On the mechanism of the domino reaction of 2-methyl-2-benzyloxycarbonyl-1-indanone mediated by palladium, hydrogen and aminoalcohols

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Dedicated to Professor Jürgen Martens on the occasion of his 65th birthday

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Abstract

Whereas the Pd-catalyzed hydrogenolysis of racemic 2-methyl-2-benzyloxycarbonyl-1-indanone in the presence of an unichiral (enantiopure) aminoalcohol leads to optically active 2-methylindanone, such a domino reaction using optically active 2-methyl-2-benzyloxycarbonyl-1-indanone and an achiral aminoalcohol affords racemic 2-methylindanone. According to these results, the ketone is obtained from the aminoalcohol-mediated protonation of an enolic species.

Keywords: Palladocatalysis, organocatalysis, hydrogenolysis, decarboxylation, ammonium enolate

Introduction

The asymmetric protonation of prochiral enolic species is an attractive route to prepare optically active carbonyl compounds.¹⁻⁶ Over the past years, we contributed to this topic using various substrates and procedures.⁷ With 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE**) as the substrate, the procedure, studied in collaboration with Martens team,^{8,9} involves a Pd-catalyzed hydrogenolysis in the presence of an unichiral¹⁰ β -aminoalcohol (**AH***) (Scheme 1). In the present paper, we discuss the nature of the intermediate responsible of the enantioselection, and the result of the reaction occurring with optically active 2-methyl-2-benzyloxycarbonyl-1-indanone and an achiral β -aminoalcohol (**AH**).

Scheme 1

Results and Discussion

In 1994, we proposed that, from **KE**, the Pd/AH* procedure leads to optically active 2-methylindanone (**K***) via the asymmetric protonation of an enolic species.⁸ Subsequent studies using different substrates and procedures led us to conclude that the main enolic species involved in the enantioselection is the ammonium enolate **^AE*** (Scheme 2).⁷ This latter, which is formed from hydridopalladium β -ketocarboxylate **^{Pd}KC** or/and β -ketoacid **KA** through various pathways,⁷ affords **K*** via either an intramolecular proton transfer or an intermolecular reaction with a protic source, especially the aminoalcohol.

Scheme 2

In the absence of an aminoalcohol, we revealed that the Pd-catalyzed hydrogenolysis of such benzyl β -ketoesters affords the ketones via the successive formation of the corresponding β -ketoacids and enols.^{11,12} Interestingly, Baiker and co-workers showed that the reaction of such a β -ketoacid with AH* leads to the corresponding diastereomeric ammonium β -ketocarboxylates, and that their subsequent evolution towards the ketone proceeds at different rates.¹³ According to these authors, this evolution would implicate the protonation of the ammonium salts by a second molecule of AH*, which would occur from the side opposed to their carboxylate unit and simultaneously with the breaking of the C-CO₂ bond.¹³ They also assumed that the Pd/AH*-mediated domino reaction of a benzyl β -ketoester involves the corresponding β -ketoacid as the

only intermediate responsible of the enantioselection, and its transformation via their concerted mechanism proposal.¹³

We were not confident in this mechanism of the enantioselective reaction of benzyl β -ketoesters, which was based on computational studies from Strassner et al. on the enantioselective decarboxylation of a Naproxen intermediate.¹⁴ Moreover, Brunner and Baur have denied the Strassner proposal.¹⁵ To remove the ambiguity on the nature of the intermediate which suffers protonation, we studied the hydrogenolysis of optically active 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE**^{*}) using an achiral aminoalcohol (**AH**) as protonating species.¹⁶ Indeed, the above concerted mechanism would imply a chirality transfer through the protonation of ammonium β -ketocarboxylate ^A**KC**^{*} to afford **K**^{*} (Scheme 3, path *a*), while the formation of ammonium enolate ^A**E** as intermediate would lead to racemic 2-methylindanone (**K**) (Scheme 3, path *b*). ^A**E** could be obtained via various pathways, one of them being the decarboxylation of ^A**KC**^{*}.⁷

Scheme 3

The synthesis of **KE**^{*} was tentatively carried out via the corresponding chiral ketimines. Using the **TiCl**₄ procedure,¹⁷ we however observed that the two enantiomers of **KE** react with (*S*)- α -methylbenzylamine at different rates. Consequently, this kinetic resolution of **KE** has been used to prepare **KE**^{*}. With a substoichiometric amount of **TiCl**₄ in benzene at 0 °C, **KE**^{*} was isolated with 30% e.e. (Scheme 4).

Scheme 4

As unichiral β -aminoalcohols having a secondary amino group were used for the synthesis of **K*** from **KE**,^{8,9,18} the Pd-catalyzed hydrogenolysis of **KE*** was carried out with 2-(methylamino)ethanol as the protonating species. At room temperature under these conditions, **KE*** afforded 2-methylindanone in high yield but without optical activity (Scheme 5). This result highly contrasts with the formation, under similar conditions, of **K*** from the hydrogenolysis of **KE** in the presence of **AH*** (Scheme 1),^{8,9,18,19} and agrees with an enantioselection depending on the asymmetric protonation of the ammonium enolate (Scheme 3, path *b*). As the enantioselectivity obtained from **KE** using the Pd/**AH*** procedure depends on the experimental conditions,^{8,9,18,19} we have however to remember that competitive pathways, such as the reductive elimination of Pd^0 from hydridopalladium enolate $\text{Pd}^{\text{H}}\text{E}$ and the tautomerisation of enol **E**,^{7,18} can also lead to **K** (Scheme 6).

Scheme 5

Scheme 6

Conclusions

The protonation of an enolic species is involved in the formation of 2-methylindanone from the domino reaction initiated by the Pd-catalyzed hydrogenolysis of 2-methyl-2-benzyloxycarbonyl-1-indanone in the presence of a β -aminoalcohol. This species is best depicted as the ammonium enolate of 2-methylindanone.⁷ Consequently, when the aminoalcohol is unichiral, the enantioselection depends on the discrimination between the two faces of the corresponding chiral ammonium enolate.

Experimental Section

General. 5% Pd/C was from Engelhard Company Ref. 5011; this catalyst has a surface area of 1100 m²/g and contains 50% of water, the carbon type being activated wood (Technical information from Engelhard Company). Spectroscopic properties of **K**²⁰ and **KE**¹¹ have already been described. The enantioselectivities were determined by HPLC using chiral columns from Daicel, eluted with *n*-hexane/isopropanol (9:1), and UV detection at 254 nm.

Preparation of optically active 2-methyl-2-benzyloxycarbonyl-1-indanone (KE*). A 1 M solution of TiCl₄ (0.9 mmol) in CH₂Cl₂ was added to a solution, at 0 °C, of **KE**¹¹ (458 mg, 1.63 mmol) and (*S*)- α -methylbenzylamine (592 mg, 4.89 mmol) in benzene (10 mL). After stirring at 0 °C for 45 min, the mixture was concentrated under reduced pressure. Flash-chromatography of the residue, eluted with petroleum ether/ethyl acetate (98:2), led to **KE*** (183 mg). The enantiomeric excess (30%) was determined using a Chiralcel OD column (flow rate: 0.5 mL/min, retention times: 13.2 and 14.4 min).

Hydrogenolysis of optically active 2-methyl-2-benzyloxycarbonyl-1-indanone (KE*). To a solution, at room temperature, of **KE*** (30% e.e., 50 mg, 0.178 mmol) and 2-(methylamino)ethanol (4 mg, 0.053 mmol) in MeCN (4 mL) was added 5% Pd/C (20 mg). A slow stream of hydrogen was immediately bubbled into the stirred mixture. After 1 h, the solvent was evaporated under reduced pressure. Purification of the residue by flash-chromatography eluted with petroleum ether/ethyl acetate (9:1) afforded 2-methyl-1-indanone (24 mg), which was racemic according to its analysis using a Chiralcel OB-H column (flow rate: 0.7 mL/min, retention times: 13.3 and 19.4 min).

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