

# 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 65<sup>th</sup> birthday

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## Abstract

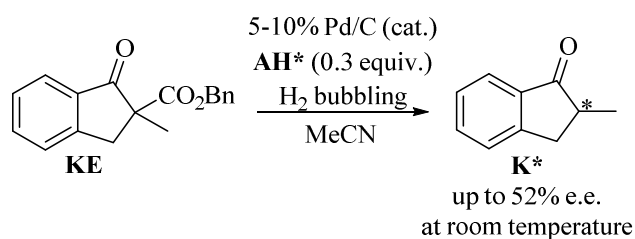
Whereas the Pd-catalyzed hydrogenolysis of racemic 2-methyl-2-benzyloxycarbonyl-1-indanone in the presence of an unichiral (enantiopure) aminoalcohol leads to optically active 2-methylindanone, such a domino reaction using optically active 2-methyl-2-benzyloxycarbonyl-1-indanone and an achiral aminoalcohol 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

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## Introduction

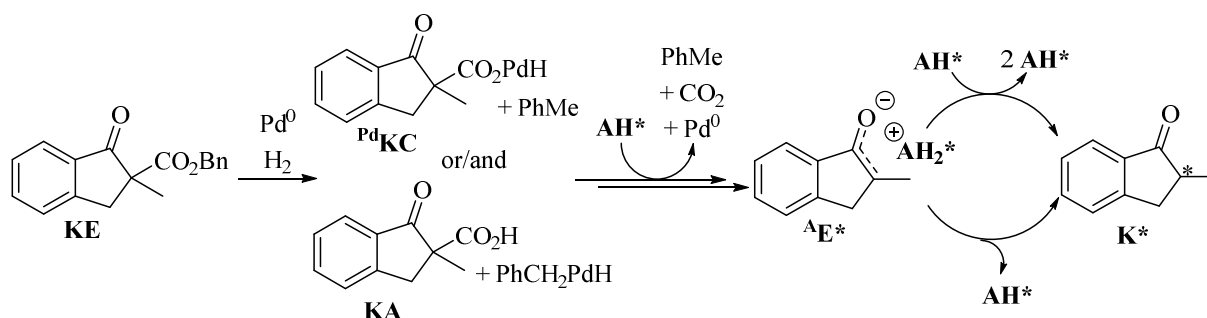
The asymmetric protonation of prochiral enolic species is an attractive route to prepare optically active carbonyl compounds.<sup>1-6</sup> Over the past years, we contributed to this topic using various substrates and procedures.<sup>7</sup> With 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE**) as the substrate, the procedure, studied in collaboration with Martens team,<sup>8,9</sup> involves a Pd-catalyzed hydrogenolysis in the presence of an unichiral<sup>10</sup>  $\beta$ -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  $\beta$ -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.<sup>8</sup> Subsequent studies using different substrates and procedures led us to conclude that the main enolic species involved in the enantioselection is the ammonium enolate <sup>A</sup>**E\*** (Scheme 2).<sup>7</sup> This latter, which is formed from hydridopalladium β-ketocarboxylate <sup>Pd</sup>**KC** or/and β-ketoacid **KA** through various pathways,<sup>7</sup> affords **K\*** via either an intramolecular proton transfer or an intermolecular reaction with a protic source, especially the aminoalcohol.

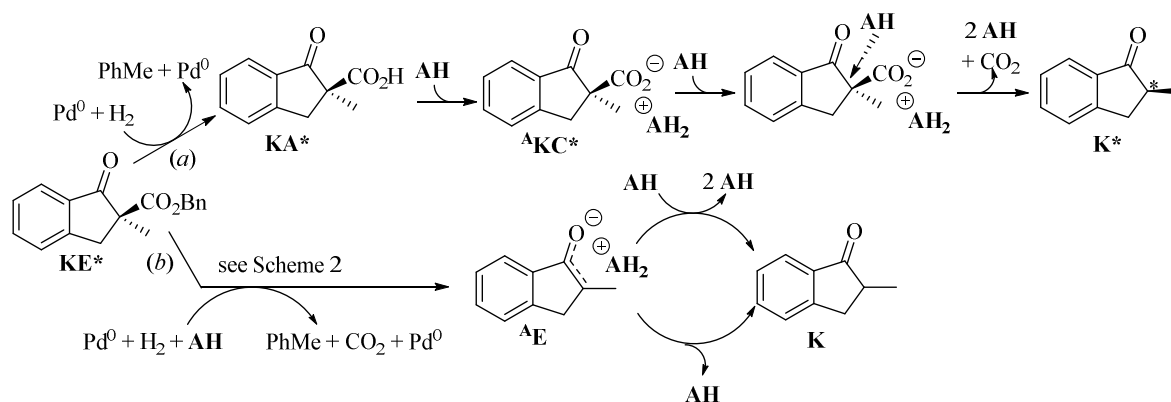


Scheme 2

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.<sup>11,12</sup> 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.<sup>13</sup> 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-CO<sub>2</sub> bond.<sup>13</sup> They also assumed that the Pd/**AH\***-mediated domino reaction of a benzyl β-ketoester involves the corresponding β-ketoacid as the

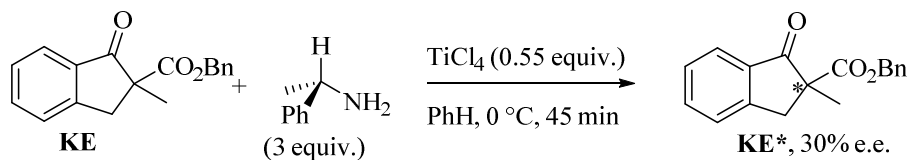
only intermediate responsible of the enantioselection, and its transformation via their concerted mechanism proposal.<sup>13</sup>

We were not confident in this mechanism of the enantioselective reaction of benzyl  $\beta$ -ketoesters, which was based on computational studies from Strassner et al. on the enantioselective decarboxylation of a Naproxen intermediate.<sup>14</sup> Moreover, Brunner and Baur have denied the Strassner proposal.<sup>15</sup> 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.<sup>16</sup> Indeed, the above concerted mechanism would imply a chirality transfer through the protonation of ammonium  $\beta$ -ketocarboxylate **<sup>A</sup>KC\*** to afford **K\*** (Scheme 3, path *a*), while the formation of ammonium enolate **<sup>A</sup>E** as intermediate would lead to racemic 2-methylindanone (**K**) (Scheme 3, path *b*). **<sup>A</sup>E** could be obtained via various pathways, one of them being the decarboxylation of **<sup>A</sup>KC\***.<sup>7</sup>



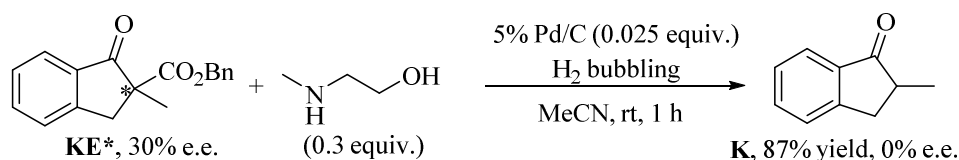
### Scheme 3

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

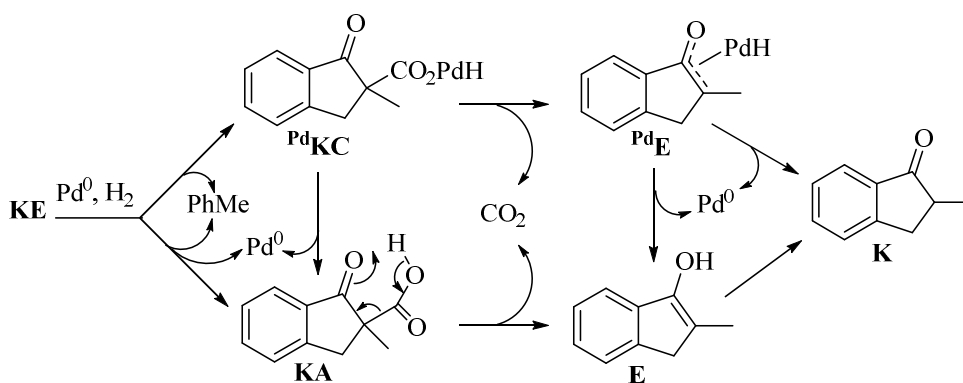


### Scheme 4

As unichiral  $\beta$ -aminoalcohols having a secondary amino group were used for the synthesis of  $\mathbf{K}^*$  from  $\mathbf{KE}$ ,<sup>8,9,18</sup> the Pd-catalyzed hydrogenolysis of  $\mathbf{KE}^*$  was carried out with 2-(methylamino)ethanol as the protonating species. At room temperature under these conditions,  $\mathbf{KE}^*$  afforded 2-methylindanone in high yield but without optical activity (Scheme 5). This result highly contrasts with the formation, under similar conditions, of  $\mathbf{K}^*$  from the hydrogenolysis of  $\mathbf{KE}$  in the presence of  $\mathbf{AH}^*$  (Scheme 1),<sup>8,9,18,19</sup> and agrees with an enantioselection depending on the asymmetric protonation of the ammonium enolate (Scheme 3, path *b*). As the enantioselectivity obtained from  $\mathbf{KE}$  using the Pd/ $\mathbf{AH}^*$  procedure depends on the experimental conditions,<sup>8,9,18,19</sup> we have however to remember that competitive pathways, such as the reductive elimination of  $\text{Pd}^0$  from hydridopalladium enolate  $\text{Pd}^{\text{d}}\mathbf{E}$  and the tautomerisation of enol  $\mathbf{E}$ ,<sup>7,18</sup> can also lead to  $\mathbf{K}$  (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  $\beta$ -aminoalcohol. This species is best depicted as the ammonium enolate of 2-methylindanone.<sup>7</sup> 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 m<sup>2</sup>/g and contains 50% of water, the carbon type being activated wood (Technical information from Engelhard Company). Spectroscopic properties of **K**<sup>20</sup> and **KE**<sup>11</sup> 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 TiCl<sub>4</sub> (0.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added to a solution, at 0 °C, of **KE**<sup>11</sup> (458 mg, 1.63 mmol) and (*S*)- $\alpha$ -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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