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Production of Optically Active Ketones by a Palladium-Induced Cascade Reaction from Racemic β-Ketoesters.[#]

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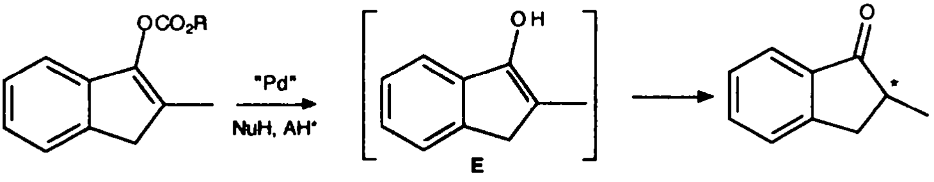
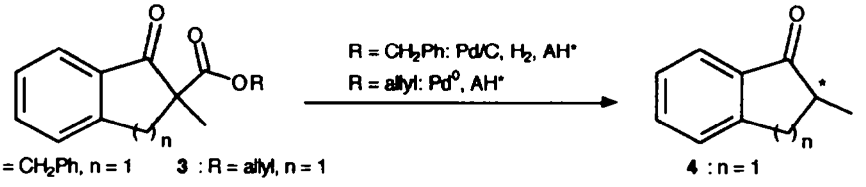
Abstract : 2-Methyl-1-indanone and 2-methyl-1-tetralone have been obtained with enantiomeric excesses of up to 52% from the corresponding benzyl and allyl β-ketoesters by a multistep reaction: palladium-catalyzed cleavage / decarboxylation / chiral aminoalcohol-mediated enantioselective protonation. The success of the process and particularly of the first step can be very dependent on the nature of the palladium catalyst used.

Recently, we have disclosed that the palladium-catalyzed cleavage of prochiral enol carbonates in a chiral medium could afford optically active ketones (Eq. 1).[1] It has been assumed that the asymmetric step was involved at the level of the tautomerization of the enol **E** catalyzed by the chiral protic species (AH*).[2] Despite the intensive research efforts currently devoted to the asymmetric protonation of enolates,[3] this work exhibited one of the rare examples of asymmetric protonation of a simple enol.[4,5] Therefore, it seemed to us that it was of interest to pursue research oriented towards new possibilities to access prochiral enols. We now report that a multistep reaction "cleavage / decarboxylation / enantioselective ketonisation" is produced from the β-ketoesters **1** to **3** in the presence of palladium and chiral aminoalcohols (Eq. 2).



(1)



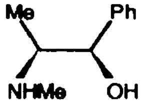
(2)

1 : R = CH_2Ph, n = 1 **3** : R = allyl, n = 1
2 : R = CH_2Ph, n = 2

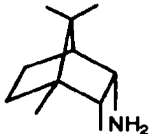
4 : n = 1
5 : n = 2

[#] Part of this work has been presented as poster at Europacat-1, Montpellier, September, 12-17, 1993.

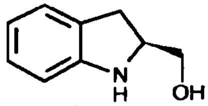
The palladium-catalyzed cleavage of allyl- and benzyl β-ketoesters to the corresponding ketones has been widely reported in the literature.[6] Therefore, we suspected that such procedures applied to the β-ketoesters **1** - **3** would afford the keto-compounds **4** and **5** under an optically active form when carried out in the presence of chiral protic sources. Our long experience in the asymmetric tautomerization of enols[1,2,7] led us to choose mainly β-aminoalcohols as chiral protic sources. The main results obtained in using **i-1** to **i-6** are reported in Tables 1 and 2.



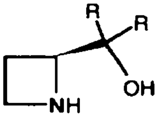
i-1



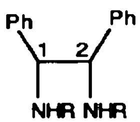
i-2



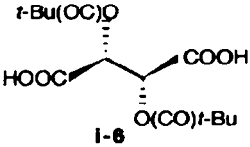
i-3



i-4a R : H
i-4b R : Ph
i-4c R: β -Naphth



i-5a R : H (1*R*, 2*R*)
i-5b R : *i*-Pr (1*S*, 2*S*)



i-6

The deprotection of **1** was initially carried out at room temperature in acetonitrile in the presence of 10% palladium on charcoal purchased from Aldrich- or Janssen-Chimica, with various amounts of (-) ephedrine (**i-1**), and continuous bubbling of hydrogen into the mixture (Table 1, entries 1 to 6). Thus, it appears that the best enantiomeric excess (*ee*) was obtained in using around 0.3 equiv. of the aminoalcohol (entry 3). Switching to a 5% Pd/C supplied by Engelhard Company afforded a similar result (entry 7). The use of toluene or ethyl acetate as solvent led to lower *ee*'s, the reaction being sluggish in AcOEt (entries 8 and 9). The addition of minute amounts of water to the ethyl acetate slurry increased the rate of the reaction but larger quantities proved detrimental to the *ee* (entries 10 and 11). The aminoalcohols **i-2**, **i-3**, **i-4b** and **i-4c** were less efficient (entries 12, 13, 15 and 16). Surprisingly, the aminoalcohol **i-4a** which bears a primary hydroxy group provided an improvment in the enantioselectivity (entry 14). The use of diamines such as **i-5a** and **i-5b** (entries 17 to 19) instead of an aminoalcohol led to lower *ee*'s even when using 0.3 equiv. of it. As suspected, the use of the diacid **i-6** was disappointing (entry 20).

We encountered great difficulties in observing a reaction of **2** under similar conditions, the nature of the palladium catalyst thus being crucial. Indeed, various samples of Pd/C from different companies under various experimental conditions failed to give rise efficiently to **5** (Table 1, entry 21). The use of a home-made catalyst, 20% $Pd(OH)_2/C$,[9] well known for its capacity to cleave the benzyl-heteroatom bond[10] led easily to **5** with high yields but with low *ee*'s, even when performing the reaction in the presence of molecular sieves (entries 22 and 23). Fortunately, one of the 5% Pd/C samples supplied by Engelhard Company[11] proved to be effective (entries 24 to 30). As above observed for **1**, the optimum amount of **i-1** was then around 0.3 equiv. (entry 27). Interstingly, **i-2** gave 50% *ee* (entry 30).

Table 1: Reaction of **1** and **2** under hydrogen atmosphere.

Entry	$\text{Palladium}_{\text{Manufacturer Reference}}$ (equiv.)	AH* (equiv.)	Solvent	Time h	Yield %	e.e.[a] %
Reaction of **1** *(concentration ≈ 3.4 10^{-2} M)*					**4**	
1	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ (0.06)	**i-1** (0.1)	MeCN	23	89	11
2	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0. 02)	**i-1** (0.15)	MeCN	16	92	13
3	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0. 02)	**i-1** (0.3)	MeCN	4	87	48
4	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.02)	**i-1** (0.5)	MeCN	4	80	33
5	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.06)	**i-1** (0.8)	MeCN	16	55	23
6	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.06)	**i-1** (2.1)	MeCN	16	65	6
7	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.3)	MeCN	5.5	68	44
8	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.04)	**i-1** (0.3)	PhMe	8	83	33
9	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ ([b])	**i-1** (0.3)	AcOEt	24	92	31
10	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ ([b])	**i-1** (0.3)	AcOEt/H_2O (100/1)	7	94	30
11	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ ([b])	**i-1** (0.3)	AcOEt/H_2O (10/1)	1.5	85	21
12	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-2** (0.3)	MeCN	1	82	25
13	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.05)	**i-3** (0.3)	MeCN	8	70	9
14	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.05)	**i-4a** (0.3)	MeCN	7.5	75	52
15	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.05)	**i-4b** (0.3)	MeCN	4	72	0
16	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.05)	**i-4c** (0.3)	MeCN	7	66	24
17	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ (0.06)	**i-5a** (0.1)	MeCN	6	70	17[c]
18	10% $\text{Pd/C}_{\text{Janssen 19.503.06}}$ (0.05)	**i-5a** (0.3)	MeCN	20.5	67	25[c]
19	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.0025)	**i-5b** (0.3)	MeCN	5	90	3
20	10% $\text{Pd/C}_{\text{Aldrich 20,569-9}}$ (0.06)	**i-6** (1)	MeCN	16	79	2[c]
Reaction of **2** *(concentration ≈ 1.7 10^{-2} M)*					**5**	
21	10% $\text{Pd/C}_{\text{Aldrich 20,569-9, Janssen 19.503.06, Johnson Matthey 390 or 490}}$ (0.02-0.17)	**i-1** (0.2-0.5)	PhMe, THF or MeCN	25 to 48	d	
22	20% $Pd(OH)_2/C$ (0.05-0.1)	**i-1** (0.3)	MeCN or PhMe	1.5-4	80-90	3-5
23[e]	20% $Pd(OH)_2/C$ (0.06)	**i-1** (0.3)	MeCN	10	80	8
24	5% $\text{Pd/C}_{\text{Engelhard 5105}}$ (0.025)	**i-1** (0.3)	MeCN	4.5	95	0
25	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.1)	MeCN	5	78	17
26	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.2)	MeCN	4.5	72	19
27	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.3)	MeCN	4	78	32
28	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.4)	MeCN	4	81	26
29	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-1** (0.5)	MeCN	4	90	22
30	5% $\text{Pd/C}_{\text{Engelhard 5011}}$ (0.025)	**i-2** (0.3)	MeCN	5	79	50[f]

[a]e.e. (± 3%) and (*R*) configuration determined by polarimetry comparisons.[8] [b]Sample not weighed. [c]The main enantiomer has the (*S*) configuration. [d]No reaction of **2** or less than 10% of conversion to **5**. [e]Reaction carried out in the presence of molecular sieves. [f]Also determined from ^1H NMR in the presence of $Eu(hfc)_3$.

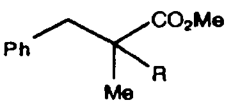
As previously disclosed for the palladium-catalyzed deprotection of allyl enolcarbonates,[1] the reaction of **3** requires at least stoichiometric amounts of the aminoalcohol. Therefore, the study of the transformation of **3** to **4** was restricted to the use of (-) ephedrine as aminoalcohol which is easily available at a relatively low price. The catalytic system was a mixture of $Pd(OAc)_2/L$ (Pd/L = 1/2, L = PPh_3, $P(OPh)_3$ or $P(OEt)_3$). In acetonitrile and with L = PPh_3, it has appeared that 0.05 equiv. of palladium was sufficient and that *ee*'s were superior in using two equiv. of **i-1** rather than 1.1 equiv. or in working at room temperature instead of 0°C (Table 2, entries 1 to 4). No reaction was observed in THF (entry 5) while ethyl acetate and toluene as solvents afforded results similar to those obtained in acetonitrile (entries 6 to 10). The use of a phosphite ligand provided lower *ee*'s (entries 11 to 13) particularly from triethyl phosphite where a large increase of the reaction time was required to reach full consumption of **3**. Attempts to carry out the transformation of **3** in using less than one equiv. of **i-1** and then a nucleophilic additive to trap the allyl group, led to racemic **4** with moderate yields (entry 14 as example). When the palladium(0) catalyst -$Pd_2(dba)_3.CHCl_3$- was directly used *in lieu* of Pd(II), the chemical yield was improved while the enantioselectivity was somewhat decreased (entry 15).

Table 2: Production of **4** from **3** (concentration: 2 10^{-2} M).

Entry	$Pd(OAc)_2$ Equiv.	Ligand (equiv.)	**i-1** Equiv.	Solvent	Tempe-rature	Time h	Yield %	e.e.[a] %
1	0.05	PPh_3 (0.1)	2	MeCN	RT	6	62	43
2	0.1	PPh_3 (0.2)	2	MeCN	RT	8	69	39
3	0.1	PPh_3 (0.2)	1.1	MeCN	RT	24	84	28
4	0.1	PPh_3 (0.2)	2	MeCN	0°C	24	78	24
5	0.05	PPh_3 (0.1)	2	THF	RT	20	[b]	
6	0.05	PPh_3 (0.1)	2	AcOEt	RT	6	48	46
7	0.1	PPh_3 (0.2)	2	AcOEt	RT	8	61	28
8	0.05	PPh_3 (0.1)	2	PhMe	RT	6.5	50	50
9	0.07	PPh_3 (0.14)	2	PhMe	RT	5	81	42
10	0.1	PPh_3 (0.2)	2	PhMe	RT	7	53	40
11	0.05	$P(OPh)_3$ (0.1)	2	PhMe	RT	5	82	35
12	0.05	$P(OPh)_3$ (0.1)	2	PhH	RT	1.75	91	35
13	0.05	$P(OEt)_3$ (0.1)	2	PhMe	RT	48	60	20
14[c]	0.05	PPh_3 (0.1)	0.5	PhMe	RT	21	80	0
15[d]	0.03[d]	PPh_3 (0.12)	2	PhMe	RT	5	91	36

[a] See note (a) in Table 1. [b] No reaction of **3**. [c] Reaction carried out in the presence of 1.1 equiv. of ammonium formate. [d] $Pd_2(dba)_3.CHCl_3$ was used as catalyst.

Finally, we envisaged to subject the β-diesters **7** and **8** to similar processes. Indeed, a related transformation has been previously performed in using a copper catalyst but heating of the mixture and excess quantities of the chiral protic agent were required.[12]



7 : R = CO_2CH_2Ph
8 : R = CO_2allyl
9 : R = CO_2H
10 : R = H

No reaction was observed when **7** was subjected to hydrogen and catalytic amounts of both Pd/C and **i-1** even at 40°C. The use of a hydrogen transfer method, Pd/C plus cyclohexene at reflux of EtOH,[13] led to the acidester **9**. Similarly, the allylester **8** led to **9** in the presence of $Pd(OAc)_2/PPh_3$/**i-1**. The high stabilities of **7** and **9** under these conditions are relatively surprising from literature data.[14,15] However, the use of a $Pd(PPh_3)_4$/**i-1** mixture in toluene at 100°C has allowed us to obtain **10** from **8** (60% yield) but the isolated monoester was thus racemic.

The mechanism of the transformation of **1**, **2** and **3** to the optically active ketones **4** and **5** is presumably similar to the one described previously from enol carbonates.[1] Indeed, we have observed that the reaction did not involve a kinetic resolution since optically inactive β-ketoester was recovered when the reaction was carried out to incomplete conversion.[16] Work is now in progress to improve the enantioselectivity of the process and to determine its limits.

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