuum/argon manifold through a glass stopcock vacuum adaptor, is equipped with a 2-cm Teflon-coated magnetic stirring bar. A solution of 0.025 M $In(OTf)_3$ in acetonitrile (2.0 mL, 0.050 mmol) is introduced into the flask via a syringe under argon, and the remaining two necks of the flask are equipped with glass stoppers. The solution is stirred under reduced pressure (1.0-1.5 mm Hg) at room temperature for 1 h to remove acetonitrile. The flask is flushed with argon, and one of the glass stoppers is replaced with a rubber septum. Ethyl 2-methyl-3-oxobutanoate (14.48 g, 14.2 mL, 0.1 mol) (Notes 7 and 8) and phenylacetylene (12.26 g, 13.2 mL, 0.12 mol) (Note 9) are introduced into the flask via syringe under argon, and the septum is

replaced with the glass stopper. The resulting clear yellow solution is stirred and the flask is immersed in an oil bath (140 °C).

After stirring for 3 h at 140 °C, the reaction mixture is cooled to ambient temperature (Note 10). The vacuum adaptor is replaced with a distillation head. Distillation of the reaction mixture under reduced pressure (1.0–1.5 mmHg) at 150–160 °C (oil bath temperature) gives the title compound as a pale yellow liquid (22.2–23.0 g, 0.090–0.093 mol) in 90-93% yield (>99.9% purity, non-calibrated GC area ratio) (Notes 11 and 12).

2. Notes

1. All glassware was dried in an oven (110 °C), assembled while hot, and allowed to cool to room temperature under argon atmosphere.

2. The checkers used the mass of $In(OTf)_3$ prior to drying for determination of the concentration of the resulting acetonitrile solution.

3. $In(OTf)_3$ (complexiometric EDTA specification of 19.2-21.7% indium, 19.5% for the batch used by the checkers, theory for $In(OTf)_3$ = 20.4%) was purchased from Aldrich and used as received. Alternatively, the submitters report that it can be made from In_2O_3 and TfOH in boiling water.[4] In_2O_3 was purchased from Kanto Kagaku. TfOH was purchased from Wako Pure Chemical Industries, Ltd. Both reagents were used as received. In order to dispose of trifluoromethanesulfonic acid, the acid should be carefully introduced into water in a dropwise fashion.

4. $In(OTf)_3$ is extremely hygroscopic.

5. Rapid increase of the oil bath temperature causes the decomposition of hydrated $In(OTf)_3$.

6. Anhydrous acetonitrile (<50 ppm water) was purchased from EMD Chemicals (Merck KGaA) and used as received.

7. Ethyl 2-methyl-3-oxobutanoate was purchased from Acros and was purified by silica gel flash column chromatography (5% ethyl acetate in hexane as eluent) and distillation (bp 80 °C/20 mmHg) before use. The chromatographic purification is necessary to remove ethyl 3-oxobutanoate.

8. The exact mass of keto ester was determined by weight of the syringe before and after the addition.

9. Phenylacetylene was purchased from Aldrich Inc. and purified by vacuum distillation before use (bp 60 °C/20 mmHg). The exact mass of the

charge was determined as in Note 8.

10. The reaction was monitored by GC/MS on an HP-1 capillary column (0.2 mm x 12 m, 0.33μm) at 30 °C to 290 °C raised at 30 °C /min. Typical retention time of product is 5.7 min. The submitters monitored the reaction by TLC on glass plates coated with 0.25 mm of 230-400 mesh silica gel containing a fluorescent indicator (Merck #1.05715.0009). Plates were visualized with UV light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on a hot plate.

11. The purity was determined by GC/MS analysis, per Note 10.

12. The product displays the following physicochemical properties: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 2.28 (s, 3 H), 4.16 (q, J = 7.0, 2 H), 5.26 (s, 1 H), 5.41 (s, 1 H) 7.16–7.30 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.5, 27.6, 61.8, 66.1, 119.0, 127.8, 128.0 (2C), 128.3 (2C), 140.6, 148.2, 172.0, 205.5; IR (neat) cm^{-1}; 1710, 1355, 1092, 1021, 915, 776; Anal. Calcd. For $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.00; H, 7.22.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

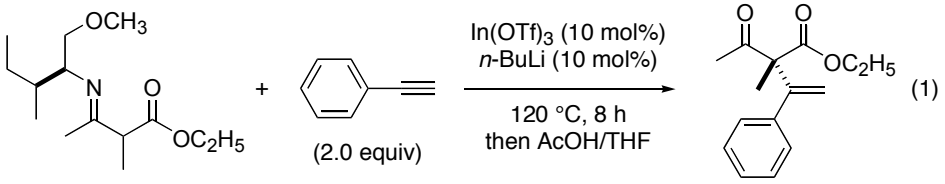
The present procedure provides a simple and efficient way to produce α-alkenyl carbonyl compounds through addition of an active methylene compound to an unactivated alkyne or acetylene catalyzed by indium(III) tris(trifluoromethanesulfonate) [$In(OTf)_3$]. The reaction does not necessarily require solvent, and, as the result, the 20-g scale synthesis can be carried out in a 50- to 100-mL flask. When viscous or solid keto esters are used, the reaction mixture can be diluted with a solvent such as toluene. The reaction also represents a method for the construction of a quaternary carbon center.

The reaction takes place smoothly at room temperature if one uses 20 mol % of $In(OTf)_3$, which however consumes the same amount of the alkyne. For the reaction to be performed with low catalyst loading (0.05

mol % catalyst), higher temperature is needed, but the reaction still shows good functional group tolerance as shown in Table 1.[5] Acid sensitive compounds such as benzyl propargyl ether (entry 5) and ethyl 2-allylacetoacetate (entry 9) require the presence of triethylamine as a base. The reaction of ethynylsilane requires $In(OTf)_3$ (5 mol %) and DBU (6 mol %) at 100 °C for 16 hours (entry 8). The addition of DBU is essential to prevent the desilylation of the vinylsilane product. The *trans*-stereochemistry of the double bond in the product indicates the *cis*-addition of an indium(III) enolate intermediate to the triple bond.

1,3-Diketones also take part in the reaction under slightly modified conditions. The addition of 3-methyl-2,4-pentanedione to phenylacetylene takes place in the presence of $In(OTf)_3$ (5 mol %), Et_3N (5 mol %), and *n*-BuLi (5 mol %) in 32 hours at 100 °C to give the desired product in 88% yield (entry 11). The presence of Et_3N and *n*-BuLi suppresses the formation of side products. As suggested by the data in Table 1, the present reaction is the most suited for creation of a quaternary carbon center, where there is no possibility of enolization. However, the creation of a tertiary center may be achieved in some limited examples of 3,3-diprotio-2,4-pentanedione congeners.[5a,d,e]

The present reaction can also be used for the creation of chiral quaternary carbon stereocenters (eq. 1).[5g] An indium(III) enamide intermediate bearing a chiral auxiliary undergoes highly diastereoselective addition to an alkyne. Intramolecular version of the reaction shows remarkable generality, creating six to fifteen membered rings in good to excellent yields (eq. 2).[5e,h,i]



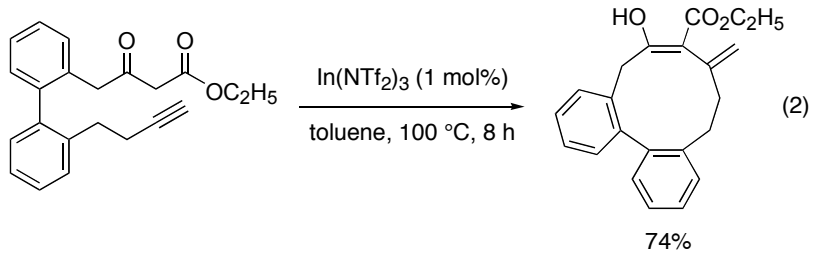


Table 1. Addition of Active Methylene Compounds to Alkynes

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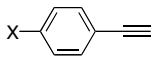
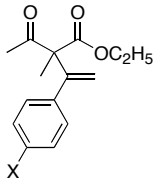
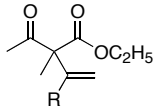
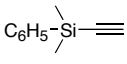
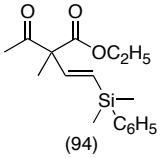
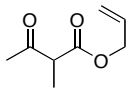
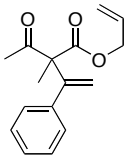
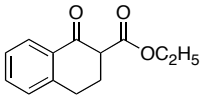
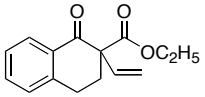
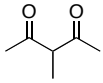
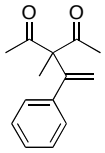
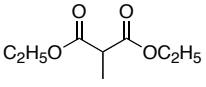
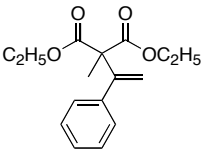
	1	 (1.2)	
1			**2**, X = -H (99)
2			X = -CO_2CH_3 (97)
3[b]			X = -OCH_3 (98)
	1	 (2.0–5.0)	
4			R = C_6H_{13} (2.0) (99)
5[c]			R = -CH_2OBn (3.0) (90)
6[d]			R = -$(CH_2)_4$NPht (2.0) (89)
7[e]			R = 1-cyclohexene (5.0) (94)
8[f]	**1**	 (2.0)	 (94)
9		**2** (1.2)	 (93)
10[g]		acetylene (balloon)	 (100)
11[h]		**2** (5.0)	 (88)
12		**2** (1.2)	 (99)

a) Isolated yield. b) $In(OTf)_3$ (1 mol%) was used at 100 °C in toluene (1 M) for 2 h. c) $In(OTf)_3$ (5 mol%) and Et_3N (5 mol%) were used at 80 °C for 22 h. d) NPht is the abbreviation of phthalamide. $In(OTf)_3$ (1 mol%) was used at 100 °C in toluene (2 M) for 10 h. e) $In(OTf)_3$ (2 mol%) was used at 60 °C for 4 h. f) $In(OTf)_3$ (5 mol%) and 1,8-diazabicyclo[5. 4. 0]undec-7-ene, DBU (6 mol%) were used at 100 °C for 16 h. g) $In(OTf)_3$ (20 mol%), DBU (20 mol%), and MS 3A were used in toluene (1 M) at 100 °C. h) $In(OTf)_3$ (5 mol%), Et_3N (5 mol%), and *n*-BuLi (5 mol%) were used at 100 °C for 32 h.

In summary, the present procedure is useful for the introduction of an alkenyl group, featuring such synthetically convenient attributes as 1) perfect regioselectivity as to the alkyne acceptor, 2) good functional group compatibility, 3) high catalytic performance, 4) requirement of no solvent and 5) good atom economy.

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4. Koshima, H.; Kubota, M. *Synth*. *Commun*. **2003**, *33*, 3983–3988.

5. (a) Nakamura, M.; Endo, K.; Nakamura, E. *J*. *Am*. *Chem*. *Soc*. **2003**, *125*, 13002–13003. (b) Nakamura, M.; Endo, K.; Nakamura, E. *Org*. *Lett*. **2005**, *7*, 3279–3281. (c) Nakamura, M.; Endo, K.; Nakamura, E. *Adv*. *Synth*. *Catal*. **2005**, *347*, 1681–1686. (d) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 5264–5271. (e) Tsuji, H.; Yamagata, K.; Ito, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew*. *Chem*. *Int*. *Ed*. **2007**, *46*, 8060–8062; highlighted by *Synfact*, **2008**, 0077. (f) Tsuji, H.; Fujimoto, T.; Endo, K.; Nakamura, M.; Nakamura, E. *Org*. *Lett*. **2008**, *10*, 1219–1221. (g) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 4492–4496. (h) Ito, Y.; Yamagata, K.-i.; Tsuji, H.; Endo, K.; Nakamura, M.; Nakamura, E. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 17161–17167. (i) Tsuji, H.; Tanaka, I.; Endo, K.; Yamagata, K.-i.; Nakamura, M.; Nakamura, E. *Org*. *Lett*. **2009**, *11*, 1845–1847.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Ethyl 2-methylacetoacetate: Butanoic acid, 2-methyl-3-oxo-, ethyl ester; (609-14-3)

Phenylacetylene: Benzene, ethynyl-; (536-74-3)

Indium(III) tris(trifluoromethanesulfonate): Methanesulfonic acid, trifluoro-, indium(3+) salt; (128008-30-0)

Eiichi Nakamura received his Ph.D. degree from Tokyo Institute of Technology in 1978. He became assistant professor in the same institute in 1980 after two-year post doc at Columbia University, and rose to the rank of professor. Since 1995, he has been professor of chemistry in the University of Tokyo. He is currently directing JST Nakamura Functional Carbon Cluster ERATO project. He received the Chemical Society of Japan Award (2003) and the Humboldt Research Award (2006), and is elected Fellow of the American Association for the Advancement of Science (1998), Fellow of the Royal Society of Chemistry (2005) and Honorary Foreign Member of the American Academy of Arts and Sciences (2008). His research focuses on physical organic chemistry, organic synthesis, material science and use of electron microscopy in chemistry.

Taisuke Fujimoto was born in Sendai, Japan in 1980. Under the direction of Prof. Eiichi Nakamura, he received his bachelor's degree in 2004 and his Ph. D. degree in 2008 from The University of Tokyo, where he worked on the development of Zn or In-mediated reactions. Currently he works for Fujifilm Corporation as organic synthetic chemist, engaging in the syntheses of functional dyes and medicinal chemicals.

Kohei Endo was born in Yokohama, Kanagawa in 1979. He received his bachelor's degree in 2001 from Tokyo Institute of Technology. Under the direction of Eiichi Nakamura he received his Ph. D. degree from The University of Tokyo in 2006. He joined the Noyori laboratory at Nagoya University as COE postdoctoral researcher in the same year. In 2007, he became an assistant professor at Waseda University. His research interest includes development of multi-functionalized molecular catalyst and catalysis system.

Masaharu Nakamura was born in Asagaya, Tokyo in 1967. He received his bachelor's degree in 1991 from Science University of Tokyo. Under the direction of Eiichi Nakamura he received his Ph. D. degree from Tokyo Institute of Technology in 1996. He became an assistant professor at The University of Tokyo in the same year. After promotions to a lecturer (2002) and an associate professor (2004) he moved to Kyoto. Since 2006, he has been a professor of Institute for Chemical Research at Kyoto University, where his research focuses on the development of future molecular/material transformations toward full utilization of chemical resources.

Mark Webster was born in 1956 in Newport, Kentucky. He received his B.S. degree from Northern Kentucky University in 1979 and began working at Hilton-Davis Chemical Company. While working at Hilton-Davis as a process chemist he attended Xavier University and received his M.S. degree in 1986. He began working in the pharmaceutical industry in 1987 at Merrell Dow Pharmaceuticals. He then worked at Procter and Gamble before joining Pfizer's Chemical Research and Development group where he currently works as a process chemist.

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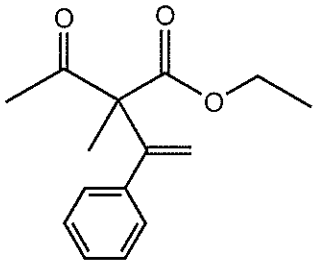

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