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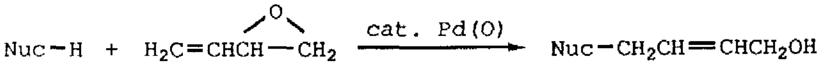
HIGHLY STEREOSELECTIVE SYNTHESIS OF DI- AND TRISUBSTITUTED HOMOALLYLIC ALCOHOLS VIA PALLADIUM(0)-CATALYZED NUCLEOPHILIC OPENING OF VINYLIC OXETANES

Richard C. Larock* and Sandra K. Stolz-Dunn
Department of Chemistry, Iowa State University, Ames, Iowa 50011

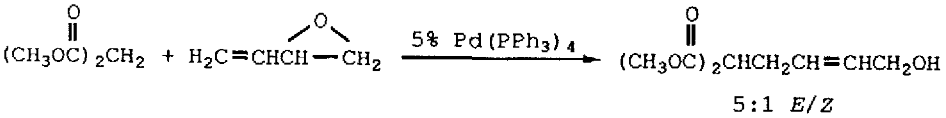
Summary. Vinylic oxetanes react in an S_N2' manner with a variety of potential nucleophiles in the presence of catalytic amounts of $Pd(PPh_3)_4$ to afford the corresponding highly functionalized, di- and trisubstituted homoallylic alcohols with high stereoselectivity.

Vinylic epoxides have been reacted with a variety of carbon,[1] oxygen,[2] nitrogen[1b,3] and sulfur[4] nucleophiles in the presence of palladium(0) catalysts to afford a convenient route to allylic alcohols (eq. 1). The reactions of carbon nucleophiles have recently found considerable synthetic utility in the synthesis of macrocycles,[5] prostaglandins,[6] steroids,[7] terpenes,[8] vitamin D_3[9] and digitoxigenin.[10] We wish to report the first such reactions of vinylic oxetanes and the observation that these reactions are highly stereoselective for the formation of di- and trisubstituted homoallylic alcohols.



$$\text{Nuc}{-}H + H_2C{=}CH\overset{O}{\overline{CH{-}CH_2}} \xrightarrow{\text{cat. Pd(0)}} \text{Nuc}{-}CH_2CH{=}CHCH_2OH \qquad (1)$$

Using a procedure similar to those reported in the literature for epoxides, we have had considerable success with a wide variety of carbon nucleophiles and vinylic oxetanes which afford disubstituted homoallylic alcohols (Table I, entries 1, 2, 5, 6, and 9-11). A wide variety of functional groups are accommodated in the nucleophile and variously substituted oxetanes[11,12] may be utilized. Unlike the analogous epoxide reactions which give a mixture of stereoisomers with the parent epoxide (eq. 2),[1a] all of these reactions with carbon nucleophiles give exclusively the _E_-disubstituted isomer, as established by ^1H and ^{13}C NMR, and IR spectroscopy.



$$(CH_3O\overset{\overset{O}{\|}}{C})_2CH_2 + H_2C{=}CH\overset{O}{\overline{CH{-}CH_2}} \xrightarrow{5\%\ Pd(PPh_3)_4} (CH_3O\overset{\overset{O}{\|}}{C})_2CHCH_2CH{=}CHCH_2OH \qquad (2)$$

$$5{:}1\ E/Z$$

Most interestingly, when vinylic oxetanes which generate trisubstituted double bonds were employed (entries 3, 4, 7, 8 and 12), only the _E_-trisubstituted homoallylic alcohols were observed, even when the new double bond is exocyclic to a ring (entry 7). This contrasts sharply with analogous reactions of epoxides which have been reported to give bad mixtures of _E_- and _Z_-allylic alcohols.[1a,1b] Best results on these systems were obtained by modifying our earlier procedure by using 9% $Pd(PPh_3)_4$, 9% $Ph_2PCH_2CH_2PPh_2$ and 1.2 equiv. of Et_3N.

As with vinylic epoxides,[13] one can also employ β-keto acids to obtain the decarboxylated ketone product (entries 11 and 12). Again the _E_-isomer is the only observed product and di-

TABLE I. SYNTHESIS OF HOMOALLYLIC ALCOHOLS

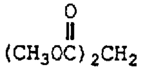
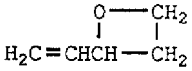
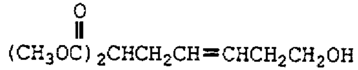
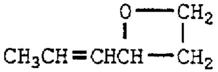
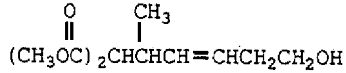
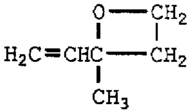
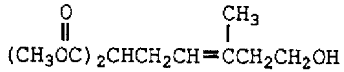
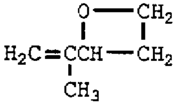
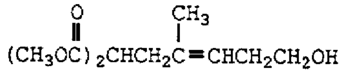
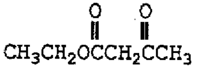
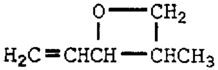
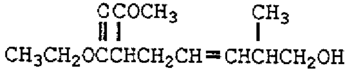
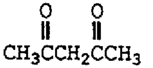
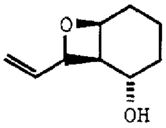
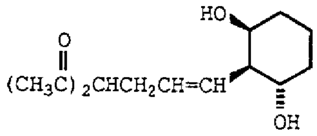
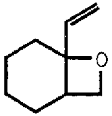
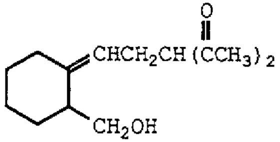
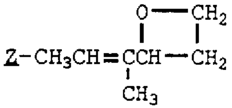
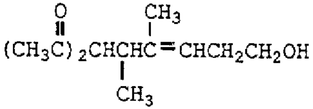
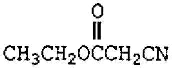
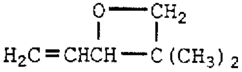
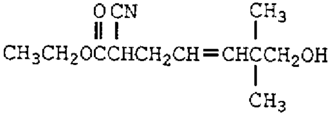
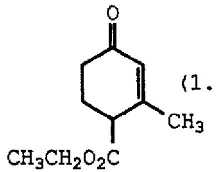
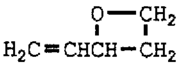
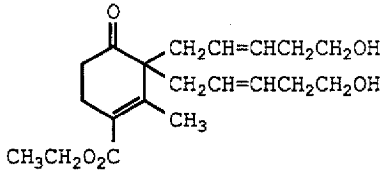
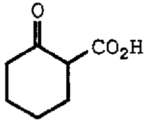
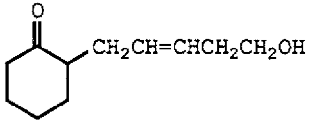
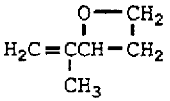
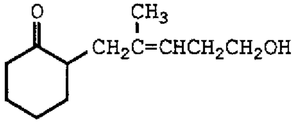
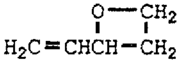
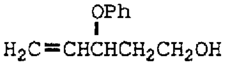
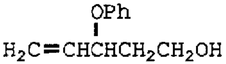
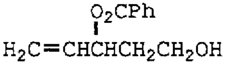
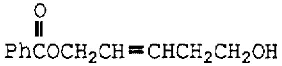
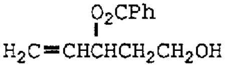
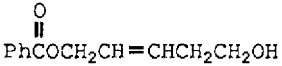
Entry	Nucleophile (equivalents)	Oxetane	% Pd(PPh$_3$)$_4$	Reaction Conditions^a	Product(s)^b	% Yield^c
1	 $(CH_3O\overset{O}{\overset{\|}{C}})_2CH_2$ (1.2)		5	40°C, 7 hr	E-  $(CH_3O\overset{O}{\overset{\|}{C}})_2CHCH_2CH{=}CHCH_2CH_2OH$	81
2	—		—	—	E-  $(CH_3O\overset{O}{\overset{\|}{C}})_2CH\overset{CH_3}{\overset{\|}{C}H}CH{=}CHCH_2CH_2OH$	72
3	—		9	40°C, 6 hr	E-  $(CH_3O\overset{O}{\overset{\|}{C}})_2CHCH_2CH{=}\overset{CH_3}{\overset{\|}{C}}CH_2CH_2OH$	82
4	—		—	—	E-  $(CH_3O\overset{O}{\overset{\|}{C}})_2CHCH_2\overset{CH_3}{\overset{\|}{C}}{=}CHCH_2CH_2OH$	89
5	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$ (1.2)		5	40°C, 7 hr	E-  $CH_3CH_2O\overset{O}{\overset{\|}{C}}\overset{COCH_3}{\overset{\|}{C}H}CH_2CH{=}CH\overset{CH_3}{\overset{\|}{C}H}CH_2OH$	85
6	 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$ (2.4)		—	40°C, 3.5 hr	E- 	82
7	—		9	40°C, 6 hr	E- 	76
8	—	E + 	—	—	E-  $(CH_3\overset{O}{\overset{\|}{C}})_2CH\underset{CH_3}{\underset{\|}{C}H}\overset{CH_3}{\overset{\|}{C}}{=}CHCH_2CH_2OH$	67
9	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2CN$ (2.4)		5	40°C, 3.5 hr	E-  $CH_3CH_2O\overset{O}{\overset{\|}{C}}\overset{CN}{\overset{\|}{C}H}CH_2CH{=}CH\overset{CH_3}{\underset{CH_3}{C}}CH_2OH$	62

TABLE I. CONTINUED

Entry	Nucleophile (equivalents)	Oxetane	% Pd(PPh$_3$)$_4$	Reaction Conditions[a]	Product(s)[b]	% Yield[c]
10	 (1.2)	 $\begin{array}{l}\quad O{-}CH_2\\ H_2C{=}CHCH{-}CH_2\end{array}$	—	40°C, 7 hr	E- 	70
11	 (1.2)	—	—	—	E- 	91
12	—	 $\begin{array}{l}\quad O{-}CH_2\\ H_2C{=}CCH{-}CH_2\\ \quad CH_3\end{array}$	9	40°C, 6 hr[d]	E- 	59
13	PhOH (1.2)	 $\begin{array}{l}\quad O{-}CH_2\\ H_2C{=}CHCH{-}CH_2\end{array}$	2	25°C, 2.5 hr	 $H_2C{=}CH\overset{OPh}{C}HCH_2CH_2OH$ + $PhOCH_2CH{=}CHCH_2CH_2OH$ (*E*/*Z* mixture, ratio undetermined)	(84) + (16)
14	PhOH (2.4)	—	9	40°C, 3.5 hr	 $H_2C{=}CH\overset{OPh}{C}HCH_2CH_2OH$ + $PhOCH_2CH{=}CHCH_2CH_2OH$ (87:13 *E*/*Z*)	(23) + (58)
15	PhCO$_2$H (1.2)	—	2	0°C, 1.5 hr[e]	 $H_2C{=}CH\overset{O_2CPh}{C}HCH_2CH_2OH$ +  $Ph\overset{O}{\overset{\|}{C}}OCH_2CH{=}CHCH_2CH_2OH$ (*E*/*Z* mixture, ratio undetermined)	(84) + (16)
16	PhCO$_2$H (2.4)	—	5	0°C, 2.5 hr	 $H_2C{=}CH\overset{O_2CPh}{C}HCH_2CH_2OH$ +  $Ph\overset{O}{\overset{\|}{C}}OCH_2CH{=}CHCH_2CH_2OH$ (88:12 *E*/*Z*)	(27) + (50)
17	$(CH_3CH_2)_2NH$ (2.4)	—	—	40°C, 7 hr	$(CH_3CH_2)_2NCH_2CH{=}CHCH_2CH_2OH$ (79:21 *E*/*Z*)	(98)

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[a] All reactions to form disubstituted alkenes were run using 0.02 mmol of Pd(PPh$_3$)$_4$, 0.40 mmol of oxetane, 0.48 or 0.96 mmol of nucleophile and 2.0 ml of tetrahydrofuran (THF) unless otherwise indicated. Trisubstituted alkenes were prepared using 9% Pd(PPh$_3$)$_4$, 9% $Ph_2PCH_2CH_2PPh_2$ and 1.2 equiv. of Et$_3$N. [b] All new compounds gave correct ^1H and ^{13}C NMR, IR and exact mass spectral or combustion analysis data. [c] Yield of isolated, purified product (yield determined by gas chromatographic analysis). [d] No Et$_3$N added. [e] The benzoic acid was dissolved in 1.0 ml of THF and added dropwise to the other reagents over a 20 minute period.

and trisubstituted products are formed highly stereoselectively.

Reactions with heteroatom-containing nucleophiles afford quite different results. With oxygen nucleophiles, mixtures of regio- and stereoisomers are observed under all conditions examined. With limited amounts of the palladium catalyst and either phenol or benzoic acid as the nucleophile (entries 13 and 15), the major product is the S_N2 ring-opened product. Only recently has palladium-promoted proximal attack of an oxygen nucleophile on vinylic epoxides been reported.[14] At higher concentrations of nucleophile and palladium catalyst, longer reaction times and higher temperatures, the S_N2' product is observed to predominate (entries 14 and 16). In all cases this product is a mixture of stereoisomers.

With diethylamine as the nucleophile (entry 17), the S_N2' product, as a mixture of stereoisomers, is virtually the exclusive product. This is consistent with previous work on nucleophilic opening of epoxides by amines,[1b,3a] although proximal attack by nitrogen nucleophiles has been observed.[3b,3c]

In conclusion, we have observed the first palladium-catalyzed S_N2' ring opening of vinylic oxetanes by acidic hydrocarbons, a β-keto acid, phenol, benzoic acid and diethylamine. The carbon-carbon bond forming reactions are highly regio- and stereoselective. The amine reacts in a regio-, but not stereoselective, manner while the oxygen substrates afford regio- and stereoisomeric mixtures. These reactions provide a convenient new synthetic route to homoallylic alcohols.

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