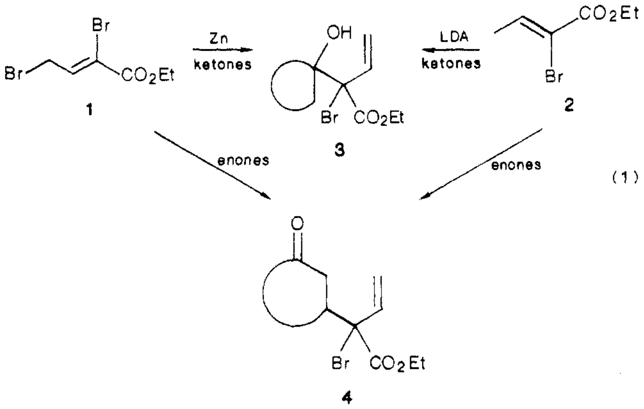
4746 *J. Org. Chem.* 1986, *51*, 4746-4748

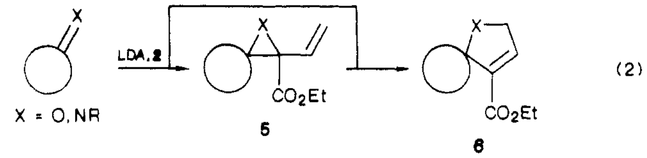
New Vinylcyclopropanation Methodology and Reagents for Potential [2 + 3] Cyclopentene, Dihydrofuran, and Pyrroline Annulations

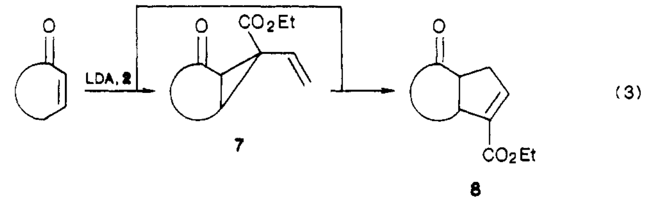
Summary: The additions of the lithium dienolate anion derived from ethyl 2-bromocrotonate to several ketones, aldehydes, and enones were investigated. The products were analyzed in terms of yields, regioselectivity, and stereoselectivity of this reaction. The potential for cyclopentene annulation is indicated.

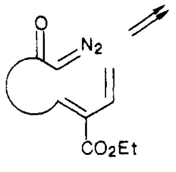
Sir: The regioselectivity in the additions of the ambidently nucleophilic Reformatsky reagent derived from ethyl 4-bromocrotonate to aldehydes and ketones,[2] as well as to enones,[3] has been established. In an effort to broaden the scope of this mild carbon–carbon bond-forming reaction, we investigated the vinylogous Darzen–Reformatsky combination through the use of reagents **1** and **2**, whose additions to ketones and enones could provide adducts **3** and **4**, respectively (eq 1). The substrates **3** and **4** are convertible to annulated dihydrofurans and cyclopentenes, respectively, by internal allylic displacement of the halide.



The condensation of **1** with several carbonyl compounds provided complex mixtures of products with **3** or **4** being present in low yields.[4] The presence of α-halogen altered the reactivity of **1** under the conditions of the vinylogous Reformatsky reaction to such an extent that no predictions about the regioselectivity of this reagent could be made. We turned instead to the investigations of additions of **2** to carbonyl compounds with the ultimate objective of providing a [2 + 3] *intermolecular* annulation scheme as shown in eq 2 and 3. Such methodology would complement the existing methods of preparation of cyclopentene-annulated systems, such as **8**, which are currently available by the use of intramolecular [4 + 1] cyclopentene annulation of diazo ketones of type **9**.[5]

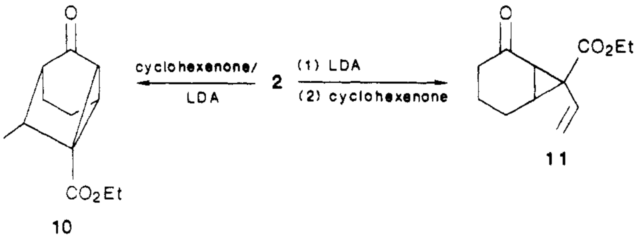






9

The uses of reagent **2**[6] as a bisannulating agent in its interaction with enones[7-9] and as a heterocyclic annulation agent with pyridine α-imines[10] have been reported previously. Thus **2** added to LDA and cyclohexenone gave the tricyclic ketone **10** as a consequence of the kinetic enolate of the enone adding to **2** in the crucial first step of this sequence.[7,9]



When cyclohexenone was added to a lithium dienolate of **2** essentially quantitative yield of **11** was obtained as a 60/40 mixture of exo/endo isomers. This experiment bodes well for a simple vinylcyclopropanation scheme emanating from the use of dienolates equipped with a leaving group at the α-position.

The literature contains many examples of cyclopropane formation from the reagents such as **12** and various ylides acting as Michael-type nucleophiles in the reaction with unsaturated carbonyl compounds.[11] Although the use of bifunctional Michael nucleophiles is quite common, to our knowledge it has only been applied to a limited degree in a "vinylogous" sense for the synthesis of vinylcyclopropanes.[12] The use of reagents of type **2**, **2a**, **2b**, and **2c** has been reported in the literature in the context of bi-

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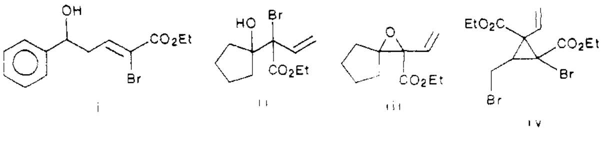
(1) Fellow of the Alfred P. Sloan Foundation, 1981-5; recipient of the NIH Research Career Development Award, 1984-9.

(2) Hudlicky, T.; Rice, L.; Boston, M. C.; Finklea, H. O.; Suder, B. J. *J. Org. Chem.* **1984**, *49*, 1845.

(3) Hudlicky, T.; Natchus, M. G.; Kwart, L. D.; Colwell, B. *J. Org. Chem.* **1985**, *50*, 4300.

(4) For example, the addition of 1 to benzaldehyde and cyclopentanone under the conditions of the Reformatsky reaction yielded compounds i-iii as major products. Both reaction mixtures contained substantial amounts of iv.



(5) See, for example: Short, R. P.; Ranu, B. C.; Revol, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

(6) Prepared from ethyl crotonate by addition of Br_2/HOAC and elimination using DBU.

(7) Hagiwara, H.; Uda, H.; Kodama, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 963.

(8) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48* 3769.

(9) Hagiwara, H.; Kodama, T.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1976**, 413.

(10) Kakehi, A.; Ito, S. *J. Org. Chem.* **1974**, *39*, 1542.

(11) See, for example: (a) Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Academic: New York, 1975. (b) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1979**, 4603 (cyclopropane formation). (c) Durst, T. *J. Am. Chem. Soc.* **1969**, *91*, 1034. (d) Becker, G.; Gosselck, J. *Tetrahedron Lett.* **1971**, 4081. (e) Tsuchihashi, G.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2023 (oxirane formation). (f) Hendrickson, J. B.; Griga, A.; Wareing, J. *J. Am. Chem. Soc.* **1974**, *96*, 2275. (g) Cohen, T.; Yu, L. C. *J. Am. Chem. Soc.* 1983, *105*, 2811.

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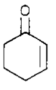
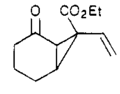
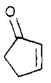
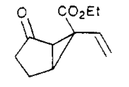
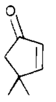
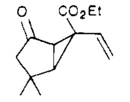
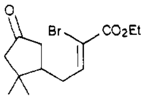
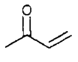
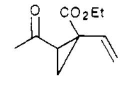
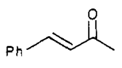
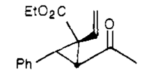
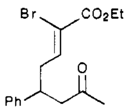
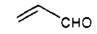
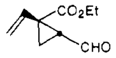
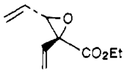
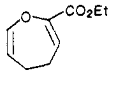
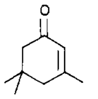
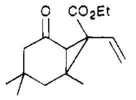
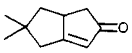
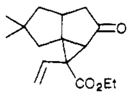
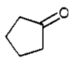
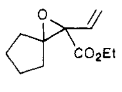
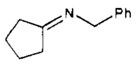
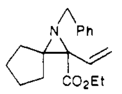
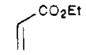
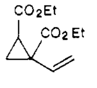
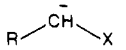
Table I. Condensation of 2 with Carbonyl Compounds

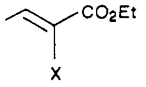
carbonyl substrate	product(s) and % yield[a] (exo/endo)				conditions
 13	 11	93% (60/40)	7% s.m.		-78 °C, 15 min
 14	 15[18]	100% (70/30)			-78 °C, 15 min
 16	 17	45% (50/50) 45% s.m.	 18	trace	-78 °C, 15 min
 19	 20	50% (50/50)	no s.m., 50% unknown		-78 °C, 15 min
 21	 22	(73% *trans*-vinylacetyl/ 27% *cis*-vinylacetyl)	 23, 45%	40% s.m.	-78 °C, 15 min
 24	 25	trace	 26, 35%	 27, 20%	-78 °C, 15 min
 28	 29	12% (35/65) 30% (55/45)	86% s.m. 60%		25 °C, 15 min BF$_3$ added, -78 °C, 15 min
 30[14]	 31[18]	45% (50/50)	50% s.m.		0 °C, 15 min
 32	 33	70%			-78 °C, 15 min
 34	 35	trace			-78 °C, 15 min
 36	 37	75% (50/50)			-78 °C, 20 min

[a] s.m. = starting material.

sannulation reagents.[6-10,13] In this report we outline their utility as versatile vinylcyclopropanation reagents.



12, X = SO$_2$Ph
SOPh, SPh



2, X = Br
2a, X = Cl
b, X = SPh
c, X = SO$_2$Ph
d, X = OTs

The temperature of reaction and timing of additions were crucial in determining the pathway of the reaction. Attempts at early quenching or trapping of the presumed intermediate of type 4 were unsuccessful even at -100 °C

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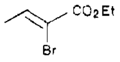
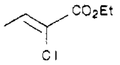
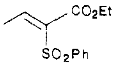
(12) (a) Few cases of vinylcyclopropanation using methyl 2-chlorobut-3-enoate, NaH and methyl-2 chloroacrylate or methyl acrylate have been reported in yields of 5-50%. Ducher, S.; Sudre, J. P.; Vessiere, R. *C. R. Seances Acad. Sci. Ser. C* **1974**, *278*, 537; **1973**, *277*, 575. This work constituted the use of a vinylogous McCoy reaction (McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568; *J. Org. Chem.* **1960**, *25*, 2078). (b) A case of vinylcyclopropanation using ambident sulfur-stabilized allyl anions has been investigated by Prof. T. Cohen, University of Pittsburg, and reported at the 2nd Symposium on the Latest Trends in Organic Synthesis, Blacksburg, VA 24061 in May 1986: Cohen, T.; Myers, M.; Ramig, K.; Bhupathy, M. *Novel One-Pot Methods for the Cyclopropanation and Vinylcyclopropanation of Enones.*

Table II. Condensation of Cyclohexenone with 2a-c

halocrotonate[a]	% yield of 11 (exo/endo)[b]	
	93% (60/40)	7% s.m.
	70% (59/41)	17% s.m.
	18% (0/100)	44% s.m.

[a] All reactions run at -78 °C. [b] Yields determined by NMR or GC methods. s.m. = starting material.

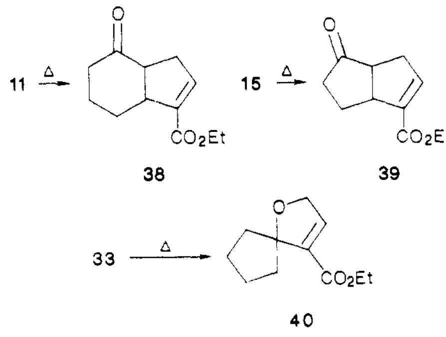
Table III. Temperature Profile for Cyclohexenone

T, °C	% yield of 11	exo/endo
-100	70-90	65/35
-78		60/40
-40		70/30
-20		70/30
0		30/70
25		30/70

with a 5-s quench (vinylcyclopropane formation was instantaneous).[15]

Table I summarizes the results of our initial experiments. As expected, with additional substitution at the β-carbon of the enone, the reaction either became sluggish or followed competing avenues such as 1,2-additions, which predominated with some enones or unsaturated aldehydes. Activation of enones with $BF_3 \cdot OEt_2$ enhanced yields of cyclopropanes in some cases. In the case of acrolein, the initially formed *cis*-divinyloxirane rearranged in situ to carboxyoxepin **27**, which was isolated. The results in Table I are reported on a comparative basis, as no attempts were made to optimize the conditions of each case at this time. The effects of time, temperature, and leaving group were briefly investigated for cyclohexenone, to determine how the exo/endo ratio was affected (Tables II and III). In the case of simple ketones, cyclopentanone gave vinyloxirane **33** exclusively, and its Schiff base adduct provided a trace of vinylaziridine **35**. Ethyl acrylate gave a good yield of vinylcyclopropane **37**.

These results, coupled with the facile vinylcyclopropanation of enones, are delightful since they provide the basis of a new [2 + 3] annulation methodology. Thus **11** and **15** (both isomers) were pyrolyzed at 550 °C (Vycor/$PbCO_3$) to provide the bicyclic keto acrylates **38** and **39**. Similarly, pyrolysis of vinyloxirane **33** afforded dihydrofuran **40**.[16,17] Further results from active research on the applications of this methodology to the synthesis of five-membered annulated ring systems will be reported in due course.



Experimental Section

General. A solution of lithium diisopropylamide (prepared from 0.48 g (4.7 mmol) of diisopropylamine in 4.7 mL of THF and 1.9 mL of *n*-BuLi (2.4 M in hexane) at 0 °C) was cooled to -78 °C and HMPA (0.9 mL; 5.2 mmol) was added. After 30 min ethyl 2-bromocrotonate (0.91 g; 4.7 mmol) was introduced via a syringe. The dark brown solution was stirred for 10 min whereupon cyclopentenone (0.34 g; 4.2 mmol) was added via a syringe. After 15 min the reaction was quenched at (-78 °C) with saturated NH_4Cl solution (5 mL), diluted with Et_2O and washed with 3 N HCl. The aqueous layers were extracted twice with Et_2O, the organic layers were combined, washed with brine, dried (Na_2SO_4), and evaporated to yield **15** (0.80 g; 99%) as a mixture of exo/endo isomers (70/30) which were separated by chromatography (silica; hexane) Et_2O (80/20) [R_f (exo) = 0.16; R_f (endo) = 0.26].

This procedure was followed for other carbonyl compounds with appropriate time temperature adjustments as noted in Table I.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Jeffress Trust, the NIH (AI-19749, AI-05564), the Chemistry Department, Virginia Polytechnic Institute and State University, and TDC Research, Inc. for generous financial support of this work.

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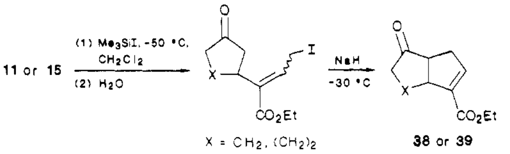
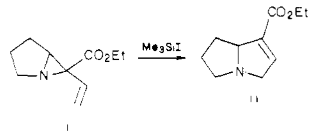
(13) Review of sulfur based cyclopropanation reagents: Conia, J. M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 570. See also ref 11a above.

(14) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, 4851.

(15) Carbenoid nature of this process was excluded upon observation that the dienolate of **2** did not react with cyclohexene.

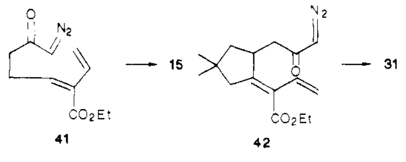
(16) Vinylcyclopropanes **11** and **15** were treated with Me_3SiI at -30 °C to provide allylic iodides which could be cyclized to **38** and **39** on treatment with NaH at -78 °C. In view of this mild equivalent of cyclopentene annulation, similar investigation of such alkylative ring opening will be performed on vinyloxiranes. As of this writing, several vinyloxiranes have been prepared and converted to dihydrofurans of type **40** by thermolysis. Although no viable method was found to prepare vinylaziridines of the type **35** by employing reagent **2**, the Me_3SiI opening of vinylaziridines **i** prepared by other means provided quantitatively fused pyrolines of type **ii** (Hudlicky, T.; Sinai-Zingde, G.; Seoane, G. *Tetrahedron Lett.*, in press).





(17) All compounds were assigned using IR, ^1H NMR, ^{13}C NMR and mass spectra. These will be reported in a full paper in the near future.

(18) Vinylcyclopropanes **15** and **31** were previously obtained from diazo ketones **41** and **42**. The current method of preparation is superior in brevity and yield.



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