

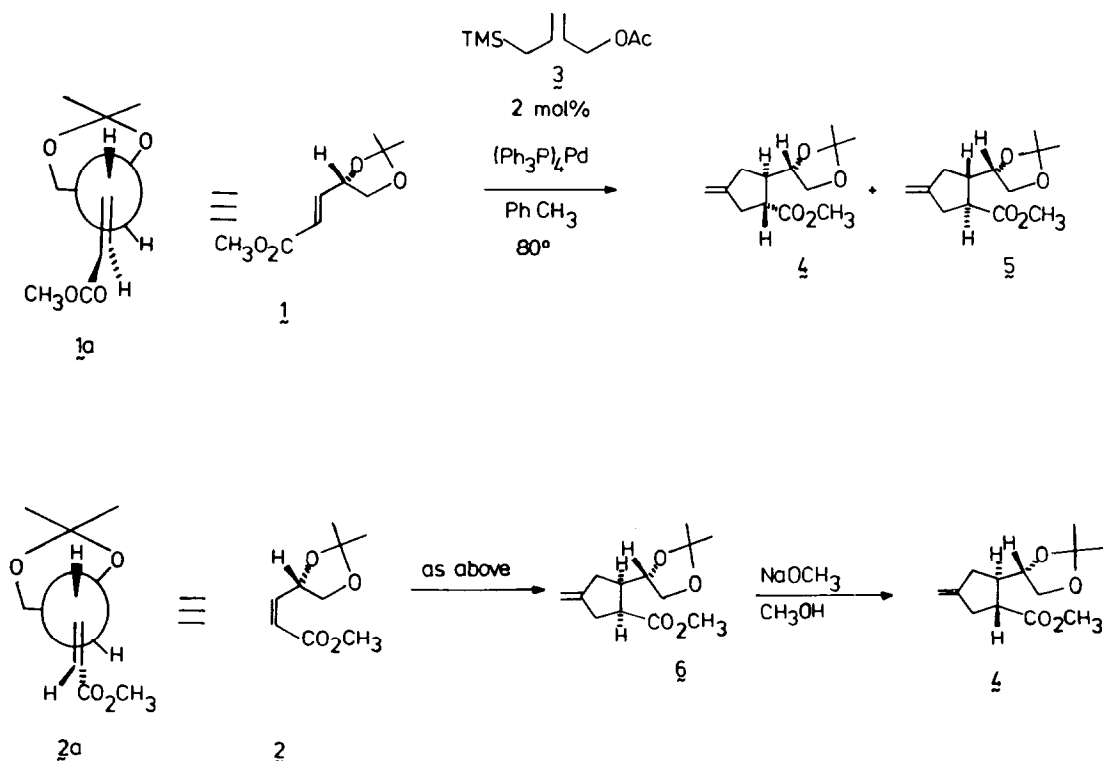
A STEREOSPECIFIC PALLADIUM MEDIATED [3+2] CYCLOADDITION

Barry M. Trost* and Serge M. Mignani

McElvain Laboratories of Organic Chemistry, Department of Chemistry
 University of Wisconsin, 1101 University Avenue, Madison, WI 53706

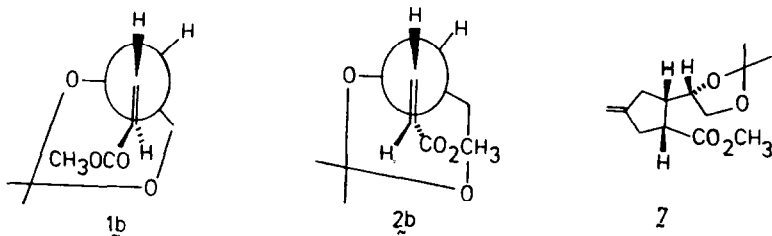
SUMMARY: The [3+2] palladium mediated cycloaddition to methyl (E)- and (Z)- (R)-4,5-di-O-isopropylidene-pent-2-enoates parallels the Diels-Alder reactions of these same acceptors.

The cycloadditions of 2-trimethylsilylmethylallyl acetate in the presence of palladium (0) catalysts¹ have been interpreted as a two step process largely on the basis that methyl Z-crotonate led to a 1.7:1 Z:E mixture of the cycloadducts and that during this reaction, there was no obvious isomerization of the starting material². However, the fact that the Z:E rate ratio is not known and is anticipated to be greater than 1 for a concerted cycloaddition³ leads to the possibility that a lack of the build-up of the E isomer during cycloaddition occurs because it is consumed rapidly. We wish to report that in contrast to



our earlier observations, the cycloaddition can be stereospecific and, in addition, have very high diastereofacial selectivity. The parallel between the palladium catalyzed [3+2] cycloaddition and the corresponding Diels-Alder reaction of the same enoate pair⁴ suggest that the current bias in favor of the stepwise mechanism should be rethought.

We explored the $\underline{E}^{5,6}$ and $\underline{Z}^{5C,6,7}$ enoates 1 and 2 because of the use of the \underline{E} enoate in our synthesis of brefeldin A.^{8,9} Using a standard set of conditions of 2 mol% $(\text{Ph}_3\text{P})_4\text{Pd}$ in toluene at 80°C, 1 gave the two cycloadducts 4 and 5 in a 76:24 ratio in 78% yield - in good agreement with our earlier observations. We interpreted the major isomer as deriving from 1a as the reactive conformer based upon consideration of dipole - dipole and non-bonded steric interactions. The Felkin - Anh conformer 1b would predict the same facial selectivity as 1a.



However, if the latter is the reactive conformer, then the \underline{Z} olefin should exhibit lower diastereoselectivity, since 2b should be disfavored. On the other hand, if 2a is the reactive conformer, then the \underline{Z} olefin should enhance the facial selectivity.

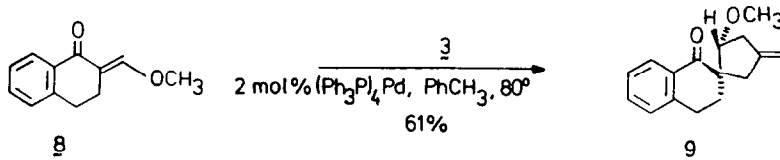
Cycloaddition of the \underline{Z} -enoate with 3 under identical conditions as above gave a single cycloadduct (>50:1) in 69% yields in contrast to the earlier case of a \underline{Z} -enoate! Furthermore, this adduct does not correspond to either 4 nor 5 indicating that it must be a \underline{Z} -methylene cyclopentane, either 6 or 7. That it corresponds to 6 was easily demonstrated since base catalyzed equilibration quantitatively converts 6 into 4.

The exclusive formation of the \underline{Z} cyclopentane 6 from the \underline{Z} -enoate 3 requires either a concerted cycloaddition or a two step process in which the ratio of the rate constants for ring closure versus bond rotation is more favorable here than in the crotonate case. There does not appear to be any obvious reason why the latter should be true. On the other hand, if the cycloaddition is concerted, the discrepancy between the current result and our earlier one is easily accounted for by the difficulty in evaluating the control experiment in the

absence of actual rate constants for cycloaddition for the E and Z crotonates.

The extremely high facial selectivity for cycloaddition of 2 is best in accord with 2a as the reactive conformation and, correspondingly, 1a in the case of the E enoate 1. The similarity of this pair of cycloadditions to the Diels-Alder reactions of this same pair of enoates is striking. The facial selectivity of the Diels-Alder reactions has also been interpreted in terms of the same reactive conformations 1a and 2a⁴. The increased steric demands in forming a six membered ring versus a five membered ring may account for the higher degree of facial selectivity seen for the Diels-Alder reaction of 1 versus this [3+2] cycloaddition.

Another example of a diastereoselective cycloaddition was briefly examined in which an additional complication arising from a possible β -elimination in a stepwise mechanism exists. The E-methoxymethylenetetralone 8¹¹ (8:1, E:Z) gave



the E-cyclopentane 9 (7:1, E:Z). The absence of β -substitution of methoxide combined with retention of geometry in the product may be interpreted as reflecting a concerted rather than a stepwise process.

While it is premature to conclude that these reactions are concerted, the present results clearly require reconsideration of such a possibility. The correspondence of these results with the Diels-Alder reaction suggests mechanistic similarities may exist. Orbital symmetry considerations do not refute a concerted pathway.¹² While mechanistic conclusions must await more information, the present results have an immediate synthetic consequence. Since 6 and, by simple base equilibration, 4 are now available as single diastereomers and enantiomers, our synthesis of (+)-brefeldin A now becomes completely enantioselective.¹³ The ability to enhance diastereoselectivity by using the Z-olefin may also be a more generally useful tool in these cycloadditions.

Acknowledgment: We wish to thank the National Institutes of Health and Rhone-Poulenc for their generous support of our programs.

References

1. Trost, B.M. Angew. Chem. Internat. Ed. Engl., **1986**, 25, 1

2. Trost, B.M.; Chan, D.M.T. J. Am. Chem. Soc., 1983, 105, 2315
3. Huisgen, R. Angew. Chem. Internat. Ed. Engl., 1963, 2, 565, 633
4. Mulzer, J.; Kappert, M.; Hultner, G.; Jibril, I. Tetrahedron Lett., 1985, 26, 1631
5. a) For ethyl ester: Minami, N.; Ko, S.S.; Kishi, Y.; J. Am. Chem. Soc., 1982, 104, 1109. B) For methyl ester: Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y.; Tetrahedron Lett., 1983, 24, 3009. c) Mulzer, J.; Kappert, M. Angew. Chem. Suppl., 1982, 23; idem., Angew. Chem. Internat. Ed. Engl., 1983, 22, 63; 1984, 23, 704
6. Kametani, T.; Suzuki, T.; Nishimura, M.; Sato, E.; Unno, K. Heterocycles, 1982, 19, 205.
7. We synthesized the Z isomer by performing the Emmons - Wadsworth -Horner reaction with methyl dimethoxyphosphonoacetate using lithium diisopropylamide in THF with the initial presence of acetic acid. Renault, P. unpublished work in these laboratories.
8. Trost, B.M.; Lunch, J.; Renault, P.; Steinman, D.H. J. Am. Chem. Soc., 1986, 108, 284
9. In an earlier study, we explored the effect of diol protecting group on the facial selectivity in the E enoate. Trost, B.M.; Lynch, J.; Renault, P. Tetrahedron Lett., 1985, 26, 6313
10. $6: [\alpha]_D^{25} - 9.83^\circ$ (c 3.5, CHCl_3): Ir (CHCl_3): 1730, 1660 cm^{-1} . Nmr (CDCl_3 , 500 MHz): 4.93 (bs, 1H), 4.89 (bs, 1H), 4.03 (q, $J=6.6 \text{ Hz}$, 1H), 3.98 (dd, $J=7.8, 6.1 \text{ Hz}$, 1H), 3.47 (dd, $J=7.8, 6.8 \text{ Hz}$, 1H), 3.21 (s, 3H), 2.72 (m, 2H), 2.53 (m, 2H), 2.22 (ddm, $J=16.7, 7.9 \text{ Hz}$, 1H), 2.03 (p, $J=7.9 \text{ Hz}$, 1H), 1.37 (s, 3H), 1.27 (s, 3H). Calc'd for $\text{C}_{13}\text{H}_{20}\text{O}_4$: 240.1362 Found: 240.1378
 $4: [\alpha]_D^{25} - 29.04^\circ$ (c 0.83, CHCl_3). For spectral data see ref. 8.
11. Brady, W.T.; Agho, M.O. J. Org. Chem., 1983, 48, 5337
12. Albright, T.A.; J. Organomet. Chem., 1980, 198, 159
13. In our earlier paper⁸, it should be noted that the syntheses of ref. 8 of that paper are for enantiomerically pure brefeldin A and that optically pure 13 of that same paper has been independently synthesized by a different route by Gais (ref. 8a of that paper).

(Received in USA 5 May 1986)