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On the Extent of Racemization of Allylic Esters During Palladium-mediated Alkylation with Homochiral 3-Methyl-γ-butyrolactone Derivatives[1]

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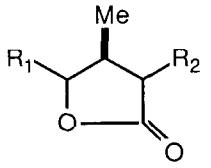
Abstract: The allylic phosphate **4e** has been shown to racemize ~4-6% upon alkylation with the sodium lactone enolates of **1c** and **ent-1c** in the presence of $Pd(Ph_3P)_4$. The acetate **4d** racemizes 11%.

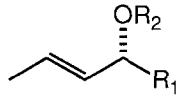
The Claisen rearrangements of lactone **1a**[2,3] (via its diethyl ortholactone) with alcohols **4a-c**[4] afford only the lactones **2a-c**, respectively, while the diastereomeric reactions (**1a** + **ent-4a-c**) give an ~50/50 mixture of lactones **5a-c/6a-c**, respectively.[5] When the lactone bears an alkyl substituent at C-4 (**1b**), attempted ortholactone formation with triethyloxonium tetrafluoroborate[3] provides a complex mixture of desired product and unsaturated ethyl esters arising from ring cleavage.[6]

The Claisen rearrangement may be considered an intramolecular, suprafacial, S_N2' alkylation. The operational equivalent (Scheme) of the rearrangement is the palladium-catalyzed alkylation of the activated allylic alcohol with the carbomethoxylated lactone enolate followed by decarboxylation. This type of alkylation has been studied extensively by Tsuji,[7] Trost,[8] and Bosnich;[9] and Keinan[10] has demonstrated high regioselective addition of sodiomalonic ester at the methyl terminus of acetate **rac-4d**. Racemization of π-allyl complexes during alkylations has been observed by Tsuji,[11] Bosnich,[9b] and Hayashi.[12] The racemization arises by palladium(0) displacement on the π-allyl complex, a process which is catalyst concentration dependent. We report in this Letter the extent of racemization in the palladium-catalyzed alkylation and the suitability of the alkylation as an alternative to the Claisen rearrangement.

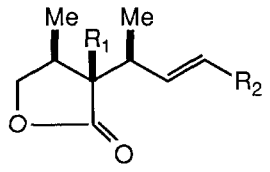
The purity of lactone **1a** (%ee=96.4) and **ent-1a** (%ee=97.4) was determined by hplc integration (electronic) of the diastereomeric hydroxyamides from R-(+)-phenethylamine (%ee=98.6),[13] as described by Helmchen.[14] Carbomethoxy lactones **1c** and **ent-1c** were prepared



1a, R_1 = H, R_2 = H
b, R_1 = alkyl, R_2 = H
c, R_1 = H, R_2 = CO_2Me



4a, R_1 = Me, R_2 = H
b, R_1 = n-Bu, R_2 = H
c, R_1 = i-Pr, R_2 = H
d, R_1 = i-Pr, R_2 = Ac
e, R_1 = i-Pr, R_2 = $PO(OEt)_2$



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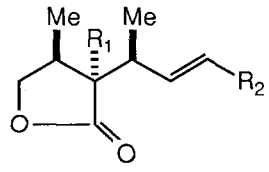

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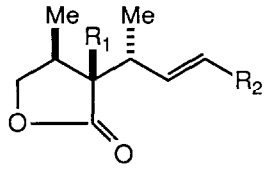

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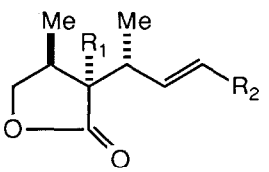

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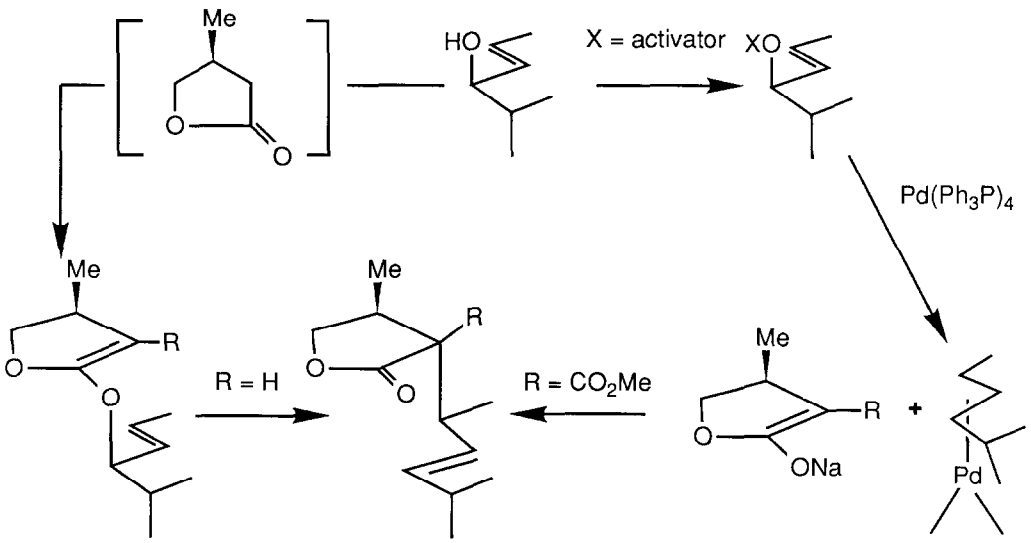
a, R_1 = H, R_2 = Me; b, R_1 = H, R_2 = n-Bu;
c, R_1 = H, R_2 = i-Pr; d, R_1 = CO_2Me, R_2 = i-Pr

Table[a]

Entry	Lactone	Conditions	Temp(°C)[b]	Time(h)[b]	Products[c]	Ratio[d]	%Rac[e]
1	ent-1a	4c, toluene, H^+	110	48	2/3/ent-5/ent-6 1.3/0/53.6/45.1	98.7/1.3[f]	-
2	ent-1c	4e, 2.0 equiv. 5% $Pd(Ph_3P)_4$ 5% Ph_3P	25	2	ent-(2/3/5/6) 3.4/0.9/79.3/16.4	95.7/4.3[g]	6.2
3	ent-1c	4e, 2.0 equiv. 10% $Pd(Ph_3P)_4$ 10% Ph_3P	25	2	ent-(2/3/5/6) 3.0/0.9/78.8/17.3	96.1/3.9[g]	5.4
4	ent-1c	4d, 2.5 equiv. 10% $Pd(Ph_3P)_4$ 10% Ph_3P 10% 15-crown-5	65	18	ent-(2/3/5/6) 5.8/1.1/79.4/13.7	93.1/6.9[g]	11.4
5	1c	4e, 2.0 equiv. 5% $Pd(Ph_3P)_4$ 5% Ph_3P	25	2	2/3/5/6[h] 94.8/1.3/3.9/0	96.1/3.9[i]	4.4[j]

a) THF solvent; yields are in excess of 80%, b) required for complete reaction, c) values reflect kinetic decarboxylation products; capillary gc, Carbowax 20M, 25 m, 3 injection average, d) see footnote 18, e) %rac=200[(98.7-(ent-5+ent-6)]/(98.7-1.3), f) ratio=(ent-5+ent-6)/(2+3), g) ratio=ent-[(5+6)/(2+3)], h) After t-BuOK/t-BuOH equilibration, i) ratio=(2+3)/(5+6), j) 1a/ent-1a=98.2/1.8; %rac=200[98.2-(2+3)]/(98.2-1.8).

Scheme



by the method of Mander[15] using 2 equivalents of LDA, and were converted into their anions with sodium hydride. Decarboxylation was accomplished by the method of Krapcho (LiCl, aq. DMSO, 190°C).[16] The Table presents the results of the study.

The Claisen rearrangement of lactone **ent-1a** with alcohol **4c** (entry 1) reveals a ratio of diastereomeric products, **(ent-5+ent-6)/(2+3)**, of 98.7/1.3. Since this ratio is the same as the ratio of enantiomeric lactones **ent-1a/1a**, the alcohol **4c** is virtually 100% enantiomerically pure. This diastereomer ratio is the optimum ratio that can be obtained in the palladium-catalyzed alkylations employing activated esters of alcohol **4c**. The increased reactivity of phosphate esters over acetates mandated the former ester as the activator of choice.[17] The comparison of entries 2 and 3 with entry 4 confirms the greater reactivity of the allylic phosphate over the acetate. In the latter case, crown ether is required to solubilize the ester enolate, whereas the phosphate alkylation does not require the complexing agent. Entries 2 and 3 demonstrate that increased catalyst concentration does not increase the extent of racemization, while entry 5 shows that the absolute homochirality of the lactone has no bearing upon the extent of racemization. The phosphate **4e** suffers ~4-6% racemization while the elevated temperature and extended reaction time required for complete reaction of

entry 4, employing acetate **4d**, cause 11% racemization.

The following Letters illustrate synthetic applications of this methodology.

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References and Notes:

1. In this Letter and the two that follow, homochiral means enantiomerically pure, Masamune, S., Heterocycles **1984**, 21, 107. All structures are the enantiomers shown, unless the structure numbers are prefixed by ent- or rac.
2. Mori, K., Tetrahedron **1983**, 39, 3107.
3. Chapleo, C. B.; Hallett, P.; Lythgoe, B.; Waterhouse, I.; Wright, P. W. J., Chem. Soc., Perkin Trans. I **1977**, 1211.
4. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ideda, M.; Sharpless, K. B., J. Am. Chem. Soc. **1981**, 103, 6237.
5. a) Ziegler, F. E.; Thottathil, J. K., Tetrahedron Lett. **1982**, 23, 3531; b) Ziegler, F. E.; Wester, R. T., Ibid. **1984**, 25, 617; c) Ziegler, F. E.; Kneisley, A., Ibid. **1985**, 26, 263.
6. Cf. Kaloustian, M. K.; Khouri, F., Tetrahedron Lett. **1981**, 22, 413.
7. Tsuji, J., Fortschritte Chem. **1980**, 91, 29; Idem., Pure Appl. Chem. **1982**, 54, 197.
8. a) Trost, B. M., Tetrahedron **1977**, 33, 2615; b) Trost, B. M.; Verhoeven, T. R., J. Am. Chem. Soc. **1980**, 102, 4730; c) Trost, B. M.; Klun, T. P., Ibid. **1981**, 103, 1864.
9. Bosnich, B., Pure Appl. Chem. **1982**, 54, 189; b) Auburn, P. R.; Mackenzie, P. B.; and Bosnich, B., J. Am. Chem. Soc. **1985**, 107, 2033.
10. Keinan, E.; Sahai, M., J. Chem. Soc., Chem. Commun. **1984**, 648.
11. Takahashi, J.; Jinbo, Y.; Kitamura,K.; Tsuji, J., Tetrahedron Lett. **1984**, 25, 5921.
12. a) Hayashi, T.; Konishi, M.; Kumada, M., J. Chem. Soc., Chem. Commun. **1984**, 107; b) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M., J. Am. Chem. Soc. **1983**, 105, 7767.
13. The enantiomeric purity of R-(+)-α-phenethylamine was determined by measuring the NMR ratio of the methyl doublet of the S-enantiomer and the upfield ^{13}C methyl doublet satellite of the R-enantiomer in the presence of $Eu(thfc)_3$. The ratio of the R-methyl doublet to the S- methyl doublet is 99.3/0.7.
14. Helmchen, G.; Nill, G., Angew. Chem., Int. Ed. Eng., **1979**, 18, 65. All reactions were checked for lack of kinetic resolution using a racemic partner.
15. Mander, L. N.; Sethi, S. P., Tetrahedron Lett., **1983**, 24, 5425.
16. Krapcho, A. P., Synthesis **1982**, 805.
17. Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S., Tetrahedron Lett. **1982**, 23, 5549.
18. The diastereomers comprising the numerator of the ratio of entries 2-5 have %ee>99.8; the components of the denominator are partially racemized. The major enantiomers are listed under Products. Cf. Midland, M. M.; Gabriel, J. J., J. Org. Chem., **1985**, 50, 1143 (footnote 9); Hoye, T. R.; Suhadolnik, J. C., J. Am. Chem. Soc., **1985**, 107, 5312.

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