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DIASTEREOCONTROL VIA THE PHENOL- AND PALLADIUM(II)-CATALYZED CLAISEN REARRANGEMENT WITH CYCLIC ENOL ETHERS

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SUMMARY: Taking the judicious choice of either 2,6-dimethylphenol or $PdCl_2(RCN)_2$ as the catalyst, the Claisen rearrangements with the enol ethers of cyclic ketones are shown to proceed with a high level of either anti or syn diastereoselection, respectively.

The Claisen rearrangement is an important synthetic tool for acyclic stereoselection, where the olefinic stereocontrol of the enol ether part involved is the key to diastereocontrol over the newly created chiral centers of the product.[1] The acyclic enol ether Claisen variants, however, show no significant diastereoselectivity because of the lack of the olefinic stereoselectivity in the enol ether formation.[1] Herein we wish to report that the cyclic (stereo-defined) enol ether Claisen variant permits the highly stereoselective formation of either syn- or anti-product through the judicious choice of the catalyst employed, 2,6-dimethylphenol (DMP) or $PdCl_2(RCN)_2$ (Scheme 1).[2,3]

Scheme 1

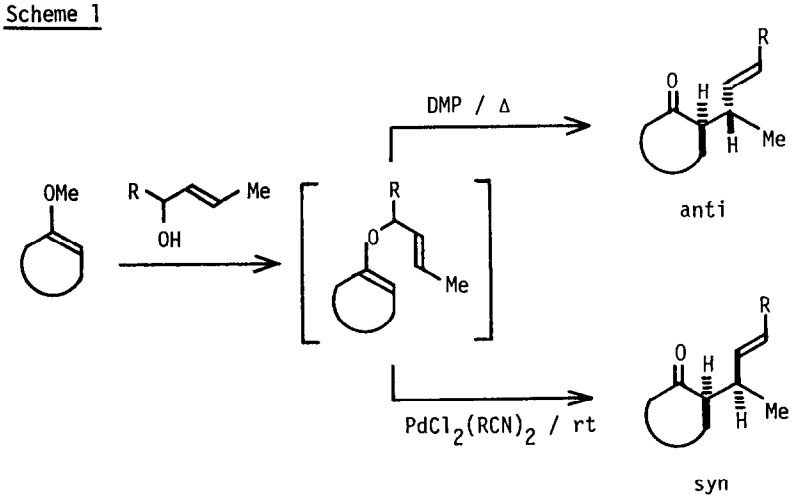
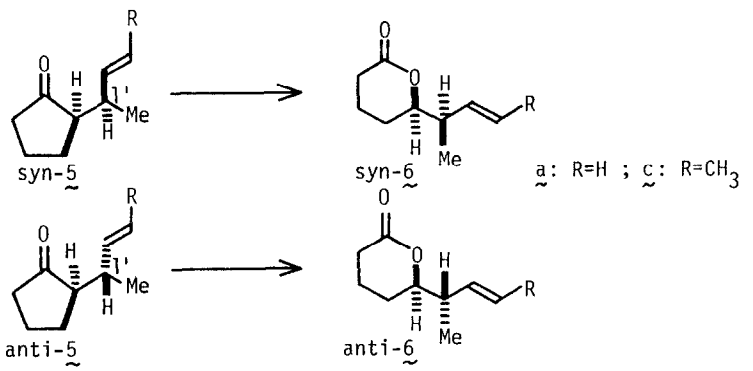


Table 1 summarizes the representative results of the Claisen rearrangements of allylic alcohols (1a - c) with the two cyclic enol ethers 2[4] and 3[5]. All reactions were carried out in toluene solution (0.2 M each) in the presence of the catalyst (10 mol%) such as $Hg(OAc)_2$, DMP[6], and $PdCl_2L_2$ (L = PhCN or MeCN).[7,8]

Inspection of Table I reveals several significant features of the present Claisen variants. (1) The conventional Claisen procedure using $Hg(OAc)_2$ as the catalyst shows only a moderate syn/anti-selectivity (runs 1 and 2) presumably because the acetic acid once formed causes epimerization to some extent.[9] (2) The rearrangement catalyzed by DMP exhibits a remarkably enhanced E→anti selectivity (runs 3, 5, 7, and 9).[10] (3) Surprisingly enough, the Pd(II)-catalyzed rearrangement not only proceeds smoothly even at room temperature but also exhibits the opposite sense of stereoselection, i.e., the E→syn selectivity (runs 4, 6, and 8).[11] (4) In all cases where an internal olefin is formed, an extremely high E selectivity is observed for both the DMP- and Pd(II)-catalyzed rearrangements (runs 5, 6, and 9).

The stereochemical assignments of the diastereomeric Claisen products deserve special comments.[12] The stereochemistry of 5c was confirmed through its conversion to the known pentanolide diastereomer 6c[13] via Baeyer-Villiger oxidation with peracetic acid (Scheme 2). Thus, syn-5c of which the 1'-methyl NMR signal appears at a lower field compared to that of anti-5c[14] was correlated to syn-6c of which the oxy-methine NMR signal appears at a higher field compared to that of anti-6c. The stereochemistry of 5a[15] was also confirmed through its similar conversion to the pentanolide 6a which shows a similar NMR trend to that for 6c.[16] On the other hand, the stereochemical assignments of 4a and 4b were made, though not vigorously, based on similar NMR trends to those observed for 5a and 5c.[17] Further notable is that the syn/anti pair of all the products (4 and 5) show systematic differences in their HPLC.[18]

Scheme 2



Particularly noteworthy is the dramatic changeover in diastereoselection observed by changing the catalyst from DMP to $PdCl_2(RCN)_2$. The E→anti selectivity of the DMP-catalyzed rearrangement is easily visualized by the well-established chairlike transition states (A),[1] whereas the E→syn selectivity of the Pd(II)-catalyzed rearrangement can be explained by the boatlike transition state (B) where the diene moiety may act as a bidentate ligand.[19]

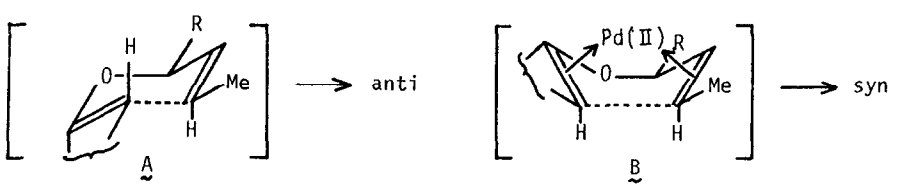


Table 1. Cyclic Enol Ether Claisen Rearrangements.

run	alcohol	catalyst	temp.(°C)/time(h)	product	anti/syn[a]	%yield[b]
						
	1 + 2 → 4					
1	(E)-1a (R=H)[c]	$Hg(OAc)_2$	140 / 10	4a (R=H)	61 : 39	>95
2			100 / 17		77 : 23	91
3[d]		DMP	100 / 17		94 : 6	94
4[e]		$PdCl_2(PhCN)_2$	rt / 3		13 : 87	>95
5	(E)-1b (R=i-Bu)[f]	DMP	100 / 10	4b (R=i-Bu)	>98 : <2[g]	>95
6		$PdCl_2(PhCN)_2$	rt / <1		<2 : >98[g]	>95
						
	1 + 3 → 5					
7[h]	(E)-1a (R=H)[c]	DMP	120 / 14	5a (R=H)	88 : 12	>95
8[i]		$PdCl_2(MeCN)_2$	rt / 10		12 : 88	78
9[j]	(E)-1c (R=Me)[k]	DMP	120 / 14	5c (R=Me)	81 : 19[g]	>95

[a] The stereoisomeric ratio was determined by HPLC and/or ^1H NMR. [b] Isolated yield after silica gel chromatography. [c] The geometric purity was of 94%. [d] A similar reaction of the Z-counterpart (93% Z) provided the anti- and syn-4a in a ratio of 15 : 85. [e] A similar reaction of the Z-counterpart was sluggish to afford only 40% of the rearranged product even after 24 h. [f] The geometric purity was of 100%. [g] The (E)-olefin was formed exclusively. [h] A similar reaction of the Z-counterpart (93% Z) provided the anti- and syn-5a in a ratio of 25 : 75. [i] The substrate used is 1-crotyloxy-1-cyclopentene (94% E) which was prepared by the literature procedure: K. Takai, I. Mori, K. Oshima, and H. Nozaki, Bull. Chem. Soc. Jpn., 57, 446 (1984). [j] A similar reaction of the Z-counterpart (98% Z) afforded the anti- and syn-5c in a ratio of 11 : 89. [k] The geometric purity was of 94%.

This work has demonstrated that the newly-developed Claisen procedures provide a useful approach to the introduction of an α-side chain onto cyclic ketones with a high level of either anti or syn diastereoselectivity. Application of the present methodology to natural product synthesis is now in progress.

REFERENCES AND NOTES

1. P. A. Bartlett, Tetrahedron, 36, 2 (1980); F. E. Ziegler, Acc. Chem. Res., 10, 227 (1977).
2. The Claisen variant with cyclic orthoesters has already been reported: B. Lythgoe, Chem. Soc. Rev., 10, 449 (1981).
3. No example of the Claisen rearrangement with cyclic enol ether had been reported. After completion of this work, the two reports dealing with the Claisen variant with ketals of cyclic ketones have appeared: (a) J. L. Baan and F. Bickelhaupt, Tetrahedron Lett., 27, 6267 (1986); (b) G. W. Daub and D. A. Griffith, ibid., 27, 6311 (1986).
4. The enol ether 2 was prepared by applying the literature procedure: R. B. Miller and C. G. Gutierres, J. Org. Chem., 43, 1569 (1978).
5. For the preparation, see: R. A. Wohl, Synthesis, 1974, 38.
6. DMP has been used as a catalyst for ortho ester Claisen rearrangement: Y. Fujita, T. Onishi, and T. Nishida, Synthesis, 1978, 532.
7. Reviews on catalysis of the Cope and Claisen rearrangements: L. E. Overman, Angew. Chem. Int. Ed. Engl., 23, 579 (1984); R. P. Lutz, Chem. Rev., 84, 205 (1984). In these reviews, however, no example of Pd(II)-catalyzed Claisen rearrangement is recorded.
8. (a) After completion of this work, Baan and Bickelhaupt has reported a similar Pd(II)-catalyzed Claisen rearrangement (ref 3a). In this paper, however, no stereochemical data is available. (b) Also see: A. Yamamoto and T. Hayashi, Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1985, 2W35.
9. Recently, the syn/anti-selectivity of the cyclic ketal Claisen has been reported to be attenuated by propionic acid via epimerization of the products; cf. ref 3b.
10. Apparently the smaller acidity of DMP is responsible for the enhanced stereoselectivity.
11. No rearrangement, however, occurred with β-substituted allylic alcohols such as 2-methyl-2-buten-1-ol. This failure parallels the significant limitation reported for the Pd(II)-catalyzed Cope rearrangement of 2,5-disubstituted 1,5-dienes (ref 7).
12. It should be noted that the product stereochemistry of the Hg(II)- and acid-catalyzed Claisen process is readily assignable to the E→anti configuration based on the well-established chairlike transition state (ref 1).
13. For the ^{1}H NMR data of the pentanolide diastereomers 6c, see: C. S.-Rouvier, Tetrahedron Lett., 25, 4371 (1984).
14. Syn-5c: δ 1.07 (d, 1'-Me), 5.10-5.60 (m, 2'- and 3'-H); anti-5c: δ 0.91 (d, 1'-Me), 5.20-5.70 (m, 2'- and 3'-H).
15. Syn-5a: δ 1.11 (d, 1'-Me), 5.66 (ddd, 2'-H); anti-5a: δ 0.93 (d, 1'-Me), 5.83 (ddd, 2'-H).
16. Syn-6a shows the oxy-methine proton at a higher field (δ 4.13 ppm) than anti-6a (δ 4.20 ppm).
17. Syn-4a: δ 1.10 (d, 1'-Me), 5.72 (ddd, 2'-H); anti-4a: δ 0.99 (d, 1'-Me), 5.91 (ddd, 2'-H); syn-4b: δ 1.04 (d, 1'-Me), 5.13-5.50 (m, 2'- and 3'-H); anti-4b: δ 0.95 (d, 1'-Me), 5.26-5.63 (m, 2'- and 3'-H).
18. Syn-4a: R_t=12.1 min; anti-4a: R_t=11.1 min; syn-4b: R_t=12.9 min; anti-4b: R_t=11.6 min; syn-5a: R_t=18.1 min; anti-5a: R_t=17.7 min; syn-5c: R_t=16.7 min; anti-5c: R_t=15.9 min.
19. A similar boatlike transition state has been proposed for the $PdCl_2(PhCN)_2$-catalyzed Cope rearrangement of cis-1,2-divinylcyclobutane: P. Heimbach and M. Molin, J. Organomet. Chem., 49, 477 (1973).

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