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# Chiral Pd organometallic complexes as catalysts in cyclopropanation reactions

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**Abstract**

Asymmetric cyclopropanation of styrene with diazoacetic esters is performed firstly using chiral amino acidato complexes of Pd(II) containing a C,N-cyclometallated group as an ancillary ligand as catalyst precursors. In general these catalytic systems provide good conversion to the corresponding cyclopropyl derivatives with a moderate *trans* selectivity, although the stereoselectivities obtained were low. With the use of chiral catalysts and chiral diazoacetic esters the diastereoselectivities were slightly improved.

*Keywords*: Asymmetric reactions; Cyclopropanation; Palladium

## 1. Introduction

The use of organotransition metal complexes as intermediates or catalysts in organic synthesis is a research field of recent interest which is undergoing rapid development, the success of these metal-mediated organic syntheses being mainly due to the unique ability of the metal to activate ligands to which it is directly bound [1]. A known example is the cyclopropanation of alkenes with diazoalkanes employing a transition metal as a catalyst. This reaction has wide application in the preparation of cyclopropanes which are of great interest in organic chemistry due to their frequent occurrence in biologically active compounds and their use as valuable synthetic intermediates [2]. However, as often in the preparation of biological materials, only one of the resulting isomers has high biological activity and work must be directed to selective formation of this isomer. Asymmetric cyclopropanation is important in this context and different chiral catalysts (Co, Cu, Rh, Ru, ...) have been used [3].

Organopalladium complexes are also known to be efficient catalysts in metal-mediated organic synthesis [4](a,b) but their use in cyclopropanation reactions has been scarcely treated [4](a,c). Moreover, the presence of chiral ligands bonded to palladium centres does not seem to promote appreciable enantioselective reactions [4](d). In our current research work we are interested in the synthesis and reactivity of chiral palladium complexes and we have recently reported [5] the syn-

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thesis of new chiral aminoacidato derivatives of Pd (II) which contain a C,N-cyclometallated group as an ancillary ligand. In this paper we report their use as catalysts in a model cyclopropanation reaction as well as a comparison of their catalytic properties with other related cationic and neutral palladium complexes.

## 2. Experimental

### 2.1. General methods

Solvents were distilled and deoxygenated before use. The C, H, N, analyses were carried out using a Perkin Elmer 2400 CHNS microanalyzer. IR spectra (4000–200 $cm^{-1}$) were recorded on a Perkin Elmer 883 infrared spectrophotometer in Nujol mulls between polyethylene plates. $^1H$ and $^{13}C\{^1H\}$ NMR spectra were recorded on Varian Unity-300 and on Bruker ARX-300 spectrometers at 300.13 MHz and 75.47 MHz respectively in $CDCl_3$ or DMSO-$d_6$ using the solvent signal as internal standard. Optical rotations were measured at the sodium-D line (589 nm) on the specific solutions in a 1-dm cell at 20°C with a Perkin Elmer Model 241 C polarimeter. Gas chromatography analysis was performed using a Hewlett-Packard 5890 II with a flame ionisation detector in a cross-linked methylsilicone column (25 m × 0.2 mm × 0.3 μm). High performance liquid chromatography analysis was performed with a Waters 600-E chromatograph equipped with a photodiode array detector in a chiral column derived from the 3,5-dimethylcarbamate of cellulose fixed on silica gel (15 cm × 0.46 cm ø).

The complexes $[Pd(dmba)(NCCH_3)_2]ClO_4$ (**1**) [6](a), [Pd(dmba)(acac)] (**2**) and [Pd(*S*-dmphea)(acac)] (**3**) [6](b) [dmba = *N*,*N*-dimethylbenzylamine-$C^2$,N; *S*-dmphea = *N*,*N*-dimethyl-(*S*-α-phenylethyl)-amine-$C^2$,N; acac = acetylacetonate-*O*,*O'*] were prepared by a slight modification of the previously described procedure. The aminoacidate catalysts (**4a–d**) (**5a–d**) (see Scheme 3) were synthesized as previously reported [5].

### 2.2. General procedure for cyclopropanation with diazoacetates

A solution of ethyl diazoacetate in dichloromethane was added dropwise over a period of 30 min to a solution of the catalyst precursor, styrene and n-decane in dichloromethane. The reaction was carried out at room temperature with magnetic stirring. After 24 h, the products were isolated by filtration of the reaction mixture through a Celite pad and evaporation of the solvent under reduced pressure. The percentage of conversion and *cis*/*trans* selectivity were determined by GLC using n-decane as internal standard. Enantiomeric excess was measured by chiral HPLC.

### 2.3. Measurement of cis/trans selectivity

*Cis*/*trans* selectivity in the reaction between ethyl diazoacetate or menthyl diazoacetate and styrene was determined by GLC on a cross linked methylsilicone column (25 m × 0.2 mm 0.3 μm) using helium as carrier gas (18 psi). The injector temperature was 230°C and the detector temperature was 250°C. For ethyl esters the gas chromatography experiment was run using the following oven programme: 70°C (3 min)—15°C/min—190°C (15 min) and under these conditions we observed the following retention times: ethyl diazoacetate 3.7 min, styrene 4.4 min, decane 6.3 min, *cis*-ethyl cyclopropancarboxylate 11.2 min and *trans*-ethyl cyclopropancarboxylate 11.8 min. For menthyl esters the gas chromatography experiment was run using the following oven programme: 100°C (3 min)—4°C/min—200°C (30 min) and under these conditions we observed the following retention times: styrene 3.3 min, decane 4.9 min, (+) or (−) menthyl diazoacetate 22 min, (1*R*,2*S*) (+) menthyl cyclopropancarboxylate or (1*S*,2*R*) (−) menthyl cyclopropancarboxylate 38.9 min, (1*S*,2*R*) (+) menthyl cyclopropancarboxylate or (1*R*,2*S*) (−) menthyl cyclopropancarboxylate 39.50 min, (1*S*,2*S*) (+) menthyl cyclopropancarboxylate or (1*R*,2*R*) (−) menthyl cyclopropancarboxylate 42.1 min and (1*R*,2*R*) (+) menthyl cyclopropan-

carboxylate or (1*S*,2*S*)(−) menthyl cyclopropancarboxylate 43.1 min.

### 2.4. Measurement of enantiomeric excess

Enantioselectivity in the reaction between ethyl diazoacetate and styrene was determined by HPLC with a recently developed chiral column derived from the 3,5-dimethylphenylcarbamate of cellulose fixed on a silica gel matrix [7] (15 cm×0.46 cm ø) using isopropanol/hexane (0.001%) as eluent with a flow rate of 3.5 ml/min. Detection was done at 220 nm with a photodiode array detector. In these conditions we observed the following retention times: (1*S*,2*S*) ethyl cyclopropancarboxylate 7.3 min, (1*R*,2*R*) ethyl cyclopropancarboxylate 8.4 min, (1*R*,2*S*) and (1*S*,2*R*)ethyl cyclopropancarboxylate 11.5 min.

### 2.5. Measurement of diastereomeric excess

Diastereoselectivity in the reaction between menthyl diazoacetate and styrene was determined by GLC under the above described conditions by integration of the diastereoisomer signals.

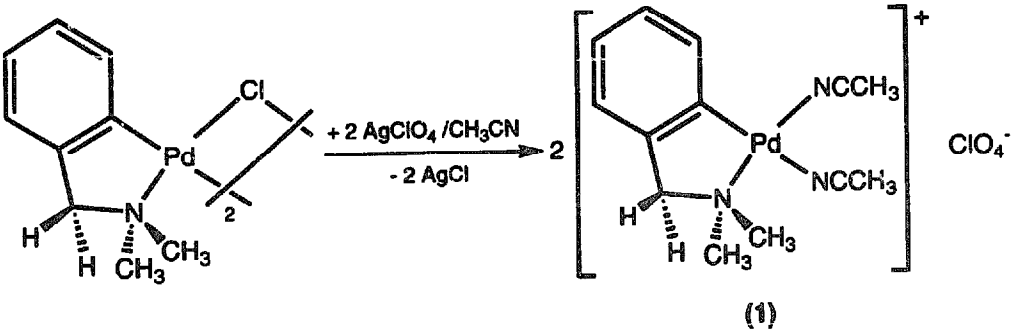
### 2.6. Determination of absolute configuration

To determine the absolute configuration of the major *trans* compound in the reaction between ethyl diazoacetate and styrene the crude product is filtered through silica gel to remove styrene and decane and afterwards eluted on a silica gel column to isolate the major *trans* compound. Measurement of the optical rotation of the *trans* mixture and comparison of its sign with the literature data [8,9] for (1*R*, 2*R*) methyl cyclopropancarboxylate allowed us to state that this was the absolute configuration for the major *trans* compound.

## 3. Results and discussion

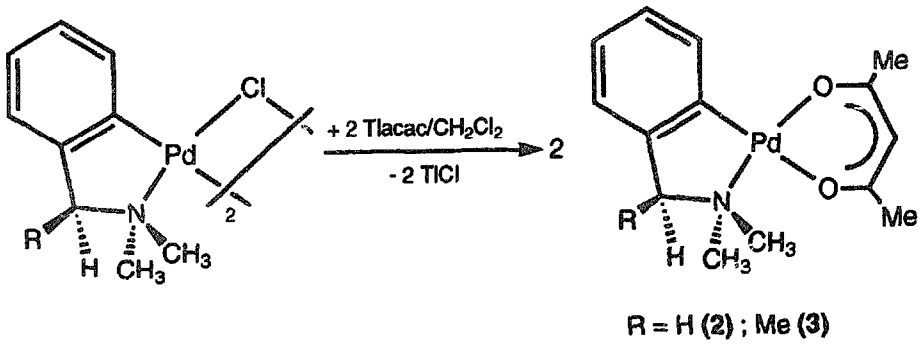
### 3.1. Synthesis of the precursors and of the amino acidato complexes of Pd(II) containing a C,N-cyclometallated group as an ancillary ligand

The cationic complex [Pd(dmba)($NCCH_3$)$_2$]($ClO_4$) (**1**) was synthesized by reaction of the chlorine bridged [Pd(μ-Cl)(dmba)]$_2$ with a stoichiometric amount of $AgClO_4$ in acetonitrile [6](a). After removal of the precipitated AgCl, solvent evaporation and $Et_2O$ addition, complex (**1**) was obtained as a white solid (see Scheme 1). The acetylacetonato complexes [Pd(dmba)(acac)] (**2**) and [Pd(*S*-dmphea)(acac)] (**3**) were obtained by reaction of the corresponding chlorine-bridged derivatives with Tl(acac) (see Scheme 2) following the procedure described in [6](b). The aminoacidato complexes [Pd(dmba)(Aa)] (**4a–d**) and [Pd(*S*-dmphea)(Aa)] (**5a–d**) (Aa = aminoacidate) were prepared by reaction of the acetylacetonato complexes (**2**) and (**3**) with the corresponding amino acid (see Scheme 3) by a previously reported procedure [5].

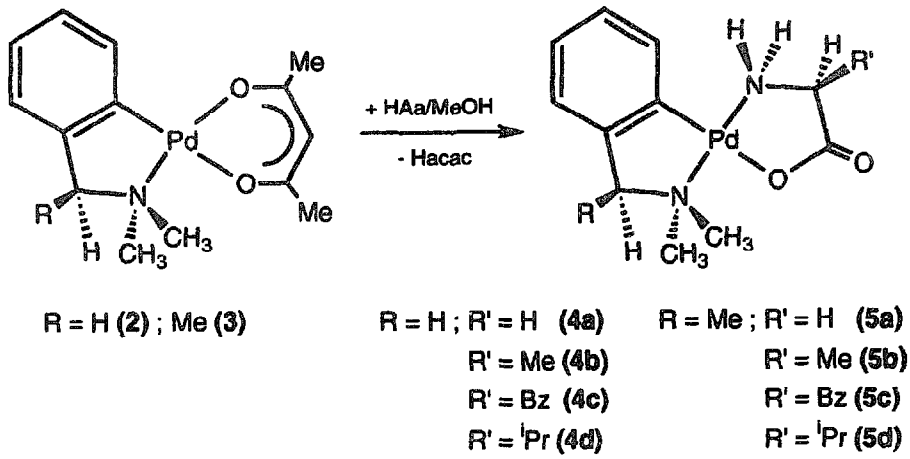



(1)

Scheme 1.




Scheme 2.




Scheme 3.

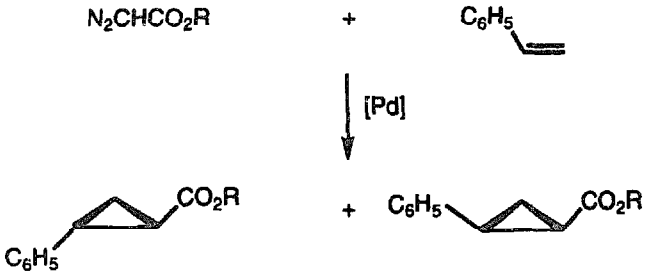
Table 1
Cyclopropanation reaction between ethyl diazoacetate and styrene catalysed by palladium complexes [a]

| Catalyst | Yield (%) [b] | *trans*/*cis* | % ee [c] (*trans*) | Configuration [d] |
|---|---|---|---|---|
| (1) | 60 | 1.80 | – | – |
| (2) | 55 | 1.85 | – | – |
| (4a) | 52 | 1.88 | – | – |
| (3) | 63 | 1.87 | 4 | 1*R*,2*R* |
| (5a) | 60 | 1.90 | 6 | 1*R*,2*R* |
| (4b) | 47 | 1.89 | 6 | 1*R*,2*R* |
| (4c) | 32 | 1.86 | 4 | 1*R*,2*R* |
| (4d) | 50 | 1.87 | 8 | 1*R*,2*R* |
| (5b) | 49 | 1.86 | 4 | 1*R*,2*R* |
| (5c) | 56 | 1.87 | 3 | 1*R*,2*R* |
| (5d) | 49 | 1.88 | 8 | 1*R*,2*R* |

[a] Reaction conditions: styrene (3 mmol), ethyl diazoacetate (1.5 mmol), palladium complex (0.05 mmol), methylene chloride (20 ml), room temperature, reaction time 24 h.
[b] Yield based on ethyl diazoacetate and determined by GLC with *n*-decane as internal standard.
[c] Measured by chiral HPLC.
[d] Absolute configuration of the major *trans* compound.

### 3.2. Catalytic cyclopropanation

The observed results in the cyclopropanation reaction between styrene and ethyl diazoacetate (see Eq. 1, R = ethyl and Table 1) are the following:




R = Ethyl, Menthyl

In the absence of the catalyst there is no reaction but in the presence of catalytic amounts of the achiral complexes [Pd(dmba) ($NCCH_3$)$_2$]

($ClO_4$) (**1**), [Pd(dmba) (acac)] (**2**) or {Pd(dmba) (gly)] (**4a**) up to 63% conversion can be obtained in 24 h at room temperature and with a styrene/catalyst ratio of 60/1. Better results were obtained working in refluxing methylene chloride allowing about 80% conversion as was tested for different cases. It is worth noting that deactivation of the catalyst does not occur since the addition of more reactant is possible, although the use of a large amount of catalyst does not improve the yield of the reaction. A slow addition of the diazocompound is recommended; otherwise the usual presence of dimerization products of the diazocompound (basically ethyl fumarate) is increased. In all cases the observed *trans/cis* ratio of the corresponding cyclopropane derivative is about 1.8, similar to that observed previously with other catalysts [3]. The cationic derivative (**1**) reacted faster than the neutral ones (**2**) or (**4a**) allowing a conversion of 60% in only 1 h. However, at the same time, an important increase in the formation of the dimerization products was observed so in this way the use of this type of catalyst does not seem recommendable.

From these results, it is clear that these compounds can be used as catalysts in the cyclopropanation reaction. In consequence, we should expect that the incorporation of a chiral ligand in the palladium catalyst would improve the enantioselective synthesis of the desired cyclopropyl derivatives, taking into account that the use of chiral catalysts in organic reactions is one of the most interesting tools in modern chemistry. Chiral compounds were prepared incorporating the chiral ligand either in the cyclometallated amine or in the amino acidate moiety. The first complexes using [Pd(*S*-dmphea)(acac)] (**3**) and [Pd(*S*-dmphea)(gly)] (**5a**) showed a similar behaviour to the achiral ones and a low enantioselectivity (about 5%) was observed. In all cases the major *trans* compound had a (1*R*,2*R*) configuration when (*S*)-phenylethyl amine was used.

Alternatively compounds with a chiral amino acidate ligand (**4b**), (**4c**) and (**4d**) were used. In these cases similar results (*trans/cis* ratios of 1.9 and enantioselectivities of about 10% for the *trans* isomers) were observed with again (1*R*,2*R*) being the configuration for the major *trans* stereoisomer when *S*-amino acids were used as ligands. These results were also independent of the nature of the amino acid despite employing different types of amino acids in order to study the influence of substituents with different steric requirements and the presence of a phenyl group since it has been reported that the enantioselectivity of a reaction can in some cases be increased when $\pi$-stacking interactions are present [10].

Taking into account that the direction of the asymmetric induction was the same when either (*S*)-phenylethyl amine or *S*-amino acids were used, we decided to use both chiral ligands in the same catalyst to improve the enantioselectivity of the reaction since, in some cases, it has been reported that a matched effect occurs for a pair of ligands working in the same direction when they are on the same molecule [11]. Thus ,compounds (**5b**), (**5c**) and (**5d**) were prepared and used as catalysts in the cyclopropanation reaction. However, unfortunately, no change was observed: similar rates, the same *trans/cis* ratio and, if a slight increase in the enantioselectivity occurred, it was in the error range for the apparatus and maintained the same configuration for the major *trans* enantiomer.

We also tried the achiral catalysts in a diastereoselective cyclopropanation reaction with the chiral auxiliary directly linked to one of the reagents, with the aim of improving the preceding results. In order to study the influence of the chirality of the reagent on the reaction rate and stereoselectivity we decided to use (+) or (−)menthyl diazoacetate as the chiral reagent (see Eq. 1, R = menthyl).

Both enantiomers were prepared and used with complexes (**1**) and (**2**) as catalyst precursors. The results (see Table 2) were quite similar to those previously obtained, the conversion was in the range 60–70% and the *trans/cis* ratio was about 2.3 in all cases. The stereoselectivity of the cyclopropanation was slightly better reaching up to 20% when complex (**2**) was used as catalyst precursor. When (+)-menthyl diazoacetate was

Table 2
Cyclopropanation reaction between (+) or (−)menthyl diazoacetate and styrene catalysed by palladium complexes [a]

| Catalyst | Menthol | Yield (%)[b] | *trans*/*cis* | % de[c] (*trans*) | Configuration[d] |
|---|---|---|---|---|---|
| (1) | (+) | 60 | 1.70 | 15 | 1*R*,2*R* |
| (1) | (−) | 77 | 1.71 | 16 | 1*S*,2*S* |
| (2) | (+) | 40 | 2.30 | 19 | 1*R*,2*R* |
| (4a) | (+) | 55 | 2.37 | 13 | 1*R*,2*R* |
| (3) | (+) | 60 | 2.33 | 20 | 1*R*,2*R* |
| (3) | (−) | 80 | 1.84 | 14 | 1*S*,2*S* |
| (4b) | (+) | 34 | 2.29 | 15 | 1*R*,2*R* |
| (5b) | (+) | 57 | 2.33 | 16 | 1*R*,2*R* |

[a] Reaction conditions: styrene (1.5 mmol), menthyl diazoacetate (0.3 mmol), palladium complex (0.015 mmol), methylene chloride (7 ml), room temperature, reaction time 24 h.
[b] Yield based on menthyl diazoacetate and determined by GLC with *n*-decane as internal standard.
[c] Measured by GLC.
[d] Absolute configuration of the cyclopropane ring of the major *trans* compound.

used as reagent the major *trans* compound had a (1*R*,2*R*) configuration on the cyclopropane ring, so we tried to combine the effects using catalysts (3), (4b) or (5b). In all cases the diastereoselectivity was again similar, showing that the menthyl frame (usually not a good auxiliary) is probably mainly responsible for the asymmetric induction.

## 4. Conclusions

We have shown that these new catalytic systems can be valuable in cyclopropanation reactions and although a high asymmetric induction cannot be obtained for the moment, the use of new chiral auxiliaries should allow an improvement in the diastereoselectivity of the reaction.

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