SHORT COMMUNICATION

FACILE ENANTIOSELECTIVE PALLADIUM CATALYSED TRANSFER HYDROGENATION OF α-METHYLCINNAMIC ACID IN THE PRESENCE OF OPTICAL PURE ORGANIC ACIDS

Reginah N. Bwire, Runner R. T. Majinda and Ishmael B. Masesane[*]

Chemistry Department, University of Botswana, P/Bag UB00704, Gaborone, Botswana

ABSTRACT. An efficient and enantioselective method for catalytic transfer hydrogenation of the C=C double bond of α-methylcinnamic acid with the aid of chiral organic acids as the hydrogen donors and palladium(II) chloride as the catalyst is reported. Enantiomeric excess was assayed using optical rotation measurements. The best stereoselectivity was achieved when L-(+)-tartaric acid was used as the hydrogen donor and acetonitrile as the solvent.

KEYWORDS: Enantioselective, Chiral, α-Methylcinnamic acid, Transfer hydrogenation, Palladium(II) chloride

INTRODUCTION

Asymmetric metal catalysis has emerged in the last decade as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Asymmetric transition metal catalysed hydrogenation reactions in particular have featured prominently in last fifteen years and it was not surprising that in 2001 the Royal Swedish Academy of Sciences awarded the Nobel Price of Chemistry to William S. Knowles and Ryori Noyori for their development of chirally catalysed hydrogenation reactions together with Barry K. Sharpless for his work on asymmetric oxidation reactions [1]. The widely studied reducing agent in asymmetric metal catalysis is hydrogen and due to the safety issues associated with compressed gases there is need to extend this work to other reducing agents. A promising alternative method which avoids some of the technical and safety concerns associated with using compressed hydrogen gas is catalytic transfer hydrogenation [2].

In connection with a project exploiting the use of palladium as a catalyst in organic synthesis, we have explored the palladium catalysed reduction of alkenes in the presence of zinc powder and various achiral organic acids [3]. In this paper we report the results of the study of the palladium catalysed transfer hydrogenation of α-methylcinnamic acid **1** in the presence of zinc powder and optical pure organic acids.

RESULT AND DISCUSSION

We have early proposed that the catalytic cycle of the palladium catalysed transfer hydrogenation involved reduction of Pd(II) to Pd(0) by the zinc powder followed by oxidative addition of the organic acid to the palladium to give a Pd(II) hydride species which acts as the reducing agent [3]. Consequently, the use of an optical pure organic acid would give a chiral Pd(II) hydride species which would potentially make the reduction reaction favour either enantiomer **2** or **3**, Figure 1.

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*Corresponding author. E-mail: masesane@mopipi.ub.bw

The results for the palladium-catalysed reduction of the pro-chiral alkene α-methylcinnamic acid **1** in the presence of chiral acids and different solvents are summarized in Table 1. When a solution of the test substrate **1** was treated with catalytic amount of $PdCl_2$, zinc powder and L-(+)-mandelic acid and stirred for 16 h under a nitrogen atmosphere, a reduction reaction with a percentage conversion of 79% was observed [4]. Analysis of the reduced product using optical rotation measurements showed 98% ee in favour of enantiomer **2**, Table 1, entry 1. The absolute configuration of the products **2** and **3** were determined by comparison of the specific rotation with reported values [4]. The fact that reduction occurred with good enantioselectivity suggested that indeed the reaction proceeded through oxidative addition of the chiral acid to the palladium to generate in *situ* a chiral palladium hydride catalyst [5-7]. When an achiral acid such as acetic acid is uses as the hydrogen donor, no enantioselectivity was observed, entry 6.
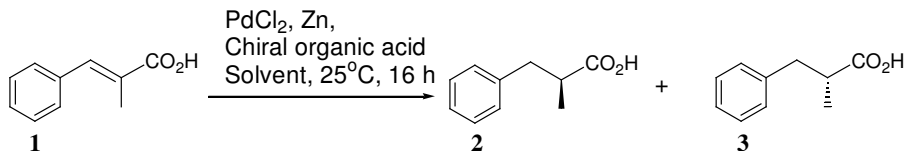

Figure 1. Palladium-catalysed reduction of the pro-chiral alkene α-methylcinnamic acid **1**.

Table 1. Asymmetric reduction of **1** catalysed by palladium.

Entry	Solvent	Acid	Conversion (%)	Yield (%)	$[\alpha]_D$ (C, 1; $CHCl_3$)	ee (%)
1	CH_3CN	L(+)-Mandelic acid	79	42	+28.5	98
2	CH_3CN/H_2O (9:1)	L (+)-Mandelic acid	75	32	+18.3	63
3	EtOH	L (+)-Mandelic acid	80	94	+11.0	37
4	MeOH	L (+)-Mandelic acid	46	88	+16.0	55
5	Toluene	L (+)-Mandelic acid	76	86	+20.0	69
6	CH_3CN	CH_3CO_2H	24	83	0.0	0
7	CH_3CN	L(+)Tartaric acid	100	71	+29.0	>99
8	CH_3CN/H_2O (9:1)	L(+)Tartaric acid	100	47	+2.0	0
9	MeOH	L(+)Tartaric acid	45	80	+10.7	37
11	CH_3CN	Proline	70	96	+2.0	9
12	EtOH	Proline	38	72	+2.0	9

Literature optical rotation measurement for (+)-2-methyl-3-phenylpropanoic acid $[\alpha]_D$ +25.9 (c, 1 $CHCl_3$) [4]. Optical rotation measurement for commercial (+)-2-methyl-3-phenylpropanoic acid $[\alpha]_D$ +29.0 (c,1; $CHCl_3$).

In an effort to extend the utility of this method to reduction of α,β-unsaturated acid with poor solubility in CH_3CN, we investigated the effect of different solvents on the percentage conversion and enantioselectivity. When the reaction was carried out in protic solvents, such as 10% H_2O in CH_3CN, EtOH and MeOH, moderate (46 %, entry 4) to good (80 %, entry 3) conversions were achieved with moderate (63 %, entry 2) to poor (37 %, entry 3) enantioselectivity. A relative non-polar solvent toluene gave good conversion (76%) and moderate ee (69 %, entry 5).

This study was then extended to other chiral organic acids hydrogen donors. Gratifyingly, when the test substrate **1** was subjected to the reduction conditions described above with L-(+)-tartaric acid as the hydrogen donor and CH_3CN as the solvent, a highly enantioselective reaction (over 99 % ee) was observed with a conversion of 100 %, entry 7. It is instructive to discuss the success of this reaction further. When a monoacid was used as a hydrogen donor, the last step in the catalytic cycle of this reaction was thought to involve a proton transfer from another molecule of the acid to the reduced product [3]. L-(+)-Tartaric acid has two acid groups, consequently the proton transfer step in the mechanism of the reaction would be an intramolecular reaction. This lowers the entropy of the reaction and is responsible for the high percentage conversion and probable for the enantiospecificity. Enantioselectivity was again poor when protic solvents were used, entries 8 and 9. Selectivity was also poor when L-proline was used as the hydrogen donor, entries 11 and 12.

We have described a simple palladium catalysed transfer hydrogenation method for α,β-unsaturated organic acids. Future work will undoubtedly be aimed not only at reducing other unsaturated organic acids but also studying the chemoselectivity of this reaction.

EXPERIMENTAL

Typical procedure for the transfer hydrogenation reaction. To a solution of α-methylcinnamic acid (250 mg, 1.54 mmol) in acetonitrile (10 mL) was added an L-(+)-mandelic acid (700 mg, 4.62 mmol), $PdCl_2$ (30 mg, 0.15 mmol) and zinc powder (300 mg, 4.62 mmol). The reaction mixture was stirred for 16 h at room temperature under nitrogen gas. The mixture was then filtered and the filtrate concentrated under reduced pressure to give the product. The product was then purified using column chromatography [stationary phase: silica gel (0.0040-0.063 mm)] eluting with 7:3 mixture of petroleum ether:ethyl acetate to give 2-methyl-3-phenylpropanoic acid as a yellow oil (80 mg, 42%); v_{max} (KBr): 3027-3000 *br*, 1688, 1415 cm^{-1}; δ_H (CDCl$_3$); 1.27 (3H, *d*, J = 6.6 Hz, CH$_3$), 2.97 (1H, *m*, H-3), 2.88 (1H, t, J = 6.3 Hz, H-4), 3.20 (1H, *dd*, J = 6.3, 13.2 Hz, H-4) and 7.39 (5H, *m*, phenyl H).

Three specific rotation measurements were taken using an Autopol IV Automatic Polarimeter at 22 °C for each sample and the average of the three was recorded. Percentage enantiomeric excess (ee) was calculated by dividing the specific rotation of sample by that of commercial (+)-2-phenyl-3-phenylpropanoic acid. Percentage conversions were calculated from ^{1}H NMR spectra of the crude products.

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