Bis(2,2,2-trifluoroethyl)bromophosphonoacetate, a Novel HWE Reagent for the Preparation of (*E*)- α -Bromoacrylates: A General and Stereoselective Method for the Synthesis of Trisubstituted Alkenes

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ABSTRACT



A novel reagent, methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate (3a), was designed and prepared in order to efficiently synthesize (*E*)- α -bromoacrylates, which are useful precursors for various C–C bond formations. Honer–Wadsworth–Emmons (HWE) reaction of various aldehydes with 3a in the presence of *t*-BuOK and 18-C-6 gave the corresponding (*E*)- α -bromoacrylate derivatives with high stereoselectivity. Using the (*E*)- α -bromoacrylate as a key intermediate, a general stereoselective synthesis of trisubstituted alkenes via Pd-catalyzed cross-coupling was developed.

The highly stereoselective construction of trisubstituted alkenes is one of the most challenging problems in synthetic organic chemistry.¹ Indeed, many skillful and selective synthetic methods for the preparation of this important functional group have been devised for decades.² However, the need for a general and stereoselective method for the efficient synthesis of trisubstituted alkenes still remains.¹ At

present, vinyl bromides are widely used as precursors for C–C bond formation with conservation of olefin geometry, using reactions such as Suzuki coupling,³ or Stille coupling.⁴ Therefore, we anticipated that a stereoselective construction of trisubstituted bromoalkenes, for example, α -bromoacrylate derivatives, would provide a useful method to synthesize various trisubstituted olefins.

Although there are limitations to the stereoselective construction of tri- and tetrasubstituted alkenes, Wittig and Horner–Wadsworth–Emmons (HWE) reactions are powerful and attractive methods for the construction of various alkenes.⁵ This is because they provide a direct introduction of the C–C double bond from carbonyl compounds. It is

⁽¹⁾ Kelly, S. E. In *Comprehensive Organic Synthesis, Additions to C–X* π *Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford 1991; Vol. 1, Chapter 3.

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(d) Denmark, S. E.; Amburgey, J. J. Am. Chem. Soc. 1993, 115, 10386. (e) Pelter, A.; Colclough, M. E. Tetrahedron 1995, 51, 811. (f) Studemann, T.; Knochel, P. Angew. Chem., Int. Ed. Engl. 1997, 36, 93. (g) Kawasaki, T.; Ichige, T.; Kitazume, T. J. Org. Chem. 1998, 63, 7525.

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^{(4) (}a) Stille, J. K. Angew. Chem., Int. Ed. Engl. 1986, 25, 508. (b) Farina,

V.; Krishnamurthy, V.; Scott, W. J. Org. React. 1997, 50, 1.

known that the HWE reaction with diethoxybromophosphonoacetate **1** and Wittig reaction with the stabilized ylide **2** gave α -bromoacrylates with slightly predominant *Z*-isomer (Scheme 1).^{6,7} On the other hand, only a few procedures for



the synthesis of (E)- α -bromoacrylates have been reported in the literature.⁸ Thus, a general method for the synthesis of (E)- α -bromoacrylates would be a beneficial synthetic achievement. (E)- α -Fluoroacrylates are synthesized stereoselectively by the HWE reaction of diethoxyfluorophosphonoacetate with lithium base.⁹ However, it is apparent that fluoroalkenes cannot be used as precursors for C-C bond formation. Therefore, we investigated HWE reagents and reaction conditions to develop a stereoselective synthetic method for (*E*)- α -bromoacrylates from which precursors for C-C bond formation could be readily synthesized. In this Letter, we describe the preparation of the novel HWE reagent 3 and a general methodology for the construction of trisubstituted alkenes, which involves the stereoselective HWE reaction of 3 followed by stereospecific C-C bond formation by Pd-catalyzed cross-coupling.

While the HWE reaction using diethoxyphosphonoacetate shows a preference for the formation of more stable disubstituted *E*-olefins,^{5a,10} Still's electrophilic bis(2,2,2-trifluoroethoxy)phosphonoacetate reacts with aldehydes in the presence of KHMDS and 18-crown-6 ether (18-C-6) to afford *Z*- α , β -unsaturated esters selectively.^{2a,11,12} In view of

(7) (a) Gonzalez, M. S. P.; Aciego R. M. D.; Herrera, F. J. L. *Tetrahedron* **1988**, 44, 3715. (b) Sato, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. J. Org. *Chem.* **1991**, 56, 2278.

(8) (a) Nakamura, I.; Harada, K. *Heterocycles* **1978**, *9*, 473. (b) Kolsaker, P.; Brobakke, K. *Acta Chem. Scand. B* **1981**, *35*, 701. (c) Bestmann, H. J.; Dostalek, R.; Zimmermann, R. *Chem. Ber.* **1992**, *125*, 2081. These procedures generally lack of efficiency because of multiple steps or limitation of substrate.

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the above fact, we designed a novel reagent, bis(2,2,2-trifluoroethyl)bromophosphonoacetate, **3**, anticipating that (E)- α -bromoacrylates would be synthesized by the HWE reaction since **3** is thought to be complementary to **1** in the analogous reaction.

The novel reagent **3a** was readily prepared from methyl bis(2,2,2-trifluoroethyl)phosphonoacetate $(4)^{2a}$ using a procedure similar to that reported by McKenna et al. (Scheme 2).¹³ Treatment of **4** with freshly prepared sodium hypo-



 a (a) Aqueous NaOBr 85%; (b) SnCl_2·2H_2O (0.96 equiv), EtOH, H2O, 70%.

bromide afforded dibromide, which was subsequently reduced by 1 equiv of SnCl_{2} .¹⁴ A small amount of unreacted dibromide and over-reduced product **4** were removed by flash chromatography (dichloromethane/acetone = 50:1) using silica gel which was pretreated with dichloromethane containing 4 N HCl in ethyl acetate.¹⁵ Finally, the residue was distilled under reduced pressure (bp 85–87 °C, 0.4 mmHg) to give pure **3a** (60% yield from **4**).

The results of the HWE reaction between **1a** or **3a** and aldehydes using potassium *tert*-butoxide (*t*-BuOK) are summarized in Table 1. Excess amounts of *t*-BuOK reduced the

 Table 1. Results of the HWE Reaction with 1a or 3a and Benzaldehyde



run ^a	reagent	additive	time	yield, % ^{b}	E/Z^c
1	$\mathbf{1a}^d$	none	16 h	94	1/5
2	1a	18-C-6	16 h	93	1/14
3	3a	none	2 h	65	10/1
4	3a	18-C-6	20 min	94	30/1

^{*a*} 1 equiv of benzaldehyde, 1.1 equiv of **1a** or **3a**, 1.05 equiv of *t*-BuOK, and 1.3 equiv of additive (runs 2 and 4) were used. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR (400 MHz) analysis of the products. ^{*d*} For preparation of **1a**, see ref 13.

yield and stereoselectivity.¹⁶ Therefore, phosphonoacetates were used slightly in excess of *t*-BuOK. As we anticipated, HWE reactions with **3a** proceeded with high *E*-selectivity

⁽⁵⁾ For review to see: (a) Wadsworth, W. S. Org. React. 1977, 25, 73.
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⁽¹¹⁾ Hensel, M. J.; Fuchs, P. L. Synth. Commun. 1986, 16, 1285.

⁽¹³⁾ McKenna, C. E.; Khawli, L. A. J. Org. Chem. 1986, 51, 5467.

⁽¹⁴⁾ SnCl_2·2H_2O, which was purchased from Aldrich Chemical Co., gave the best result for reduction.

Table 2. Results of the HWE Reaction with 1a or 3a and a Range of Aldehydes

	$(R^{1}O)_{2} \xrightarrow{P} CO_{2}R^{2}$ Br			1) t-BuOK, 18-C-6, THF, -78 °C, 30min			ç	CO₂R ²					
				2) RCHO, –78 °C		Br	<u>∼</u> ¤ +	Br	٦				
1a: $R^1 = R^2 = Et$ E Z R 3a: $R^1 = CF_3CH_2$, $R^2 = Me$ E Image: Reference of the second													
Run ^a	R	Reagent	Time (h)	Yield (%) ^b	E : Z ^c	Run ^a R	Reagent	Time (h)	Yield (%) ^b	E : Z°			
1		3a	4	94	30 : 1	8	🧹 3a	5	84	15 : 1			
2	MeC	3a	1.5	98	28 : 1	9°	3a	3	75	32 : 1			
. 3		1.	15	07	10 · 1	10 ^g	3a	2	86	>50 : 1			
5		Ja	1.5	57	19.1	11 ^{<i>f.g n-</i>Bu}	1a	5	80	3:1			
4		3a	1	94	9:1	12 ^{f.g.h}	1a	5	72	1:3			
5	r ^o r	, 3a	1.5	98	25 : 1	¹³⁹	. 3a	6.5	64	>50 : 1			
c	<u></u>	0.	47		F ack d	14 ^{<i>f.g</i>}	1a	5	47	3 :1			
6	$\langle \rangle$	38	1/	quant.	E only								
7		1a	5	87	1:2	15 BnO	3a	1.5	96	26 : 1			

^{*a*} See the corresponding footnotes in Table 1. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR analysis of the products. ^{*d*} Z-product cannot be detected by ¹H NMR analysis. ^{*e*} At -20 °C. ^{*f*} At -40 °C. ^{*g*} Aldehyde was distilled before use in the reaction. ^{*h*} Without 18-C-6.

(runs 3 and 4) in contrast to the same reaction with **1a** (runs 1 and 2). Furthermore, stereoselectivity and/or yield were markedly improved using 1.3 equiv of 18-C-6 as an additive (runs 2 and 4). When using LHMDS as a base, a higher temperature (even at room temperature) was needed for the HWE reaction to proceed with **3a**, and both the yield and stereoselectivity were significantly decreased (38%, E/Z = 2:1).

For further evaluation of the applicability of this Eselective reaction, we examined the HWE reaction using 3a with various aldehydes. As shown in Table 2, olefination of most aldehydes with 3a in the presence of t-BuOK and 18-C-6 gave (*E*)- α -bromoacrylates¹⁷ with high stereoselectivities and excellent yields. The reaction with aromatic aldehydes proceeded rapidly and gave (E)- α -bromoacrylates stereoselectively with high yields (runs 1-5). Conjugated aldehydes and branched aliphatic aldehydes were slightly less reactive, but high stereoselectivity still remained (runs 6, 8, and 13). E/Z ratio and reactivities were extremely diminished when using 1a instead of 3a (runs 7, 11, 12, and 14). This HWE reagent 3a provides an efficient and highly stereoselective method to obtain various (E)- α -bromoacrylates, which are very useful precursors for various C-C bond formations.

To examine the availability of (E)- α -bromoacrylates, trisubstituted alkenes 7 and 9 were synthesized as shown in Scheme 3. From acrylate 5, a precursor for the coupling



^{*a*} (a) DIBAL-H, CH₂Cl₂, -78 °C, 88%; (b) TBSCl, imidazole, DMF, rt, 96%; (c) *n*-Bu₃SnCH=CH₂, Pd(PPh₃)₄, THF, rt, 66%; (d) **8**, 9-BBN, THF, rt then **6**, PdCl₂(dppf), Ph₃As, Cs₂CO₃, DMF, 50 °C, 81%.

reaction was readily synthesized in two steps. **7** was synthesized by Stille coupling of **6** with vinylstannane, and Suzuki coupling of **6** and **8** gave trisubstituted olefin **9** in good yields. The combination of stereoselective bromoolefination and C–C bond formation affords a useful and general synthetic method for a wide range of trisubstituted alkenes. This protocol has considerable potential for the construction of complex molecules.

In conclusion, the novel HWE reagent **3a** was designed and prepared. (*E*)- α -Bromoacrylates were synthesized stereoselectively and efficiently from **3a** with various aldehydes

⁽¹⁵⁾ Reagent **3a** is unstable even under weakly basic conditions. Usual silica gel column chromatography caused decomposition of **3a**. The purified **3a** was enough to stable to be stored in a freezer (-20 °C) over 3 years without decomposition.

⁽¹⁶⁾ Yu, W.; Su, M.; Jin, Z. Tetrahedron Lett. 1999, 40, 6725.

⁽¹⁷⁾ Geometry of α -bromoacrylates were determined by NOE analysis of the allylic alcohol which was derived from DIBAL-H reduction of corresponding ester.

in the presence of *t*-BuOK and 18-C-6. Using the product (E)- α -bromoacrylate as a key intermediate, we succeeded in developing a general protocol for the highly stereoselective synthesis of trisubstituted alkenes via Pd-catalyzed cross-coupling.

Supporting Information Available: Experimental details for the preparation of **3a**, the general procedure for the HWE

reaction, and the synthesis of 7 and 9 and the characterization of α -bromoacrylates and compounds 6, 7, and 9. This material is available free charge via the Internet at http://pubs.acs.org.

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