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Development of a palladium catalyzed addition of boronic acids to alkynyl esters: synthesis of trisubstituted olefins as single isomers

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ABSTRACT

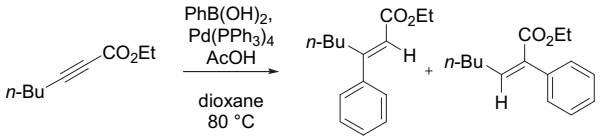
Very small phosphine ligands allow access to single isomer trisubstituted olefins from alkynyl esters with complete control of both stereochemistry and regiochemistry. This method provides a convenient synthesis of single isomer trisubstituted olefins without requiring olefin templates.

1. Introduction

The synthesis of trisubstituted olefins in a stereocontrolled manner is a challenging endeavor in organic chemistry. Direct syntheses such as the Wittig,[1] Horner–Wadsworth–Emmons,[2] or olefin metathesis reactions[3] typically produce mixtures of isomers that can be difficult to separate. To address this issue of stereoselectivity, indirect approaches have been explored.[4,5] Metal-catalyzed addition reactions of organometallic reagents to alkynes provides a direct entry to trisubstituted olefins, provided that regio- and stereochemistry can be tightly controlled.[6]

Recent work has shown that alkynes,[7] alkenes,[8] or organoboronic acids[9,10] can be added to alkynes using catalysts to generate trisubstituted olefin products. The addition of a variety of arylboronic acids to alkynyl esters was enabled by the use of copper acetate in methanol, giving regioisomers such as **2** excluseively.[10] When alkynyl esters were used as coupling partners in the presence of a palladium catalyst and under mildly acidic conditions, the corresponding trisubstituted α,β-unsaturated esters were obtained in very good yields, but as mixtures of regioisomers **2** and **3**[9a,b] (Scheme 1). Further research improved the regioselectivity using a pincer-type aryl phosphine ligand,[9c] however small amounts of regioisomeric products such as **3** were always present. In this paper we present a catalyst system that produces single isomer trisubstituted olefins by enabling the addition of boronic acids to alkynyl esters in very mild conditions. The process utilizes neutral conditions and *small* phosphine ligands, and appears to function through a palladium-hydride system.

Previous work in our laboratory had shown that single isomer trisubstituted olefins could be synthesized from (*E*)-β-chloro-α-iodo-α,β-unsaturated esters by cross-coupling with organoboronic acids.[11] As part of this work, a mechanistic study was done that involved submitting an alkynyl ester to the template cross-coupling reaction conditions. This experiment produced trisubstituted olefins such as **5** and regioisomeric products such as **6**[12] in low yield (10%). Although inefficient, the high stereoselectivity encouraged us to develop this process to produce single isomer trisubstituted olefins.



1 2 3

Scheme 1. Coupling of arylboronic acids and alkynyl esters.

2. Results and discussion

Using our previous mechanistic observation as a starting point, a 3:1 mixture of the desired product **5** and the regioisomer **6** was isolated in a 10% combined yield (Table 1, entry 1). Adding water to the reaction mixture[13] increased the yield to 50%, however, no improvement in regioselectivity was noted (entry 2). Employing $Pd(OAc)_2$ as a palladium source resulted in an increase in both yield (89%) and regioselectivity in favor of **5** over **6** (entry 3). The use of bulky ligands such as Cy_3P gave high regioselectivity (19:1) together with good overall yields (entry 4). When PPh_3 was used as the ligand, the efficiency of the process suffered (entry 5). A reaction performed with *S*-Phos (entry 6) gave very good regioselectivity (97:3) but the overall yield was moderate. The use of smaller alkyl-substituted ligands produced success. As shown in entry 7, $t\text{-}Bu_2MeP$ worked quite well as a ligand, giving high yield (95%) and excellent regioselectivity. By decreasing the size of the ligand slightly to Et_3P, we were able to suppress the formation of **6**,

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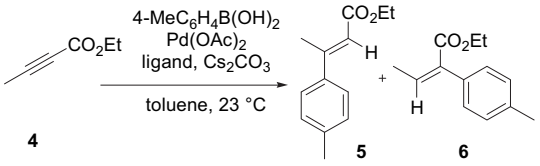
isolating only product **5** in 85% yield (entry 8).[14] The smaller ligand, Me_3P (entry 9) gave exclusive regioselectivity, however, the yield decreased to 59%.

Table 1
Optimization of the formation of trisubstituted olefins from alkynyl esters and boronic acids



Entry[a]	Ligand	Yield (%)	Ratio (**5**:**6**)
1[b,c]	*t*-$Bu_3P\cdot HBF_4$	10	75:25
2[b]	*t*-$Bu_3P\cdot HBF_4$	50	75:25
3	*t*-$Bu_3P\cdot HBF_4$	89	85:15
4	$Cy_3P\cdot HBF_4$	86	95:5
5	Ph_3P	53	93:7
6	*S*-Phos	69	97:3
7	*t*-$Bu_2MeP\cdot HBF_4$	95	96:4
8	$Et_3P\cdot HBF_4$	85	Only **5**
9	$Me_3P\cdot HBF_4$	59	Only **5**

[a] 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of ligand, 2.0 equiv of 4-$MeC_6H_4B(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of H_2O, toluene, 23 °C, 18 h.
[b] $Pd_2(dba)_3$ was used in place of $Pd(OAc)_2$.
[c] No H_2O was added.

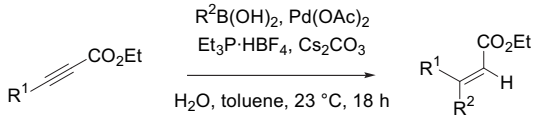
Variations in the ligand to palladium ratio were explored and it was found that a 3:1 ratio of ligand to metal was optimal. Using a 2:1 or 4:1 ratio of ligand to metal resulted in lower yields of **5** (45 and 61%, respectively).[15]

Simple boronic acids worked well under the reaction conditions, giving trisubstituted olefins in good yield (Table 2, entry 1). The presence of an electron-donating group on the boronic acid component had minimal impact on the reactivity, regardless of whether the substituent was in the *ortho*-, *meta*-, or *para*-positions (entries 2–7). Electron-withdrawing groups were compatible with the process, giving the trisubstituted products in moderate yields (entries 8 and 9). Coupling with sp^2 hybridized partners such as vinyl or styrenyl boronic acids gave moderate to good yields as shown in entries 10 and 11. No loss of olefin stereochemical information in the coupling partner was noted and these products were isolated as single isomers. The steric bulk of the boronic acid did not affect the yield of the process, as shown in entries 12 and 13 in which the use of either 1- or 2-naphthylboronic acids afforded the respective addition products in good yields. Heterocyclic boronic acids were also tolerated, as shown by the results of entry 14 employing a 3-thiophenylboronic acid.

The presence of branched substituents on the alkynyl starting material resulted in an efficient coupling as shown in entry 15 in which a cyclohexyl substituent was used. It was possible to substitute the alkyne component with a phenyl group, a modification that produced the desired trisubstituted olefin as a single isomer (entry 16). In both of these cases the newly introduced hydrogen and aryl ring were *syn* to each other, indicating that product stereochemistry was a consequence of mechanism and not of thermodynamics. The presence of substituted alkyl chains was compatible with the reaction conditions as shown in entries 18 and 19, although using methyl propyolate as a substrate did not provide useful amounts of product (entry 17). Finally, the reaction proceeded with complete selectivity when the carboxylate moiety on the alkyne was replaced with a Weinreb amide (entries 20 and 21). In all cases, the products were isolated as single isomers.[16]

In order to identify the hydrogen source, a series of isotope labeling experiments were done. Only product **7** was obtained when **4** was coupled with $PhB(OH)_2$ in C_6D_6 indicating that the solvent was not the hydrogen source (Table 3, entry 2). Performing a reaction between alkyne **4** and phenylboronic acid in the presence of D_2O gave the alkene products **7** and **34** with 70% deuterium incorporation (entry 3). Using an excess of D_2O did not significantly increase the proportion of the deuterated product **34**, as shown in entry 4. Performing a reaction with a deuterated boronic acid (40% D) resulted in almost no deuterium incorporation (entry 5). These results suggested that H_2O or boronic acid was the hydrogen source. A significant deuterium isotope effect was operative. Evidence supporting this is shown in entry 6, in which a reaction was

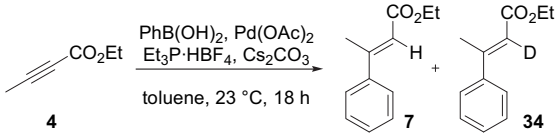
Table 2
Formation of trisubstituted olefins from alkynyl esters and boronic acids



Entry[a]	Substrate	Product[b]	Yield (%)
1	**4**: R^1=Me	**7**: R^2=C_6H_5	77
2	**4**: R^1=Me	**5**: R^2=4-MeC_6H_4	85
3	**4**: R^1=Me	**8**: R^2=3-MeC_6H_4	75
4	**4**: R^1=Me	**9**: R^2=2-MeC_6H_4	80
5	**4**: R^1=Me	**10**: R^2=4-$MeOC_6H_4$	67
6	**4**: R^1=Me	**11**: R^2=3-$MeOC_6H_4$	67
7[c]	**4**: R^1=Me	**12**: R^2=2-$MeOC_6H_4$	58
8	**4**: R^1=Me	**13**: R^2=4-FC_6H_4	58
9[c]	**4**: R^1=Me	**14**: R^2=4-$MeCOC_6H_4$	49
10	**4**: R^1=Me	**15**: R^2=C_6H_4CHCH	51
11[c]	**4**: R^1=Me	**16**: R^2=C_6H_{13}CHCH	86
12	**4**: R^1=Me	**17**: R^2=1-naphthyl	77
13	**4**: R^1=Me	**18**: R^2=2-naphthyl	78
14	**4**: R^1=Me	**19**: R^2=3-thiophene	56
15	**20**: R^1=Cy	**21**: R^2=4-MeC_6H_4	77
16	**22**: R^1=Ph	**23**: R^2=4-MeC_6H_4	66
17[d]	**24**: R^1=H	**25**: R^2=4-MeC_6H_4	10
18	**26**: R^1=$BnO(CH_2)_2$	**27**: R^2=4-MeC_6H_4	71
19	**28**: R^1=$TIPSO(CH_2)_4$	**29**: R^2=4-MeC_6H_4	68
20[e]	**30**: R^1=$Me(CH_2)_5$	**31**: R^2=4-MeC_6H_4	60
21[e]	**32**: R^1=C_6H_{12}	**33**: R^2=C_6H_5	56

[a] 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P\cdot HBF_4$, 2.0 equiv of $R^2B(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of H_2O, toluene, 23 °C, 18 h.
[b] Products were obtained as single isomers.
[c] *t*-$Bu_2MeP\cdot HBF_4$ was used in place of $Et_3P\cdot HBF_4$.
[d] Methyl ester was used.
[e] Weinreb amide was used in place of the ester.

Table 3
Source of hydrogen during trisubstituted olefin formation from alkynes



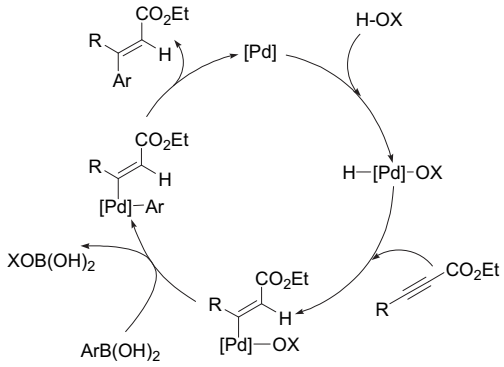
Entry[a]	Boronic acid	Additive	Yield (%)	Ratio (**7**:**34**)[b]
1	$PhB(OH)_2$	H_2O	77	100:0
2[c]	$PhB(OH)_2$	H_2O	64	100:0
3	$PhB(OH)_2$	D_2O	66	30:70
4[d]	$PhB(OH)_2$	D_2O	72	27:73
5	$PhB(OD)_2$[e]	H_2O	63	97:3
6	$PhB(OD)_2$[e]	D_2O	68	30:70
7	$PhB(pin)_2$	None	Trace	
8	$PhB(pin)_2$	H_2O	36	100:0
9	$PhB(pin)_2$	D_2O	30	40:60
10	$C_6D_5B(OH)_2$	H_2O	78	100:0

[a] 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P\cdot HBF_4$, 2.0 equiv of $PhB(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of additive, toluene, 23 °C, 18 h.
[b] Products were obtained as single isomers.
[c] Reaction performed in C_6D_6.
[d] 30 equiv of D_2O were used.
[e] 40% D.

done using both deuterated boronic acid (40% D) and D_2O that gave only 70% deuterium incorporation.[17]

Using the pinacol ester of phenylboronic acid, the reaction did not proceed. However when water was added to the mixture a moderate yield of product **7** was noted (entries 7 and 8). Performing a coupling with the pinacol ester and D_2O, we observed 60% deuterium incorporation in the product. The remaining 40% (product **7**) could possibly have arisen from the $Et_3P{\cdot}HBF_4$ salt. As a final control experiment, we performed a reaction with $C_6D_5B(OH)_2$ and H_2O in order to see if the hydrogen could have been derived from a 1,4-Pd shift on the aryl group of the product.[18] No deuterium incorporation was observed under these conditions (entry 10).

Based on these experiments and on previous proposals,[8,9,19] the following mechanism is proposed (Scheme 2). Palladium undergoes oxidative insertion into an OH bond to form an initial H–Pd–OX species. This step is suggested by the observation of an isotope effect for hydrogen transfer and by the fact that pinacol boronic esters do not undergo the process in the absence of water. The HOX species may be water as a fast exchange between boronic acid and water would account for the observed isotope effect.[20] Following the oxidative insertion, there occurs a *syn* carbopalladation into the triple bond of the alkynyl ester, forming a palladium intermediate with the observed regio- and stereochemistry. Transmetallation of the arylboronic acid is followed by reductive elimination to regenerate the palladium catalyst and produce the final product.



Scheme 2. Proposed mechanism.

3. Conclusion

By using the sterically unencumbered phosphine ligand, Et_3P, single isomer trisubstituted olefins have been generated from alkynyl esters by coupling with either aryl or alkenyl boronic acids. The reactions proceeded easily at room temperature under very mild conditions and in all cases produced the products as single isomers. Ligand size proved to be critical in this process as only small ligands such as Me_3P or Et_3P resulted in the production of single isomers. This new methodology provides a convenient synthesis of trisubstituted olefins without the need to generate olefin templates.

4. Experimental

4.1. General

Reactions were performed under nitrogen in flame-dried glassware equipped with a magnetic stir bar and a rubber septum. Solvents were freshly distilled prior to use as follows: THF and toluene over sodium/benzophenone; dioxane over calcium hydride. All other reagents were obtained from commercial sources and used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates precoated with silica gel 60 F_{254}. The plates were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or *p*-anisaldehyde stains. Flash chromatography was carried out on 230–400 mesh silica gel 60. ^1H and ^{13}C NMR spectra were acquired on a Bruker Advance 400 MHz instrument in the specified solvent, reporting chemical shifts downfield from tetramethylsilane. Infrared spectra were acquired from neat films on a sodium chloride cell using a Bomen Michaelson 100 FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer using either electron impact (EI) or chemical ionization (CI). High resolution mass spectroscopy (HRMS) was performed with an electron beam of 70 eV, or using a double focusing magnetic sector mass spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected.

4.2. General procedure for the preparation of trisubstituted alkenes. (*E*)-Ethyl-3-*p*-tolylbut-2-enoate (5)[11]

To a flame-dried vial equipped with a Teflon-coated stir bar were added $Pd(OAc)_2$ (4.8 mg, 0.007 mmol), $Et_3P{\cdot}HBF_4$ (4.1 mg, 0.02 mmol), 4-tolylboronic acid (29.9 mg, 0.22 mmol), and Cs_2CO_3 (74.9 mg, 0.23 mmol). Freshly distilled toluene was introduced (2.0 mL) followed by H_2O (20.0 μL, 1.1 mmol) and ethyl 2-butynoate **4** (12.5 mg, 0.112 mmol). The solution was stirred for 18 h at room temperature, then diluted with Et_2O, and washed three times with H_2O. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The pure product **5**[11] (20.1 mg, 88%) was obtained as a clear oil by flash chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether). ^1H NMR (400 MHz, acetone-d_6) δ 7.46 (d, J=8.0 Hz, 2H), 7.23 (d, J=7.8 Hz, 2H), 6.12 (q, J=1.2 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.55 (d, J=1.2 Hz, 3H), 2.35 (s, 3H), 1.27 (t, J=7.2 Hz, 3H).

4.3. (*E*)-Ethyl 3-(3-methylphenyl)-but-2-enoate (8)

Prepared from ethyl 2-butynoate (12.5 mg, 0.112 mmol) and 3-tolylboronic acid (29.9 mg, 0.22 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (17.2 mg, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 3H), 7.19–7.16 (m, 1H), 6.13 (q, J=1.2 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 2.57 (d, J=1.2 Hz, 3H), 2.38 (s, 3H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 155.7 (C), 142.2 (C), 138.1 (C), 129.7 (CH), 128.4 (CH), 127.0 (CH), 123.4 (CH), 116.9 (CH), 59.8 (CH_2), 21.4 (CH_3), 18.0 (CH_3), 14.3 (CH_3); IR (neat) 1713, 1631 cm^{-1}; MS 175.1 ($M^+-C_2H_5$); HRMS calcd for $C_{11}H_{11}O_2$ ($M^+-C_2H_5$) 175.0759, found 175.0754.

4.4. (*E*)-Ethyl 3-(2-methylphenyl)-but-2-enoate (9)

Prepared from ethyl 2-butynoate (12.5 mg, 0.112 mmol) and 2-tolylboronic acid (29.9 mg, 0.22 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound as a colorless oil (18.3 mg, 80%) after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.13 (m, 3H), 7.06–7.04 (m, 1H), 5.74 (q, J=1.6 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 2.43 (d, J=1.6 Hz, 3H), 2.72 (s, 3H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C), 158.2 (C), 143.9 (C), 133.9 (C), 130.4 (CH), 127.6 (CH), 127.1 (CH), 125.7 (CH), 119.4 (CH), 59.8 (CH_2), 20.8 (CH_3), 19.7 (CH_3), 14.3 (CH_3); IR (neat) 1716, 1635 cm^{-1}; MS 189.1 (M^+-CH_3); HRMS calcd for $C_{12}H_{13}O_2$ (M^+-CH_3) 189.0910, found 189.0902.

4.5. (2*E*,4*E*)-Ethyl 3-methylundeca-2,4-dienoate (16)

Prepared from ethyl 2-butynoate (12.5 mg, 0.112 mmol) and 1-octenylboronic acid (34.3 mg, 0.22 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (21.1 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (m, 2H), 5.69 (d, J=1.2 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.26 (d, J=1.2 Hz, 3H), 2.18–2.13 (m, 2H), 1.45–1.38 (m, 2H), 1.34–1.25 (m, 9H), 0.89 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 152.7 (C), 137.5 (CH), 133.6 (CH), 117.5 (CH), 59.6 (CH_2), 33.0 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 13.8 (CH_3); IR (neat) 1714, 1638 cm^{-1}; MS 224.2 (M+); HRMS calcd for $C_{12}H_{19}O$ ($M^+-C_2H_5O$) 179.1436, found 179.1438.

4.6. (*E*)-Ethyl 3-(thiophen-3-yl)-but-2-enoate (19)

Prepared from ethyl 2-butynoate (12.5 mg, 0.112 mmol) and 3-thiofuranylboronic acid (28.2 mg, 0.22 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (12.3 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.48 (m, 1H), 7.32–7.31 (m, 2H), 6.23 (q, J=1.6 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 2.57 (d, J=1.6 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 148.9 (C), 143.4 (C), 126.1 (CH), 125.2 (CH), 124.1 (CH), 115.3 (CH), 59.8 (CH_2), 17.2 (CH_3), 14.3 (CH_3); IR (neat) 1709, 1621 cm^{-1}; MS 196.1 (M^+); HRMS calcd for $C_{10}H_{12}O_2S$ (M^+) 196.0558, found 196.0558.

4.7. (*E*)-Ethyl 3-cyclohexyl-3-p-tolylacrylate (21)

Prepared from ethyl 3-cyclohexylpropiolate[21] (40.2 mg, 0.223 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (46.7 mg, 77%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.19–7.17 (m, 2H), 7.12–7.10 (m, 2H), 5.60 (s, 1H), 4.15 (q, J=7.2 Hz, 2H), 3.81–3.74 (m, 1H), 2.33 (s, 3H), 1.75–1.62 (m, 5H), 1.41–1.23 (m, 8H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3 (C), 167.3 (C), 140.3 (C), 139.0 (C), 130.3 (CH), 129.3 (CH), 120.1 (CH), 61.2 (CH_2), 42.3 (CH), 33.3 (CH_2), 28.2 (CH_2), 27.6 (CH_2), 22.1 (CH_3), 15.6 (CH_3); IR (neat) 1715, 1626 cm^{-1}; MS 272.2 (M+); HRMS calcd for $C_{17}H_{21}O_2$ (M^+-CH_3) 257.1542, found 257.1535.

4.8. (*E*)-Ethyl 5-(benzyloxy)-3-p-tolylpent-2-enoate (27)

Prepared from ethyl 5-(benzyloxy)-pent-2-ynoate[22] (26.4 mg, 0.112 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (26.2 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=8.5 Hz, 2H), 7.35–7.25 (m, 5H), 7.17 (d, J=8.0 Hz, 2H), 6.12 (s, 1H), 4.49 (s, 2H), 4.20 (q, J=7.0 Hz, 2H), 3.64 (t, J=7.0 Hz, 2H), 3.45 (t, J=7.0 Hz, 2H), 2.37 (s, 3H), 1.31 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 156.8 (C), 139.1 (C), 138.5 (C), 138.2 (C), 129.2 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 117.9 (CH), 72.6 (CH_2), 69.3 (CH_2), 59.9 (CH_2), 31.6 (CH_2), 21.2 (CH_3), 14.3 (CH_3); IR (neat) 1705, 1618 cm^{-1}; MS 279.1 ($M^+-C_2H_5O$); HRMS calcd for $C_{19}H_{19}O_2$ ($M^+-C_2H_5O$) 279.1385, found 279.1389.

4.9. Ethyl 7-(triisopropylsilyloxy)-hept-2-ynoate (28)

To an oven-dried round bottom flask equipped with a Teflon-coated stir bar was added freshly distilled THF (50 mL) and (hex-5-ynyloxy)-triisopropylsilane (4.9 g, 19.3 mmol). The resulting solution was cooled to −78 °C and butyllithium (9.2 mL, 23.1 mmol) was added by syringe pump over 10 min. After all the butyllithium had been added, a solution of ethyl chloroformate (3.7 mL, 38.5 mmol) in THF (15 mL) was added by syringe pump over 45 min. After the addition of the ethyl chloroformate was complete, the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl solution and extracted thrice with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by flash chromatography (1% ether in petroleum ether) to afford the title compound as a clear oil (4.53 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, J=6.9 Hz, 2H), 3.71 (t, J=6.0 Hz, 2H), 2.78 (t, J=6.9 Hz, 2H), 1.62–1.73 (m, 4H), 1.30 (t, J=7.2 Hz, 3H), 1.02–1.11 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (C), 89.3 (C), 73.3 (C), 62.6 (CH_2), 61.7 (CH_2), 31.9 (CH_2), 24.2 (CH_2), 18.5 (CH_2), 18.0 (CH_3), 14.0 (CH), 11.9 (CH_3); IR (neat) 2240, 1714 cm^{-1}; MS 283.2 ($M^+-C_3H_7$); HRMS calcd for $C_{15}H_{27}O_3Si$ ($M^+-C_3H_7$) 283.1729, found 283.1739.

4.10. (*E*)-Ethyl 3-p-tolyl-5-(triisopropylsilyloxy)-pent-2-enoate (29)

Prepared from ethyl 7-(triisopropylsilyloxy)pent-2-ynoate **28** (72.3 mg, 0.221 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colorless oil (62.9 mg, 68%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.43 (d, J=8.4 Hz, 2H), 7.22 (d, J=8.4 Hz, 2H), 6.03 (s, 1H), 4.16 (q, J=7.2 Hz, 2H), 3.70 (t, J=6.0 Hz, 2H), 3.18 (t, J=7.6 Hz, 2H), 2.35 (s, 3H), 1.62–1.51 (m, 4H), 1.27 (t, J=7.2 Hz, 3H), 1.08–1.02 (m, 21H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.7 (C), 162.1 (C), 140.8 (C), 140.0 (C), 131.1 (CH), 128.4 (CH), 118.2 (CH), 64.7 (CH_2), 61.1 (CH_2), 34.6 (CH_2), 31.6 (CH_2), 27.1 (CH_2), 22.2 (CH_3), 19.4 (CH_3), 15.7 (CH_3), 13.7 (CH_3); IR (neat) 1715, 1623 cm^{-1}; MS 375.2 ($M^+-C_3H_7$); HRMS calcd for $C_{22}H_{35}O_3Si$ ($M^+-C_3H_7$) 375.2355, found 375.2346.

4.11. (*E*)-*N*-Methoxy-*N*-methyl-3-*p*-tolylnon-2-enamide (31)

Prepared from *N*-methoxy-*N*-methylnon-2-ynamide **30**[23] (20.6 mg, 0.104 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound after purification by flash column chromatography (3% EtOAc in petroleum ether followed by 5% EtOAc in petroleum ether) as a colorless oil (18.0 mg, 60%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.40 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.4 Hz, 2H), 6.49 (s, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 3.06 (t, J=7.2 Hz, 2H), 2.34 (s, 3H), 1.42–1.23 (m, 8H), 0.85 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 169.2 (C), 158.2 (C), 141.0 (C), 140.1 (C), 131.0 (CH), 128.4 (CH), 117.6 (CH), 62.8 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.0 (CH_2), 30.7 (CH_2), 24.2 (CH_2), 22.1 (CH_3), 15.3 (CH_3); IR (neat) 1650; MS 229.2 ($M^+-C_2H_6NO$); HRMS calcd for $C_{16}H_{21}O$ ($M^+-C_2H_6NO$) 229.1592, found 229.1586.

4.12. 3-Cyclohexyl-*N*-methoxy-*N*-methylpropiolamide (32)

To an oven-dried round bottom flask equipped with a Teflon-coated stir bar was added ethynylcyclohexane (0.35 mL, 2.7 mmol) in freshly distilled THF (25 mL). The solution was cooled to −78 °C and butyllithium (1.2 mL, 3.0 mmol) was added via syringe pump over 30 min. After stirring for 30 min, methoxy(methyl)carbamic chloride[24] (0.52 mL, 5.4 mmol) was added via cannula, rinsing the flask once with THF (10 mL), and the resulting solution was stirred

for 60 min at −78 °C. After warming the reaction to room temperature and stirring overnight, the reaction was quenched with 10% HCl solution (50 mL) then extracted three times with EtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ followed by brine and then dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (1% Et_2O in hexanes followed by 4% Et_2O in hexanes) to afford the title compound as a clear oil (458.2 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.24 (s, 3H), 2.54–2.59 (m, 1H), 1.81–1.85 (m, 2H), 1.67–1.74 (m, 2H), 1.48–1.56 (m, 3H), 1.30–1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.1 (C), 77.2 (CH_3), 73.1 (C), 61.8 (CH_3), 31.5 (CH_2), 29.0 (CH), 25.6 (CH_2), 24.5 (CH_2); IR (neat) 2232, 1643 cm^{-1}; MS 195.1 (M^+); HRMS calcd for $C_{11}H_{17}NO_2$ (M^+) 195.1259, found 195.1259.

4.13. (*E*)-3-Cyclohexyl-*N*-methoxy-*N*-methyl-3-phenylacrylamide (33)

Prepared from 3-cyclohexyl-*N*-methoxy-*N*-methylpropiolamide **32** (22.5 mg, 0.115 mmol) using a procedure similar to that described for (*E*)-ethyl 3-(4-methylphenyl)-but-2-enoate **5** that provided the title compound as a colorless oil (17.2 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.35 (m, 3H), 7.18–7.21 (m, 2H), 6.07 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H), 1.61–1.77 (m, 5H), 1.33–1.43 (m, 2H), 1.19–1.29 (m, 3H), 1.02–1.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1 (C), 127.8 (CH), 127.6 (CH), 127.1 (CH), 117.4 (CH), 61.4 (CH_3), 40.8 (CH_3), 32.6 (CH_2), 31.7 (CH_2), 26.4 (CH_2), 26.0 (CH_2); IR (neat) 1645 cm^{-1}; MS 273.2 (M^+); HRMS calcd for $C_{15}H_{17}O$ ($M^+-C_2H_6NO$) 213.1279, found 213.1285.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.029.

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15. A small amount (5–7%) of the homo-coupled product 4,4′-dimethyl-biphenyl was detected in these reactions.
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