Access to optically active linear ketones by one-pot catalytic deprotection, decarboxylation, asymmetric tautomerization from racemic benzyl β-ketoesters

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Benzyl 2-benzoyl-2-phenylpropanoate **1b** subjected to heterogeneous hydrogenolysis conditions in the presence of catalytic amounts of commercially available cinchona alkaloids as chiral protic source, led to (*R*)-1,2-diphenylpropanone with up to 71% ee, through a cascade reaction involving deprotection, decarboxylation and asymmetric tautomerization of enolic species.

Numerous diastereoselective methods exist in enol chemistry to prepare linear ketones bearing an α-stereogenic centre: they use various protecting groups as chiral auxiliaries[1,2] or an alkylating reagent having a chiral leaving group.[3,4] Another efficient way involves the asymmetric protonation of metal enolates generated from ketones[5] or ketenes[6] by stoichiometric quantities of a chiral protic source. In some cases, these latter methods become catalytic in chiral inducing entity,[7,8] but meticulous adjustments of the experimental conditions are then required. The development of catalytic methods in asymmetric protonation of open chain ketone enolates can be complicated by two main factors: i) in contrast to ester or amide derivatives, these simple enolates have no additional chelation sites able to enhance the rigidity of a transition state in coordinating the chiral protic source[9] and ii) *Z*- and *E*-enolates can provide similar[10] or opposite[4] enantiomers. Currently no rule can predict the olefin configuration effect; thus, the preparation of a single enol geometrical isomer is required and is difficult to achieve.

We have shown that 2-carboxy-2-methyltetralone provided optically active 2-methyltetralone in a two step reaction consisting of a decarboxylation and an asymmetric protonation of the resulting enolic species assisted by catalytic amounts of enantiopure aminoalcohols.[11] In acyclic series, a similar methodology has been studied by Brunner's group and was also effective starting from malonic substrates[12] [eqn. (1)]; fur-

E = COOH, CO₂R, CN

AH* = cinchonia derivatives
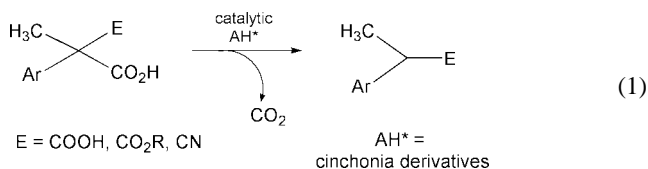
thermore, this has been applied to the preparation of optically active naproxen derivatives, the selectivity being higher, starting from 2-cyano-2-arylpropionic acid[13] than from 2-ethoxycarbonyl-2-arylpropionic acid.[14]

Using this methodology, we envisaged to prepare aliphatic non racemic ketones. Since we have observed that solutions of 2-carboxy-2-methyltetralone where the acidic group is tertiary were not stable at rt,[11] we decided to start from protected β-ketoacids. The acidic group was protected as benzylic ester as the reductive cleavage of the benzyl group would allow a gradual generation of the acid and of the enolic species. The *in situ* generation of the intermediates under palladium–aminoalcohol catalysis[15] could improve both chemical and optical yields. We present here our results [eqn. (2)].

1a: R = CH₂Ph,
1b: R = Ph

(2)
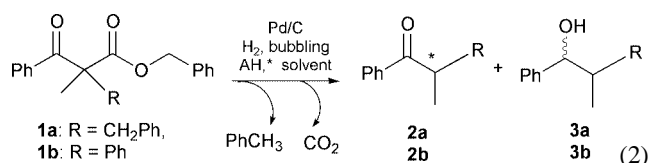
In the first experiments, we applied the conditions previously defined from cyclic substrates:[15] to an acetonitrile solution of substrate **1a**† and chiral aminoalcohol (0.3 eq.) was added palladium on charcoal (0.025 eq., Ref. 5011 from Engelhard Company), then, H₂ was continuously bubbled into the mixture for the time indicated in Table 1. From the results assembled in

Table 1 Enantioselective hydrogenolysis–decarboxylation–tautomerization from **1a**

				2a		3a
Run	AH* 0.3 eq.	T °C	Time[a]/h	Yield[b](%)	ee (config.)[c]	Yiled[b] (%)
1	**4**	22	0.25	79	2 (*S*)	17
2	**4**	22	1	71	4 (*S*)	22
3	**4**	50	0.25	58	6 (*S*)	11
4	**5**	22	0.5	74	5 (*S*)	n.d.[d]
5	**5**	50	0.25	60	10 (*S*)	n.d.[d]
6	**5**	80	0.17	62	10 (*S*)	n.d.[d]
7	**6**	0	7[e]	19	16 (*S*)	n.d.[d]
8	**6**	22	1	89	10 (*S*)	n.d.[d]
9	**6**	50	0.37	81	9 (*S*)	n.d.[d]
10	**7**	22	1.1	82	5 (*R*)	n.d.[d]

[a] Reaction time to reach full conversion of the substrate, as indicated by TLC. [b] Isolated yields of purified products. [c] Enantiomeric excess determined by HPLC (column Daicel, Chiralcel OD; n-hexane–*i*-PrOH = 99:1, 0.6 mL min⁻¹, t_r (*R*) = 14.1 min, t_r (*S*) = 15.5 min, α = 1.2); configuration determined by optical rotation comparison:[2,17] $[\alpha]_D^{20}$ = +5 (c 1 CHCl₃, ee$_{HPLC}$ = 10%). [d] Not determined. [e] Conversion: 35%.

Table 1, it appears that ketone **2a** was obtained with good chemical yields but usually accompanied by alcohol **3a**,[16] which corresponds to an over-reduction of **2a**, the amount of **3a** increasing slowly with the reaction time (runs 1 and 2). As aminoalcohols, we used (−)-ephedrine (**4**) and aminoborneol (**5**) which gave satisfying results from cyclic substrates,[15] and also cinchonia alkaloids **6** or **7** which afforded good enantioselectivities from malonic substrates.[12–14] However these chiral inducing entities led to poor enantioselectivities even in varying the reaction temperature (Table 1); the results were not improved by modifying the nature of the supported palladium catalyst or the solvent (toluene and THF instead of acetonitrile).

Then we examined substrate **1b**† where the benzyl group in the 2-position was replaced by a phenyl substituent capable of stabilizing the enolic species (Table 2). From this substrate compared to **1a**, the chemical yield of ketone **2b** increased since alcohol **3b** was not produced. Again the use of **4** and **5** led to no or low enantioselectivity (runs 11 and 12). In contrast, the enantiomeric excess of **2b** increased dramatically with cincho-
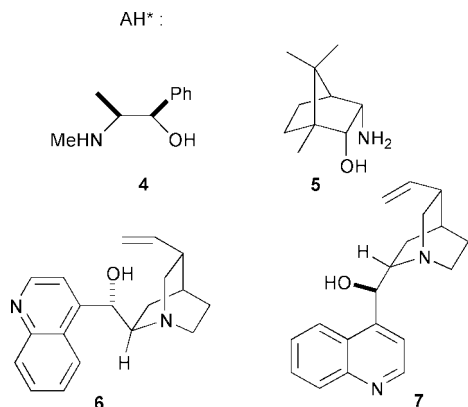
AH* :

4   5

6   7

Table 2 Enantioselective cleavage–decarboxylation–tautomerization from **1b** at room temperature

Run	Solvent	AH* (eq.)	Time[a]/h	2b Yield[a] (%)	ee (config.)[b]
11	MeCN	**4** (0.3)	1	97	0
12	”	**5** (0.3)	0.5	85	16 (S)
13	”	**6** (0.3)	0.5	70	49 (S)
14	”	**7** (0.3)	1	94	56 (R)
15	”	**7** (0.5)	1	100	56 (R)
16	”	**7** (0.1)	1	100	61 (R)
17	”	Adsorbed[c] **7** (0.3)	7	95	64 (R)
18	THF	**7** (0.3)	17	85	52 (R)
19	AcOEt	**7** (0.3)	1	100	71 (R)
20	”	**7** (0.05)	2	100	68 (R)
21	”	Adsorbed[c] **7** (0.3)	8	49[d]	70 (R)

[a] See Table 1. [b] Enantiomeric excess determined by HPLC (column Daicel, Chiralcel OD; n-hexane–i-PrOH = 99:1, 0.6 mL min^{-1}, t_r (R) = 11.8 min, t_r (S) = 13.9 min, α = 1.46); configuration determined by optical rotation comparison:[2,18] $[\alpha]_D^{20}$ = +167 (c 1.2 CHCl$_3$, ee$_{HPLC}$ = 71%). [c] The suspension is prepared as following: the palladium on charcoal is added to a solution of **7** in chloroform; then the solvent is evaporated under reduced pressure and replaced by the solution of the substrate in MeCN or AcOEt. [d] Only 49% of conversion.

nia aminoalcohols; indeed we observed 49 and 56% ee with cinchonidine (**6**) (run 13) and cinchonine (**7**) (run 14) respectively. As these latter chirality inductors were insoluble in acetonitrile, we studied the effects of the amount of **7** and of its distribution in the medium. As expected, increasing the amount of **7** from 0.3 (run 14) to 0.5 eq. (run 15) did not change the selectivity. Dropping to 0.1 eq. the amount of **7** was not detrimental to both chemical yield and ee (run 16). Adsorbing **7** on the supported catalyst by its dissolution in chloroform followed by a solvent exchange allowed a slight increase of the enantioselectivity, but a concomitant decrease of the reaction rate (run 17). Switching from acetonitrile to THF led to a slower reaction and a decreased ee (run 18). The best solvent for both yield and ee was ethyl acetate, since ee could reach 71% for a quantitative chemical yield (runs 19); even in the presence of only 0.05 eq. of **7**, ee remained high (68%, run 20). In this solvent however, the adsorption of **7** on palladium on charcoal was detrimental to the conversion without change of the ee.

Thus we have shown that, in spite of their non-fixed geometry, enolic species corresponding to open chain ketones could be asymmetrically protonated in using a catalytic amount of commercial cinchonine, the one pot procedure starting from **1** being easily carried out.

References and notes

† *Selected data for* **1**: **1a**: δ_H (250 MHz, CDCl$_3$) 7.7–7.8 (m, 2H), 6.9–7.4 (m, 13H), 5.09 (br s, 2H, OCH$_2$Ph), 3.44 (d, 1H, CHHPh, J = 13.7 Hz), 3.35 (d, 1H, CHHPh, J = 13.7 Hz), 1.50 (s, 3H, CH$_3$). **1b**: δ_H (250 MHz, CDCl$_3$) 7.62–7.66 (m, 2H), 7.06–7.50 (m, 13H), 5.16 (d, 1H, OCHHPh, J = 12.6 Hz), 5.08 (d, 1H, OCHHPh, J = 12.6 Hz), 1.94 (s, 3H, CH$_3$).

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