

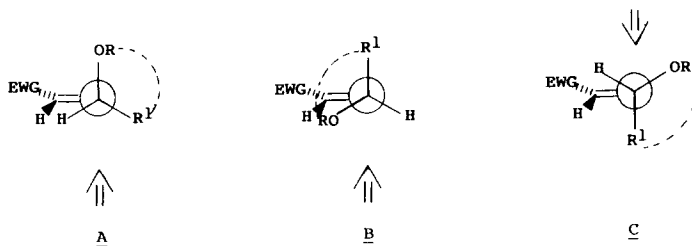
Diastereoselectivity of a [3+2]Annulation. On the Question
of a Dipole Effect on Diastereoselectivity of Olefin Addition

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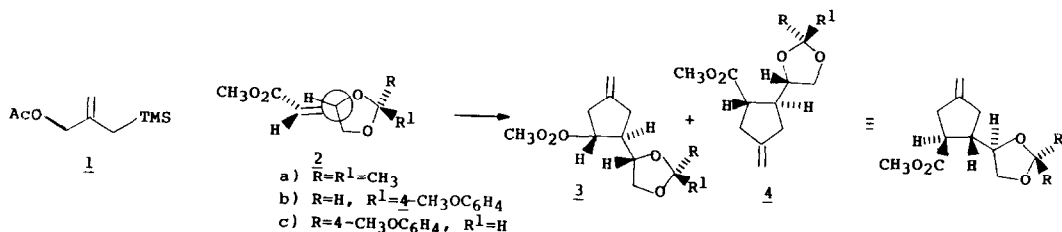
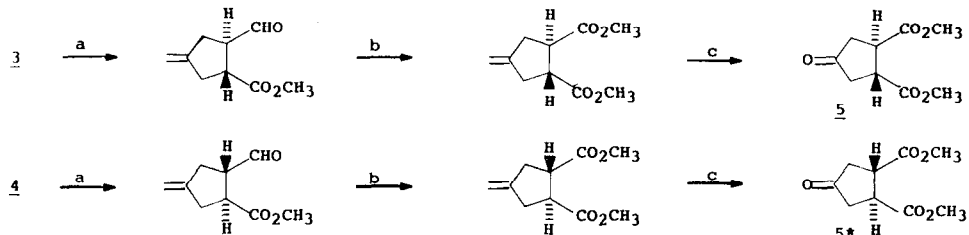
SUMMARY: The stereochemistry of addition to γ -alkoxy- α,β -unsaturated carbonyl systems is examined in the context of a palladium catalyzed cycloaddition.

The question of diastereoselectivity of addition to olefins bearing an oxygen substituent at the allylic position has been considered from both a theoretical and experimental point of view. Some additions to an α,β -unsaturated carbonyl system have been interpreted in terms of a modified Felkin-Anh model as in A.¹ On



the other hand, calculations and nmr data suggest that conformer B would be preferred.² While the preferred ground state and the reactive conformer need not be the same, the diastereoselectivity observed does not allow differentiation between which of these two conformers represents the more reactive one. In cases where R and R¹ are incorporated into a ring, the opposite diastereoselectivity sometimes prevails³ and may be interpreted as arising via addition to conformer C. Such a change in diastereoselectivity appears very reasonable if B is the normally reactive conformer in the absence of such a ring. The very unfavorable steric interactions in B when R and R¹ are tied together in a ring would strongly destabilize B in favor of C. Such an effect could be reinforced by consideration of internal dipole effects where minimization of dipole-dipole interactions also favor C. We wish to report that such an unrecognized effect may indeed be important in controlling diastereoselectivity of a palladium catalyzed cycloaddition.

The cycloaddition of equimolar quantities of (2-acetoxymethyl)allyltrimethylsilane (1) with acrylate 2 (R = R¹ = CH₃)⁴ utilizing 5-10 mol% palladium acetate and 25-50 mol% of triisopropyl phosphite⁵ produces a mixture of diastereomer 3⁶ and 4 which depended on solvent (eq. 1). In refluxing toluene (87% yield), dioxane (45% yield), and hexane (94% yield), the ratio was approximately 3:1 for 3:4.⁷ The stereochemistry was assigned by degrading the mixture of 3 and 4 to 5 and its mirror image isomer 5* (Scheme 1). The rotation of the mixture, [α]_D²⁵ = -44°, indicated the absolute stereochemistry depicted

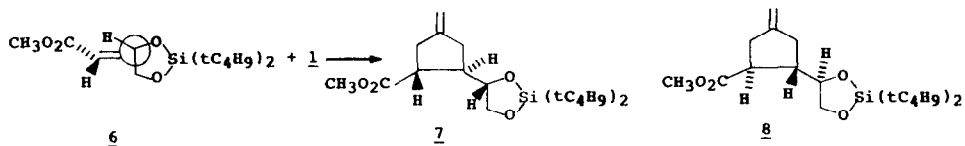
Scheme 1. Degradation of Adducts 3 and 4

a) i. TsOH, CH_3OH , rt; ii. Pb(OAc)_4 , PhH , rt; b) i. PDC, DMF, rt; ii. CH_2N_2^* , ether; c) O_3 , CH_3OH , CH_2Cl_2 then $(\text{CH}_3)_2\text{S}$

in 5 for the major component of the mixture.⁸

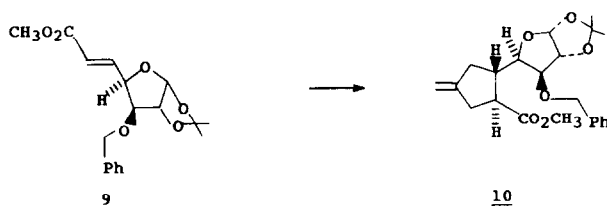
Dramatically, the ratio of 3:4 dropped to 1:1 in DMF as solvent even though the temperature was reduced to ambient.⁷ This unanticipated result suggested that polar effects on the diastereoselectivity may be important. An explanation of this polar effect reflects the anticipation that any internal dipole-dipole effect favoring C as the reactive conformer would be swamped by the switch from relatively non-polar solvents such as toluene to the very polar DMF. An alternative explanation invokes involvement of DMF as a ligand to Pd. Such an explanation appears less likely since phosphine complexation to Pd is a requirement for cycloaddition⁴ and selectivities in palladium catalyzed allylic alkylation are unaltered by such a solvent change - an observation that suggests that the same phosphine ligated palladium species is involved in both non-polar and polar solvents.⁹

Reasoning that a silyl ether should increase such a dipole effect and therefore increase the diastereoselectivity, we performed the cycloaddition with the di-*t*-butylsilylene derivative 6.^{6,10} Gratifyingly the ratio of 7 to 8, which was correlated with 3a and 4a respectively (TsOH, TBAF, acetone then PPTS, $(\text{CH}_3)_2\text{C}(\text{CH}_3)_2$) jumped to 7.5:1 (92% isolated yield).^{7,11} To probe how much of a

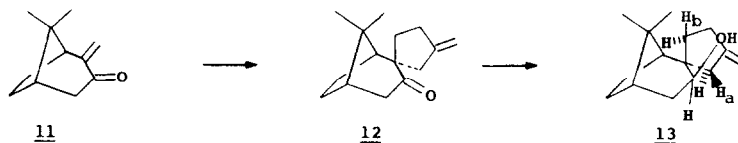


steric effect might be reflected in this increase, we prepared¹² 2b, R = H and R¹ = 4-CH₃OC₆H₄, and 2c, R = 4-CH₃OC₆H₄ and R¹ = H. Both isomers underwent cycloaddition in excellent yields (91 and 95%) but the diastereomeric ratio was identical (i.e. 3b:4b⁶ = 2.6:1⁷ and 3c:4c⁶ = 2.6:1⁷) regardless of the stereochemistry of the protecting group. Assignment of the cyclopentane stereochemistry involved conversion to the acetonides 3a and 4a (TsOH, acetone, rt) which were obtained also in a 2.6:1 ratio. The independence of the diastereoselectivity on the steric bulk of the substituents on the protecting group suggest that the silylene effect is more electronic than steric in nature.

To check the generality of the diastereoselectivity of the TMM-Pd reaction, the glucose derived acrylate 9¹³ was subjected to the standard cycloaddition conditions. A single product 10,⁶ homogeneous by tlc and ¹H and ¹³C nmr



spectroscopy, was isolated in 88% yield (100% based upon recovered 9). In an ancillary study, the diastereoselectivity of cycloaddition to α -pinenone (11)¹⁴



was examined. Again only a single isomer, 12⁶ forms in 64% isolated yield. The stereochemistry is assigned based upon Eu(+3) induced shifts of the corresponding alcohol 13¹⁵ and mechanistic grounds, where steric effects would dictate attack.

The results indicate that good to excellent diastereoselectivity characterizes the palladium catalyzed cycloaddition approach to cyclopentane rings. Furthermore, with neighboring oxygen groups, the silylene protecting group enhances diastereoselectivity relative to acetals or ketals - an observation that may be generally useful. For γ -alkoxy- α,β -unsaturated carbonyl and related systems (e.g. sulfone, nitro, etc.), dipole effects and solvent effects upon them^{16,17} should also be considered in interpreting diastereoselectivity of additions to the unsaturation. While the results reported herein do not prove that such a dipole effect is the causative factor, it is most consistent with our observations.

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