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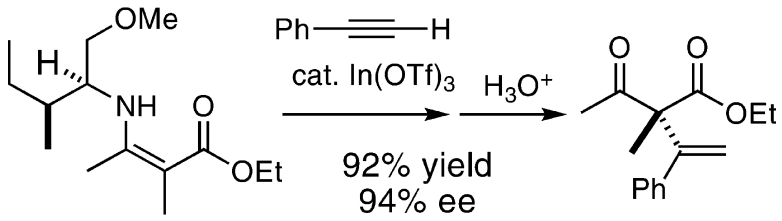

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Construction of a Chiral Quaternary Carbon Center by Indium-Catalyzed Asymmetric α-Alkenylation of β-Ketoesters

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Abstract: Construction of a nonracemic all-carbon quaternary stereocenter at the α-position of β-ketoesters was achieved by way of an indium(III)-catalyzed diastereoselective α-alkenylation reaction of chiral enamines with 1-alkynes. The enamine bearing a chiral auxiliary derived from L-isoleucine was added to the alkyne to give an α-alkenylated product in excellent yield and with a stereoselectivity better than 90% ee. One can ascribe the high selectivity to a chelate intermediate involving the auxiliary and the metal atom and the high yield to efficient interactions between the indium(III) atom and the alkyne. The selectivity increased as the reaction temperature was raised to 120 °C and decreased at higher temperatures.

Introduction

We expended a considerable effort in the past decade to achieve the addition of enolate anions or their nitrogen congeners to unactivated olefins[1] and acetylenes.[2] Such reactions are unique among the reactions that allow the formation of a C−C bond at the α-position of carbonyl compounds because simple olefins and acetylenes are not polarized and hence have been considered to be unreactive toward a stabilized carbanionic nucleophile such as enolate anions. In a series of papers, we demonstrated that zinc(II) enolates and enamides add smoothly to simple olefins in a stoichiometric manner[1] and that zinc(II)[3] or indium(III)[2] enolates or enamides, generated from 1,3-dicarbonyl compounds, react catalytically with simple 1-alkynes to produce α-alkenylated or α-alkylidenated β-dicarbonyl compounds.[4] One important outcome of the former reactions is the possibility of stereoselective synthesis of quaternary carbon centers,[5] which has attracted much attention of chemists because of the difficulty to achieve a high yield and high enantioselectivity. Following the pioneering work by Meyers et al. on the reactions of chiral metal enamides,[6] various reactions were developed including asymmetric α-alkylation,[7,8] 1,4-addition,[9,10] Tsuji−Trost allylation,[11] and arylation.[12] Introduction of an alkenyl group also was reported, although much less frequently. For instance, conjugated addition to alkynones[13] and acylation of silyl ketene acetals[14] are such examples. A recent example by Toste and Corkey on an enantioselective Pd-catalyzed Conia-ene reaction[15] is an intramolecular variant of the α-alkenylation achieved by the addition of a metal enolate to an alkyne. We report herein an asymmetric indium(III)-catalyzed alkenylation of chiral enamines to unactivated alkynes that creates an all-carbon

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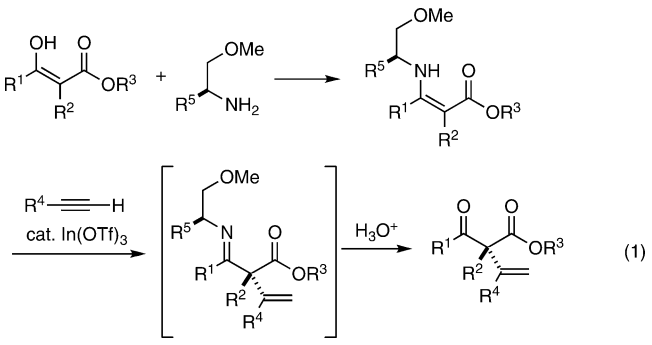
quaternary stereocenter with high efficiency. The synthetic scheme is summarized in eq 1: the addition reaction of an α-substituted β-enaminoester to an alkyne takes place in the presence of an indium(III) catalyst, and acidic workup affords optically active β-ketoesters. This reaction was inspired by a stoichiometric analogue of the reaction that utilized an optically active zinc(II) enamide and an unactivated olefin as reaction partners,[1b] which, however, cannot be applied to quaternary carbon center construction because of our inability to regioselectively generate the necessary but sterically encumbered enolate from α,α-disubstituted ketone or imine starting materials.



(1)

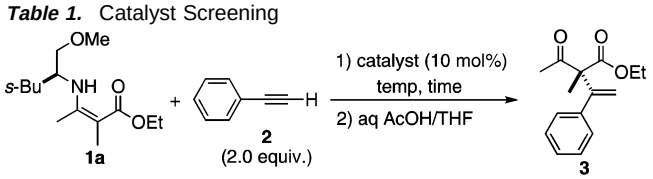
Results and Discussion

General. A variety of enamines **1** bearing a chiral auxiliary was synthesized in 80−90% yield by dehydrative condensation of a dicarbonyl compound and a chiral amine derived from an α-amino acid. They were obtained mostly as a single isomer, a *Z*-enamine form, but no further structure determination was carried out because this geometry is of no consequence in the subsequent reaction.

Screening of the catalyst was carried out for the reaction of a β-enaminoester **1a** derived from L-isoleucine (Table 1). The addition reaction of the enamine **1a** and phenylacetylene **2** was carried out using various catalysts, some of which are shown in Table 1, and subsequent acidic hydrolysis provided the α-alkenylated products. It is noteworthy that the reaction does not require the use of a solvent, although it tolerates the use of aromatic solvents (e.g., toluene; Table 5, entries 5 and 6) when necessary. The reaction in the presence of diethylzinc (10 mol %)[3b] at 70 °C for 8 h gave the corresponding product **3** in 96% yield with 15% ee (entry 1 in Table 1). A combination of zinc(II) bis(trifluoromethanesulfonate), $Zn(OTf)_2$ (10 mol %), and triethylamine, Et_3N (10 mol %),[3a] at 100 °C for 18 h improved the selectivity to 53% ee (entry 2 in Table 1). The reaction with an $In(OTf)_3$ catalyst[2] took place faster than the zinc reaction and gave better enantioselectivity (entry 3 in Table 1). However, the presence of triethylamine reduced the activity of the $In(OTf)_3$ catalyst (entry 4 in Table 1). When a small amount of butyllithium in hexane (10 mol %) was added,[2c] the reaction became faster, and the product was obtained in 92% yield with 94% ee (entry 5 in Table 1). Such beneficial effects of basic additives were also observed for LiOTf (10 mol %, 93% ee) (entry 6 in Table 1). A larger amount of LiOTf (25 mol %) slightly improved the enantioselectivity to 95% ee at the expense of the reaction rate (entry 7 in Table 1). $Mg(OTf)_2$ (10 mol %) behaved similarly to LiOTf (entry 8 in Table 1).

Interestingly, the selectivity increased markedly as the temperature was raised (Table 2f). It increased from 70 to 120 °C

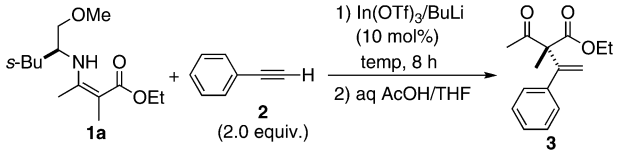
Table 1. Catalyst Screening



entry	catalyst[a]	temp (°C)	time (h)	% yield[b]	% ee[c]
1	Et_2Zn	70	8	96	15
2	$Zn(OTf)_2/Et_3N$	100	18	98	53
3	$In(OTf)_3$	120	6	95	89
4	$In(OTf)_3/Et_3N$	120	12	12	53
5	$In(OTf)_3$/BuLi	120	8	92	94
6	$In(OTf)_3$/LiOTf	120	12	88	93
7	$In(OTf)_3$/LiOTf[d]	120	12	75	95
8	$In(OTf)_3/Mg(OTf)_2$	120	12	90	94

[a] Ratio of zinc or indium salt and additive is 1:1 unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 2.5 equiv of LiOTf vs indium salt was used.

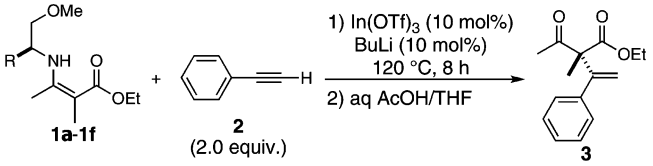
Table 2. Temperature Effect on Stereoselectivity



Entry	temp (°C)	% yield[a]	% ee[b]
1	70	87	68
2	100	94	83
3	120	92	94
4	140	93	91

[a] Isolated yield. [b] Determined by HPLC analysis.

Table 3. Chiral Auxiliary Screening



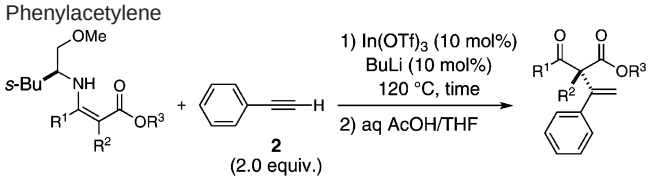
Entry	R	% yield[a]	% ee[b]
1	Bn (**1b**)	93	68
2	*i*-Bu (**1c**)	92	70
3	Ph (**1d**)	87	81
4	*s*-Bu (**1a**)	92	94
5	*i*-Pr (**1e**)	89	89
6	*t*-Bu (**1f**)	91	91

[a] Isolated yield. [b] Determined by HPLC analysis.

(entries 1−3 in Table 2) and decreased again when heated further up to 140 °C (entry 4 in Table 2). Such a temperature effect suggests that the selectivity is controlled by an entropy factor.

Chiral auxiliary screening was performed using the reaction of β-aminocrotonate **1a**−**1f** and phenylacetylene **2** (2.0 equiv) in the presence of $In(OTf)_3$ (10 mol %) and butyllithium (10 mol %) at 120 °C for 8 h (Table 3). All substrates examined herein afforded the desired product **3** in high yields while the enantioselectivity was dependent on the structure of the chiral auxiliaries. Selectivity was low with chiral auxiliaries lacking a branched substituent (68% ee with **1b**, entry 1 in Table 3, and 70% ee with **1c**, entry 2 in Table 3), and the enantioselectivity slightly increased with a phenyl group (derived from L-phenylglycine; 81% ee, entry 3 in Table 3). We finally found

Table 4. Reaction of Various Ketoester Derivatives with Phenylacetylene

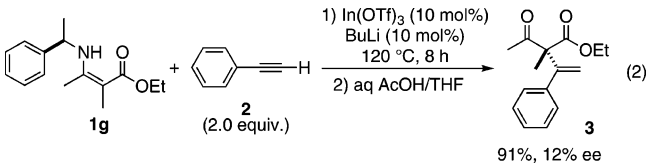


	Enamine						
entry	R^1	R^2	R^3	product	time (h)	% yield[a]	% ee[b]
1	Me	Me	Et (**1a**)	**3**	8	92	94
2	Me	allyl	Et (**4**)	**5**	18	82	94
3	Me	Bn	Et (**6**)	**7**	18	85	95
4	-$(CH_2)_4$-		Et (**8**)	**9**	8	92	97
5	-$(CH_2)_3$-		Me (**10**)	**11**	8	94	96
6	-$(CH_2)_3$-		Et (**12**)	**13**	8	93	94
7	-$(CH_2)_3$-		*i*-Pr (**14**)	**15**	8	93	94
8	-$(CH_2)_3$-		allyl (**16**)	**17**	8	84	92
9	-$(CH_2)_3$-		Bn (**18**)	**19**	8	81	81

[a] Isolated yield. [b] Determined by HPLC analysis.

that the L-isoleucine derivative **1a** gave the best enantioselectivity (94% ee, entry 4 in Table 3). The isopropyl (**1e**) and *t*-butyl (**1f**) substituents are of comparable efficiency: 89% ee (entry 5 in Table 3) and 91% ee (entry 6 in Table 3), respectively.

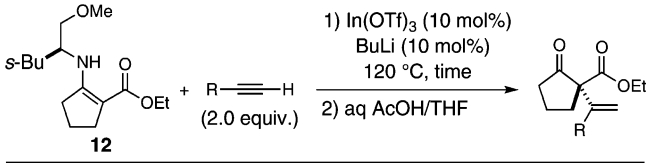
The importance of the methoxy group in the chiral auxiliary already has been documented for a long time[6] and is illustrated here experimentally by the very poor enantioselectivity for the auxiliary without the methoxy group (eq 2).[16] The reaction rate was found to be rather insensitive to the absence of the methoxy group.



Next, we examined the scope of the β-enaminoester substrates under optimized conditions (Table 4). The reactions took place in high yield and with a high enantioselectivity whether or not the enamine moiety was a part of the ring structure. For acyclic substrates **1a**, **4**, and **6**, the substrates with a bulkier α-substituent were rather unreactive but showed higher selectivities (up to 95% ee, entries 1−3 in Table 4). Cyclic substrates underwent the addition reaction as well. The cyclohexanone derivative **8** furnished the product **9** with a higher yield and selectivity (92% yield, 97% ee, entry 4 in Table 4). The 2-oxocyclopentancarboxylate derivatives **10**, **12**, and **14** provided the products **11**, **13**, and **15**, respectively, in good yields with high enantioselectivities (entries 5−7 in Table 4). The allyl ester **16** and the benzyl ester **18** afforded the corresponding product in 84% yield with 92% ee (entry 8 in Table 4) and 81% yield with 81% ee (entry 9 in Table 4), respectively.

Table 5 summarizes the scope of the alkyne substrates. The reaction of **12** with an alkyne (2.0 equiv) was carried out under standard conditions with the use of $In(OTf)_3$ and butyllithium at 120 °C. The reaction with a simple aliphatic alkyne, 1-octyne (**20**), required a somewhat longer reaction time (24 h) to give the corresponding product **21** in 78% yield with 94% ee (entry 2 in Table 5). We found no evidence of either isomerization of the terminal alkene produced to internal alkenes.[2d] The reaction of 1-ethynylcyclohexene (**22**) took place to form the C−C bond in the internal carbon atom to give a diene product **23** that survived nicely under the reaction conditions (88% yield with 88% ee, entry 3 in Table 5). The reaction with electron-donating *p*-methoxyphenylacethylene (**24**) was completed in 4 h to afford the product **25** in 82% yield with 96% ee (entry 4 in Table 5). The electron-withdrawing *p*-methoxycarbonylphenylacetylene (**26**) and *p*-bromoethynylbenzene (**28**) required longer reaction times to provide the corresponding products in 91% yield with 94% ee (**27**) and 93% yield with 94% ee (**29**), respectively (entries 5 and 6 in Table 5). Comparison of the electron-rich and deficient alkynes indicated that the electron-rich alkyne reacts faster than the deficient alkyne, while the yield and enantioselectivity of the product were unaffected by the substituent. This rate profile suggests strongly that Lewis acidic activation of the alkyne by the indium metal is an important step in this reaction.

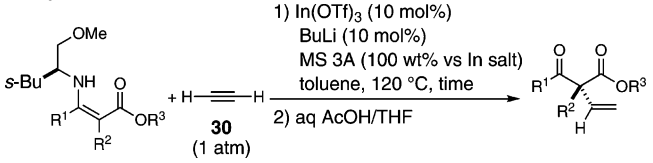
Table 5. Reaction with Various Alkynes



entry	R	product	time (h)	% yield[a]	% ee[b]
1	Ph (**2**)	**13**	8	93	94
2	*n*-Hex (**20**)	**21**	24	78	94
3	1-cyclohexenyl (**22**)	**23**	12	88	88
4	4-$MeOC_6H_4$ (**24**)	**25**	4	82	96
5[c]	4-$MeOCOC_6H_4$ (**26**)	**27**	24	91	94
6[c]	4-BrC_6H_4 (**28**)	**29**	24	93	94

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Reaction was carried out in toluene.

Table 6. Reaction of Various Ketoester Derivatives with Gaseous Acetylene



	Enamine						
entry	R^1	R^2	R^3	time (h)	product	% yield[a]	% ee[b]
1	Me	Bn	Et (**6**)	48	**31**	72	28
2	-$(CH_2)_4$-		Et (**8**)	32	**32**	81	39
3	-$(CH_2)_3$-		Et (**12**)	33	**33**	84	86
4	-$(CH_2)_3$-		Bn (**18**)	34	**34**	79	64

[a] Isolated yield. [b] Determined by HPLC analysis.

The addition to acetylene posed some problems due to the gaseous nature of the compound and the low purity of the acetylene gas that are cheaply available. The reaction, however, took place smoothly under conditions previously developed for the corresponding racemic reaction (Table 6).[2b] Thus, the reaction was carried out under an atmospheric pressure of acetylene gas (welding grade) in the presence of $In(OTf)_3$ (10 mol %), butyllithium (10 mol %), and molecular sieves 3A (100 wt % for the indium catalyst). While the reaction of an acyclic substrate **6** and cyclohexanone derivative **8** resulted in being poorly selective (28% ee, entry 1 in Table 6 and 39% ee, entry

(16) This auxiliary is used for a diastereoselective 1,4-addition reaction. (a) Guingant, A. *Tetrahedron: Asymmetry* **1991**, *2*, 415−418. (b) Cavé, C.; Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 4361−4368.

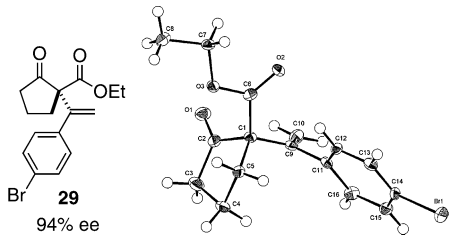


Figure 1. ORTEP drawing of single-crystal structure of **29**.

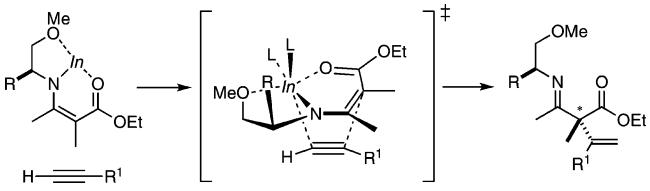


Figure 2. Proposed transition state structure.

2 in Table 6), the cyclopentanone derivatives **12** and **18** afforded the corresponding α-vinyl product in high yield with acceptable selectivity (entries 3 and 4 in Table 6). The poor selectivity with acetylene gas indicates in turn that the steric bulk of the substituent of the 1-alkyne plays a key role in the highly enantioselective reactions described previously.

Absolute Configuration and Mechanistic Considerations. A single crystal of compound **29** was obtained, and its absolute configuration was determined to be *R* by X-ray structural analysis using anomalous dispersion effects (Figure 1).[17] The Flack parameter of the *R* enantiomer was 0.015(7), while that of the *S* enantiomer was close to 1.0.[18]

We previously proposed a transition state model of the racemic version of the present reaction (β-ketoester addition to alkyne) on the basis of a computational study.[2c] Considering this model and the observed *R* configuration of the product to the present system, we can build a reasonable transition state structure as shown in Figure 2. The methoxy group forms a rigid bicyclic ring system with the indium(III) center, which forces the alkyne substituent away from the side chain (R) on the chiral auxiliary. The poor selectivity with acetylene gas conforms to this analysis. The electrophilic nature of the reaction suggested by the data in Table 5 supports the proposed mechanism that is driven by the strong interaction between the indium(III) atom and an alkyne carbon atom.

Conclusion

We have developed an asymmetric indium(III)-catalyzed α-alkenylation reaction of β-ketoesters through the addition of enamides bearing a chiral auxiliary to unactivated 1-alkynes. While the reaction is a catalytic alkyne version of the stoichiometric reaction of the enamides derived from ketones that add to unactivated 1-alkenes, we have so far been unable to apply this catalytic reaction to unactivated alkenes. The origin of the high reactivity is the strong electrophilic interaction of the indium(III) atom to the alkyne that makes the reaction electrophilic in its character and makes the transition state tight enough to attain high enantioselectivity. Despite the high temperature and Lewis acidity of the indium(III) metal atom, the reaction tolerates a considerable range of functional groups. We therefore consider that indium(III), which serves as a Lewis acid, activates specifically a C−C triple bond toward nucleophiles in the presence of certain basic functional groups.

Experimental Procedures

Representative Procedure for Preparation of Chiral Enamine. (*Z*)-Ethyl 3-[(2*S*,3*R*)-1-Methoxy-3-methylpentan-2-ylamino]-2-methylbut-2-enoate (1a). Molecular sieves 4A (5.0 g) was added to a hexane solution (30 mL) of ethyl 2-methylacetoacetate (4.32 g, 30.0 mmol) and (*S*)-1-methoxypentan-2-amine[19] (4.32 g, 33.0 mmol), and the mixture was heated at 50 °C for 12 h. The resulting suspension was cooled to ambient temperature and was filtered through a pad of Celite. The residue was washed with ethyl acetate, and the filtrate was concentrated. The crude product was purified by distillation (13 Pa, 76−77 °C) to afford compound **1a** as a colorless liquid (5.1 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 1.19 (m, 1H), 1.24 (t, J = 6.8 Hz, 3H), 1.55 (m, 1H), 1.62 (m, 1H), 1.79 (s, 3H), 1.97 (s, 3H), 3.32 (m, 1H), 3.33 (s, 3H), 3.45 (dd, J = 9.2 Hz, 6.9 Hz, 1H), 3.52 (m, 1H), 4.23 (m, 2H), 9.42 (d, J = 9.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.9, 12.8, 14.6, 15.5, 15.6, 24.7, 37.4, 57.4, 58.6, 59.2, 74.5, 86.5, 159.6, 171.0. IR (cm^{-1}) 3249 (br), 2970 (w), 2894 (w), 1640 (m), 1590 (s), 1478 (m), 1250 (vs), 1173 (w), 1102 (vs), 780 (m). Anal. calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44; Found: C, 65.26; H, 10.75; N, 5.31.

Representative Procedure for Asymmetric Alkenylation Reaction. (*R*)-Isopropyl 2-Oxo-1-(1-phenylvinyl)cyclopentanecarboxylate (15). Indium(III) triflate was dried under reduced pressure (26 Pa) at 60 °C for 2 h and then at 160 °C for 10 h before use. To the dried indium triflate (16.8 mg, 0.030 mmol) was added 19 μL of butyllithium (1.60 M hexane solution, 0.030 mmol) to afford a white paste. To this mixture was added enamine **14** (849 mg, 3.0 mmol) and phenylacetylene **2** (612 mg, 6.0 mmol) successively to afford a pale-yellow homogeneous liquid. This mixture was heated immediately at 120 °C. The color of the reaction mixture gradually turned orange. The reaction was monitored by TLC analysis. After stirring for 8 h, enamine **14** was completely consumed. The mixture was cooled to room temperature and diluted with THF (3.0 mL). To the mixture was added an aqueous solution of acetic acid (ca. 1 M, 3.0 mL). After stirring for 6 h, the solution was neutralized by a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt, and the combined organic layer was dried over Na_2SO_4. Concentration and silica gel column chromatography afforded pure product **15** as a pale-yellow oil (741 mg, 91% yield). When the reaction was run in a 0.3 mmol scale, the yield was 93%, which is shown in Table 4 (entry 7). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.73−1.82 (m, 1H), 1.86−1.94 (m, 1H), 2.09−2.14 (m, 1H), 2.33−2.44 (m, 2H), 2.64 (ddd, J = 13.2 Hz, 8.9 Hz, 6.9 Hz, 1H), 5.04 (hept, J = 6.3 Hz, 1H), 5.27 (s, 1H), 5.46 (s, 1H), 7.23−7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9, 21.2, 21.5, 34.0, 37.2, 66.7, 69.4, 118.8, 127.5 (2C), 127.6 (2C), 128.1, 140.0, 144.9, 169.8, 212.1. IR (cm^{-1}) 3057 (w), 2980 (m), 2897 (w), 1749 (vs), 1714 (vs), 1621 (w), 1494 (w), 1455 (w), 1374 (w), 1251 (vs), 1181 (m), 1139 (m), 1104 (vs), 1031 (w), 992 (w), 957 (w), 911 (s), 826 (m), 776 (s), 730 (m), 703 (w). Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40; Found: C, 75.21; H, 7.59. Chiral HPLC: CHIRALPAK AD-H (Daicel), hexane/*i*-PrOH = 95:5, 1 mL/min, 20 °C, 254 nm, 9.4 min (major)/14.3 min (minor). $[\alpha]^{29}_D$ −61.0 (*c* 0.30, $CHCl_3$, 94% ee).

Representative Procedure for Addition to Acetylene Gas. (*R*)-Ethyl 2-Benzyl-2-ethanoylbut-3-enoate (31). Dried indium(III) triflate (12.9 mg, 0.024 mmol) and molecular sieves 3A (12.9 mg) were placed into a flame-dried reaction vessel (15 mL) equipped with a balloon

(17) Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876−881.
(18) Single crystal used for the X-ray structural analysis was analyzed by HPLC to provide the same retention time as the major enantiomer.
(19) (*S*)-1-Methoxypentan-2-amine was prepared by methylation of L-(+)-isoleucinol with NaH/MeI according to Meyers et al.'s procedure: Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 3081−3087.

filled with 1 atm pressure of welding-grade acetylene gas. The solids were treated with butyllithium (1.6 M, 15 μL, 0.024 mmol) under argon, and the vessel was evacuated and then acetylene was introduced via the balloon. Under acetylenic atmosphere, enamine **6** (0.24 mmol) and toluene (240 μL) were added, and the resulting suspension was heated at 120 °C for 48 h. The resulting mixture was cooled to room temperature, diluted with THF (500 μL), and treated with an aqueous solution of acetic acid (ca. 1 M, 500 μL). After stirring for 6 h, the mixture was neutralized with an aqueous $NaHCO_3$ solution, extracted with ethyl acetate, and concentrated. The crude product was purified by silica gel column chromatography to afford pure product **31** as a pale-yellow oil (43 mg, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, J = 7.5 Hz, 3H), 2.12 (s, 3H), 3.23 (d, J = 13.7 Hz, 1H), 3.39 (d, J = 13.7 Hz, 1H), 4.14 (dq, J = 10.9 Hz, 7.5 Hz, 1H), 4.20 (dq, J = 10.9 Hz, 7.5 Hz, 1H), 5.15 (d, J = 17.7 Hz, 1H), 5.38 (d, J = 10.9 Hz, 1H), 6.31 (dd, J = 17.7 Hz, 10.9 Hz, 1H), 7.09 (dd, J = 7.2 Hz, 1.8 Hz, 2H), 7.19−7.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 27.3, 41.3, 61.5, 67.3, 117.9, 126.7, 128.0 (2C), 130.0 (2C), 135.3, 136.1, 170.5, 201.8. IR (cm^{-1}) 3031 (w), 2983 (w), 2939 (w), 1713 (vs), 1497 (w), 1455 (w), 1355 (w), 1260 (m), 1173 (s), 1084 (m), 1017 (m), 996 (m), 928 (m), 857 (w), 739 (w), 700 (vs). Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 73.17; H, 7.62. Chiral HPLC: CHIRALPAK OJ-H (Daicel), hexane/*i*-PrOH = 99.9:0.1, 0.5 mL/min, 20 °C, 275 nm, 34.1 min (major)/39.3 min (minor). $[\alpha]^{23}_D$ −4.28 (*c* 0.73, $CHCl_3$, 28% ee).

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

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