Palladium(0)-mediated Intramolecular Lactonization of Allylic Alcohol Derivatives; Unusual Substituent Effect of the Trifluoromethyl Group on δ-Lactone Formation

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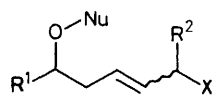
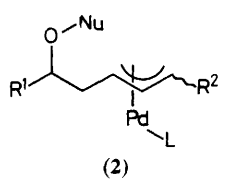
In the intramolecular lactonization of allylic alcohol derivatives catalysed by a palladium(0) complex, selective formation of 4,6-*cis*-disubstituted δ-lactones and the unusual effect of a trifluoromethyl group in the homoallylic position were observed.

Recent advances in the chemistry of palladium-catalysed substitution reactions of allylic alcohol derivatives with soft carbon nucleophiles have demonstrated many applications in synthetic chemistry.[1] One stereochemical aspect of palladium-catalysed allylic substitution reactions is characteristic: the double inversion of the configuration at the centre of substitution in allylic alcohol derivatives. By applying this characteristic, the effect of 1,3-chirality transfer in the intramolecular lactonization of optically active allylic alcohol derivatives (**1**) *via* the π-allyl complex (**2**) has been reported.[2]



(**1**) R^1 = H, R^2 = alkyl
(**3a**) R^1 = Pr^i, R^2 = H
(**3b**) R^1 = Me, R^2 = H
(**3c**) R^1 = Ph, R^2 = H
(**3d**) R^1 = CF_3, R^2 = H

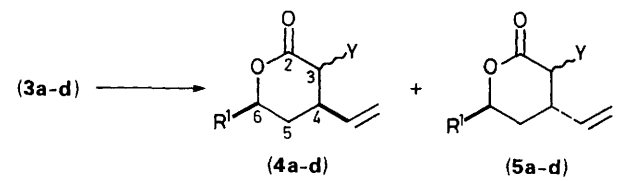
X = OCO_2Et or OAc; Nu = $COCH_2CO_2Et$



(**2**)

We report herein the intramolecular lactonization of the allylic alcohol systems (**3a—d**) and the effect of the substituent (R^1) at the homoallylic position.

The cyclization of (**3a—d**) {5 mol% $Pd_2(dba)_3$·$CHCl_3$ (dba = dibenzylideneacetone),[3] 15 mol% 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane, Me_2SO, 40 °C} was effected within 5 min to give the 6-membered ring lactone; the regiochemical isomer (8-membered ring lactone) could not be isolated (Scheme 1).[4] The stereochemistry of the starting material and generation of the anion with base (NaH) in tetrahydrofuran (THF) prior to the addition to the catalytic system had no effect on the regio- and stereo-chemistry of the product.



Scheme 1. *Reagents and conditions:* $P(OCH_2)_3CEt$, $Pd(dba)_3$·$CHCl_3$, then NaI, HMPA.

Table 1. Intramolecular lactonization of (**3**) at 40 °C (5 min).

R	X	*E*/*Z*	Base	% Yield	(**4**)/(**5**)[a]
(**3a**)	OAc	*E*	NaH	67	4/1
(**3a**)	OCO_2Et	*E*		43	3.5/1
(**3a**)	OCO_2Et	*Z*		67	3.6/1
(**3b**)	OCO_2Et	*E*		84	2.5/1
(**3c**)	OAc	*E*	NaH	69	2/1
(**3c**)	OCO_2Et	*Z*		50	2.3/1
(**3d**)	OCO_2Et	*E*		56 (Y = CO_2Et)[b]	
(**3d**)	OCO_2Et	*Z*		58 (Y = CO_2Et)[b]	

[a] Determined by ^1H NMR spectroscopy and GLC analysis (OV-101, 0.25 mm, 25 m). [b] Diastereoisomeric mixture of (**4d**).

The stereochemistry of the de-ethoxycarbonylated products (**4, 5**; Y = H) [NaI–hexamethylphosphoric triamide (HMPA) 160 °C, 6 h][5] showed moderate 4,6-*cis*-stereoselectivity (*cis* : *trans*; 2 : 1–4 : 1) except for the trifluoromethylated compound (**3d**) (Table 1). In the case of the trifluoromethylated compound (**3d**), owing to the instability of the product, the ^1H and ^{19}F NMR spectra of the two isomeric mixture (**4d**, Y = CO_2Et) obtained initially by cyclization were analysed. The results clearly indicated that the two isomers (9 : 1 ratio)† (**4d**; Y = CO_2Et) are diastereoisomers arising from the chiral centre at C-3 and both the C-4 and C-6 substituents (vinyl and CF_3) are equatorial.‡ The reason for the formation of the 4,6-*cis*-lactone without the 4,6-*trans*-isomer for the trifluoromethylated compound (**3d**) may not be the simple steric bulkiness of the trifluoromethyl group but the sum of the steric and the strong electronic effect of the trifluoromethyl group, since the isopropyl group, considered similar to the trifluoromethyl group in steric bulkiness,[7] gave a moderate *cis* : *trans*-ratio (4 : 1). Thus we believe that in the trifluoromethylated compound, the trifluoromethyl group played an important role in determining the conformation of the transition state by its steric and electronic effects. In the reaction described herein, the 4,6-*cis*- to 4,6-*trans*-isomer ratio stayed constant regardless of the reaction time (5 min to 48 h) and the temperature (room temp. to 48 °C).[6] These facts show that the reaction is not reversible under the conditions examined, and that it proceeded through a favoured transition state (**A**) which involves less steric and electronic repulsion between the R group and the enolate anion than the transition state (**B**).

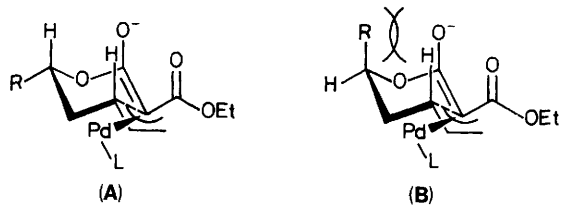


Figure 1. Transition state for cyclization of (**3**).

This 4,6-*cis*-lactone formation is of considerable interest when it is considered that Michael-type addition of organometallic reagents to α,β-unsaturated lactone derivatives gives the 4,6-*trans*-lactone as the major product.[8] The present results are significant not only with regard to the formation of the 4,6-*cis*-lactones but also for the 1,3-transfer of the homoallylic chirality, especially in the trifluoromethylated compound.

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† The ratio was determined by ^1H and ^{19}F NMR integration. No other isomers were detected in the ^{19}F NMR spectrum of the crude reaction mixture.

‡ Major isomer of (**4d**): ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (1H, ddd, *J* 13.93, 12.24, 12.24 Hz, 5-H_{ax}), 2.26 (1H, ddd, *J* 13.93, 3.72, 3.72 Hz, 5-H_{eq}), 3.07 (1H, m, 4-H), 3.32 (1H, d, *J* 11.34 Hz, 3-H), and 4.78 (1H, m, 6-H); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ 15.5 (d, *J* 5.64 Hz) p.p.m. to high field of external $PhCF_3$.

Minor isomer of (**4d**): ^1H NMR δ 2.09 (1H, m, 5-H_{eq}), 2.43 (1H, ddd, *J* 13.10, 12.46, 12.46 Hz, 5-H_{ax}), 2.93 (1H, m, 4-H), 3.77 (1H, dd, *J* 6.32, 1.28 Hz, 3-H), and 4.73 (1H, m, 6-H); ^{19}F NMR δ 15.3 (d, *J* 5.64 Hz) p.p.m.

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