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Bu_4N^+-Controlled Addition and Olefination with Ethyl 2-(Trimethylsilyl)acetate via Silicon Activation

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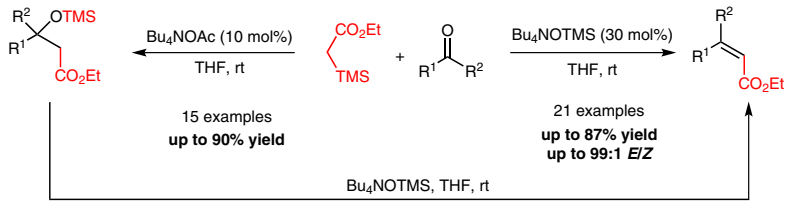

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Abstract Catalytic Bu_4NOAc as silicon activator of ethyl 2-(trimethylsilyl)acetate, in THF, was utilized for the synthesis of β-hydroxy esters, whereas employing catalytic Bu_4NOTMS gave α,β-unsaturated esters. The established reaction conditions were applicable to a diverse range of aromatic, heteroaromatic, aliphatic aldehydes and ketones. Reactions were achieved at room temperature without taking any of the specialized precautions that are in place for other organometallics. A stepwise olefination pathway via silylated β-hydroxy esters with subsequent elimination to form the α,β-unsaturated ester has been demonstrated. The key to selective product formation lies in use of the weaker acetate activator which suppresses subsequent elimination whereas stronger $TMSO^-$ activator (and base) facilitates both addition and elimination steps. The use of tetrabutyl ammonium salts for both acetate and trimethylsilyloxide activators provide enhanced silicon activation when compared to their inorganic cation counterparts.

Key words tetrabutyl ammonium, acetate, trimethylsilyl oxide, silicon activation, addition, olefination

β-Hydroxy esters and α,β-unsaturated esters are important structural motifs for a wide range of industrial applications, such as flavors, graphics, plasticizers, lubricants, perfumes, and cosmetics. For example, 2-ethylhexyl-4-methoxycinnamate is the most common ingredient of sunscreen lotions and cosmetic formulations. α,β-Unsaturated esters also possess various pharmacological activities including antioxidant, antimicrobial, and anticancer activities. These moieties also serve as fundamentally important building blocks for the synthesis of various naturally occurring and biologically active compounds.[1,2]

Several methodologies have been reported for the synthesis of β-hydroxy esters. Historically, Reformatsky reaction of ethyl 2-haloacetates and carbonyls with zinc reagents has been one of the most studied protocols,[3–5] although this method demands in situ formation of the organometallic reagent and immediate use owing to their instability.[6] Alternative organometallic nucleophiles containing metals such as magnesium, iron, nickel, manganese, and indium have also been shown to successfully participate in addition reactions.[7] However, employment of stoichiometric amount of metal reagents is a drawback and these protocols are associated with numerous complexities.[7] As an alternative, the use of α-silyl ester metalloids, such as ethyl 2-(trimethylsilyl)acetate (**1**), as bench-stable pro-nucleophiles, has been studied (Figure 1).[8,9] In the first seminal reports, the nucleophilic character of **1** was revealed through a fluoride activation of silicon using tetrabutylammonium fluoride (TBAF).[8] After these initial successes with fluoride activation for the synthesis of β-hydroxy esters, several successful alternative activation conditions, such as proazaphosphatranes $P(i\text{-}PrNCH_2CH_2)_3N$ in THF,[9a] Schwesinger imino phosphorene base P_4-*t*-Bu in MeCN,[9b] CsF in DMF,[9c,d] tris(2,4,6-trimethoxyphenyl)phosphine in DMF,[9e] and $K[Al(OMe)_4]$ in pyridine[9f] have been reported by different authors for the addition of α-silyl ester to carbonyls.

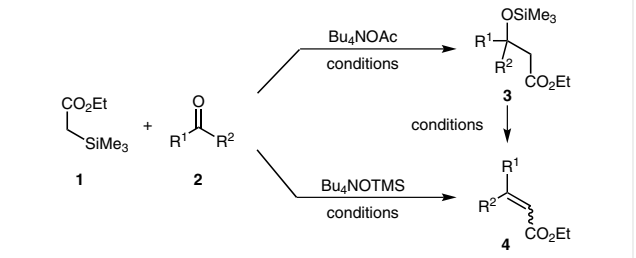


Figure 1 Reaction of ethyl 2-(trimethylsilyl) acetate and carbonyl compounds under Lewis basic conditions

Mild and efficient routes to α,β-unsaturated esters remain a popular topic of research for chemists as they often play the role of key synthetic intermediate in multistep synthetic programs.[10] Among them, the olefination of carbonyl compounds provides the most common routes. Wittig,[11] Horner–Wadsworth–Emmons,[12] and Peterson olefination (PO)[13,14] reactions have been the most widely exploited methods for the synthesis of α,β-unsaturated esters. However, the use of an equivalent of strong base can be limiting and in some cases the removal of crystalline byproduct can be challenging for olefin purification. Specifically for the PO reaction the necessity to perform an α-silyl carbanion by employing a strong base has restricted its widespread application.[13] As such, the use of bench-stable trimethylsilylacetate (**1**) in a silicon-activated addition with subsequent elimination reaction sequence is synthetically attractive (Figure 1). Recently, Verkade and co-workers reported the use of catalytic proazaphosphatranes P(*i*-PrNCH$_2$CH$_2$)$_3$N as effective base for the condensation of **1** with aryl aldehydes to produce α,β-unsaturated esters.[9a]

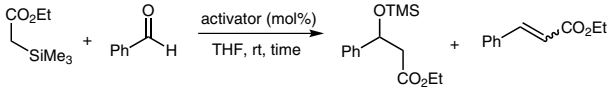
Kondo et al. also have reported the employment of catalytic P$_4$-*t*-Bu superbase at –78 °C in the synthesis of α,β-unsaturated esters from **1** and corresponding aldehydes and ketones.[9b] In the first report on this topic, Bellassoued et al. reported an addition–elimination process to synthesize olefins in which **1** and nonenolizable aldehydes were reacted at 100 °C in polar DMSO utilizing catalytic amount of CsF.[9c] It occurred to us that the need for very strong specialized bases such as P(*i*-PrNCH$_2$CH$_2$)$_3$N (pK_a = 33.6)[14] or P$_4$-*t*-Bu (pK_a = 42.7)[15] may not be necessary for such reactions and that the high temperatures required for elimination with CsF/DMSO conditions could be avoided by selection of more suitable inexpensive bases.

As part of our research program into pro-nucleophile trimethylsilane reagents, the use of Me$_3$SiO$^-$/Bu$_4$N$^+$ as a general activator of a wide range of organotrimethylsilanes for addition reactions[16] and organobis(trimethylsilanes) for olefination reactions[17] has been established. Using the pK_a of EtOAc at 25.6[18] as a guide, it could be anticipated that the activation of silicon in **1** would not require a strong base and that both addition and olefination reactions could be achieved with a high degree of selectivity under mild conditions. In this report, we illustrate room-temperature strategies which utilize acetate and trimethylsilyloxide bases, as their Bu$_4$N$^+$ salts, to produce either the addition β-hydroxy esters or unsaturated esters olefination products, respectively, in a highly selective manner (Figure 1).

In previously reported work we have shown that carbonyl addition reactions with ethyl 2-(trimethylsilyl)acetate (**1**) at 0 °C in THF were very rapid (within 15 min) when Bu$_4$NOTMS was used to promote the reaction.[16a] At that time it was noted that reactions needed to be closely monitored and stopped as soon as completion had been reached or olefin impurities would form. We started this investigation by employing **1** and benzaldehyde with 10 mol% TMSOK/Bu$_4$NCl in THF at room temperature for two hours from which ethyl 3-phenyl-3-[(trimethylsilyl)oxy]propanoate (**3a**) was isolated in 5% yield as minor product and ethyl cinnamate (**4a**) obtained as the major product in 82% yield (*E*/*Z* = 99:1; Table 1, entry 1). In an attempt to achieve complete conversion into olefin, an increased amount of activator (30 mol%) was employed and the olefin **4a** obtained in 87% yield (*E*/*Z* = 99:1; Table 1, entry 2) with no silylether **3a** identified. The use of stoichiometric amount of activator was attempted under the same conditions, though it showed no further improvement in yield (85%, *E*/*Z* = 99:1, Table 1, entry 3). As illustration of the effect of the Bu$_4$N$^+$ counterion, when stoichiometric amount of TMSOK alone was used as activator in THF at room temperature for a prolonged reaction time of 16 hours, a mixture of addition product **3a** (32%), and olefin **4a** (41%) was isolated, illustrating a loss in selectivity between the two possible reaction outcomes (Table 1, entry 4). To establish a general method for the synthesis of addition products, Bu$_4$NOAc was selected as a weaker base for investigation. Gratifyingly, under the same reaction conditions, the use of catalytic (10 mol%) Bu$_4$NOAc provided the silylether **3a** in 90% yield with a trace amount of the corresponding alkene **4a** (Table 1, entry 5). Employment of stoichiometric Bu$_4$NOAc gave the similar reaction outcome, showing the preference for addition rather than olefination product (Table 1, entry 6). Reaction utilizing one equivalent of KOAc for 16 hours failed to provide effective addition conditions, emphasizing the requirement of the ammonium cation (Table 1, entry 7). This stark reactivity difference between the organic and inorganic counterion is clearly revealed in this case of acetate activation. Also of note, the use of one equivalent Bu$_4$NCl as an even weaker silicon activator also produced the silylether **3a**, though in a low 35% yield after 20 hours (Table 1, entry 8). From the screening of reaction conditions, it became apparent that 10 mol% Bu$_4$NOAc in THF at room temperature would be ideal to explore substrate scope for the synthesis of β-hydroxy esters, whereas 30 mol% TMSOK/Bu$_4$NCl in THF at room temperature would be optimal to determine the scope for diverse α,β-unsaturated ester synthesis.

After establishing reaction conditions for the synthesis of β-hydroxy esters, we next evaluated the addition of **1** to various structurally and electronically different aromatic, heteroaromatic, α,β- unsaturated, organometallic, and aliphatic carbonyls (Scheme 1). Addition of **1** to a diverse range of aromatic aldehydes was achieved selectively, providing products **3b–g** in good to excellent yields. Aromatic aldehydes having *ortho*, *meta*, and *para* substitution or trisubstitution all worked very well under the same reaction conditions. Moreover, the addition to ferrocenecarboxaldehyde to produce **3h** showcased the versatility of this method. Synthesis of β-hydroxy esters containing heterocyclic rings **3i,j** showed the tolerance of furan and pyridine moi-

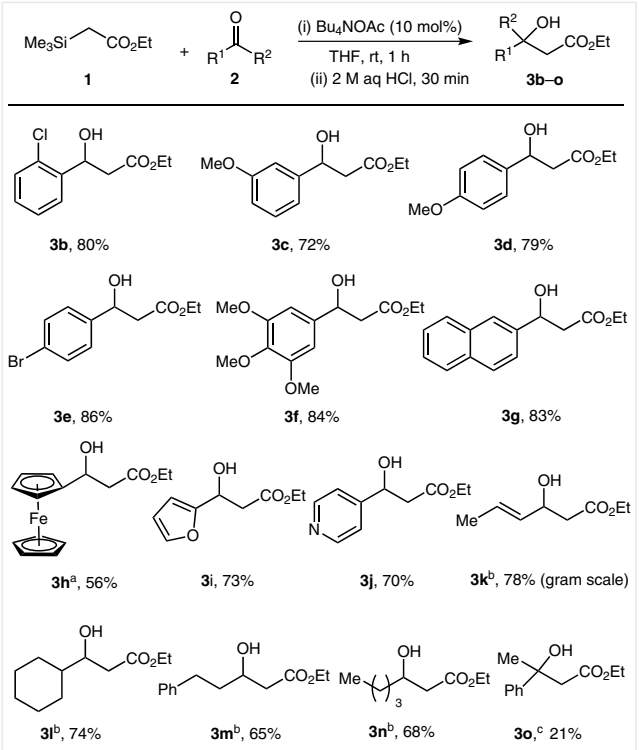
Table 1 Optimization of Reaction Conditions[a]



1 2a 3a 4a

Entry	Activator (mol%)	Time (h)	Yield of **3a** (%)[b,c]	Yield of **4a** (%)[c]	*E*/*Z* of **4a**[d]
1	TMSOK/Bu_4NCl (10)	2	5	82	99:1
2	TMSOK/Bu_4NCl (30)	2	–	87	99:1
3	TMSOK/Bu_4NCl (100)	2	–	85	99:1
4	TMSOK (100)	16	32	41	93:7
5	Bu_4NOAc (10)	2	90	trace	–
6	Bu_4NOAc (100)	2	88	trace	–
7	KOAc	16	–	–	–
8	Bu_4NCl (100)	20	35	–	–

[a] Conditions: Benzaldehyde (0.5 mmol), ethyltrimethylsilyl acetate (0.75 mmol), solvent (2.5 mL).
[b] Silylether was hydrolyzed by aqueous acid workup to transform to β-hydroxy ester and isolated.
[c] Yield of product after chromatography.
[d] Determined by ^1H NMR analysis.



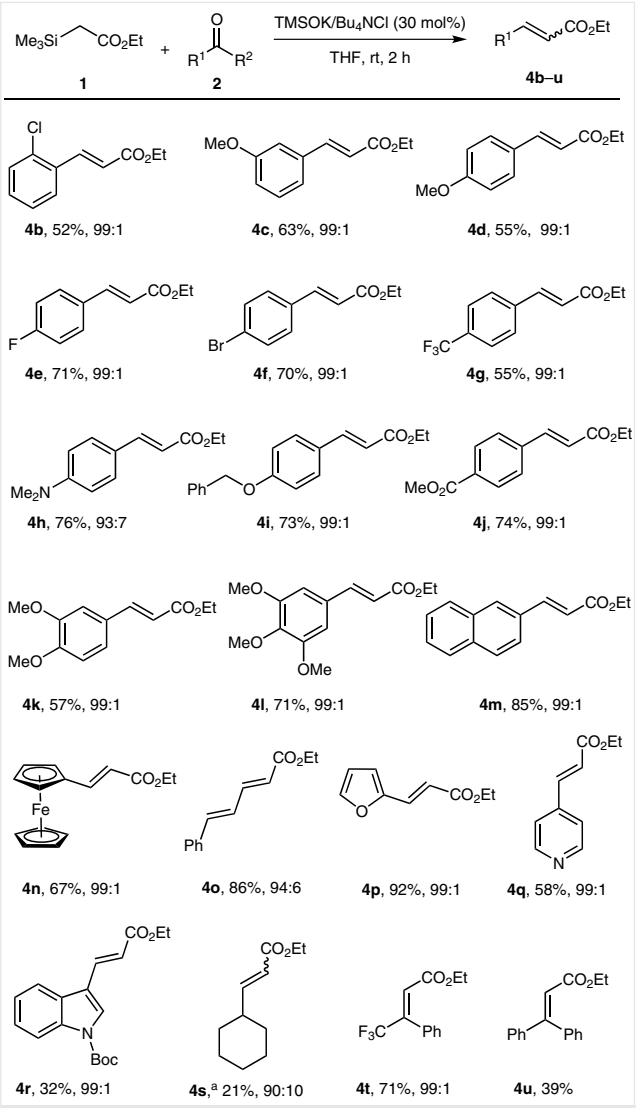
Scheme 1 Addition reactions with carbonyl compounds. *Reagents and conditions*: benzaldehyde (0.5 mmol), ethyltrimethylsilyl acetate (0.75 mmol), solvent (2.5 mL); yield of product after chromatography. [a] 1.0 equiv Bu_4NOAc used, reaction time: 30 min. [b] 20 mol% Bu_4NOAc used. [c] 1.5 equiv Bu_4NOAc used under reflux; reaction time: 4 h.

eties. Using crotonaldehyde as a test substrate, it was found that the addition reaction performed equally well as a gram-scale reaction, providing the ethyl (*E*)-3-hydroxyhex-4-enoate (**3k**) in 78% (1.85 g) yield. The procedure was also successful for enolizable aliphatic aldehydes with addition of **1** to cyclohexanecarbaldehyde, 3-phenylproponal, and pentanal providing **3l–n** in good yields. Furthermore, **1** was also added successfully to acetophenone to provide a β-hydroxy ester **3o** with a quaternary carbon, though under slightly more forcing reflux conditions and with unreacted starting material remaining. In general, the substituent tolerance was broad, with only traces of olefin observed in the crude products.

Next, the use of Bu_4NOTMS to achieve olefination products under comparable conditions was evaluated by reaction of **1** with a series of structurally and electronically different carbonyls. Olefination of electron-neutral, -rich, and -poor aromatic aldehydes having *ortho*, *meta*, or *para* substituents was achieved in each case, providing the corresponding alkenes **4b–l** in good to high yields and with excellent *E*/*Z* ratios ranging from 93:7 to 99:1 (Scheme 2). Bicyclic aromatic aldehyde, ferrocene aldehyde, and α,β-unsaturated aldehyde all worked well under this protocol to yield the diversely substituted alkenes (**4m–o**). Moreover, pharmaceutically important alkenes (**4p**,**q**) containing heterocycles were also accessible with near perfect stereoselectivity in moderate to excellent yields. For more challenging aliphatic cyclohexanecarbaldehyde, an elevated amount of activator was used under reflux conditions to get the olefin **4s** with *E*/*Z* ratio of 90:10. 2,2,2-Trifluoro-1-phenylethan-1-one also underwent olefination, providing the corresponding alkene **4t** in 71% yield and with *E*/*Z* ratio of 99:1. Olefination of benzophenone gave the corresponding product **4u** in 39% yield with unreacted starting material remaining.

From the results of Scheme 1 and Scheme 2 it is evident that synthesis of β-hydroxy esters with Bu_4NOAc activation and α,β-unsaturated esters with $TMSO^-/Bu_4N^+$ activation both worked well in selectively delivering their respective products. Hence, gaining an understanding of the interrelationship of both methods and their reaction pathways is important such that they may be applied to other trimethylsilane reagents.

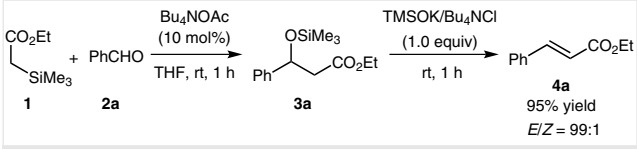
As both activators are bases and nucleophiles, theoretically two pathways could be envisaged. The first being the PO pathway in which deprotonation of **1** yields **5** which upon addition to aldehyde generates **6** with in situ elimination of $TMSO^-$ giving olefin **4** (Scheme 3).[13] LDA is a typical base used to achieve the deprotonation of **1** in THF at low temperature.[19] Both of our chosen activators are relatively weak bases, with acetate having pK_a of 4.7 and trimethylsilyloxide at 12.7,[20] so it could be expected that silicon activation to form hypervalent silicate **7**, as in route B, would be favored over deprotonation (Scheme 3).



Scheme 2 Survey of scope for α,β-unsaturated esters. *Reagents and conditions*: aldehydes or ketones (0.5 mmol), ethyltrimethylsilyl acetate (0.75 mmol), solvent (2.5 mL), TMSOK (0.015 mmol), Bu_4NCl (0.015 mmol). [a] TMSOK (0.50 mmol), Bu_4NCl (0.50 mmol) at reflux.

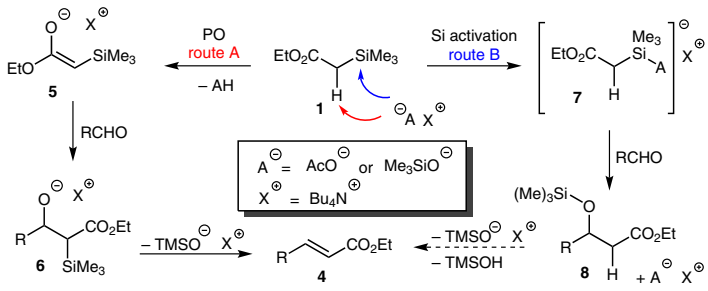
Aldehyde addition of **7** (or its corresponding carbanion) would lead to the silylated ether product **8**. If **8** was not the final product but was to proceed to olefin product **4** then this would require the base elimination of trimethylsilyloxide. That would indicate that the differentiating feature of the two activators used in this study is their ability to effect the elimination of $TMSO^-$ from **8**. Control of this pivot point was achieved as Bu_4NOTMS, being the stronger of the two base systems used, is capable of doing this olefin forming–elimination step but, under room-temperature THF conditions, the weaker Bu_4NOAc is not.

Illustration of the singular silicon activating role of acetate versus the dual roles of trimethylsilyloxide was achieved in a one-pot approach as shown in Scheme 4. First, addition of **1** to benzaldehyde was carried out using 10 mol% Bu_4NOAc as silicon activator in THF at room temperature for one hour, with ^1H NMR analysis confirming that complete conversion into the silylated β-hydroxy ester **3a** had occurred. At this stage, stoichiometric amount of TMSOK/Bu_4NCl was added to the same reaction flask and stirred for one hour at room temperature. After workup, ^1H NMR analysis showed complete conversion into the corresponding α,β-unsaturated ester **4a**.



Scheme 4 Formation of silylated β-hydroxy ester and then transformation to the corresponding olefin in one pot

In conclusion, we have demonstrated very mild and highly selective methods for addition[21] and olefination[22,23] reactions with ethyl 2-(trimethylsilyl)acetate. Silicon activation of the pro-nucleophile was achieved with either Bu_4NOAc or Bu_4OTMS in THF at room temperature, with the former giving addition β-hydroxy ester products and the latter proceeding to α,β-unsaturated esters. The use of Bu_4N^+ as counterion to the nucleophilic activator is key to successful reaction outcomes, the basis for which is currently under detailed investigation as is the potential use of



Scheme 3 Possible pathways leading to the formation of silylated β-hydroxy esters and α,β-unsaturated esters

chiral ammonium salts to achieve enantioselective additions. Insight into the controlled and mild activation of trimethylsilane pro-nucleophiles will allow for the continued expansion of their use in general synthetic chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588805.

References and Notes

(1) (a) Sánchez, M.; Bermejo, F. *Tetrahedron Lett.* **1997**, *38*, 5057. (b) Gabriel, T.; Wessjohann, L. A. *Tetrahedron Lett.* **1997**, *38*, 1363. (c) Wittenberg, R.; Beier, C.; Drager, G.; Jas, G.; Jasper, C.; Monenschein, H.; Kirschning, A. *Tetrahedron Lett.* **2004**, *45*, 4457.

(2) (a) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405. (b) Chen, D.; Guo, L.; Liu, J.; Kirtane, S.; Cannon, J. F.; Li, G. *Org. Lett.* **2005**, *7*, 921. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752. (e) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (f) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(3) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210.

(4) (a) Gensler, W. J. *Chem. Rev.* **1957**, *57*, 191. (b) Diaper, D. G. M.; Kuksis, A. *Chem. Rev.* **1959**, *59*, 89.

(5) (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325. (c) Orsini, F.; Sello, G. *Curr. Org. Synth.* **2004**, *1*, 111.

(6) (a) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452. (b) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698. (c) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775.

(7) (a) Moriwake, T. *J. Org. Chem.* **1996**, *31*, 983. (b) Durandetti, M.; Périchon, J. *Synthesis* **2006**, 1542. (c) Inaba, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155. (d) Suh, Y. S.; Rieke, R. D. *Tetrahedron Lett.* **2004**, *45*, 1807. (e) Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (f) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408.

(8) (a) Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett.* **1976**, *20*, 1699. (b) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932. (c) Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1998**, *39*, 2585.

(9) (a) Wadhwa, K.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 4368. (b) Kobayashi, K.; Ueno, M.; Kondo, Y. *Chem. Commun.* **2006**, 3128. (c) Bellassoued, M.; Ozanne, N. *J. Org. Chem.* **1995**, *60*, 6582. (d) Latouche, R.; Texier-Boullet, F.; Hamelin, J. *Bull. Soc. Chim. Fr.* **1993**, *130*, 535. (e) Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* **2000**, *41*, 103. (f) Birkofer, L.; Ritter, A.; Wieden, H. *Chem. Ber.* **1962**, *95*, 971.

(10) For general reviews on the synthesis of unsaturated esters, see: (a) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451. (b) Shen, Y. *Acc. Chem. Res.* **1998**, *31*, 584.

(11) (a) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654. (c) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1. (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (e) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049.

(12) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Motoyoshiya, J. *Trends Org. Chem.* **1998**, *7*, 63. (c) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recl.* **1997**, *7*, 1283. (d) Ando, K.; Yamada, K. *Green Chem.* **2011**, *13*, 1143. (e) Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.

(13) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464. (c) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195. (d) Ager, D. J. *Science of Synthesis*; Thieme: Stuttgart, **2010**, 85.

(14) Kisanga, P. B.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.

(15) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G. Z.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055.

(16) (a) Das, M.; O'Shea, D. F. *J. Org. Chem.* **2014**, *79*, 5595. (b) Das, M.; O'Shea, D. F. *Chem. Eur. J.* **2015**, *21*, 18723. (c) Das, M.; O'Shea, D. F. *Org. Lett.* **2015**, *17*, 1962. (d) Das, M.; O'Shea, D. F. *Tetrahedron* **2013**, *69*, 6448.

(17) (a) Das, M.; Manvar, A.; Jacolot, M.; Blangetti, M.; Jones, R. C.; O'Shea, D. F. *Chem. Eur. J.* **2015**, *21*, 8737. (b) Manvar, A.; O'Shea, D. F. *Eur. J. Org. Chem.* **2015**, 7259. (c) Das, M.; O'Shea, D. F. *Org. Lett.* **2016**, *18*, 336.

(18) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129.

(19) For example, see: Sikervar, V.; Fleet, J. C.; Fuchs, P. L. *J. Org. Chem.* **2012**, *77*, 5132.

(20) Baker-Glenn, C. A. G.; Barrett, A. G. M.; Gray, A. A.; Procopiou, P. A.; Ruston, M. *Tetrahedron Lett.* **2005**, *46*, 7427.

(21) **General Procedure for Addition Reactions**

A solution of ethyl 2-(trimethylsilyl)acetate (**1**, 137 µL, 0.75 mmol) and aldehyde (0.50 mmol) in anhydrous THF (2.5 mL) was treated with dried Bu_4NOAc (0.05 mmol) under N_2. The resulting solution was stirred at r.t. for 1 h. Aqueous HCl (2 M, 10 mL) was added and stirred for 30 min. The residue was extracted with Et_2O (3 × 15 mL), organic layers combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure gave the crude product.

Ethyl 3-(2-chlorophenyl)-3-hydroxypropanoate (3b)

A solution of ethyl 2-(trimethylsilyl)acetate (**1**, 137 µL, 0.75 mmol) and 2-chlorobenzaldehyde (70 mg, 0.50 mmol) in anhydrous THF (2.5 mL) was treated with dried Bu_4NOAc (15 mg, 0.05 mmol) under N_2. The resulting solution was stirred at r.t. for 1 h. Aqueous HCl (2 M, 10 mL) was added and stirred for 30 min. The residue was extracted with Et_2O (3 × 15 mL), organic layers combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography eluting with cyclohexane–EtOAc (90:10) afforded **3b** as a colorless oil (91 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.36–7.27 (m, 2 H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1 H), 5.49 (dd, *J* = 9.7, 2.5 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.61 (br s, 1 H), 2.86 (dd, *J* = 16.6, 2.7 Hz, 1 H), 2.58 (dd, *J* = 16.6, 9.7 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 140.0, 131.5, 129.5, 128.9, 127.3, 127.2, 67.2, 61.1, 41.5, 14.3 ppm. ESI–MS: m/z cald for $C_{11}H_{14}O_3Cl$ $[M + H]^+$: 229.1; found: 229.0.

(22) **General Procedure for Olefination Reactions**
A solution of ethyl trimethylsilylacetate (**1**, 137 µL, 0.75 mmol) and aldehyde (0.50 mmol) in THF (2.5 mL) was treated with dried Bu_4NCl (0.15 mmol) and TMSOK (0.15 mmol) under N_2, and the resulting reaction mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with aq 2 M HCl (10 mL) and stirred for 5 min at r.t. The residue was extracted with EtOAc (3 × 15 mL). Organic layers were combined and washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude product.

(23) **(*E*)-Ethyl-3-(3,4,5-trimethoxyphenyl)acrylate (4l)**
A solution of 3,4,5-trimethoxybenzaldehyde (98 mg, 0.50 mmol) and ethyl trimethylsilylacetate (**1**, 137 µL, 0.75 mmol) in THF (2.5 mL) was treated with dried Bu_4NCl (42 mg, 0.15 mmol) and TMSOK (19 mg, 0.15 mmol) under N_2, and the resulting reaction mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with 2 M aq HCl (10 mL) and stirred for 5 min at r.t. The residue was extracted with EtOAc (3 × 15 mL). Organic layers were combined and washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by Al_2O_3 chromatography eluting with cyclohexane–EtOAc (90:10) yielded **4l** (95 mg, 71%) as a colorless solid, mp 53–55 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 16.0 Hz, 1 H), 6.74 (s, 2 H), 6.33 (d, *J* = 16.0 Hz, 1 H), 4.25 (q, 2 H), 3.87 (s, 9 H), 1.33 (t, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 153.4, 144.5, 140.1, 129.9, 117.5, 105.2, 60.9, 60.4, 56.1, 26.9, 14.3. MS (EI): *m/z* calcd for $C_{14}H_{18}O_5$ $[M]^+$: 266.1; found: 266.2.