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β-Amino tertiary cycloalkanols for the enantioselective protonation of enolic species produced by a palladium-induced cascade reaction

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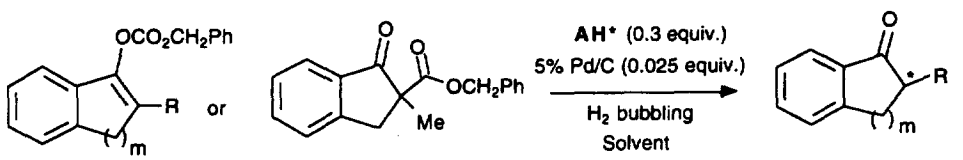
Abstract

The palladium-induced cleavage of β-ketoesters and enol carbonates derived from α-alkylated 1-indanones and 1-tetralones in the presence of substoichiometric amounts of various (*S*)-aminocycloalkanols led to optically active (*R*)-α-alkylated indanones and tetralones with enantiomeric excesses of up to 72%.

We have recently been studying the enantioselective protonation of prochiral enolic species produced from enol carbonates (**EC**) and β-ketoesters (**KE**) by palladium catalysis (Eq. 1).[1,2] This type of approach to the formation of optically active ketones (**K**) differs from the majority of work devoted to the enantioselective protonation of enolates.[3,4] Under our conditions, the enantioselectivity is induced by catalytic amounts of enantiopure β-aminoalcohols (**AH***'s) having amino and hydroxy groups directly bound to stereogenic centers. In other words, these **AH***'s have at least two stereogenic centers: C*–OH and C*–NHR. We have observed that the absolute configuration of **K** is dependent on the absolute configuration of C*–NHR but not on the stereochemistry of C*–OH.



(1)

EC 5*i*-Bu: m= 1, R= *i*-Bu
EC 5Me: m= 1, R= Me
EC 6Me: m= 2, R= Me

KE 5Me

K 5*i*-Bu: m= 1, R= *i*-Bu
K 5Me: m= 1, R= Me
K 6Me: m= 2, R= Me

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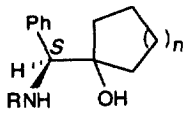
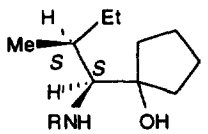
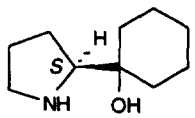
In work on other projects[5] we have prepared various β-aminocycloalkanols (**1–8**) having no chirality at the OH position but with an (*S*)-configuration of C*–NHR. Thus, it became desirable to examine the chirality induced by these **AH***'s. This has been carried out with **EC 5*i*-Bu**, **EC 5Me**, **EC 6Me** or **KE 5Me** as substrates.



1 : n= 1, R= H
2 : n= 1, R= Me
3 : n= 2, R= H



4 : R= H
5 : R= Me



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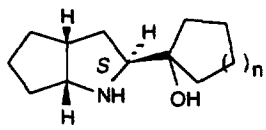

7 : n= 2
8 : n= 3

Since we recently observed that in using (+)-*endo*-2-hydroxy-*endo*-3-aminobornane as **AH***, the enantioselectivity (*e.e.*) was surprisingly increased when the reaction is carried out between 45 and 70°C rather than at room temperature,[2] most experiments were carried out in this temperature range. As exemplified in Table 1, the ketones were produced in good chemical yields.† Although the *e.e.*'s were extremely dependent on the structure of **AH***, the main enantiomer always had the (*R*)-configuration. The aminocycloalkanols **1–6** led to low *e.e.*'s; the comparison of the results obtained with **1** and **2**, and **4** and **5** showed that the *e.e.*'s were slightly better when the amino group was primary (runs 1 and 4) rather than secondary (runs 2 and 5). Nevertheless, the best *e.e.*'s were obtained with the use of **7** and **8** which have a secondary amino group, this being indeed part of a more strained bicyclic framework.

EC 5Me and **KE 5Me** led to the the same optically active ketone but even under similar experimental conditions (runs 8 and 9/19 and 13/21), the enantioselectivity of the process depended on the nature of the starting substrate. This confirms that the mechanistic scheme we previously proposed[1a,1b] was oversimplified.‡

A few runs showed that the reaction temperature influenced the *e.e.* (runs 8–12 and 19 and 20). Using **EC 5Me** and **7**, lowering the temperature from 58°C to 50°C increased the *e.e.* but this diminished with a further reduction of the temperature.

In conclusion, the present study has;

(i) exemplified the relationship between the configurations of **K** and C*–NHR;
(ii) shown that fair *e.e.*'s and the unusual increase of *e.e.*'s with temperature[2] can also been observed with β-aminocycloalkanols.

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This study was carried out in the framework of a PROCOPE program. We thank Engelhard and Hoechst AG Companies for repeated generous loans of Pd catalysts and fine chemicals respectively, S. Lanthony (Reims laboratory) for help with HPLC analysis, Dr. G. Bird (Zeneca Pharmaceuticals, Reims) for help with the manuscript.

† Following a referee's question, we have to point out that racemic **K 5Me** was also produced from **EC 5Me** and **KE 5Me** in the absence of **AH***.[6]

‡ These cascade reactions which involve deprotection, decarboxylation and enantioselective protonation, seem to depend on many limiting factors; see Ref.[2] for a partial rationalization.

Table 1
Cascade reaction of **EC 5*i*-Bu**, **EC 5Me**, **EC 6Me** and **KE 5Me**[a]

Run	Substrate	AH*	t°C	Time, min	Yield %	*e.e.* %	Conf.
1	**EC 5*i*-Bu**	**1**	55	20	71	11[b]	*R*[c,d]
2	"	**2**	"	25	90	6[b]	"
3	"	**3**	"	25	70	14[b]	"
4	"	**4**	"	"	77	18[b]	"
5	"	**5**	"	20	81	10[b]	"
6	"	**6**	"	25	60	10[b]	"
7	"	**7**	"	"	69	42[b]	"
8	**EC 5Me**	**7**	58	20	89	48[b]	*R*[c]
9	"	"	50	"	91	60[b]	"
10	"	"	42	"	84	52[b]	"
11	"	"	35	25	69	48[b]	
12	"	"	22	"	74	46[b]	"
13	"	**8**	55	20	79	48[c]	"
14[e]	**EC 6Me**	**1**	"	360	85	2[c]	"
15[e]	"	**4**	"	"	76	7[c]	"
16	"	**7**	70	14	58	56[c]	"
17	"	**8**	"	11	81	17[c]	"
18	**KE 5Me**	**6**	55	22	63	<3[b]	"
19	"	**7**	"	23	67	66[b]	"
20	"	"	22	130	72	9[b]	"
21	"	**8**	55	67	64	72[b]	"

[a]Reaction carried out in MeCN while bubbling hydrogen in the presence of 5% Pd/C (Ref.5011 from Engehard Company wasused for this work [1a,1b]) (0.025 equiv.) and **AH*** (0.3 equiv.). [b]Determined by HPLC using a Chiralcel OB-H column (*n*-hexane/*i*-PrOH 90:10, 0.5 ml/min.). [c]Determined by polarimetry comparisons.[7] [d]Determined by circular dichroism.[2] [e]CH_2Cl_2 was used as solvent.

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