On the mechanism of the domino reaction of 2-methyl-2-benzylxoycarbonyl-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-benzylxoycarbonyl-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-benzylxoycarbonyl-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-benzylxoycarbonyl-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-benzylxoycarbonyl-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. 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). This latter, which is formed from hydridopalladium β-ketocarboxylate PDKC or/and β-ketoacid KA through various pathways, 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. 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. 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. 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.\textsuperscript{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.\textsuperscript{14} Moreover, Brunner and Baur have denied the Strassner proposal.\textsuperscript{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.\textsuperscript{16} Indeed, the above concerted mechanism would imply a chirality transfer through the protonation of ammonium β-ketocarboxylate \( ^{\Delta}KC* \) to afford K* (Scheme 3, path a), while the formation of ammonium enolate \( ^{\Delta}E \) as intermediate would lead to racemic 2-methylindanone (K) (Scheme 3, path b). \( ^{\Delta}E \) could be obtained via various pathways, one of them being the decarboxylation of \( ^{\Delta}KC* \).\textsuperscript{7}

\[ \text{Scheme 3} \]

The synthesis of KE* was tentatively carried out via the corresponding chiral ketimines. Using the TiCl\(_4\) procedure,\textsuperscript{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).

\[ \text{Scheme 4} \]
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 Pd0 from hydridopalladium enolate PdE and the tautomerisation of enol E,7,18 can also lead to K (Scheme 6).

![Scheme 5](image)

**Scheme 5**

![Scheme 6](image)

**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-benzyloxy carbonyl-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 K²⁰ and Kε¹¹ 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-benzyloxy carbonyl-1-indanone (KE*).** A 1 M solution of TiCl₄ (0.9 mmol) in CH₂Cl₂ was added to a solution, at 0 °C, of KE¹¹ (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-benzyloxy carbonyl-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).

**References**

3. Eames, J.; Weerasooriya, N. Tetrahedron: Asymmetry 2001, 12, 1-24. [http://dx.doi.org/10.1016/S0957-4166(00)00496-1](http://dx.doi.org/10.1016/S0957-4166(00)00496-1)
   [http://dx.doi.org/10.1016/j.tetasy.2014.02.017](http://dx.doi.org/10.1016/j.tetasy.2014.02.017)

   [http://dx.doi.org/10.1016/0957-4166(94)80173-8](http://dx.doi.org/10.1016/0957-4166(94)80173-8)

   [http://dx.doi.org/10.1016/S0957-4166(98)00189-X](http://dx.doi.org/10.1016/S0957-4166(98)00189-X)


   [http://dx.doi.org/10.1021/jo049464w](http://dx.doi.org/10.1021/jo049464w)

   [http://dx.doi.org/10.1039/c3nj00457k](http://dx.doi.org/10.1039/c3nj00457k)

   [http://dx.doi.org/10.1002/chem.200701652](http://dx.doi.org/10.1002/chem.200701652)

   [http://dx.doi.org/10.1002/1099-0690(200207)2002:14<2405::AID-EJOC2405>3.0.CO;2-1](http://dx.doi.org/10.1002/1099-0690(200207)2002:14<2405::AID-EJOC2405>3.0.CO;2-1)

   [http://dx.doi.org/10.1002/ejoc.200300206](http://dx.doi.org/10.1002/ejoc.200300206)

16. The absolute configuration of the used KE* has not been determined. Thus, the use of KE* with (S)-configuration in Scheme 3 is only to highlight the two plausible reactive pathways.

   [http://dx.doi.org/10.1021/jo01285a088](http://dx.doi.org/10.1021/jo01285a088)

   [http://dx.doi.org/10.1016/S0957-4166(97)84908-7](http://dx.doi.org/10.1016/S0957-4166(97)84908-7)

   [http://dx.doi.org/10.1016/j.tetasy.2007.11.017](http://dx.doi.org/10.1016/j.tetasy.2007.11.017)

   [http://dx.doi.org/10.1016/S0040-4020(01)86998-2](http://dx.doi.org/10.1016/S0040-4020(01)86998-2)