Palladium-catalysed Addition of Chiral Nucleophiles to Non-conjugated Dienes: Enantioselective Oxidative Cyclization of *cis*-1,2-Divinylcyclohexane

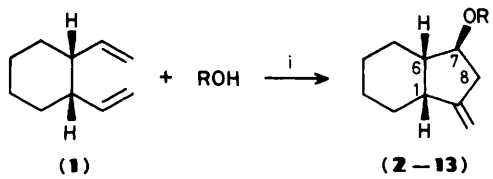
Andreas Heumann[a] and Christina Moberg[b]

[a] *Université d'Aix-Marseille, UA 126, IPSOI, F13397 Marseille Cedex 13, France*
[b] *Department of Organic Chemistry, Royal Institute of Technology, S 10044 Stockholm, Sweden*

Carboxylic acids react readily with *cis*-1,2-divinylcyclohexane; in the case of chiral acids, modest, but significant asymmetric inductions are observed during the palladium catalysed oxidation reaction.

Chiral oxidation is currently a problem under study in selective organic synthesis,[1] and effort has been devoted to the development of efficient systems which are highly enantioselective and catalytic at the same time. Metal-catalysed reactions of olefins are potential models for this purpose, provided they proceed in a highly selective manner.

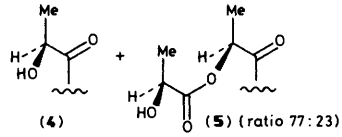
During our studies[2] of the oxidation of 1,5-dienes with palladium(II) and various reoxidation combinations we have observed the diastereoselective cyclization of *cis*-1,2-



(1) (2—13)

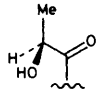
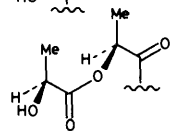
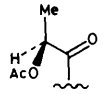
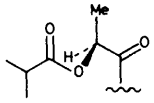
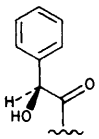
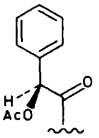
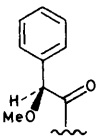
Scheme 1. *Reagents:* i, $Pd(OAc)_2$ (1—5 mol%), MnO_2–benzoquinone.

Table 1.

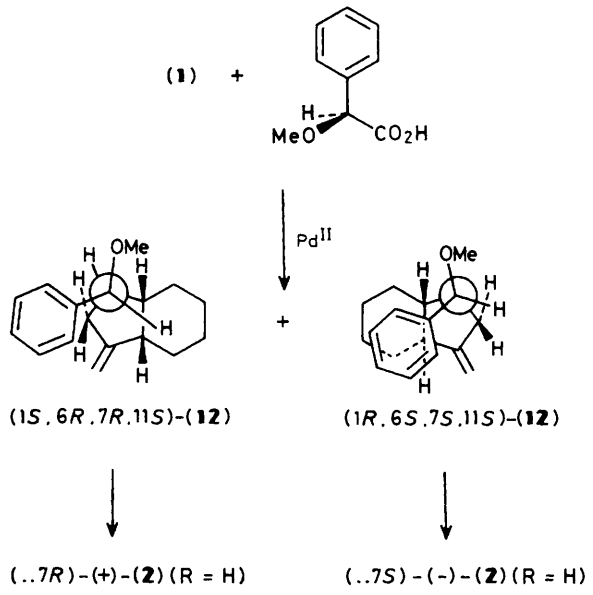
Solvent	Nucleophile	*t* (days)	Products (R)	% Yield[a]
HOAc	AcO^-	1	(**2**) Ac	70 (ref. 3)
Acetone	$PhCO_2^-$	6	(**3**) PhCO	39
Acetone	L-Lactic acid[b]	2—3	 (**4**) + (**5**) (ratio 77 : 23)	48—72
THF	"	3	(**4**) + (**5**)	27
CH_2Cl_2	"	3	(**4**) + (**5**)	19
MeOH	"	3	No reaction	

[a] Isolated and purified products (silica gel); all new products gave correct spectroscopic and analytical data. [b] Ref. 5.

Table 2. Cyclization of *cis*-1,2-divinylcyclohexane (**1**) with chiral acids $*RCO_2H$.[a]

Acid (*R)	Configuration	% Yield[b]	Product	D.e.[c]	α of (**2**) (R = H)
L-Lactic acid (ref. 5)	*S*	48—72	(**4**) + (**5**)		(+)
	*S*		(**4**)	6—7[d]	(+)
	*S*		(**5**)	18	(+)
	*S*	51	(**6**)	9	(+)
	*S*	46	(**7**)[e]	16	(−)
	*S*	21	(**10**)	8.4	(−)
	*S*	45	(**11**)	22	(−)
	*S*	31	(**12**)	11	(−)
Camphanic acid (*R = $C_{10}H_{13}O_3$)	*R*	43	(**13**)	18.9[f]	(−)

[a] 10—50 ml solvent, 0.2 M (**1**), 0.01 M $Pd(OAc)_2$, 0.05 M benzoquinone, 0.2 M MnO_2, 0.4—0.8 M *RCOOH, room temperature, 2—5 days. [b] Isolated products, purified on silica gel. [c] Determined by capillary g.l.c.: SE-30 type or CP-SIL 88 columns; we thank G. Muchow, Ecole Supérieure de Chimie de Marseille for valuable help with the g.l.c. analyses. [d] Determined by ^1H n.m.r. (200 MHz). [e] Two other acyloxylated L-lactic acids (*S*)-MeCH(OCO-Bu^t)-CO_2H and MeCH($OCOCH_2$-Bu^t)CO_2H gave cyclised products (**8**) (R = $C_9H_{13}O_3$; d.e. = 5.6%) and (**9**) (R = $C_{10}H_{15}O_3$; d.e. = 10%), respectively. [f] According to $[\alpha]_D$.



divinylcyclohexane (**1**) to the *exo-cis*-hydrindane compound (**2**) (R = COMe),[3] Scheme 1. The selective formation of ester (**2**) (R = COMe) with three asymmetric centres from the symmetric (*meso*) diene (**1**) seemed to us to be an attractive model to study the possibility of chiral discrimination during catalytic olefin oxidation reactions.

In the catalytic system used for the cyclization of (**1**), at least three factors can be considered to affect the palladation reaction, which is the regio- and diastereo-selective step in this reaction: i, the nature of the palladium(II) species, ii, the type of nucleophile, and iii, the quinone.† Here we report preliminary results on chiral cyclization reactions, using different chiral nucleophiles,‡ which can be used in place of acetic acid.[4]

A rapid screening (Table 1) showed that in the formation of the bicyclic framework (**2**), acetic acid was unnecessary and the reaction could be performed with benzoic acid§ in solvents such as acetone, tetrahydrofuran (THF), or methylene chloride. As a consequence of lower nucleophile concentration and lower nucleophilicity, yields became poorer and the reaction times increased. However, it was interesting to find that L-lactic acid[5] could also be added to divinylcyclohexane (**1**). Two pairs of diastereoisomeric esters were formed in a ratio of 77:23. After separation by column chromatography, the n.m.r. spectra revealed the structures of lactate (**4**) and lactic acid lactate (**5**). Hydrolysis (NaOH/MeOH, 60 °C, 15 min) of (**4**) and (**5**) gave the same bicyclic alcohol (**2**) (R = H). While the diastereoisomeric excess (d.e.) was easily determined for (**5**) (18%) by g.l.c. (25 m, SE-30 type or CP-sil 88 capillary column), the value for the lactate (**4**) (d.e. = 6—7%) could only roughly be estimated from the 200 MHz n.m.r. spectra. The results with other chiral acids, mainly derivatives of L-lactic- and (*S*)-mandelic acid are listed in Table 2.

The chiral inductions realized due to the asymmetry of the chiral acids are in the range 5—22%, and therefore comparable to the palladium-catalysed chiral oxidative cyclization of 2-allylphenols,[6] one of the rare 'Wacker type' oxidation reactions with appreciable chiral induction. However, in the case of the chiral acid-mediated cyclization of (**1**), the diastereoisomeric products can be separated by conventional chromatographic methods,¶ thus giving access to enantiomerically pure alcohols after hydrolysis.

The analysis of the ^{1}H n.m.r. spectra of the products from *O*-methylmandelic acid permits the direct assignment of the absolute configuration[7] of the different diastereoisomers (**12**) ‖ ** and, consequently, of the chiral alcohols (+)- and (−)-(**2**).

It can be seen from these results (Table 2) that an (*S*)-configuration in the acid molecule does not necessarily induce an (*S*)-configuration at C(7) in the bicyclic compound (**2**). As demonstrated by the formation of chiral esters (**4**—**6**), the presence of a free OH, acetyl, or lactate group in asymmetric propanoic acids with (*S*)-configuration gives rise to the opposite (*R*)-configuration at C(7) in the bicyclic molecules.

Although the chiral recognition in this catalytic oxidation is still weak, the easy access to a great number of chiral acids, their controllable modification by derivatisation, and last but not least, their ready recycling are promising factors for further developments. Preliminary experiments have shown that lactic acid also reacts with other non-conjugated dienes (hexa-1,5-diene), and a number of other palladium-catalysed oxidative functionalization reactions should be possible with aliphatic and alicyclic mono-olefins, 1,3-dienes *etc.*, and chiral acids as nucleophiles.

† One might also consider MnO_2, which is the ultimate oxidant; however the latter is supposed to be too far away from the reaction centre.

‡ We have also tried using a chiral palladium(II) catalyst in the oxidation. For example, the use of (+)-(η^3-pinene)-Pd^{II} complexes, instead of $Pd(OAc)_2$, gave (**2**; R = COMe) in fair chemical, but extremely low optical yields.

§ Formation of (**3**) (R = COPh), ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 5.11 (dt, J_1 6.5; $J_2 = J_3 = 2.5$ Hz, 1H), 4.97 (dd, m, J_1 3, J_2 2 Hz, 1H), 4.89 (br. q, J 2.5, 1H), 2.97 (ddq, part of an AB, J_1 18.5, J_2 6.5, J_3 2 Hz, 1H), 2.82 (m, $w_{\frac{1}{2}}$ 15 Hz, 1H), 2.54 (d,m-9 lines, part of an AB, J 18.5 Hz, 1H), 2.21 (m, $w_{\frac{1}{2}}$ 18 Hz, 1H), 1.82 (dq, part of an AB, J_1 14, J_2 4 Hz, 1H); 1.54—1.66 (m, 3H), 1.32—1.40 (m, 2H), 1.19—1.30 (m, 1H), 0.95—1.06 (m, 1H). ^{13}C n.m.r., δ 166.3 (CO), 150.4 (C_9), 130.7 (arom. C), 132.7, 129.5, 128.2 (arom. C–H), 106.0 (C_{10}), 77.9 (C_7), 45.1 (C_6), 41.3 (C_1), 25.5, 25.3, 24.2 (C_2, C_3, C_5), 21.6 (C_4).

¶ Separation of (**6**) by means of microcrystalline cellulose triacetate (medium pressure) chromatography; the hydrolysis (NaOH/MeOH) gave the enantiomerically pure alcohols (−)-(1*R*,6*S*,7*S*)-(**2**) (R = H) and (+)-(1*S*,6*R*,7*R*)-(**2**) (R = H), $[\alpha]_D$ +33.12 (*c* 0.004, CH_2Cl_2; separation of (**12**) [R = CO–CH(OMe)Ph] on silica gel (h.p.l.c.).

‖ Drawn in the 'extended' Newman projection, *cf.* ref. 7.

** ^{1}H N.m.r. shifts of C(1)-H_a, C(6)-H_b (bridgehead) and C(8)-H *endo* and *exo* protons:

Compound		H_a[a]	H_b[a]	C(8) H_{exo}[a]	C(8) H_{endo}[a]
	(**2**) (R = OAc)	2.67	2.05	2.35	2.83
(1*R*,6*S*,7*S*,11*S*)	(**6**)	2.64	2.03	2.41	2.85
(1*S*,6*R*,7*R*,11*S*)	(**6**)	2.67	2.08	2.35	2.85
(1*R*,6*S*,7*S*,11*S*)	(**12**)	2.52	1.86	2.39	2.86
(1*S*,6*R*,7*R*,11*S*)	(**12**)	2.65	2.07	2.18	2.78

[a] Chemical shifts in p.p.m.

We thank the NFR (Sweden) and the CNRS (France) for financial support of this project (Convention d'échange).

Received, 6th June 1988; Com. 8/02247J

References

1 B. Bosnich, ed., 'Asymmetric Catalysis,' NATO ASI Series E: Applied Sciences 103, Martinus Nijhoff, Dordrecht, 1986.
2 A. Heumann, M. Reglier, and B. Waegell, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 866, 867; *Tetrahedron Lett.*, 1983, **24**, 1971.
3 T. Antonsson, A. Heumann, and C. Moberg, *J. Chem. Soc., Chem. Commun.*, 1986, 518; T. Antonsson, C. Moberg, L. Tottie, and A. Heumann, work to be published.
4 A chiral olefin-mercuration reaction has been reported: R. M. Carlson and A. H. Funk, *Tetrahedron Lett.*, 1971, 3661; J. Barluenga, J. M. Martinez-Gallo, C. Najera, and M. Yus, *J. Chem. Res. (S)*, 1985, 266.
5 L-Lactic acid is one of the cheapest chiral starting materials available; the commercial product is a mixture of (*S*)-(+)-2-hydroxypropanoic acid and (*S*)-(+)-2-hydroxypropanoic acid 1-carboxyethylester (lactic acid lactate) as well as of varying amounts of cyclic and polymeric lactides; *cf.* M. Brin and R. H. Dunlop, 'Chemistry and Metabolism of L- and D-Lactic Acids,' *Ann. N.Y. Acad. Sci.*, 1965, **119**, pp. 851—1165.
6 T. Hosokawa, T. Uno, S. Inui, and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1981, **103**, 2318; T. Hosokawa, Y. Imada, and S.-I. Murahashi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3282; T. Hosokawa, C. Okuda, and S.-I. Murahashi, *J. Org. Chem.*, 1985, **50**, 1282.
7 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; B. L. Roy and P. Deslongchamps, *Can. J. Chem.*, 1985, **63**, 651; B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, and J. M. Balkovec, *J. Org. Chem.*, 1986, **51**, 2370.