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Practical Approach to α- or γ-Heterosubstituted Enoic Acids

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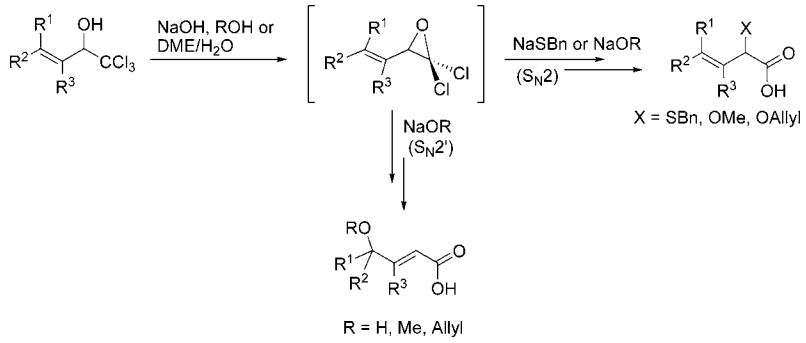
ABSTRACT

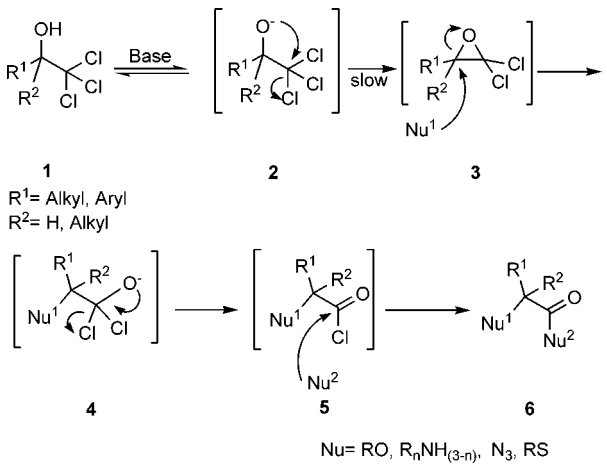


The reaction of alkenyl trichloromethyl carbinols with various nucleophiles under protic basic conditions reveals that mercaptans participate by α-substitution (S_N2) of the intermediate alkenyl *gem*-dichloroepoxides. Conversely, hydroxide results in preferential γ-substitution with stereoselective allylic transposition (S_N2'). Regioselectivity with alkoxides depends upon the level of alkene substitution.

The Jocic reaction involves the treatment of trichloromethyl carbinols (**1**) with hydroxide to furnish 2-substituted carboxylic acids (Scheme 1).[1] Nucleophilic addition to the α-carbon of a reactive geminal dichloroepoxide (**3**), formed from the corresponding trichloromethyl alkoxide (**2**), leads to subsequent elimination of chloride. The resulting acid chloride (**5**) then undergoes acylation with a second or tethered nucleophile.

Studies by Reeve helped clarify the mechanism of the Jocic reaction as outlined in Scheme 1.[2] Reeve's work with aryl trichloromethyl carbinols and other analogues also showcased the utility of dichloroepoxides as latent dielectrophiles.[3] Corey and Link established an efficient preparation of trichloromethyl carbinols from carbonyl compounds by reacting them with trichloroacetic acid/sodium trichloroacetate in DMF.[4] They also reported the first preparation of asymmetric trichloromethyl carbinols using an enantioselective oxazaborolidine-based reduction of the correspond-

Scheme 1. Mechanism of the Jocic Reaction



(1) (a) Jocic, Z. Z. *Zh. Russ. Fiz. Khim. Ova.* **1897**, *29*, 97. (b) Gukasyan, A. O.; Galstyan, L. K.; Avetisyan, A. A. *Russ. Chem. Rev.* **1991**, *60*, 1318.
(2) (a) Reeve, W.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem.* **1980**, *58*, 485. (b) Reeve, W.; Bianchi, R. J.; McKee, J. R. *J. Org. Chem.* **1975**, *40*, 339. (c) For another mechanistic consideration, see: Benner, J. P.; Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 331.
(3) Reeve, W. *Synthesis* **1971**, 131 and references therein.

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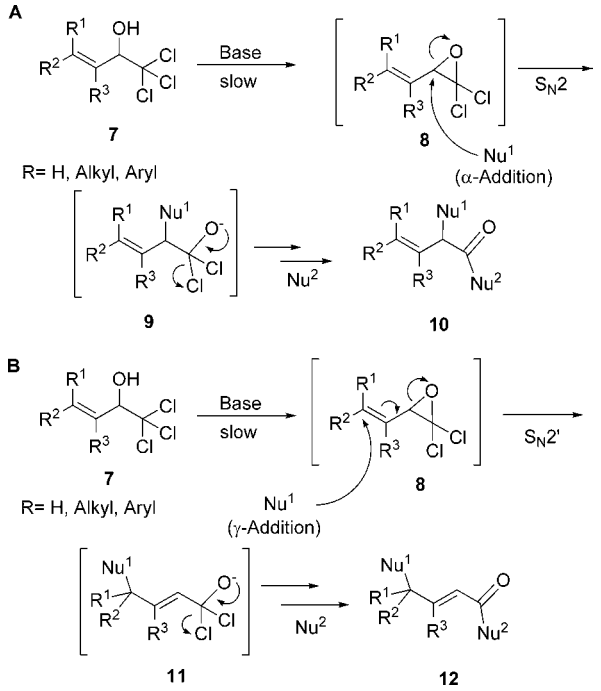
ing trichloromethyl ketones.[5] Although these investigators have made notable contributions toward the application of trichloromethyl carbinols in Jocic-type reactions, examinations into the reactivity of alkenyl trichloromethyl carbinols in such reactions are conspicuously lacking.[6]

Herein, we report the first exploration into the regioselectivity of nucleophilic additions with alkenyl *gem*-dichloroepoxides in the Jocic-type reaction. We reasoned that various nucleophiles might display a preference for direct epoxide substitution, ultimately leading to β,γ-unsaturated α-substituted carboxylic acids (Scheme 2A), or proceed via

Scheme 2. Regiochemical Considerations during Reactions of Nucleophiles with Alkenyl Trichloromethyl Carbinols

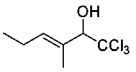
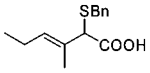
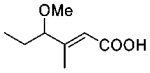
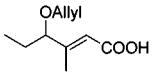
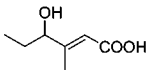
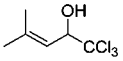
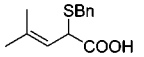
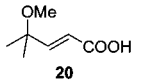
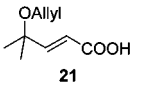
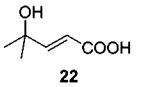
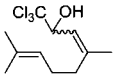
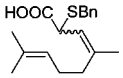
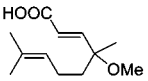
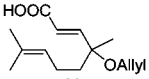
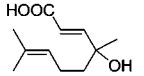


an S_N2' pathway resulting in γ-substituted enoic acids (Scheme 2B). In either case, the results would offer a convenient approach to disparate heterosubstituted unsaturated carboxylic acids that are not readily accessible by conventional methods.

Alkenyl trichloromethyl carbinols (Tables 1, 2, and 3) were prepared from the corresponding enals by the method of Corey and Link.[4] We employed commercially available enals except those used to afford **35** and **39**, which were prepared by the method of Hon.[7] The resulting carbinols featured a range of olefin substitution and alkene configurations.

Protic solvent plays a pivotal role in the formation of the reactive alkenyl dichloroepoxide **8** (Scheme 2). Conducting

Table 1. Reactions of Trisubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles

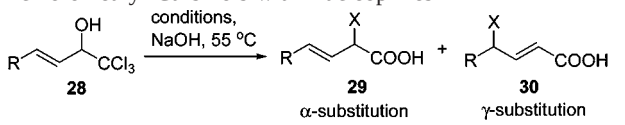
entry	substrate	conditions[a]	product	yield (%)[b]
1	 **13**	BnSH, MeOH	 **14**	85
2		MeOH	 **15**	76
3			 **16**	63[c]
4		DME/H_2O	 **17**	75
5	 **18**	BnSH, MeOH	 **19**	75
6		MeOH	 **20**	80
7			 **21**	72
8		DME/H_2O	 **22**	89
9	 **23**	BnSH, MeOH	 **24**	83
10		MeOH	 **25**	85
11			 **26**	70
12		DME/H_2O	 **27**	84

[a] Reactions were conducted with 1 mmol of substrate at 55 °C using 6 equiv of NaOH. DME/H_2O ratios were 4:3 (v/v). A portion of 3 mmol of BnSH was used in the thiolate addition reactions. [b] Yield of a purified single alkene diastereomer shown. Alkene geometry was confirmed by 1D NOE difference spectroscopy. [c] 31% of the α-substitution product was also isolated.

the reactions in anhydrous THF, THF/HMPA, DMF, or MeCN results in little or no conversion of **1** to products.[8] This dependency on a hydrogen bond donating solvent implicates an S_N1-type mechanism in the formation of the epoxide, where substantial bond breakage between a chlorine and carbon bond in **7** facilitates the intramolecular attack of the alkoxide.

(4) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435.
(5) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431. (b) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.
(6) We are aware of only two examples, each of which involved a single alkenyl substrate: (a) Reeve, W.; Steckel, T. F. *Can. J. Chem.* **1980**, *58*, 2784. (b) Kryshtal, G. V.; Zhdankina, G. M.; Yanovskaya, L. A. *Izv. Akad. Nauk, SSSR Ser. Khim.* **1986**, *5*, 1190.
(7) Hon, Y.-S.; Chang, F.-J.; Lu, L.; Lin, W.-C. *Tetrahedron* **1998**, *54*, 5233.
(8) Other authors have reported a similar protic solvent requirement: (a) Oliver, J. E.; Waters, R. M.; Lusby, W. R. *Synthesis* **1994**, 273. (b) Khrimian, A. P.; Oliver, J. E.; Waters, R. M.; Panicker, S.; Nicholson, J. M.; Klun, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 37.

Table 2. Reactions of 1,2-Disubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles

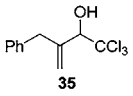
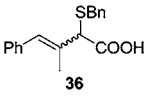
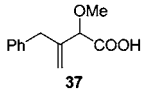
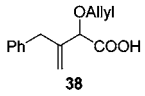
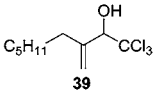
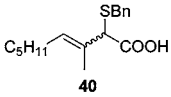
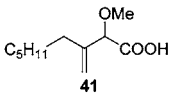
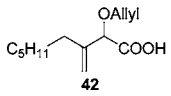


entry	R	conditions[a]	X	**29**/**30**[b]	major regioisomer yield (%)
1	**a** n-C_5H_{11}	MeOH	OMe	1.4:1	55
2	**a** n-C_5H_{11}	DME/MeOH	OMe	5:1	81
3	**a** n-C_5H_{11}	DME/H_2O	OH	1:2	64
4	**a** n-C_5H_{11}		OAllyl	>20:1	93
5	**a** n-C_5H_{11}	MeOH, BnSH	BnS	>20:1	64[c]
6	**b** Ph	MeOH	OMe	1.3:1	37
7	**b** Ph	DME/MeOH	OMe	2.5:1	47
8	**b** Ph		OAllyl	NA[d]	-
9	**b** Ph	MeOH, BnSH	BnS	1.6:1	52

[a] Reactions were conducted with 1 mmol of substrate at 55 °C using 6 equiv of NaOH. A portion of 3 mmol of BnSH was used in the thiolate addition reactions. [b] Established by ^{1}H NMR of the crude reaction mixture. [c] Alkene isomerized after α-substitution to give 2-(benzylthio)non-2-enoic acid as confirmed by 1D and 2D NMR. [d] ^{1}H NMR spectrum of the crude mixture too complex to accurately determine the relative ratio.

Benzyl thiolate, a good nucleophile in protic media, readily adds to alkenyl trichloromethyl carbinols in methanol. However, phenoxides and alcohols other than the solvent, whose nucleophilicities are attenuated by solvation, are essentially unreactive under these conditions.[9] Despite this obstacle, reactions may be efficiently conducted in alcohols where the solvent or its conjugate base serves as the nucleophile. For example, reactions conducted in methanol and allyl alcohol created useful methoxy- or allyloxy-substituted unsaturated carboxylic acids, respectively (cf. Tables 1−3). The reaction works equally well with other alcohols (e.g., EtOH, ^{i}PrOH) acting as the nucleophile and solvent, although the resulting products are generally less desirable than those presented. Unsaturated esters were not generated as products when hydroxide was employed as base, even when the reaction was conducted in an alcohol solvent. This is attributed to irreversible ester saponification which occurred under the alkaline reaction conditions.

Table 3. Reactions of 2,2-Disubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles

entry	substrate	conditions[a]	major product	yield (%)[b]
1	 **35**	BnSH, MeOH	 **36**	78
2		MeOH	 **37**	76
3			 **38**	79
4	 **39**	BnSH, MeOH	 **40**	92[c]
5		MeOH	 **41**	72
6			 **42**	76

[a] Reactions were conducted with 1 mmol of substrate at 55 °C using 6 equiv of NaOH. DME/H_2O ratios were 4:3 (v/v). A portion of 3 mmol of BnSH was used in the thiolate addition reactions. [b] Yield of a purified single alkene diastereomer shown. [c] Combined yield for the 1:1 mixture of **40** and 2-(benzylthio)-3-methylenenonanoic acid.

All substrates examined, except **28b**, underwent facile nucleophilic substitution by both sulfur and oxygen nucleophiles (yields from 70 to >97%). Substrate **28b** routinely failed to undergo complete conversion even with extended reaction times or higher temperatures. The reactions that proceeded via the S_N2' pathway led to (*E*)-enoic acids with excellent diastereocontrol. In no case was there NMR evidence of *Z*-olefin formation after examination of crude reaction mixtures.[10]

Experimental and computational evidence suggests that soft nucleophiles preferentially interact with traditional vinyl epoxides via an S_N2' mechanism, and hard nucleophiles typically undergo direct addition to the epoxide ring without allylic rearrangement.[9,11] Thus, we were initially surprised to find that benzyl mercaptan underwent an S_N2-type reaction with the alkenyl *gem*-dichloroepoxide intermediates (Scheme 2A) to ultimately produce β,γ-unsaturated-α-thiocarboxylic acids (Tables 1−3). Meanwhile, the harder hydroxide nucleophile adds preferentially by an S_N2' epoxide ring opening (Scheme 2B) affording γ-hydroxy-(*E*)-enoic acids in all cases examined. Alkoxides displayed a similar preference with trisubstituted alkenyl substrates (Table 1). However, with 1,2- or 2,2-disubstituted alkenes, methoxide preferentially reacted in an S_N2 fashion and allyloxide expressed highly regioselective α-substitution with every disubstituted alkenyl carbinol (Tables 2 and 3). Methoxide addition also exhibited a modest solvent effect in additions to 1,2-disubstituted alkenyl substrates. A greater preference for the S_N2 vs S_N2' mechanism was revealed when the reaction was conducted in a mixture of DME/MeOH rather than in neat MeOH (Table 2, entries 1, 2 and 6, 7).

The reaction of **28a** with benzylmercaptan in MeOH afforded 2-(benzylthio)non-2-enoic acid, which arose from α-substitution and alkene isomerization to the α,β-position. This presumably arises due to the increased acidity of the α-proton after installation of the sulfide. Meanwhile, treatment of **28b** with benzylmercaptan provided a mixture of α- and γ-substitution products in contrast to the high

(9) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

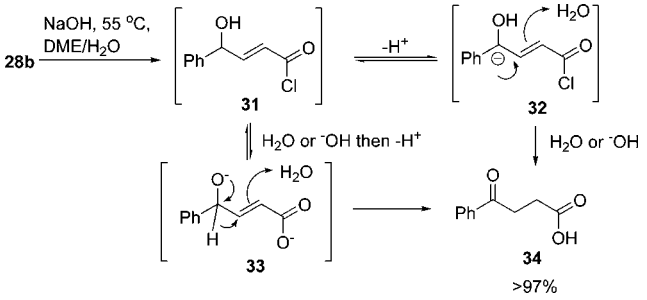
(10) This is in accord with related findings: (a) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985. (b) Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*,391.

(11) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Jaime, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139. For more recent examples, see: (c) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. (d) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574. (e) Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* **2004**, 2151.

regioselectivity observed with other substrates. Thiolate selectivity for the S_N2' pathway with **28b** may involve a higher relative charge density at the γ-benzylic position of this alkenyl *gem*-dichloroepoxide than at the corresponding position in substrates lacking a γ-aromatic substituent. Methoxide showed a similar, albeit less pronounced, preference for the γ-position relative to the reaction with **28a**.

Treatment of **28b** with NaOH in DME/H_2O led to hydroxide addition solely at the γ-carbon, affording **31** (Scheme 3). However, **31** experienced either benzylic depro-

Scheme 3. Hydroxide Addition/Oxidation on Treatment of **28b** with NaOH in DME/H_2O



tonation followed by protonation/tautomerization or a precedented 1,2-hydride shift in carboxylate intermediate **33**,[12] to afford γ-ketoacid **34** in essentially quantitative yield.

Hydroxide addition to the substrates in Table 3 generated complex mixtures of products. However, alkoxides smoothly furnished the α-alkoxy terminal alkenes without incident. Treatment of compounds **35** and **39** with thiolate afforded α-substitution with alkene isomerization from the terminal to the internal β,γ-position under the basic conditions. The isomerization was more pronounced in **35**, with its benzylic protons, than in **39**.

Although the propensity of different nucleophiles to undergo S_N2 vs S_N2' dichloroepoxide ring opening was initially surprising, the stereoselective formation of the (*E*)-enoates was predictable. This may be rationalized by assuming the alkenyl oxirane adopts either an *s-cis* or an *s-trans* early transition-state conformation during nucleophilic addition (Figure 1).[13] Either coplanar conformation is necessary to

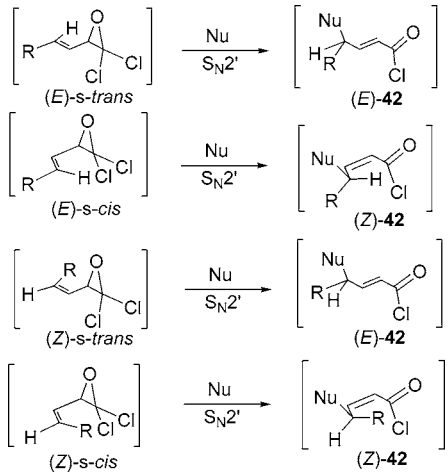


Figure 1. Conformational analysis used to rationalize stereoselective (*E*)-alkene formation.[13]

allow the proximal p-orbital to maximize the overlap with the C−O σ^*-orbital. However, the chlorine atoms attached to C_1 force the substrates to adopt the more favorable *s-trans* conformation leading to stereoselective (*E*)-alkene formation independent of the evaluated solvent, base, or reaction temperature.

The reported method offers an operationally simple, inexpensive route to γ-hydroxy- or alkoxy-(*E*)-enoic acids and β,γ-unsaturated α-substituted acids in very good yields. The reactions occurring via an S_N2' pathway afford (*E*)-olefins with excellent diastereoselectivity. The products generated feature multiple handles for further synthetic elaboration. We are in the process of evaluating additional inter- and intramolecular nucleophiles in related reactions and conducting mechanistic investigations that will be reported once completed.

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Supporting Information Available: Experimental procedures and spectroscopic data for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. Although the alkene geometry might result from thermodynamic equilibration, this seems unlikely given the lack of temperature dependence on the observed diastereoselectivity.