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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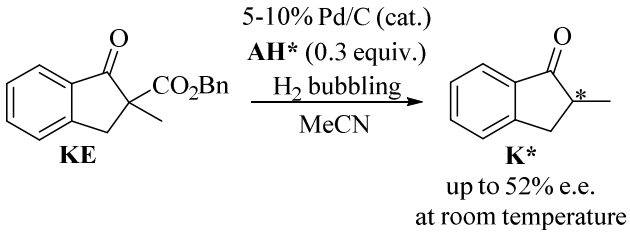
Abstract

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

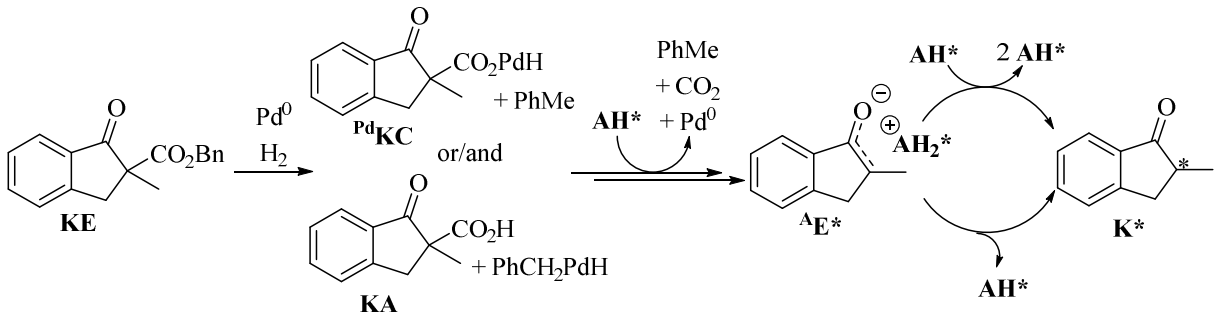
The asymmetric protonation of prochiral enolic species is an attractive route to prepare optically active carbonyl compounds.[1-6] Over the past years, we contributed to this topic using various substrates and procedures.[7] With 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE**) as the substrate, the procedure, studied in collaboration with Martens team,[8,9] involves a Pd-catalyzed hydrogenolysis in the presence of an unichiral[10] 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 ^{A}**E*** (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.

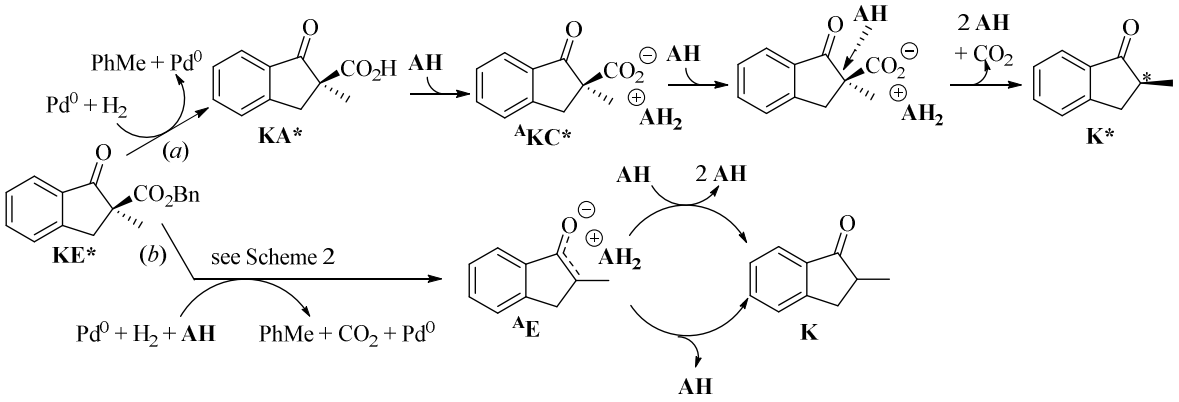


Scheme 2

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-CO_2 bond.[13] They also assumed that the Pd/**AH***-mediated domino reaction of a benzyl β-ketoester involves the corresponding β-ketoacid as the

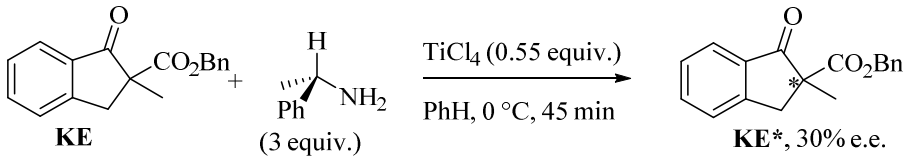
only intermediate responsible of the enantioselection, and its transformation via their concerted mechanism proposal.[13]

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]



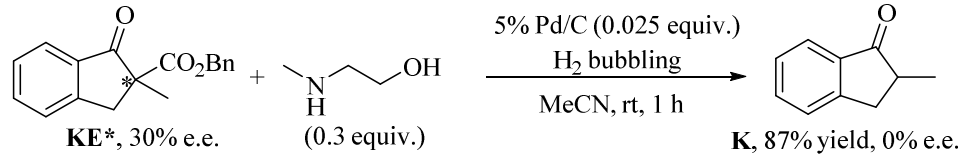
Scheme 3

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).

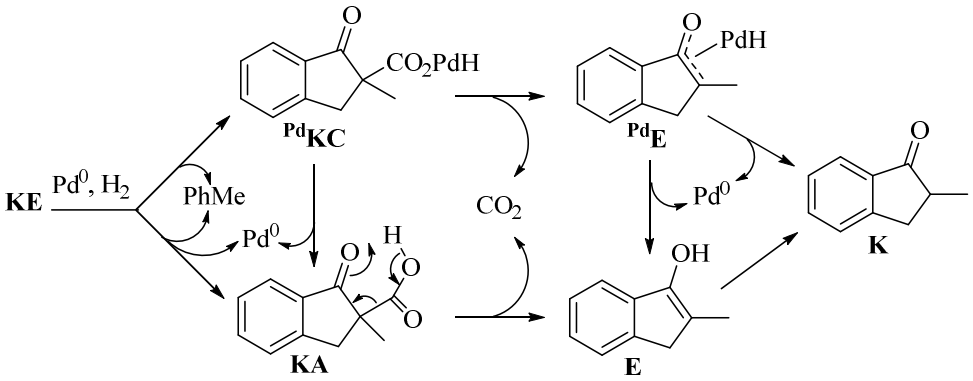


Scheme 4

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 ^{Pd}**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 m^2/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 $TiCl_4$ (0.9 mmol) in CH_2Cl_2 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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