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[2,3]-Wittig Rearrangement of Crotyl Picolyl Ethers. Evaluation of the Electronic Effect as a Stereo-Directing Factor

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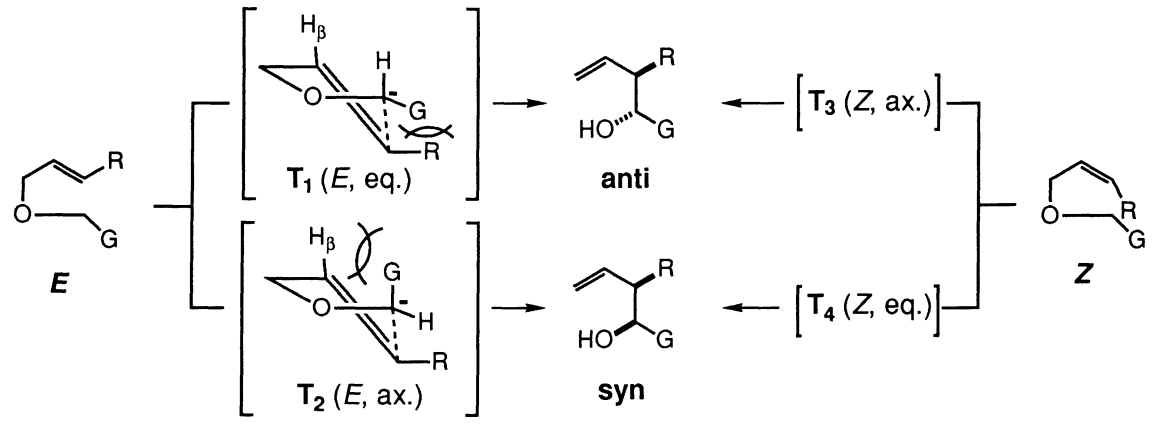
The title rearrangement is shown to exhibit syn diastereoselectivity independent of the crotyl geometry, the degree decreasing in the order: 2-> 4-> 3-picolyl ether for the *E* series and in the opposite order for the *Z* series. These trends suggest that the electronic effect plays a profound but not sole factor in governing the orientational preference of the pyridyl group in the transition states.

The [2,3]-Wittig rearrengement has enjoyed wide application as a versatile method for acyclic stereocontrol.[1] Of special interest and value is that either syn or anti stereocontrol is effectively achieved by the proper choice of the substituent (G) on the carbanion terminus (Scheme 1). For instance, G groups such as $CH{=}CH_2$ and C≡CH provide a high *E*→anti (or *Z*→syn) selectivity,[2] whereas G groups such as CO_2R and $CONR_2$ leads to a high *E*→syn selectivity.[3] Thus, the key issue to be answered is what factor(s) governs the orientational preference of G group in the five-membered transition states, which is addressed in this communication.

Two explanations have been invoked. The authors' group has argued that the G orientation is determined by the balance of the two steric parameters, *i.e.*, the 1,3-diaxial repulsion of G with H_β and the gauche repulsion



Scheme 1.

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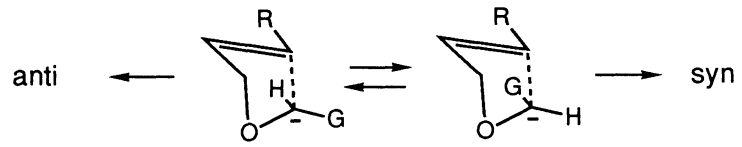
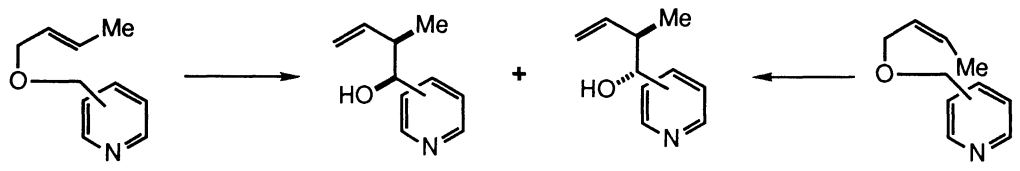
of G with R.[2b, 4] Thus, *E*→anti (or *Z*→syn) selection is explained as a result that the former is larger than the latter, whereas *E*→syn selection results in the cases where the latter prevails over the former. Based on the ab initio molecular orbital calculations, on the other hand, Houk *et al.* have suggested that the orientational preference of G is governed by the electrostatic effects involved in slightly different transition-state conformations (Scheme 2).[5] In their model, the exo position (corresponding to the equatorial position in our model) is favored for π-donor groups such as C≡CH, whereas π-acceptor groups such as CHO favors the endo position due to the electrostatic interaction between G and the olefinic bond.



T_1'(*E*, exo) T_2'(*E*, endo)

Scheme 2.

With these hypotheses in mind, we have now analyzed the stereochemistry of [2,3]-Wittig rearrengement of the 2-, 3-, and 4-picolyl ethers **1** (Scheme 3), in which the steric factors involved would be essentially identical in magnitude among the three cases, but the electronic factors around the carbanion terminus should be variable with the substitution position on the pyridine ring. The [2,3]-Wittig rearrengements of (*E*)- and (*Z*)-**1a**-**c**[6] were carried out under standard conditions (*n*-BuLi or LDA, THF/hexane, -78 °C - room temp) to give a diastereomeric mixture of the corresponding alcohols **2** in high isolated yield (>75%). Table 1 summarizes the



(*E*)-**1** syn-**2** anti-**2** (*Z*)-**1**

a, 2-Picolyl; **b**, 3-Picolyl; **c**, 4-Picolyl

Scheme 3.

diastereoselectivities thus observed.[7] These data reveal the following trends. (a) All the rearrangements show syn selectivity independent of the crotyl geometry, indicating that the orientational preferences of the pyridyl group for the *E* and *Z* series are opposite each others. (b) The *E*→syn selectivity decreases in the order: 2-> 4-> 3-picolyl > (benzyl). (c) In contrast, the *Z*→syn selectivity decreases in the opposite order. This means that the order of *Z*→anti selectivity is the same as that of *E*→syn selectivity, thus suggesting that *the axial (or endo) preference decreases in the order: 2-> 4-> 3-pyridyl> (phenyl).*[8] Trend (a) is easily explained by the authors' "steric hypothesis" that the orientational preference of G group is dependent critically on the crotyl geometry, but obviously argues against Houk's "electronic hypothesis" that the G orientation is determined by its own nature independent of the crotyl geometry. However, trends (b) and (c) are consistent with Houk's hypothesis, not with

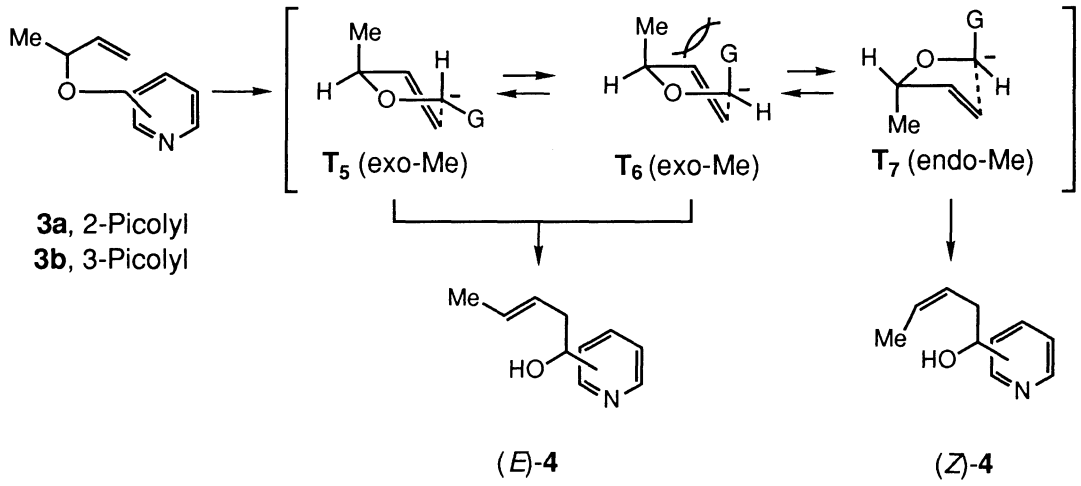
Table 1. Diastereoselectivities of (*E*)- and (*Z*)-**2**

Substrates	Base	Selectivity [a] $E \rightarrow$ syn	$Z \rightarrow$ syn ($Z \rightarrow$ anti)
2-Picolyl (**1a**)	*n*-BuLi	97%	69% (31%)
	LDA	91%	78% (22%)
3-Picolyl (**1b**)	*n*-BuLi	81%	89% (11%)
	LDA	81%	88% (12%)
4-Picolyl (**1c**)	*n*-BuLi	92%	83% (17%)
	LDA	93%	82% (18%)
cf. Benzyl [b]	*n*-BuLi	45-68%	95-98% (5-2%)

a) Determined by HPLC analysis. For the stereochemical assignments of **2**, see Ref. 7.
b) Cited from Ref. 2b.

the predictions based on the authors' hypothesis. Therefore, it is safe to conclude that the orientational preference of the G group in general is governed by the steric factors as well as the electronic factors. In other words, the electronic effects should be taken into account as a profound but not sole factor in dictating the orientations of G group in our transition-state model.

To confirm the present hypothesis, we next examined *E*/*Z* selection in the rearrangements of ethers **3a** and **3b** (Scheme 4), with the prediction that **3a** provides a much lower *E* selectivity than **3b** as a result that the larger axial preference of 2-pyridyl (more π-attractive) relative to that of 3-pyridyl would destabilize the transition state $\mathbf{T_6}$ due to the steric repulsion of G with Me. Indeed, the rearrangement of **3a** was found to show a significantly lower *E* selectivity (74%) as compared with 95% *E* of **3b** [9] (and 100% *E* of the benzyl ether [10]).



Sheme 4.

In summary, we have presented experimental proofs that the orientational preference of G group in the [2,3]-Wittig rearrangment in general is governed by the balance of the electronic and steric factors involved in the transition states. Further work is needed to elucidate the exact origin of the electronic factors concerned.

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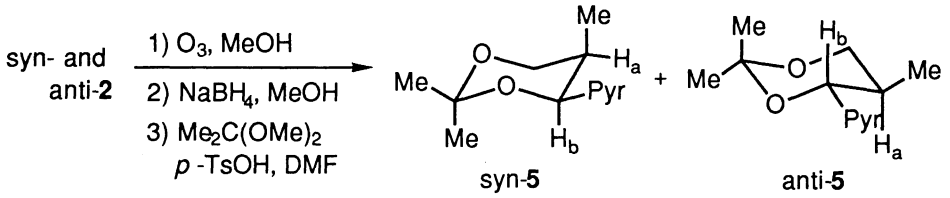
6) Prepared via reaction of (*E*)- or (*Z*)-crotyl alcohol with the corresponding hydrogen chloride salt of picolyl chloride in DMF using 2.5 equiv. of sodium hydride.
7) The stereochemistry of **2** was assigned by the ^{1}H NMR analysis of the corresponding acetonide **5** derived as depicted below. The most informative are the chemical shifts (δ) due to H_b and the coupling constants



(J_{ab}): 5.21 ppm and 2.7 Hz for syn-**5a**, 4.65 ppm and 10.4 Hz for anti-**5a**; 5.21 ppm and 2.8 Hz for syn-**5b**, 4.47 ppm and 10.2 Hz for anti-**5b**; 5.13 ppm and 2.8 Hz for syn-**5c**, 4.43 ppm and 10.4 Hz for anti-**5c**.
8) This order seems to reflect the order of the π-accepting ability of the molecular orbital (LUMO) at the site bearing the crotyloxymethyl group: *cf.* I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," John Wiley & Sons, New York (1976), p. 66-68.
9) Determined by HPLC analysis. The geometry of **4** was assigned by NMR analysis. The most informative are the ^{1}H and ^{13}C chemical shifts due to Me: 1.65 (dd) and 18.2 ppm for (*E*)-**4a**, 1.54 (dd) and 14.3 ppm for (*Z*)-**4a**; 1.65 (dd) and 18.2 ppm for (*E*)-**4b**, 1.54 (dd) and 14.3 ppm for (*Z*)-**4b**.
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