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Heterocyclic Acceptors in Diastereoselective Palladium Mediated [3+2] Cycloadditions

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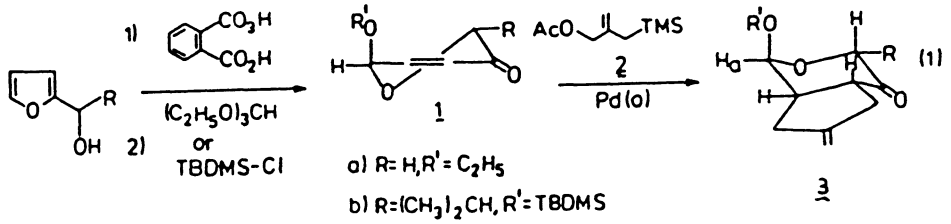
Whereas cyclohexenones and ketones are poor acceptors for palladium mediated cycloadditions of 2-trimethylsilylmethylallyl acetate, oxygen heterocycles bearing such functionality react smoothly and with high diastereoselectivity.

Our recently developed [3+2] cycloaddition[1] to generate five membered ring heterocycles[2] and carbocycles[3] either failed or proceeded in unsatisfactory yields with ketones and cyclohexenones. In probing the source of this limitation, we believed the steric and electronic properties of oxygen heterocycles would increase their reactivity as acceptors. In this letter, we report that such acceptors indeed participate in these cycloadditions with high stereocontrol.

The poor reactivity of cyclohexenones in the [3+2] cycloaddition may derive from steric hindrance to approach resulting from the 3-axial substituent. We

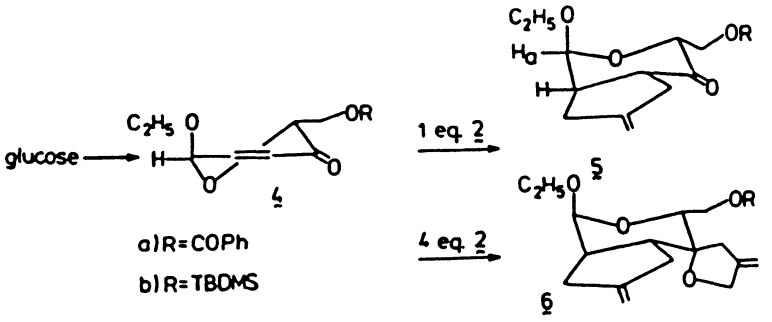
reasoned that replacement of the carbon with oxygen minimizes such unfavorable steric interactions. Furthermore, the electronic properties of oxygen may enhance the reactivity of the enone. A requisite substrate is readily available from furfuryl alcohols according to Eq. 1.[4,5] The stereochemistry of 1 simply reflects thermodynamics and is supported by its spectral data.[4] Cycloaddition of 1 with the bifunctional conjunctive reagent 2 (THF, reflux) used an *in situ* prepared Pd(0) catalyst [$Pd(OAc)_2$, Ph_3P, $n\text{-}C_4H_9Li$].[6] The cycloadduct 3a formed in only 25% yield. Attributing the low yield to the kinetic acidity of the α-methylene group of 1a, we carried out the cycloaddition of the substituted dihydropyranone 1b. Under identical conditions as above, the cycloadduct 3b[7,8] formed in 94% yield as a single stereoisomer! The stereochemistry as that derived



Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

from attack on 1 derives from spectral comparisons.[9] Of special note was the appearance of the signal for H_a as a doublet, J=2.3 Hz, at δ 5.34.

Such δ-oxaenones are also available from carbohydrates;[10] for example 4 is readily available from glucose.[11] Palladium catalyzed cycloadditions of 2 with

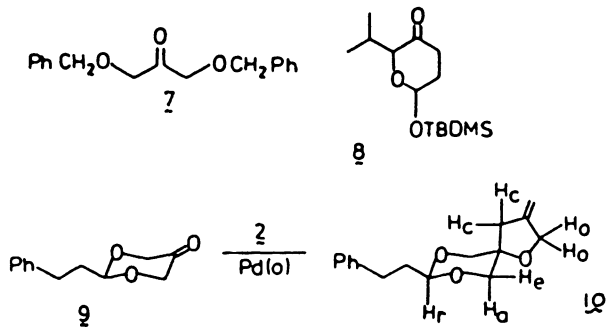


4a and 4b again produced single stereoisomeric cycloadducts 5a[7] and 5b[7,8] in 70% yield each. The appearance of H_a as a slightly broadend singlet (J < 1 Hz) supports the configuration of the methylenecyclopentane as assigned.

Use of excess TMM precursor 2 in the cycloaddition of 4a led to incorporation of two TMM fragments. Spectral analysis established that cycloaddition occurred both at the double bond and at the carbonyl group to give the diadduct 6[7] in 54% yield. Since reaction of 4 with a stoichiometric amount of 2 produced the expected cycloadduct 5 in good yield, the diadduct must arise from further reactions of the monoadduct. While 6 is again a single stereoisomer, the tentatively assigned stereochemistry simply derives from attack on the less hindered face of the ketone.

The formation of 6 was quite surprising since we previously noted[2] that only a tin version of 2 undergoes palladium catalyzed additions to aldehydes and neither 2 nor its tin version undergoes such additions to ketones. We have subsequently established that the silicon reagent 2 will also undergo a cycloaddition to a limited number of aldehydes but not ketones.[12] It appeared that the oxygen functionality of 5 enhanced the reactivity of this ketone to permit it to serve as an acceptor in [3+2] TMM cycloadditions.

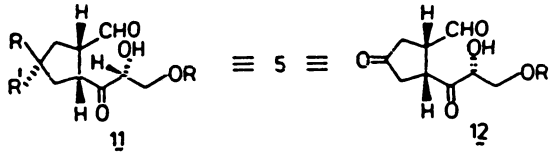
To test the structural requirements for such a cycloaddition, we examined three oxygenated carbonyl partners 7 - 9. Neither 7 nor 8 participated as acceptors. On the other hand, ketone 9 provided a single stereoisomeric



cycloadduct 10[7,8] in 59% yield using $dba_3Pd_2.CHCl_3$ and Ph_3P as catalyst in refluxing THF. The assignment of the stereochemistry as that derived from axial attack derives from NOE experiments. Irradiation of H_a caused an enhancement of H_r (8.4%) and H_o (6.12) but not H_c; whereas, irradiation of H_e causes enhancement of H_c (4.7%) and H_o (6.5%) but not H_r.

The current studies clearly demonstrate the enhanced reactivity imparted to both enones and carbonyl groups towards palladium catalyzed [3+2] cycloaddition by oxygen substitution. Such enhanced reactivity of an enone in Diels-Alder reactions has also been recently noted.[13] While minimizing steric effects undoubtedly account for part of the enhanced reactivity, it is likely that electronic effects also play a role. In a simplistic picture, the inductive effect of oxygen should increase the electrophilicity of the acceptors. Althernatively, the oxygen substitution may lower the LUMO energy and thereby enhance reactivity in such cycloadditions.

Accompanying enhanced reactivity is the excellent diastereoselectivity. The preference for α-attack on the enolones directly mirrors the Diels-Alder reaction of these same acceptors.[9b,10a] The axial selectivity for carbonyl addition is quite striking but it, too, mirrors the addition of organolithiums to such ketones.[14] These selectivities obviously derive from the intrinsic reactivity preferences of these acceptors which may, in turn, derive from the effect of the oxygen substitution. Synthetically, the methylenecyclopentanes are cyclopentanone



equivalents. The easy availability of the starting enones from carbohydrates, therefore, corresponds to an easy access to enantiomerically pure cyclopentanes and cyclopentanones. Thus, 5 may be considered to be a synthon for enantiomerically pure 11 or 12. The parallel between this [3+2] cycloaddition and Diels-Alder reaction with these substrates is also striking.[9b-d,13]

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References

1) B.M. Trost, Angew. Chem., Int. Ed. Engl., 25, 1 (1986).
2) B.M. Trost and P. Bonk, J. Am. Chem. Soc., 107, 8277 (1985).
3) B.M. Trost and D.M.T. Chan, J. Am. Chem. Soc., 105, 2315 (1983).
4) O. Achmatowitz and R. Bielski, Carbohydr. Res., 55, 165 (1977); Piancatelli, A. Scettri, and M. D'Auria, Tetrahedron, 36, 661 (1980); J.B. Henrickson, J.S. Farina, J. Org. Chem., 45, 3359 (1980); P.G. Sammes and L. Street, J. Chem., Soc. Chem. Commun., 1980, 666; P. De Shong, S. Ramesh, V. Elango, and J.J.

Perez, J. Am. Chem. Soc., 107, 5219 (1985).

5) We find that use of monoperphthalic acid provides the most convenient work-up in the oxidation of the furfuryl alcohols.

6) B.M. Trost and T.N. Nanninga, J. Am. Chem. Soc., 107, 1293 (1985).

7) All new compounds have been fully characterized and elemental composition determined by either mass spectroscopy and/or combustion analysis. Partial spectral data for some adducts appear in Ref. 8.

8) 3b: IR($CDCl_3$): 1713, 1660, 1380, 1367 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.34 (d, J=2.3 Hz, 1H), 4.86 (m, 2H), 3.68 (d, J=4.2 Hz, 1H), 2.92 (d, J=16.2 Hz, 1H), 2.78-2.70 (m, 2H), 2.51-2.25 (m, 4H), 1.00 (d, J=6.8 Hz, 3H), 0.90 (s, 9H), 0.87 (d, J=6.8 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.7, 148.8, 100.5, 95.3, 84.6, 49.4, 47.3, 34.1, 31.5, 28.2, 25.8, 19.8, 17.9, 17.0, -3.9, -5.4.
5b: IR ($CDCl_3$): 1720, 1663, 1375, 1361 cm^{-1}. ^1H NMR (C_6D_6, 270 MHz): δ 4.84 (bs, 2H), 4.58 (s, 1H), 4.14 (t, J=4.1 Hz, 1H), 3.96 (m, 2H), 3.70 (m, 1H), 3.28 (m, 1H), 3.09 (d, J=17 Hz, 1H), 2.73 (m, 1H), 2.38 (m, 2H), 2.12 (m, 2H), 1.07 (t, J=7.0 Hz, 3H), 0.94 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.6, 148.2, 106.7, 98.2, 75.7, 47.8, 45.8, 36.1, 33.4, 25.9(3), 18.4, 15.0, -5.4(2).
6a: IR ($CHCl_3$): 1715 cm^{-1}. ^{1}1H NMR ($CDCl_3$, 270 MHz): δ 8.01 (dd, J=6.8, 1.0 Hz, 2H), 7.53 (m, 1H), 7.40 (m, 2H), 5.00 (bs, 1H), 4.93 (bs, 1H), 4.80 (bs, 3H), 4.62 (dd, J=11.3, 2.2 Hz, 1H), 4.38 (bs, 2H), 4.20 (dd, J=11.3, 8.1 Hz, 1H), 4.05 (dd, J=8.1, 2.2 Hz, 11H), 3.75 (dq, J=9.1, 7.3 Hz, 1H), 3.44 (dq, J=9.1, 7.3 Hz, 1H), 2.71 (d, J=16.8 Hz, 1H), 2.58 (d, J=16.8 Hz, 1H), 2.40-2.25 (m, 3H), 2.16 (m, 1H), 1.10 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.3, 151.4, 147.4, 132.8, 104.9, 104.3, 98.2, 83.0, 74.2, 72.9, 64.9, 62.7, 44.4, 44.0, 40.6, 36.1, 34.6, 15.6.
10: ^1H NMR ($CDCl_3$, 270 MHz): δ 7.31-7.17 (m, 5H), 5.08 (t, J=2.2 Hz, 1H), 4.97 (t, J=2.2 Hz, 1H), 4.45 (t, J=5.1 Hz, 1H), 4.34 (bs, 2H), 3.81 (d, J=10.1 Hz, 1H), 3.55 (d, 10.1 Hz, 1H), 2.78 (bs, 2H), 2.72 (dd, J=9.7, 9.1 Hz, 2H), 1.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.2, 141.5, 137.5, 128.4, 125.8, 106.3, 101.4, 75.8, 73.4, 70.8, 40.8, 35.9, 30.2.

9) a) H. Gnichtel and L. Autenrieth-Ansorge, Annalen, 1985, 2217; b) H. Gnichtel, C. Gumprecht, and P. Luger, Annalen, 1984, 1531; c) S. Chew and R.J. Ferrier, J. Chem. Soc., Chem. Commun., 1984, 911; d) J.L. Primeau, R.C. Andersen, and B. Fraser-Reid, J. Am. Chem. Soc., 105, 5874 (1983).

10) For reviews see: B. Fraser-Reid, Acc. Chem. Res., 18, 347 (1985); 8, 192 (1975).

11) R.J. Ferrier and N. Prassad, J. Chem. Soc., C, 1969, 570; B. Fraser-Reid, A. McLean, E.W. Usherwood, and N. Yunker, Can. J. Chem., 48, 2877 (1970).

12) S. King, unpublished work in these laboratories.

13) B. Fraser-Reid, R. Underwood, M. Osterhout, J.A. Grossman, and D. Liotta, J. Org. Chem., 51, 2152 (1986).

14) Y.M. Kobayashi, J. Lambrecht, J.C. Jochims, and V. Burkert, Chem. Ber., 111, 3442 (1978).

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