Journal of Organometallic Chemistry, 285 (1985) 389–393
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

ASYMMETRIC INDUCTION DURING CARBONYLATION OF AN OPTICALLY ACTIVE ORGANOPALLADIUM. A NOVEL AND VERSATILE ROUTE TO ENANTIOMERIC GLYCERIDES

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(Received December 20th, 1984)

Summary

In the course of carbonylation of optically active $[\eta^5\text{-}C_5H_5Fe\text{-}\eta^5\text{-}C_5H_3CH_2NMe_2PdCl]_2$ (1) in prochiral diols, the asymmetric induction of a newly developed chiral centre by a chiral plane has been performed. For 2-*O*-benzylglycerol, the extent of asymmetric induction, that means diastereoselectivity, was found to be about 36%. The protection of a free hydroxyl followed by hydrolysis of a ferrocenoyl derivative resulted in enantiomeric 2-*O*-benzyl-3-*O*-trityl-*sn*-glycerol (4) which can serve as a key intermediate in the synthesis of optically active mono-, di- and tri-substituted glycerides. This methodology has been illustrated by the detailed description of the preparation of 1-palmitoyl-*sn*-glycerol.

Introduction

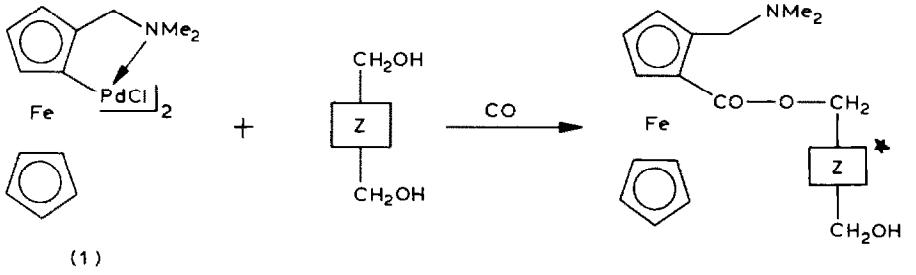
A few years ago we found that cyclopalladation of dimethylaminoalkylferrocenes in the presence of salts of optically active *N*-acylaminoacids can afford planar chiral organopalladiums with a high enantiomeric yield [1]. Replacement of palladium by other groups made it possible to obtain a series of di- and tri-substituted optically active ferrocenes [2]. Using some features of ferrocene chemistry, we were able to synthesize the analogues of prostanoids which contain a ferrocene moiety instead of cyclopentane, for example, the analogue of 11-desoxyprostaglandin-F_1 [3].

With a convenient method to prepare I in a high enantiomeric purity at our disposal, we tried to apply this compound for the asymmetric induction of a novel chiral centre. The planar chiral ferrocenes are known to be very effective ligands in asymmetric catalysis [4]; probably since they do not have planar chirality in itself but rather are of rigid three-dimensional molecular geometry which imposes the severe requirements on the transition state. This suggested the possible asymmetric influence on reactions of different kinds which involve the optically active metallocene derivatives.

0022-328X/85/$03.30

Creation of a new chiral carbon during carbonylation with the participation of prochiral diols

We now wish to report the asymmetric induction which takes place when a new chiral carbon centre arises in the course of the carbonylation of optically active **1** with prochiral diols as nucleophilic reagents. We had considered such a model as interesting and desirable one as early as 1979 [1]. During the transition state formation, one of the enantiotopic hydroxymethyl groups is preferred, and two

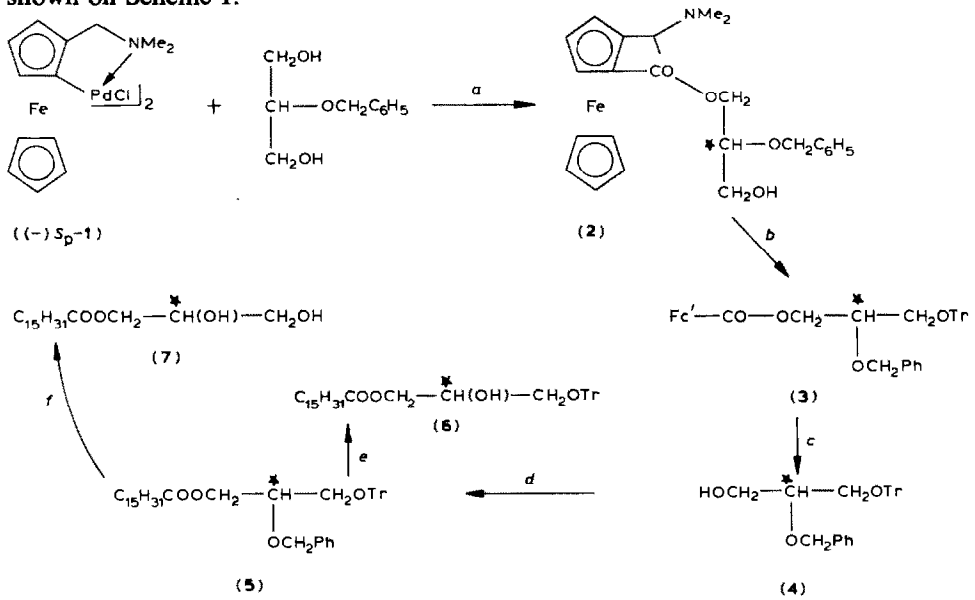


(1)

diastereomeric products form in unequal amounts. Until now it is not known whether the nucleophilic attack by an alcohol moiety takes place either on a σ-acylpalladium or on a preceding complex with a CO ligand but this is not important for the stereochemical result.

Diastereoselective carbonylation of an organopalladium as a synthetic route to enantiomeric glycerides

As an example 2-*O*-benzylglycerol has been chosen to propose the novel entry to the interesting and important class of natural glycerides. This approach has been exemplified by the synthesis of the optically active 1-palmitoyl-*sn*-glycerol (**7**) as shown on Scheme 1.



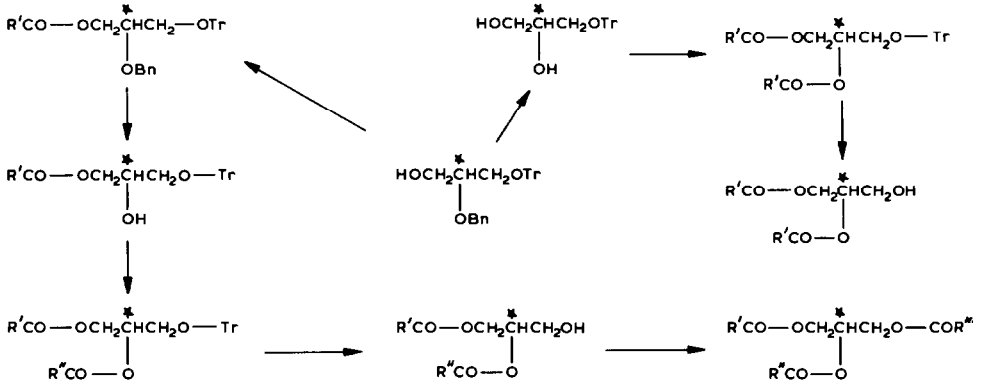
SCHEME 1. *a*: CO, C_6H_6, 20°C; *b*: TrCl, Et_3N; *c*: KOH, MeOH; *d*: $C_{15}H_{31}COCl$, py; *e*: H_2, 1 atm, Pd/C, 20°C; *f*: H_2, 1 atm, Pd/C, 50°C.

The crucial step *a* can be considered as a novel and mild preparative method for acylation under neutral conditions in an inert solvent which may be useful when susceptible alcohols are dealt with.

The primary product **2** is a mixture of unequal amounts of two diastereomers according to PMR spectroscopy. The diastereomeric ratio has been evaluated for **3** and in its ^{1}H NMR spectrum the better separation of diastereomeric NMe_2 groups was observed. Diastereoselectivity during this carbonylation is $36 \pm 2\%$ which is the extent of asymmetric induction of a chiral centre under the influence of a chiral plane. The attempt for chromatographic separation of diastereomers **2** and **3** failed. After tritylation, the ferrocenoyl group was removed by alkaline hydrolysis since as well the benzyl as the trityl groups are less reactive. Hydrolysis afforded the key compound **4** which is enantiomeric as well as compounds **5**, **6** and **7**. The conventional procedures led to an optically active monoacylglyceride **7** but it is also possible to remove the benzyl group only with formation of **6**. Absolute *S* configuration is assigned to a chiral C(2) centre on the basis of positive rotation in pyridine. 1-*O*-Acyl-*sn*-glycerols are known to exhibit the opposite signs in pyridine and other solvents as $CHCl_3$ or THF [5]. The enantiomeric excess in **7** determined by comparison with the maximum value of $[\alpha]_D$ −4.37°(pyridine) [5] is close to that calculated from PMR data taking into account the enantiomeric purity of the starting compound **1** *.

It is interesting to compare the molecular rotation of **4** in our experiment to that of a related disubstituted glycerol $HOCH_2CHO$-z-CH_2O-$C(C_6H_5)_2C_6H_4OCH_3$-*p*, z = *cis*-$(CH_2)_8HC{=}CH(CH_2)_8H$, reported recently as the *R*(+) enantiomer [6]. The rotations are $[M]_{578} - 8363°$ and $[M]_{589} + 8206°$ respectively, if corrected for optical purity this confirms as well absolute configuration as enantiomeric excess for **4**.

Diastereoselectivity could not be increased either by using different solvents such as toluene or THF or by lowering the temperature. At −20°C the reaction does not take place, probably because of the increased stability of an intermediate with a CO ligand coordinated to palladium. Enhancement of asymmetric induction can be expected if the steric hindrance in organopalladium molecules increases.



SCHEME 2

* $p = (\alpha \times \beta)/100$, where p is the enantiomeric purity of **7**, α that of **1**, and β the diastereoselectivity of carbonylation.

We may conclude that the approach proposed is shown to be useful for the preparation of optically active glycerides with an enantiomeric purity of about 40%. Obviously the enantiomeric key compound **4** can be converted into various mono-, di- and tri-substituted glycerides with different groups as shown in Scheme 2. Not only acyl but also alkyl derivatives can be obtained in a similar way.

Recently Mukaiyama et al. [7] reported a novel approach to glycerides using a tin reagent, which involved asymmetric selectivity at the chiral centre, rather than asymmetric induction, contrary to the present approach.

Experimental

2-O-Benzyl-1-O-(2-dimethylaminomethylferrocenoyl)-sn-glycerol (2). CO was bubbled through a mixture of 3.8 g (0.01 mol) of organopalladium **1** * and 3.6 g (0.02 mmol) of 2-*O*-benzylglycerol in benzene or toluene (10 ml) during 4 h while stirred. The reaction mixture was treated with aqueous $NaHCO_3$ and benzene. The organic layer was dried, then concentrated to a small volume and chromatographed on SiO_2, eluted successively with ethyl acetate, hexane/triethylamine and methanol. After the usual work-up of the last fraction, 3.7 g of **2** (82%) were obtained as a dark oil, $[\alpha]_{578}$ −62.7° (*c* 3.4; EtOH); *m/e* 451 (M^+).

^{1}H NMR ($CDCl_3$): diastereomer I, major: δ 2.19 (NMe_2, s, 6H), 3.13 (1H, d, *J* 12 Hz, CH_2NMe_2), 4.14 ppm (5H, s, C_5H_5); diastereomer II, minor: δ 2.21 (6H, s, NMe_2), 3.23 (1H, d, *J* 12 Hz, CH_2NMe_2), 4.13 ppm (5H, s, C_5H_5); complex multiplets near δ 3.75 and 4.5 ppm.

2-O-Benzyl-1-O-(2-dimethylaminomethylferrocenoyl)-3-O-trityl-sn-glycerol (3), 4.3 g of $(C_6H_5)_3CCl$ (15 mmol) and 3.4 g of **2** (7.5 mmol), and 5 ml of Et_3N in CH_2Cl_2 (40 ml) were refluxed under argon for 1.5 h. Usual chromatography on SiO_2 with benzene, then benzene/Et_3N (5/1) as eluents afforded 3.25 g of **3** (62%) as dark oil, $[\alpha]_{578}$ −38.2° (*c* 4.15; C_6H_6); −37.9° (*c* 4; EtOH). *m/e* 693 (M^+). ^{1}H NMR ($CDCl_3$): diastereomer I, major: δ 2.18 (6H, s, NMe_2), 3.93 ppm (5H, s, C_5H_5); diastereomer II, minor: δ 2.225 (6H, s, NMe_2), 3.92 (5H, s, C_5H_5); complex multiplets in the regions 3.25–3.55 (CH_2NMe_2 and CH_2OTr), 3.75 (CH–O–CH_2Ph), 4.0–4.8 and 7.0–7.6 ppm.

2-O-Benzyl-3-O-trityl-sn-glycerol (4). A solution of 2.7 g of **3** (3.9 mmol) in 100 ml of 5% KOH in MeOH was refluxed under argon for 3 h, then treated with water and ether. The ethereal extract was concentrated and chromatographed on SiO_2, eluted with benzene, then benzene/ether (5/1). 1.15 g of **4** (70%) was obtained as a yellowish oil, $[\alpha]_{578}$ + 6.55° (*c* 5.45; C_6H_6). ^{1}H NMR (C_6D_6): δ 1.9 (1H, s, O*H*), 3.35 (2H, d, *J* 4.9 Hz, CH_2OTr). 3.51 (1H, quintuplet, OCH_2–*CH*–CH_2O), 3.64 (2H, d, *J* 5.2 Hz, CH_2OH), 4.45 (2H, AB type quadruplet, *J* 11.9 Hz, CH_2Ph), complex multiplet of aromatic protons in the region 7.0–7.6 ppm.

2-O-Benzyl-1-O-palmitoyl-3-0-trityl-sn-glycerol (5). 0.6 g of freshly distilled palmitoyl chloride (> 2 mmol) in 2 ml of dry $CHCl_3$ were added dropwise at 0°C to 0.85 g (2 mmol) of **4** in 10 ml of $CHCl_3$ and 0.5 ml of dry pyridine. After 36 h the chloroform was washed with water, dried and evaporated to give 1.5 g of **5** (86.5%) which can be purified by chromatography on SiO_2 with benzene as the eluent, $[\alpha]_{578}$ + 4.72° (*c* 4.87; C_6H_6). ^{1}H NMR (C_6D_6): δ 0.91 (3H, t, CH_3CH_2), 1.15–1.60

* $[\alpha]_{578}^{20}$ −696°, *c* 2.15 in CH_2Cl_2, *p* 92.4%.

(aliphatic protons), 2.1 (2H, t, CH_2COO), 3.37 (2H, d, J 5.1 Hz, CH_2OTr), 3.67 (1H, quintuplet, J 4.5 Hz, $OCH_2-CH-CH_2O$), 4.36 and 4.38 (2H, AB system, CH_2OCO), 4.49 (2H, s, CH_2Ph), 6.95–7.60 (aromatic protons) ppm.

1-O-Palmitoyl-3-O-trityl-sn-glycerol (6). To 0.6 g of 10% Pd/C in 3 ml of dry THF at −78°C were added 0.66 g of **8** (1 mmol) in THF (7 ml) and the mixture was hydrogenated at room temperature and 1 atm H_2. After separation of the catalyst and evaporation, the residue was chromatographed on SiO_2 with benzene/ether (5/1) as eluent to afford 0.25 g of **6** (44%), m.p. 58°C, $[\alpha]_{578}$ + 3.05° (c 5.7; C_6H_6). ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, CH_3CH_2), 1.23–1.60 (aliphatic protons), 2.27 (2H, t, CH_2COO), 3.21 (2H, d, J 5.4 Hz, CH_2OTr), 3.99 (1H, m, CHOH), 4.18 (2H, dd, CH_2COO), 7.30–7.65 (aromatic protons) ppm.

1-O-Palmitoyl-sn-glycerol (7) *. A. 0.24 g of **6** (0.42 mmol) were hydrogenated in THF over 0.1 g of 10% Pd/C at 45°C and 1 atm H_2 during 4.5 h. After the usual work-up 0.07 g of **7** (50%) were obtained crystallized from benzene/ether, m.p. 68–70°C; $[\alpha]_{578}$ + 1.38° (c 4.5; pyridine).

B. Hydrogenation of **5** was performed similarly under formation of **7** but at 5 atm H_2. ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, CH_3), 1.2–1.6 (aliphatic protons), 2.32 (2H, t, CH_2COO), 3.50–3.75 (2H, m, CH_2OH), 3.93 (1H, m, CHOH).

References

1 V.I. Sokolov, L.L. Troitskaya and O.A. Reutov, J. Organomet. Chem., 182 (1979) 537.
2 V.I. Sokolov, L.L. Troitskaya and O.A. Reutov, J. Organomet. Chem., 202 (1980) 58.
3 V.I. Sokolov, L.L. Troitskaya and N.S. Khrushchova, J. Organomet. Chem., 250 (1983) 439.
4 T. Hayashi, M. Tajika, K. Tamao and M. Kumada, J. Am. Chem. Soc., 98 (1976) 3718.
5 E. Baer and H.O.L. Fischer, J. Am. Chem. Soc., 67 (1945) 2031.
6 G. Hirth, H. Saroka, W. Bannwarth and R. Barner, Helv. Chim. Acta, 66 (1983) 1210.
7 T. Mukaiyama, Y. Tanabe and M. Shimizu, Chem. Letters, (1984) 401

* Sometimes hydrogenation is accompanied by considerable racemisation of the product.