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Palladium-Mediated Enantioselective Formation of 2-Methyltetral-1-one from the Corresponding Allyl or Benzyl Enol Carbonate in the Presence of Enantiopure Aminoalcohols

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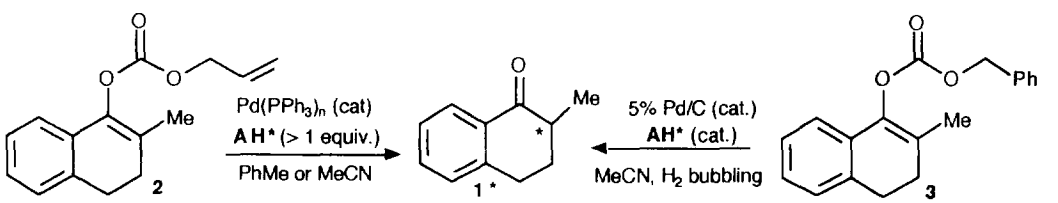
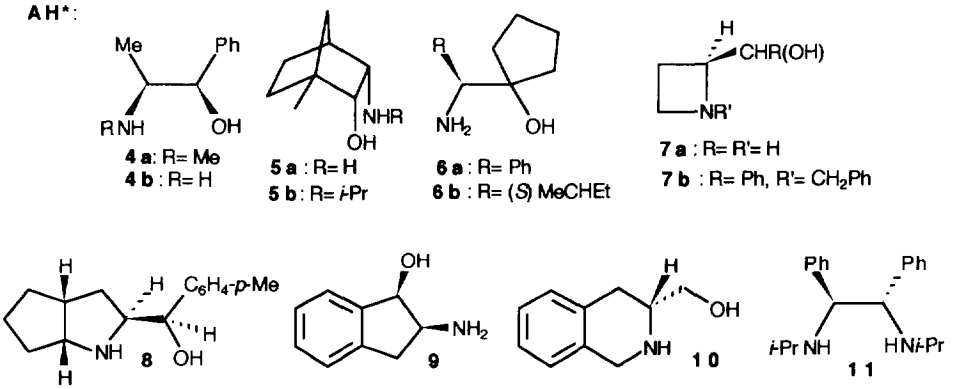
Abstract: The palladium-induced cleavage at room temperature of (2-methyl-1-tetralenyl) benzyl carbonate under bubbling of hydrogen led to (*R*) 2-methyltetral-1-one with 90% chemical yield and 64% enantiomeric excess in the presence of catalytic amounts of (+) *endo*-2-hydroxy-*endo*-3-aminobornane.

The synthesis of optically active ketones by enantioselective protonation of enol species has been the subject of great efforts during the last few years.[1,2] In the course of our work related to this topic, we have briefly described the enantioselective synthesis of 2-methylindan-1-one (*ee* ≤ 40%) from the palladium-induced cascade reaction of prochiral (2-methyl-1-indenyl) benzyl (or allyl) carbonate using mainly (+) or (-) ephedrine as source of chirality (**AH***).[3] We have also reported the formation of optically active 2-methyltetral-1-one (**1***) from either corresponding racemic β-ketoesters (2-benzyl[or allyl]oxycarbonyl-2-methyltetral-1-one) under similar conditions[4] or from racemic 2-methyl-2-isobutyl-(3,4)-dihydronaphthalen-1-one under UV irradiation in the presence of **AH***.[5] The first method led to **1*** in fair yield and enantiomeric excess (79% yield, 50% *ee*).[4] The irradiation procedure led to **1*** with a better *ee* particularly when working at low temperature but the chemical yield was lower (40% yield and 89% *ee* at -40°C for 60% conversion). Furthermore, a concurrent Norrish type I photoreaction of **1*** led to its partial racemization when the starting α-disubstituted ketone was irradiated to high conversion.[5] Other methods leading to **1*** include diastereoselective alkylation of chiral tetralone derivatives,[6] enantioselective protonation of various corresponding enolates (*ee* up to 91%)[2] and enantioselective alkylation of tetral-1-one (*ee* up to 88%).[2a,7]

In the present paper, we describe convenient access to **1*** in a high chemical yield (up to 90%) and a fair *ee* (up to 64%), using the enol carbonates **2** and **3**[8] as substrates and **4-11**[9] as **AH***.





The cleavage reaction of the allyl group of **2** has been carried out in the presence of catalytic amounts of either palladium acetate plus triphenyl phosphine ($PPh_3/Pd(OAc)_2$ = 2/1) or palladium (tetrakis)triphenyl phosphine. The main results are collected in Table 1. Excesses of protic species are required since their role is firstly to trap the allyl group and secondly to induce the enantioselective protonation step.[3] Stoichiometric or excess amounts of achiral nucleophilic species such as PhSNa,[10] PhSH,[10] PhOH[11] or $CH_2(COOMe)_2$[12] have been used in conjunction with catalytic quantities of **AH*** with the aim to carry out the first step by the achiral species and the second step by the more expensive aminoalcohol. However, we never obtained interesting results under these conditions (runs 6-10, 14 and 17). We think that these poor results are due to the competition between the additives and **AH*** in the protonation step. Presently, the best *ee* has been generated by the use of 2 equiv. of **4a** at room temperature (run 4).

Table 1: Enantioselective formation of **1*** from **2** (concentration: 2 10^{-2} M in PhMe, room temperature).

Run	**AH*** (equiv.)	Time h	Yield %	*ee* %[k]
1[a]	**4a** (0.7)	4	62	16
2[a]	**4a** (1)	4	65	36
3[a]	**4a** (1.5)	4	70	38
4[a]	**4a** (2)	4	86	50[l]
5[b]	**4a** (2)	3.75	70	42
6[b,c]	**4a** (0.1)	6	75	0
7[b,c]	**4a** (0.5)	0.5	72	21
8[b,c]	**4a** (0.5)	9	62	13
9[a,c,d]	**4a** (0.5)	9	68	15
10[b,c]	**4a** (1)	1	85	24
11[a,e]	**4a** (0.3)	1	80	10
12[a,f]	**4a** (0.3)	1	62	0
13[a,g]	**4a** (2)	9	70	41
14[b,c]	**5a** (0.4)	1	85	35
15[h]	**4a** (2)	1	76	35
16[d,i]	**4a** (1.5)	3	70	32
17[d,i,j]	**4a** (0.3)	20	60	20

[a] $Pd(OAc)_2$ (0.05 equiv.), PPh_3 (0.1 equiv.).
[b] $Pd(OAc)_2$ (0.07 equiv.), PPh_3 (0.14 equiv.).
[c] PhSNa (1 equiv.) as additive.
[d] Reaction carried out at 0°C.
[e] PhSH (1 equiv.) as additive.
[f] PhOH (1 equiv.) as additive.
[g] MeCN as solvent.
[h] $Pd(PPh_3)_4$ (0.02 equiv.), PPh_3 (0.04 equiv.).
[i] $Pd(PPh_3)_4$ (0.02 equiv.).
[j] $CH_2(COOMe)_2$ (4 equiv.) as additive.
[k] (*R*) configuration and *ee* (± 3%) determined by optical rotation comparisons.[6a]
[l] Also determined from ^1H NMR data in the presence of Eu(hfc)3.

The use of **3** as substrate is more interesting since hydrogen is employed to trap the benzyl group.

Therefore, only a substoichiometric amount of the aminoalcohol is required. However, we have previously reported that under our conditions, the cleavage step is very sensitive to the nature of the palladium catalyst.[4] We observed a similar trend with **3**. Various commercial samples of palladium on charcoal led to no reaction or to low *ee*'s of **1***. The use of 20% $Pd(OH)_2/C$[13] in acetonitrile or hexane in the presence of **4a** led to 2-methyltetral-1-one with fair yields (68-70%) but without enantioselectivity. Finally, we have obtained valuable and reproducible results in using 5% Pd/C Ref. 5011 from Engelhard Company (Table 2).[14] Thus, a high yield of **1*** was obtained at room temperature in acetonitrile in the presence of ephedrine and norephedrine (runs 1 to 4). As for benzyl β-ketoesters,[4] the increase of the quantity of the chiral protic species from 0.15 to 0.3 equiv. improves the enantioselectivity of the process (runs 1-2), a higher amount of **AH*** not being useful (run 3). Furthermore, using **5a** instead of **4** as aminoalcohol provoked a jump of *ee* to 64% (run 5). The decrease of the reaction temperature to 0°C led to a sluggish reaction and gave lower *ee* (run 7). The aminoalcohols **6a**, **6b**, **7a**, **7b**, **9** and **10** or diamine **11** were less efficient (runs 9-12 and 14-16) while **8** provided a fair *ee* (run 13).

Table 2: Enantioselective formation of **1*** from **3** (concentration: 3.4 10^{-2} M in MeCN) using 5% Pd/C Ref. 5011 from Engelhard Company (0.025 equiv. of Pd atom), catalytic amounts of **AH*** and continuous bubbling of hydrogen at room temperature.

Run	**AH*** (equiv.)	Time h	Yield %	*ee* %[d]
1	**4a** (0.15)	1	82	6
2	**4a** (0.3)	1	90	26
3	**4a** (0.5)	1	73	20
4	**4b** (0.3)	1	89	24
5	**5a** (0.3)	0.7	90	64[e]
6	**5a** (0.3)	6	91	51
7[a]	**5a** (0.3)	9	82	54
8	**5b** (0.3)	0.75	84	30
9[b]	**6a** (0.3)	6	85	2
10[b]	**6b** (0.3)	6	76	7
11	**7a** (0.3)	4	78	11
12[b]	**7b** (0.3)	3	74	8
13	**8** (0.3)	2.5	82	63[e]
14[c]	**9** (0.3)	5.7	80	0
15[b]	**10** (0.3)	14	65	8
16	**11** (0.3)	2.5	90	8

[a] Reaction carried out at 0°C.
[b] CH_2Cl_2 as solvent.
[c] $MeCN/CH_2Cl_2$ (5/1) as solvent.
[d] (*R*) configuration and *ee* (± 3%) determined by optical rotation comparisons.[6a]
[e] Also determined from ^1H NMR data in the presence of $Eu(hfc)_3$.

The difficulties vis-a-vis the enantioselectivity of the transformation of **3**, we encountered in using various palladium catalysts, led us to examine the behavior of **1*** in the presence of three different Pd-catalysts. The results summarized in Table 3 established clearly that palladium on charcoal is able to racemize **1*** and that the efficiency of this process is highly dependent on the structure of the catalyst.[14] The basicity of $Pd(OH)_2/C$ could explain its propensity to induce high racemization. The racemization could involve an oxo-η^3-allyl palladium intermediate; the formation of such complexes has already been mentioned for ketones and Pd(II) salts.[15]

Table 3: Palladium-catalyzed partial racemization of **1*** at room temperature in MeCN (equiv. of Pd atom: 0.025 for runs 1 et 2, 0.05 for run 3).

Run	*ee* of the starting sample of **1***	Pd-catalyst[13,14]	Time h	*ee* of the recovered sample of **1***
1	40%	5% Pd/C Ref. 5011	6.5	38%
2	40%	5% Pd/C Ref. 5105	6.5	27%
3	26%	20% $Pd(OH)_2/C$	5	9%

The comparison of the results of Table 2 - runs 5 and 6 and Table 3 - run 1 is informative. Indeed, the

reaction of **3** in the presence of 5% Pd/C Ref. 5011 and **5a** at room temperature in acetonitrile led to **1*** with an optical activity which decreased with the reaction time (Table 2, runs 5 and 6). As **3** has no stereogenic center, the simplest explanation of this decrease is racemization of **1*** by a palladium species. Since the initial 5% Pd/C Ref. 5011 is rather inert toward **1*** (Table 3, run 1), the observed racemization means that this catalyst has been modified in the course of the transformation of **3** to **1***.

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