JOC*Note*

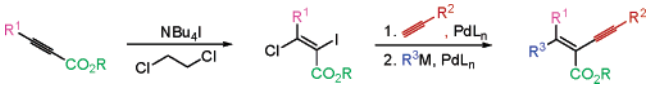
Single-Isomer Tetrasubstituted Olefins from Regioselective and Stereospecific Palladium-Catalyzed Coupling of β-Chloro-α-iodo-α,β-unsaturated Esters

Alison B. Lemay, Katarina S. Vulic, and William W. Ogilvie*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

wogilvie@science.uottawa.ca

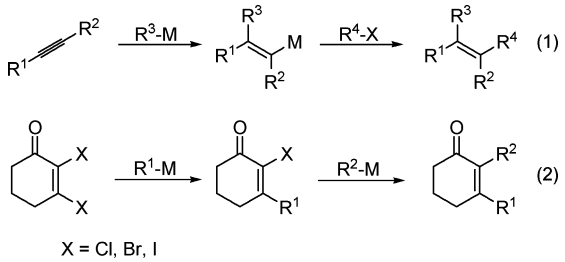
Received January 23, 2006



The efficient regioselective and stereospecific synthesis of tetrasubstituted olefins using a mild and convenient method is disclosed. 2-Alkynyl esters are selectively converted to *E*-β-chloro-α-iodo-α,β-unsaturated esters by exposure to Bu_4NI in refluxing dichloroethane. These products are produced cleanly, regio- and stereoselectively, and in high yields. Single-isomer tetrasubstituted olefins bearing four different carbon substituents are then synthesized by sequential palladium-catalyzed coupling reactions. Selectivity results from reactivity differences in the intermediate substrates.

Tetrasubstituted olefins are key structural elements of natural products and pharmaceuticals such as Nileprost[1] and Tamoxifen.[2] These moieties also serve as substrates for asymmetric transformations that generate contiguous, asymmetric, quaternary centers such as osmylations,[3] epoxidations,[4] and conjugate additions.[5] To ensure high stereocontrol in synthesis, and enantioselectivity in the latter processes, it is imperative that methods be available to prepare tetrasubstituted olefins with tight control of regio- and stereochemistry.

The efficient regio- and stereoselective synthesis of tetrasubstituted olefins is particularly challenging.[6] Steric encumbrance about the olefin and frequent lack of directing substituents contribute significantly to this problem. Classic double-bond-forming methods such as the Wittig and Horner−Wadsworth−Emmons reactions encounter serious issues of generality and stereoselectivity when used to form tetrasubstituted double bonds.[7] This has mandated the development of indirect methods to prepare these moieties, including the carbometalation of alkynes followed by organometallic coupling (eq 1)[8] and the functionalization of existing alkene templates (eq 2).[9]



Regioselectivity is often problematic in the first method, an issue often overcome by the use of directing groups. The use of alkene templates ameliorates the regiochemical difficulty; however, the preparation of the olefin template often becomes challenging. Many processes of both types give mixtures of regio- and stereoisomers.[6] There are few techniques that construct acyclic tetrasubstituted olefins,[6,10] and preparations of alkenes bearing four distinct carbon substituents are rare.[6,11]

In this paper, we describe a mild and convenient method of forming acyclic, single isomer tetrasubstituted alkenes bearing four different carbon substituents. *E*-β-Chloro-α-iodo-α,β-unsaturated esters are generated from 2-alkynyl esters by exposure to Bu_4NI in refluxing dichloroethane. This process occurs with complete selectivity and sets the foundation for the remaining steps in the method. Sequential organometallic coupling of the β-chloro-α-iodo-α,β-unsaturated esters with a variety of partners occurs with complete regioselectivity and stereospecificity,

(1) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643.

(2) (a) Mohammed, A.-H. *Synthesis* **1987**, 816. (b) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (c) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

(3) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B.*Chem. Rev.* **1994**, *94*, 2483. (b) Dobler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289.

(4) Katsuki, T.; Martin, V. *Org. React.* **1996**, *48*, 1.

(5) (a) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 224. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(6) Selected methods: (a) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M. Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576. (b) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (c) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066. (d) Pospisil, J.; Pospisil, T.; Marko, I. E. *Org. Lett.* **2005**, *7*, 2373. (e) Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367.

(7) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T. *Org. Lett.* **2005**, *7*, 1597. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

(8) (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (b) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259. (c) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993. (d) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579 and references therein. (e) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765 and references therein. (f) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317. (g) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228. (h) Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421. (i) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263. (j) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (k) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358. (l) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554 and references therein.

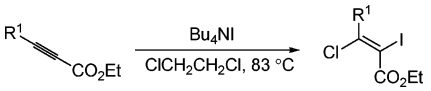
(9) Functionalization of existing alkene templates (selected examples): (a) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778. (b) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (c) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832. (d) Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290. (e) Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, *2*, 254. (f) Shao, L.-X.; Shi, M. *J. Org. Chem.* **2005**, *70*, 8635. (g) Angell, R.; Parsons, P. J.; Naylor, A. *Synlett* **1993**, 189.

(10) Selected preparations of tetrasubstituted olefins using identical vicinal olefinic halogens: (a) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095. (b) Boldi, A. M.; Anthony, J.; Knobler, C. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1240. (c) Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686. (d) Hénaff, N.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 395.

(11) Selected preparations of alkenes bearing four different carbon substituents: (a) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135. (b) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harringlton, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

10.1021/jo060144h CCC: $33.50
Published on Web 03/28/2006

TABLE 1. Formation of β-Chloro-α-iodo-α,β-unsaturated Esters



entry	R^1	product	yield (%)
1	H	**1**	89
2	CH_3	**2**	91
3	cyclohexyl	**3**	62
4	$TBSOCH_2CH_2$	**4**	67
5	Ph	**5**	76

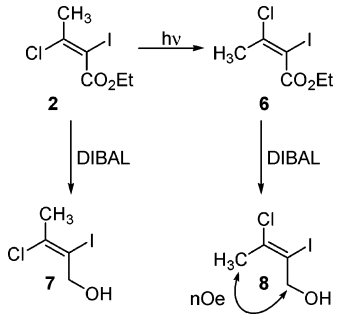
delivering the desired tetrasubstituted olefins as single isomers. This method is simple, reliable, does not require specialized equipment or substrates, and is amenable to large scale.

The required β-chloro-α-iodo-α,β-unsaturated esters were readily prepared as single isomers by treatment of the corresponding 2-alkynyl esters with Bu_4NI in refluxing dichloroethane (DCE) (Table 1). The products of the Bu_4NI process were easily obtained as pure, single isomers by simple filtration through silica gel.[12] This reaction was compatible with a variety of functionalities, including unsubstituted (entry 1), simple alkyl (entry 2), branched alkyl (entry 3), silyl ethers (entry 4), and aryl alkynyl esters (entry 5). Previously, it was reported that 2-alkynyl esters could be converted to β-chloro-α-iodo-α,β-unsaturated esters by treatment with ICl.[13,14] We found that this procedure gave side products, mixtures of *E*/*Z* isomers, required an extractive workup, and consistently gave lower yields. Exposure to Bu_4NI in DCE was superior to the ICl process, giving cleaner, higher yielding reactions from simpler workups.

Although related β-chloro-α-iodo products have been described in the literature, the stereochemistry of these products has never been unequivocally established.[13] The regiochemistry of the products in Table 1 was verified by ^{13}C NMR analysis in which the α-carbons exhibited strong upfield shifts consistent with iodine substitution.[15] The configuration of the alkene products was determined using NMR methods. In a representative example, *E*-ester **2** was briefly photolyzed to generate the corresponding *Z*-isomer **6** (Scheme 1).[16] The esters were immediately reduced with DIBAL, giving the corresponding alcohols **7** and **8**. Consistent with the structural assignments shown, NOE enhancements were observed between the methyl and methylene of compound **8**, whereas these interactions were lacking in isomer **7**. This procedure was repeated for all products described in Table 1, and in all cases, the stereochemistry shown was confirmed.

The β-chloro-α-iodo-α,β-unsaturated esters were subjected to sequential cross-coupling reactions to generate tetrasubstituted olefins. We initially investigated the selective Sonogashira coupling reaction of β-chloro-α-iodo-α,β-unsaturated esters.[17,18,19] Our initial experiments produced significant amounts of doubly coupled products. To identify conditions that would produce mono-coupling, optimization studies were done using dihalide

SCHEME 1. Confirmation of Olefin Template Stereochemistry



2 as substrate, evaluating a variety of catalysts, solvents, and bases. A screen of palladium catalysts identified $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, and $Pd(dppf)Cl_2$ as effective catalysts for the reaction, while $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave lower yields. For reasons of convenience, $Pd(PPh_3)_2Cl_2$ was selected for further investigation. Bases were examined using the same test system that showed Hünig's base (DIPEA) to be superior to NEt_3, 1,4-diazabicyclo-[2.2.2]octane (DABCO), K_2CO_3, and Cs_2CO_3. A solvent screen revealed 1,4-dioxane (0.1 M) to be the optimal solvent.[20,21]

Complete conversion and good yields were achieved in all cases examined within 2 h for a wide range of acetylenes (Table 2). The reaction was scalable[22] and tolerated a variety of substituent functionalities, including aryl (entries 1 and 2), silyl (entry 3), and alkyl groups (entry 4), as well as tethered silyl ethers of varying chain lengths (entries 5 and 6). Other substituents at R^1 were well-tolerated, and trisubstituted alkenes were prepared employing a bulky cyclohexyl group (entry 7) and a functionalized alkyl chain (entry 8). These reactions all gave single-isomer products as evidenced by GC−MS and ^1H and ^{13}C NMR analysis.

Notably, coupling was observed exclusively at the α-position. This result is in stark contrast to those reported for related substrates incorporating the same halogen at both the α and β positions.[9,10] In those substrates, the β-position was far more activated toward oxidative addition than was the α-position giving selective coupling at the β-position[23] (see also eq 2). In our substrates, the enhanced reactivity of the iodide over the chloride overrode the inherent reactivity of the system.[17] To our knowledge, this is the first time that selective coupling has been observed at the α-position of α,β-dihalo-α,β-unsaturated esters.

We then faced the challenge of forming all-carbon tetrasubstituted olefins from our trisubstituted precursors (Table 3). We were delighted with the speed and high conversion of the couplings as the formation of these congested centers is often quite

(12) On a large scale, washing with saturated $NaHSO_3$ immediately after the reaction facilitated subsequent purification by flash chromatography.

(13) Bellina, F.; Colzi, R.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2003**, *68*, 10175.

(14) For reactions of ICl with other types of alkynes, see: (a) Tendil, J.; Verney, M.; Vessiere, R. *Tetrahedron* **1974**, *30*, 579. (b) Heasley, V. L.; Buczala, D. M.; Chappell, A. E.; Hill, D. J.; Whisenand, J. M.; Shellhamer, D. F. *J. Org. Chem.* **2002**, *67*, 2183.

(15) This was confirmed by DEPT analysis of ester **1** and by subsequent NOE analysis of tetrasubstituted olefins **17**−**25**.

(16) O'Connor, J. M.; Friese, S. J.; Rodgers, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 16342.

(17) General references: (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Ltd: Chichester, West Sussex, England, 2004; and references therein. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020 and references therein.

(18) Use of different vicinal olefinic halogens in cross-coupling reactions: Organ, M. G.; Ghasemi, H. Valente, C. *Tetrahedron* **2004**, *60*, 9453 and references therein.

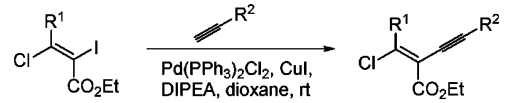
(19) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46 and references therein. (b) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056 and references therein.

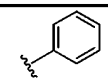
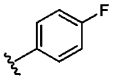
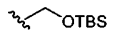
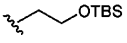
(20) Solvents screened included CH_2Cl_2, CH_3CN, DMF, 1,4-dioxane, THF, and DMSO.

(21) Glaser-type products were prominent unless the reaction was carefully degassed prior to addition of the acetylenic component. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(22) Multigram (3 g) scale reactions were performed successfully giving yields consistent with those shown.

TABLE 2. Preparation of Trisubstituted Alkenes from *β*-Chloro-α-iodo-α,*β*-unsaturated Esters[a]



entry	R^1	R^2	product	yield (%)[b]
1[c]	CH_3		**9**	78
2	CH_3		**10**	77
3	CH_3		**11**	68
4	CH_3		**12**	74
5	CH_3		**13**	76
6	CH_3		**14**	72
7[d]	c-C_6H_{11}		**15**	68
8[e]	$TBSO(CH_2)_2$		**16**	79

[a] Reaction conditions: **2** (1 equiv), alkyne (3 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (15 mol %), DIPEA (3 equiv), dioxane (0.1 M), rt, 2 h. [b] Isolated yield. [c] 0 °C. [d] **3** (1 equiv). [e] **4** (1 equiv).

difficult. Employing the optimized coupling conditions for the Sonogashira reaction, we successfully coupled phenyl acetylene to two different trisubstituted olefins (entries 1 and 2).

Seeking structural variety in the coupling partners, we next explored the Suzuki−Miyaura coupling reaction.[24] Tetrasubstituted olefins were obtained in good yields by coupling aryl- and alkenylboronic acids with our trisubstituted vinylic chlorides (Table 3). The reactions proved to be scalable[25] and tolerated aryl groups bearing electron-donating and electron-withdrawing substituents (entries 3−5). The use of styrenyl (entry 6) and alkenylboronic acids (entry 7) were also effective, smoothly

(23) α, *β*-Dibromo-α, *β*-unsaturated esters such as **i** underwent Negishi coupling to give products of type **ii** in 18−61% yield. One of these products **ii** (R = C_5H_{11}) was transformed by further Negishi coupling to **iii** (Ar = Ph-4-OMe) in 13% yield as an 88:12 mixture of *E*/*Z* isomers. Direct coupling of **i** (R = C_5H_{11}) with excess zinc reagent (ZnClPh-4-OMe) gave only **ii** and **iii** (1:1 ratio of *E*/*Z* isomers, no yield reported). In all cases, no trace of the α-coupled product was reported. Reference 10a.

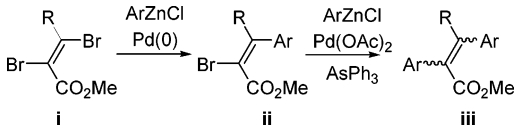
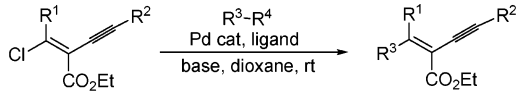
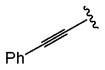
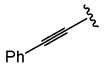
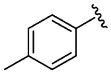
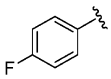
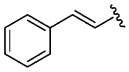
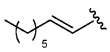


TABLE 3. Preparation of Tetrasubstituted Alkenes from *β*-Chloro-α,*β*-unsaturated Esters



entry	Substrate	R^3	R^4	product	yield (%)[a]
1[b]	**2**		H	**17**	55
2[b]	**2**		H	**18**	42
3[c]	**2**		$B(OH)_2$	**19**	77
4[c]	**2**		$B(OH)_2$	**20**	75
5[c]	**2**		$B(OH)_2$	**21**	71
6[d]	**2**		$B(OH)_2$	**22**	67
7[d]	**2**		$B(OH)_2$	**23**	64
8[c]	**3**		$B(OH)_2$	**24**	62
9[c]	**4**		$B(OH)_2$	**25**	52

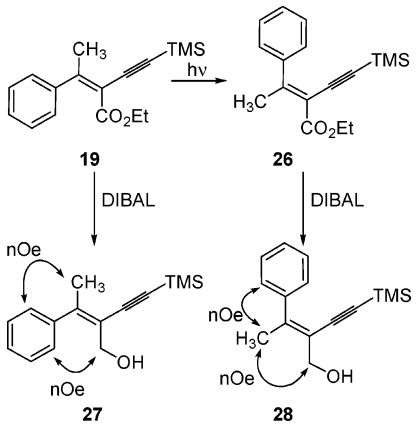
[a] Isolated yield. [b] Reaction conditions: acetylene (6 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (15 mol %), DIPEA (3 equiv), dioxane (0.1 M), rt, 18 h. [c] Reaction conditions: $R_2B(OH)_2$ (2 equiv), $Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$·HBF_4 (20 mol %), Cs_2CO_3 (2 equiv), dioxane (0.1 M), rt, 2 h. [d] Reaction conditions: $R_3B(OH)_2$ (2 equiv), $Pd_2(dba)_3$ (5 mol %), S-Phos (20 mol %), K_3PO_4 (2 equiv), THF (0.1 M), rt, 2 h.

giving rise to conjugated dienynes. The use of other R^1 groups was equally successful, and tetrasubstituted alkenes were prepared bearing a cyclohexyl group (entry 8) and a functionalized alkyl chain (entry 9). In all cases, single isomers were obtained from the process thus overcoming the most difficult hurdle in

(24) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.

(25) Reactions up to 500 mg scale were performed giving yields consistent with those shown.

SCHEME 2. Confirmation of Tetrasubstituted Olefin Configuration



the formation of tetrasubstituted olefins.[26] The regio- and stereochemistry of the final products was confirmed as before using NMR methods (Scheme 2). In a typical example, a sample of **19** was isomerized by brief photolysis and the *E*/*Z* isomers **19** and **26** were then reduced with DIBAL to give alcohols **27** and **28**.[27] NOE enhancements were observed between the methyl and methylene of alcohol **28**, indicating a cis relationship between these substituents. Alcohol **27**, corresponding to the initial product **19**, did not give enhancements between these substituents. Instead, NOE interactions were clearly noted between the Ph and CH_2 moieties. The network of NOE interactions observed for both isomers was consistent with the assignments shown and correlated exactly with the earlier structural assignments (Scheme 1). Other compounds in Table 3 were treated in a similar manner and gave consistent results. This corroborated the regiochemical assignments for compounds **1**−**5**.

We have illustrated a new, high-yielding method for the regio- and stereocontrolled formation of tetrasubstituted olefins bearing four different carbon substituents. Treatment of 2-alkynyl esters with Bu_4NI in DCE gave the corresponding *E*-*β*-chloro-α-iodo-α,*β*-unsaturated esters cleanly and selectively. These materials then served as olefin templates from which tetrasubstituted olefins were obtained by sequential cross-coupling reactions. By carefully optimizing the conditions, complete selectivity could be achieved in the first coupling. The subsequent coupling reactions all occurred under mild conditions and gave the desired olefins in good yields. In all cases investigated, the product olefins were cleanly obtained as single isomers. This method is simple, reliable, and scalable. The stereochemistry of the products was unequivocally determined by NMR analysis. Current efforts in our laboratory are being devoted to the expansion of the scope of this methodology, as well as to the application of these valuable substrates to further asymmetric transformations. Results will be reported in due course.

Experimental Section

General Procedure for the Conversion of 2-Alkynyl Esters into (*E*)-*β*-Chloro-α-iodo-α,*β*-unsaturated Esters (Table 1, Compounds 1−5). (*E*)-Methyl 3-Chloro-2-iodoacrylate (1). A solution of methyl propiolate (250 mg, 2.98 mmol, 1 equiv) and tetrabutylammonium iodide (3.25 g, 8.95 mmol, 3 equiv) in dichloroethane (25 mL) was heated at reflux for 18 h. The pure product was obtained by column chromatography on silica gel eluting with hexanes and then 5% EtOAc in hexanes to give the title compound as a colorless oil (652 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (C), 129.4 (CH), 84.3 (C), 53.2 (CH_3); IR (neat) 1728, 1567 cm^{-1}; MS (EI) 246 (M^+); HRMS calcd for $C_4H_4ClIO_2$ (M^+) 245.8945, found 245.8926.

General Procedure for the Sonogashira Coupling of (*E*)-*β*-Chloro-α-iodo-α,*β*-unsaturated Esters (Table 2, Compounds 9−16). (*Z*)-Ethyl 3-Chloro-2-(2-phenylethynyl)but-2-enoate (9). A flask was charged with $Pd(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol, 0.10 equiv) and copper iodide (5.1 mg, 0.027 mmol, 0.15 equiv). To this were added dichloromethane (2 mL) and diisopropylethylamine (0.13 mL, 0.72 mmol, 4 equiv) via syringe. (*E*)-Ethyl 3-chloro-2-iodobut-2-enoate (**2**) (50 mg, 0.18 mmol, 1 equiv) was then introduced, and the resulting yellow solution was carefully sparged with nitrogen for 10 min. Phenylacetylene (0.06 mL, 0.55 mmol, 3 equiv) was then added via syringe, and the resulting black solution was stirred for 2 h. The mixture was partitioned between water and EtOAc and the organic layer collected and then dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel eluting with hexanes then 5% EtOAc in hexanes to afford the title product (35 mg, 78%) as a clear, tan oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.35−7.34 (m, 3H), 4.33 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C), 146.6 (C), 131.4 (CH), 128.8 (CH), 128.3 (CH), 122.5 (C), 115.3 (C), 96.8 (C), 83.0 (C), 61.7 (CH_2), 26.2 (CH_3), 14.0 (CH_3); IR (neat) 2201, 1734, 1612 cm^{-1}; MS (EI) 248 (M^+); HRMS calcd for $C_{14}H_{13}ClO_2$ (M^+) 248.0604, found 248.0617.

General Procedure for the Suzuki Coupling of *β*-Chloro-α-alkynyl-α,*β*-unsaturated Esters (Table 3, Compounds 19−25). (*Z*)-Ethyl 3-Phenyl-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (19). A flame-dried round-bottom flask was charged with a solution of (*Z*)-ethyl 3-chloro-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (**11**) (50 mg, 0.20 mmol, 1 equiv) in 1,4-dioxane (2 mL), and the solution was sparged for 10 min with N_2. $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol, 0.05 equiv), phenylboronic acid (49 mg, 0.40 mmol, 2 equiv), and tri-*tert*-butylphosphine tetrafluoroborate (11.6 mg, 0.040 mmol, 0.20 equiv) were then added. The solution was sparged for an additional 5 min with N_2 before the addition of Cs_2CO_3 (130 mg, 0.40 mmol, 2 equiv). The resulting black solution was stirred for 2 h after which water was added. The mixture was extracted with EtOAc, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel, eluting with hexanes then 5% EtOAc in hexanes affording the product as a pale yellow oil (44 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 3H), 7.29−7.16 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 156.4 (C), 141.3 (C), 128.1 (CH), 128.0 (CH), 126.5 (CH), 115.0 (C), 101.5 (C), 100.5 (C), 61.0 (CH_2), 24.5 (CH_3), 13.6 (CH_3), −0.1 (CH_3); IR (neat) 2146, 1728, 1592 cm^{-1}; MS (EI) 286 (M^+); HRMS calcd for $C_{17}H_{22}O_2Si$ (M^+) 286.1389, found 286.1366.

Acknowledgment. We thank the Natural Science and Engineering Research Council of Canada (NSERC), Canada Foundation for Innovation, Ontario Innovation Trust, and the University of Ottawa for generous funding. K.S.V. thanks the University of Ottawa for an undergraduate student research award.

Supporting Information Available: Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **1**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060144H

(26) Every tetrasubstituted olefin prepared in this study was shown by ^{1}H, ^{13}C, and GC−MS analysis to be a single isomer. After a few weeks at room temperature, partial *E*/*Z* isomerization occurred, observable by ^{1}H, ^{13}C, and GC−MS. This was prevented by storing the products frozen in benzene.

(27) A pure sample of **19** was separately reduced in order to verify the identity of the corresponding alcohol isomer **27**.