

## Poly-L-leucine as an Added Chiral Ligand for the Palladium catalysed Carbonylation of Allylic Alcohols

Howard Alper\* and Nathalie Hamel

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

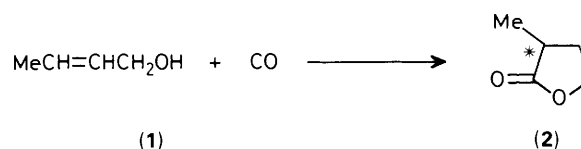
Treatment of but-2-en-1-ol with carbon monoxide, oxygen, copper(II) chloride, and hydrochloric acid in tetrahydrofuran containing palladium chloride and poly-L-leucine affords (*R*)- $\alpha$ -methyl- $\gamma$ -butyrolactone in 61% enantiomeric excess; (*L*)-diethyl tartrate and (*R*)- and (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) can also produce the optically active lactone, but in lower optical purity.

In 1985, one of us described an exceptionally mild method for the carbonylation of allylic alcohols to  $\gamma$ -butyrolactones. The reaction is catalysed by palladium chloride, and is effected in the presence of oxygen, copper(II) chloride, and hydrochloric acid.<sup>1</sup> There is considerable interest in synthesizing optically active lactones (*e.g.* by enzymatic resolution of 4-substituted- $\gamma$ -lactones).<sup>2</sup> One may anticipate that, since the unsaturated group of the allylic alcohol is prochiral, repetition of the carbonylation reaction in the presence of appropriate chiral ligands may lead to the formation of optically active lactones. We now wish to report the realization of this goal by the use of several different classes of chiral ligands including polyamino acids.

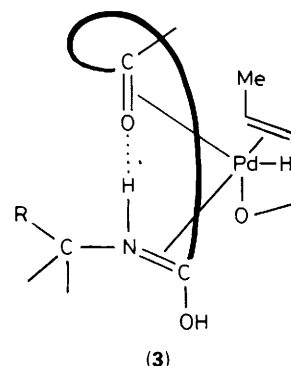
Studies were undertaken using but-2-en-1-ol (**1**) as the substrate, the reaction conditions being very similar to those previously described [except for the added chiral ligand (*L*\*)].<sup>1†</sup> This reaction, shown in Scheme 1, afforded

† Carbon monoxide was bubbled through a solution containing tetrahydrofuran (THF) (30 ml) and PdCl<sub>2</sub> (0.14 g, 0.78 mmol). Concentrated hydrochloric acid (0.5 ml) was added, the mixture was stirred until PdCl<sub>2</sub> dissolved, CuCl<sub>2</sub> (0.10 g, 1.56 mmol) was then added followed by bubbling of oxygen through the mixture. The solution was stirred until homogeneous (approximately 10 min), the chiral ligand was added (see Table 1 for proportions) followed 10 min later by 0.56 g (7.8 mmol) of but-2-en-1-ol. The reaction mixture was stirred for 18 h at room temp. and atmospheric pressure. The solvent was concentrated by rotary evaporation, and the resulting oil was extracted with hexane (3 × 30 ml). The combined hexane extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. Silica-gel thin-layer chromatography with 3 : 1 hexane-ether as developer gave pure (**2**).

$\alpha$ -methyl- $\gamma$ -butyrolactone (**2**) in 26–75% yield and 4–61% enantiomeric excess (*e.e.*) depending on the nature of the ligand (Table 1). The % *e.e.* was calculated by NMR spectroscopy using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium(III) [Eu(hfc)<sub>3</sub>] as the shift reagent.<sup>3</sup> The configuration was determined by optical rotation measurements.<sup>4</sup>



**Scheme 1.** Reagents and conditions: O<sub>2</sub>, PdCl<sub>2</sub>, CuCl<sub>2</sub>, L\*, HCl, THF, room temp., 1 atm.



**Table 1.** Asymmetric carbonylation and cyclization of (1) to (2).

Chiral agent	Ratio of (1)/L*/PdCl <sub>2</sub>	Yield of (2) <sup>a</sup> /%	% E.e. <sup>b</sup>	Configuration
D-Menthol	10/1.3/1.0	75	21	R
(R)-1,1'-Bi-2-naphthol	10/0.4/1.0	40	27	R
L-DET	10/3.8/1.0	52	51	R
D-DET	10/3.8/1.0	59	45	S
(-)-DMBT	10/1.0/1.0	69	33	R
(S,S)-CHIRAPHOS	10/0.46/1.0	45	21	R
(S)-BINAP	10/0.4/1.0	26	40	S
(R)-BINAP	10/1.9/1.0	31	36	R
Poly-L-leucine	50 mg L*	49	61	R
Poly-D-alanine	50 mg L*	32	8	S

<sup>a</sup> Isolated yield. <sup>b</sup> NMR determination with Eu(hfc)<sub>3</sub>.

While the yield of lactone was highest using the monodentate oxygen ligand, D-menthol, the degree of enantiomeric excess was modest. Of the bidentate oxygen ligands used [(R)-1,1'-bi-2-naphthol, L- and D-diethyl tartrate, (-)-dimethyl-2,3-0-benzylidene-L-tartrate {(–)-DMBT}], (L)-diethyl tartrate<sup>5</sup> was the most useful, affording (R)-(2) in 51% e.e. The phosphorus ligands, (S)- and (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [BINAP],<sup>5</sup> gave the lactone in 36–40% e.e., and the chemical yield of (2) was inferior to the case when (L)-diethyl tartrate was the chiral ligand.

The best results were obtained with the polyamino acid, poly-L-leucine.<sup>6</sup> Addition of 50 mg of poly-L-leucine [*M* ~21 700; DP = 192] to the reaction mixture gives (R)-(2) in 61% e.e. Increasing the reaction temperature is detrimental, as (R)-(2) was formed in only 11% e.e. when the reaction was repeated at 50 °C. It is known that poly-α-amino acids become denatured at elevated temperatures.<sup>7</sup> Low molecular weight polymers are of little use [*e.g.* poly-D-alanine (*M* 4 000) gives (S)-(2) in only 8% e.e.].

It is conceivable that the chiral discrimination step in the asymmetric induction process with poly-L-leucine is the intramolecular addition of palladium hydride to the co-ordinated double bond of the five-co-ordinate palladium(II) complex (3), to give a metalloxacyclopentane [carbonyl insertion followed by reductive elimination would give (2)]. It is assumed that the α-helical polyamino acid is bound to palladium as a bidentate ligand (diethyl tartrate would also complex to the metal in a bidentate fashion). It is also possible

that the secondary structure of the polyamino acid may play an important role in promoting asymmetric induction.<sup>6,8</sup>

In conclusion, use of diethyl tartrate or poly-L-leucine as the chiral ligand results in the synthesis of optically active lactones in good enantiomeric excess. Furthermore this is, to our knowledge, the first example of the use of poly-α-amino acids as added chiral ligands in homogeneous catalysis.

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