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Highly Stereoselective Synthesis of Trisubstituted Vinylcyclopropane Derivatives via Arsonium Ylides

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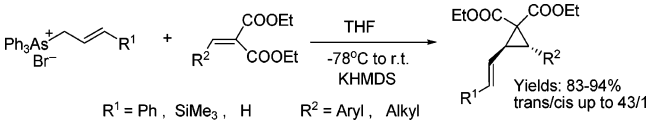
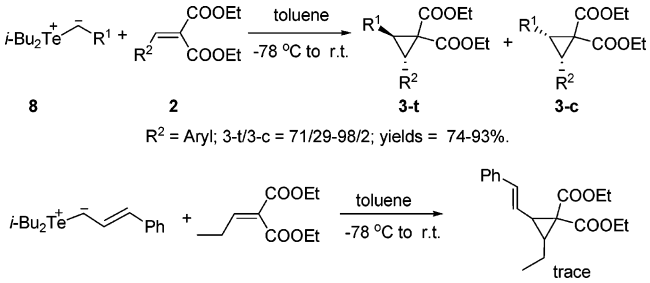


Alkylidene or arylidene malonates reacted with arsonium allylides to give *trans*-disubstituted cyclopropane-1,1-dicarboxylates with high stereoselectivity in high yields. The mechanism of the cyclopropanation reactions has also been investigated.

Vinylcyclopropane 1,1-dicarboxylic esters are very useful synthetic intermediates in construction of cyclopentane skeleton and heterocyclic compounds.[1] Although the cyclopropanation reactions of olefins using the transition-metal-catalyzed decomposition of diazoalkanes is well-studied,[2] only a few examples were reported for the preparation of these cyclopropanes, probably because the regioselectivity control is difficult and the diazoalkanes bearing two electron-withdrawing groups are substantially less reactive than diazoalkanes both without electron-withdrawing groups and with one electron-withdrawing group.[3] Of the methods developed for direct synthesis of these compounds,[2a,4] the tandem nucleophilic addition/cyclization[5] such as ylide cyclopropanation[6] of alkylidene malonates is one of the most convenient ways. In a previous study on the synthesis and application of cyclopropane derivatives,[7] we described a cyclopropanation reaction of arylidene malonates with telluronium ylides to afford disubstituted cyclopropane 1,1-dicarboxylic esters with good stereoselectivity in high yields (Scheme 1).[8] However, attempts to extend the substrates to propylidene malonate using telluronium cinnamylide gave only a trace amount of the desired cyclopropane (Scheme 1) under the same reaction conditions. Therefore, we are interested in developing a highly diastereoselective ylide cyclopropanation suitable for both alkylidene and arylidene malonates. In this paper, we wish to report the results of our studies on this subject.

SCHEME 1. Synthesis of Disubstituted Cyclopropane-1,1-dicarboxylates via Telluronium Ylides



Initial study showed that the reaction of telluronium cinnamylide with propylidene malonate gave a trace amount of the desired cyclopropane (Scheme 1). Considering that the match between ylide and substrate is crucial to the yields as well as the control of stereoselectivity in ylide cyclopropanation,[9] we tried to use the corresponding arsonium ylide[10] instead to continue the study.

Fortunately, we found that the reaction of ethyl propylidene malonate with arsonium cinnamylide, prepared in situ by deprotonation of the corresponding arsonium bromide with $KN(Me_3Si)_2$ (0.5 M in THF) at room temperature, proceeded well in THF to give the desired cyclopropane with high stereoselectivity in 71% yield (entry 3, Table 1).

As shown in Table 1, the reaction was base-dependent. When LiHMDS was used as a base, both the yield and

(1) (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057. (c)Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139. (d) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554. (e) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (f) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (g) Kotsuki, H.; Arimura, K.; Maruzawa, R.; Ohshima, R. *Synlett* **1999**, 650. (h) Beal, R. B.; Dombrowski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391.

(2) For reviews, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Davies, H. M. L.; Antoulinakis, E. *Org. React.* **2001**, *57*, 1. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(3) For cyclopropanation with a diazalkanes bearing two electron-withdrawing groups, see: (a) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327. (b) Mueller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, 779. (c) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145. (d) Koskinen, A. M. P.; Munoz, L. *J. Org. Chem.* **1993**, *58*, 879. (e) Koskinen, A. M. P.; Hassila, H. *J. Org. Chem.* **1993**, *58*, 4479. (f) Taber, D. F.; Amedio, J. C.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984.

(4) (a) Ma, S.; Jiao, N.; Yang, Q.; Zheng, Z. *J. Org. Chem.* **2004**, *69*, 6463. (b) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837.

(5) (a) Wang, Y.; Zhao, X.; Li, Y.; Lu, L. *Tetrahedron Lett.* **2004**, 7775. (b) Yamazaki, S.; Kataoka, H.; Yamabe, S. *J. Org. Chem.* **1999**, *64*, 2367. (c) Trost, B. M.; Tanimori, S.; Dunn, P. T. *J. Am. Chem. Soc.* **1997**, *119*, 2735. (d) Funaki, I.; Roel, P. L. B.; Lambertus, T.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 12253. (e) Kasatkin, A. N.; Kulak, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A. *Tetrahedron Lett.* **1990**, *31*, 4915.

(6) (a) Krief, A.; Provins, L.; Froidbise, A. *Synlett* **1999**, 1936. (b) Dauben, W. G.; Lewis, T. A. *Synlett* **1995**, 857.

(7) (a) Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2005**, *127*, 12222. (b) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030. (c) Ye, S.; Huang, Z. Z.; Xia, C. A.; Tang, Y.; Dai, L.-X. *J. Am. Chem. Soc.* **2002**, *124*, 2432. (d) Ye, S.; Yuan, L.; Huang, Z. Z.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 6257.(e) Ye, S.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2001**, *66*, 5757. (f) Ye, S.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 6257.

(8) Tang, Y.; Chi, Z.-F.; Huang, Y.-Z.; Dai, L.-X.; Yu, Y.-H. *Tetrahedron* **1996**, 8747.

(9) Tang, Y.; Huang, Y.-Z.; Dai, L.-X.; Sun, J.; Xia, W. *J. Org. Chem.* **1997**, *62*, 954.

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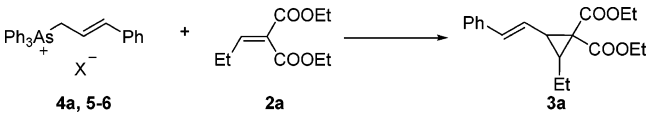
TABLE 1. Effects of Reaction Conditions on the Cycloprapanation Reaction of Propylidene Malonate[a]



4a, 5-6 **2a** **3a**

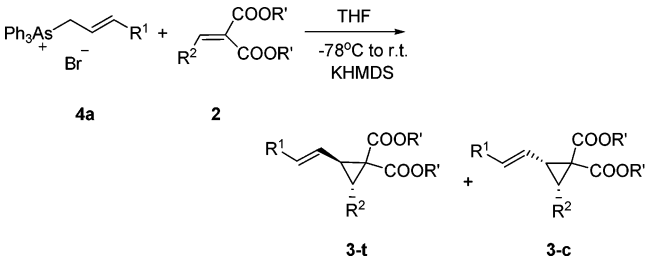
entry	base	solvent	X^-	*T* (°C)	(*trans*/*cis*)[b]	yield (%)[c]
1	LiHMDS	THF	Br^- (**4a**)	−78 to rt	1.5/1	30
2	NaHMDS	THF	Br^- (**4a**)	−78 to rt	11/1	82
3	KHMDS	THF	Br^- (**4a**)	−78 to rt	13/1	71
4	KHMDS	THF	BPh_4^- (**5**)	−78 to rt	7/1	80
5	KHMDS	THF	BF_4^- (**6**)	−78 to rt	10/1	74
6	KHMDS	THF+ 10% HMPA	Br^- (**4a**)	−78 to rt	11/1	75
7	KHMDS[d]	THF	Br^- (**4a**)	−78 to rt	16/1	88
8	KHMDS[d]	THF + LiBr[e]	Br^- (**4a**)	−78 to rt	1.5/1	37[f]
9	KHMDS[g]	THF	Br^- (**4a**)	−78	24/1	77(89[f])
10	KHMDS	THF	Br^- (**4a**)	rt	7/1	76

[a] With stirring for a further 6 h after the cooling bath was removed. [b] Determined by ^{1}H NMR. [c] Isolated yields. [d] With stirring for further 5 min after the cooling bath was removed. [e] 2.5 equiv added. [f] Conversion based on ester by ^{1}H NMR. [g] Quenched at −78 °C.

stereoselectivity decreased greatly (entry 3 versus entry 1, Table 1). NaHMDS gave good stereoselectivity in 82% yield (entry 2 in Table 1). The anions of the arsonium salts influenced both the yields and the selectivity (entries 3−5, Table 1).[11] Further studies showed that lowering the reaction temperature increased the diastereoselectivity. For instance, the ratio of *trans*-isomer and *cis*-isomer could be improved from 7/1 to 24/1 by lowering the reaction temperature from room temperature to −78 °C (entry 9 versus entry 10, Table 1). Noticeably, lithium ion decreased both the yields and diastereoselectivity greatly. In our screening conditions, the best result was achieved using KHMDS as a base and THF as a solvent. In this case, the reaction gave the cyclopropane in 88% yield with high diastereoselectivity (*trans*/*cis* = 16/1, entry 7).

The high diastereoselectivity and yield obtained with propylidene malonate encouraged us to further explore the cyclopropanation of arylidene and alkylidene malonates. As shown in Table 2, ethylene, isobutylene, and isopentylene malonates gave good to high stereoselecivity as well as excellent yields (entries 1−3, Table 2). Compared with the ethylene and isopentylene malonates, isobutylene malonate took longer to react and the selectivity decreased slightly, probably as a result of the steric hindrance (entry 2). Arylidene malonates could also be

TABLE 2. Stereoselective Synthesis of *trans*-Disubstituted Cyclopropane-1,1-dicarboxylates via Arsonium Ylides

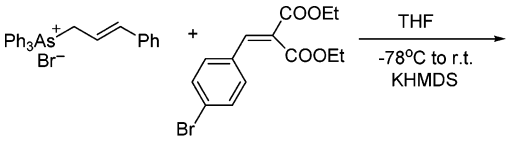


4a **2** **3-t** **3-c**

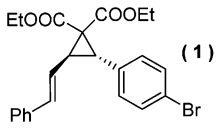
entry	R^1	R^2	R′	(*trans*/*cis*)[a]	yield (%)[b]
1	Ph (**4a**)	Me (**2b**)	Et	16/1 (**3b**)	88
2	Ph (**4a**)	i-Pr (**2c**)	Et	5/1 (**3c**)	89
3	Ph (**4a**)	i-Bu (**2d**)	Me	16/1 (**3d**)	91
4	Ph (**4a**)	Ph (**2e**)	Et	14/1 (**3e**)	93
5	Ph (**4a**)	*p*-CH_3-C_6H_4 (**2f**)	Me	25/1 (**3f**)	93
6	Ph (**4a**)	*p*-Br-C_6H_4 (**2g**)	Et	27/1 (**3g**)	94
7	H (**4b**)	Ph (**2e**)	Et	43/1 (**3h**)	88
8	H (**4b**)	Et (**2a**)	Et	13/1 (**3i**)	83
9	TMS (**4c**)	Ph (**2e**)	Et	13/1 (**3j**)	89
10	TMS (**4c**)	Et (**2a**)	Et	13/1 (**3k**)	86

[a] Determined by ^{1}H NMR. [b] Isolated yields.

highly stereoselectively converted to the corresponding cyclopropane in excellent yields (entries 4−6, Table 2). Other arsonium ylides, such as simple allylide and 3-trimethylsilylallylide, could react well with both alkylidene and arylidene malonates to give the desired cyclopropane with high stereoselectivity in high yields (entries 7−10). For example, the reactions of the arsonium allylide with benzylidene malonate and propylidene malonate gave 88% and 83% yields, respectively, with high selectivity. It is worth noting that the triphenylarsine could be recovered with high yield as shown in eq 1.



Ph_3As: recovered in 88% yield.



(1)

Yield: 94%
trans/cis = 27/1

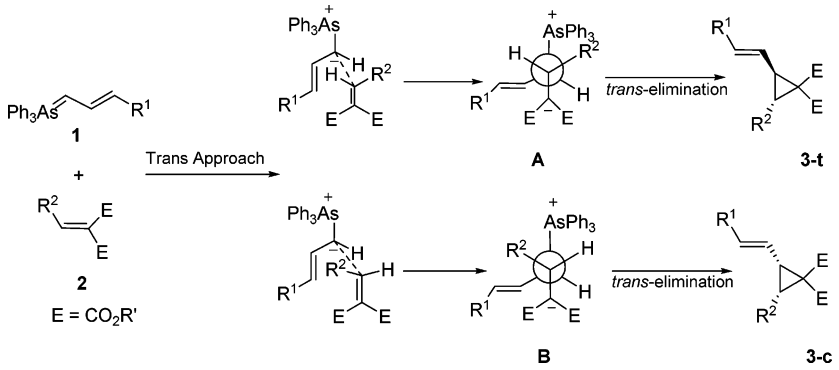
The reactions of arylidene and alkylidene malonates with arsonium allylides afforded *trans*-2,3-disubstituted 1,1-dialkoxylcarbonylcyclopropanes with high stereoselectivity. A possible mechanism as shown in Scheme 2 can rationalize the *trans*-selectivity produced.[12] Arsonium ylides **1** took a "transoid approach" in which the triphenylarsonium group and carbon carbon double bond of malonate **2** are located in an *anti*-like orientation to form intermediates **A** or **B**, followed by *trans*-elimination to provide cyclopropanes. In accordance with the mecha-

(10) Selected references on the reactions of arsonium ylides: (a) Dai, W.-M.; Wu, A.-X.; Wu, H.-F. *Tetrahedron: Asymmetry* **2002**, 2187. (b) Chen, Y.-L.; Ding, W.-Y.; Cao, W.-G.; Lu, C. *Synth. Commun.* **2002**, 1953. (c) Shen, Y.-C.; Wang, T.-L. *J. Fluorine Chem.* **1997**, *82*, 139. (d) Moorhoff, C. M. *J. Chem. Res., Synop.***1997**, 130. For reviews, see: (e) He, H. S.; Chung, C. W. Y.; But, T. Y. S.; Toy, P. H. *Tetrahedron* **2005**, 1385. (f) Huang, Y.-Z.; Shi, L.-L.; Zhou, Z.-L. Triphenylarsine. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; p 5339. The arsenic compounds described here should be handled with caution. Although triphenylarsine has been used for years as a ligand by inorganic chemists and seems to have only moderate acute toxicity, repeated exposure should be avoided by working with care in an efficient hood. Because the compounds described in this paper are nonvolatile, actual danger is minimal.

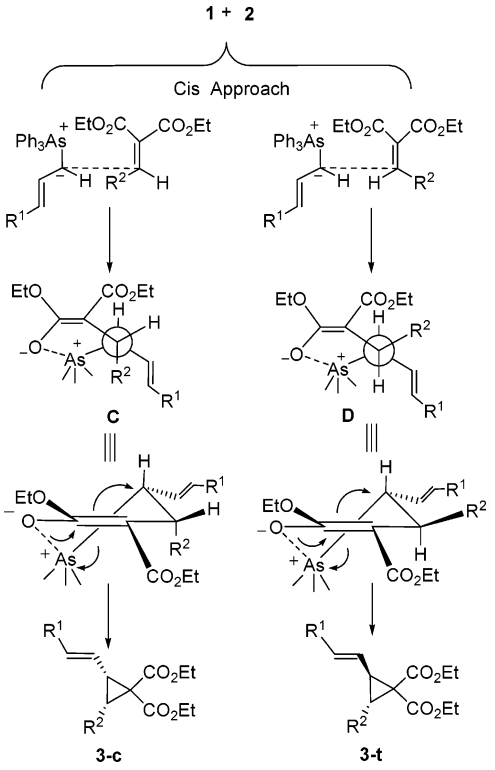
(11) A similar "salt effect" was reported in the epoxidation of arsonium ylides, Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1981**, *103*, 1283.

(12) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747.

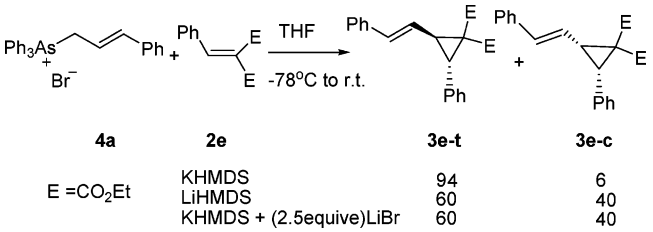
SCHEME 2. Possible Mechanism for the Cyclopropanation of Arsonium Ylide



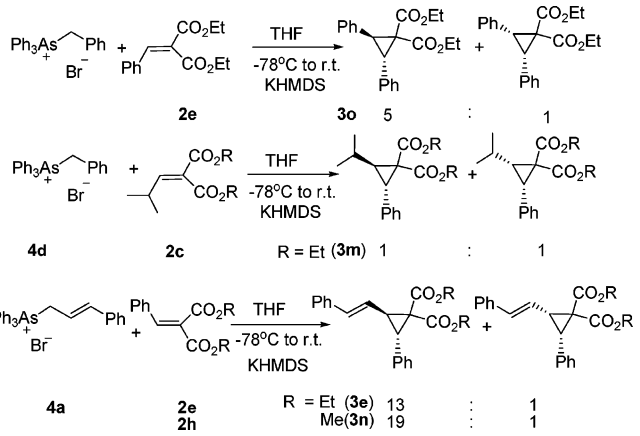
SCHEME 3. Proposed Cisoid Approach Mechanism



SCHEME 4. Effect of Lithium Ion on Stereochemistry



SCHEME 5



nism proposed in Scheme 2, it appears that intermediate **A** is more stable than intermediate **B** and thus the *trans*-disubstituted cyclopropane 1,1-dicarboxylic esters forms preferably as the major product.

Considering a possible interaction between the arsonium cation and ester oxygen,[13] an alternative mechanism is shown in Scheme 3. The ylide may approach the malonate in a manner such that the triphenylarsonium cation and carbon carbon double bond of malonate **2** are in a *cis*-like orientation to form intermediates **C** and **D**, which allows for an interaction between the triphenylarsonium cation and one of the ester oxygen atoms. Intermediates **C** and **D** can give the observed cyclopropanes by an elimination reaction. Formation of proposed intermediate **C** is disfavored on steric grounds relative to intermediate **D** and thus the *trans*-isomer is proposed to be the major product. According to the mechanism shown in Scheme 3, the presence of lithium ion should destroy the formation of intermediates **C** and **D** as a result of the strong interaction of lithium ion with oxygen anion[14] and will influence the diastereoselectivity. Thus, we investigated the effect of lithium bromide as an additive on this reaction. As expected, we found that lithium ion had a strong effect on both the yield and stereoselectivity (Scheme 4). This mechanism is also consistent with the experimental results shown in Scheme 5. Increasing the steric interaction between the R^2 group and the R^1 group or the size of the ester group decreases the selectivity. For instance, when R^2 is changed from phenyl to isopropyl, the ratio for *trans*- and *cis*-isomers is reduced from 5/1 to 1/1. Although both the proposed mechanisms could explain the stereochemistry, a clear mechanistic understanding awaits further investigation.

(13) (a) Mitsumoto, Y.; Nitta, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2268. (b) Boubia, B.; Mann, A.; Bellamy, F. D.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1454.

(14) (a)Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664. (b) Ousset, J. B.; Mioskowski, C.; Solladie, G. *Synth. Commun.* **1983**, *13*, 1193.

In summary, we have developed an efficient cyclopropanation reaction of alkylidene and arylidene malonates with arsonium allylides. This methodology provides an easy access to *trans*-2,3-disubstituted cyclopropane 1,1-dicarboxylic esters. The readily available starting material, high selectivity, and high yield make this protocol potentially useful in organic synthesis. Efforts to develop its catalytic and asymmetric version are in progress in our laboratory.

Experimental Section

General Procedure for Cyclopropanation of Alkylidene (or Arylidene) Malonic Acid Esters with Triphenylcinnamyl Arsonium Bromide. A. For Diethyl *trans*-2-Ethyl-3-styrylcyclopropane-1,1-dicarboxylate (3a). A dried vial was charged with triphenylcinnamyl arsonium bromide (160 mg, 0.318 mmol) and 2.5 mL of THF, followed by a solution of potassium bis(trimethylsilyl) amide (0.5 M in THF, 0.6 mL, 0.3 mmol) via a syringe at room temperature under N_2 atmosphere. The resulting mixture was cooled to −78 °C and stirred for 30 min, and then diethyl propylidene malonic acid ester (50 mg, 0.250 mmol) in THF (1 mL) was added. After 1 h, the cooling bath was removed. The mixture was stirred for a further 5 min and filtered rapidly through a glass funnel with a thin layer of silica gel (ethyl acetate as the elutant, 50 mL). The filtrate was concentrated and the residue was subjected to ^{1}H NMR analysis (δ 5.89 vs δ 6.10) to determine the ratio of isomers (*trans*/*cis* = 16/1). The pure product was obtained by flash chromatography (EtOAc/petroleum ether = 1/100, v/v). Yield: 70 mg (88%). ^{1}H NMR for *trans*-isomer (300 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 6.63 (d, J = 15.9 Hz, 1H), 5.89 (dd, J = 15.9, 9.0 Hz, 1H), 4.29−4.10 (m, 4H), 2.58 (t, J = 8.1 Hz, 1H), 2.13 (q, J = 7.8 Hz, 1H), 1.51−1.40 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.1, 167.8, 136.8, 132.8, 128.5, 127.3, 125.9, 125.1, 61.4, 42.1, 35.6, 34.6, 21.0, 14.1, 13.0; MS (EI) *m/z* (rel intensity) 316 (M^+, 11), 169 (100), 242 (77), 115 (73), 270 (66), 91 (60), 168 (58), 141 (58), 213 (58); IR (thin film)/cm^{-1} 2979 (m), 1723 (s), 1368 (m), 1290 (m), 1201(m), 1146 (m), 964 (m), 693(m). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.18; H, 7.76.

General Experimental Procedure for Cyclopropanation of Allyltriphenyl (3-Trimethylsilylallyltriphenyl) Arsonium Bromide with Alkylidene (or Arylidene) Malonic Acid Esters. Synthesis of Diethyl *trans*-2-Ethyl-3-vinylcyclopropane-1,1-dicarboxylate (3i). A dried vial was charged with triphenylallyl arsonium bromide (172 mg, 0.403 mmol), 2.5 mL of THF, and a solution of potassium bis(trimethylsilyl) amide (0.5 M in THF, 0.7 mL, 0.35 mmol) via a syringe at −78 °C. The resulting mixture was stirred for 30 min, and then diethyl propylidene malonic acid ester (64 mg, 0.32 mmol) in THF (1 mL) was added. After 1 h, the cooling bath was removed, and the mixture was stirred for a further 5 min and filtered rapidly through a glass funnel with a thin layer of silica gel (CH_2Cl_2 as the elutant, 60 mL). The filtrate was concentrated and the residue was subjected to ^{1}H NMR analysis (δ5.07 vs δ5.20) to determine the ratio of isomers (*trans*/*cis* = 16/1). The pure product was obtained by flash chromatography (EtOAc/30−60 °C petroleum ether = 1/100, v/v). Yield: 61 mg (83%). ^{1}H NMR (300 MHz, $CDCl_3$) for *trans*-isomer δ 5.52−5.39 (m, 1H), 5.26 (dd, J = 17.1, 1.8 Hz, 1H), 5.07 (dd, J = 10.2, 1.8 Hz, 1H), 4.30−4.06 (m, 4H), 2.42 (t, J = 8.1 Hz, 1H), 2.01 (q, J = 7.5 Hz, 1H), 1.46−1.35 (m, 2H), 1.30−1.18 (m, 6H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.0, 167.9, 133.3, 117.8, 61.4, 61.3, 41.7, 35.7, 33.9, 20.8, 14.2, 14.1, 13.0; MS (EI) *m/z* (rel intensity) 241 (MH^+, 26), 211 (100), 137 (79), 93 (77), 195 (73), 149 (62), 148 (34), 77 (34), 183 (32); IR (thin film)/cm^{-1} 2980 (m), 2936 (m), 1726 (s), 1368 (m), 1290 (m), 1204 (m), 1149 (m), 415 (m), 401 (s); HRMS (EI) calcd for $C_{13}H_{20}O_4$ [M^+] 240.1362, found 240.1350.

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Supporting Information Available: Characterization data for all compounds and experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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