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

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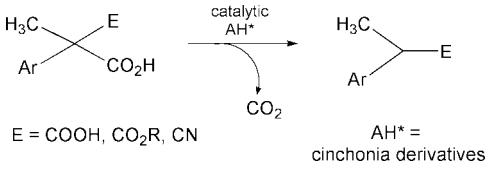
Benzyl 2-benzoyl-2-phenylpropanoate 1b subjected to heterogeneous hydrogenolysis conditions in the presence of catalytic amounts of commercially available cinchonia alkaloids as chiral protic source, led to (*R*)-1,2-diphenylpropanone with up to 71% ee, through a cascade reaction involving deprotection,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

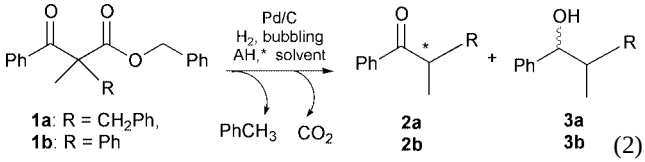
Numerous diastereoselective methods exist in enol chemistry to prepare linear ketones bearing an α-stereogenic centre: they use various protecting groups as chiral auxiliaries[1,2] or an alkylating reagent having a chiral leaving group.[3,4] Another efficient way involves the asymmetric protonation of 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)]; furthermore, 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]



(1)

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)].



(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, H_2 was continuously bubbled into the mixture for the time indicated in Table 1. From the results assembled in 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).

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 $CHCl_3$, ee_{HPLC} = 10%). [d] Not determined. [e] Conversion: 35%.

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-

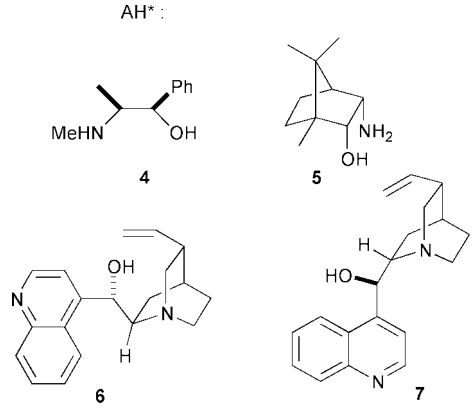


Table 2 Enantioselective cleavage–decarboxylation–tautomerization from **1b** at room temperature

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.

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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, OC*H*$_2$Ph), 3.44 (d, 1H, C*H*HPh, *J* = 13.7 Hz), 3.35 (d, 1H, CH*H*Ph, *J* = 13.7 Hz), 1.50 (s, 3H, C*H*$_3$). **1b**: δ_H (250 MHz, $CDCl_3$) 7.62–7.66 (m, 2H), 7.06–7.50 (m, 13H), 5.16 (d, 1H, OC*H*HPh, *J* = 12.6 Hz), 5.08 (d, 1H, OCH*H*Ph, *J* = 12.6 Hz), 1.94 (s, 3H, C*H*$_3$).

1 Reviews: J. S. McCallum and L. S. Liebeskind, in *Stereoselective Synthesis* (Houben-Weyl), ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme Verlag: New York, 1996, p. 916. P. Fey and W. Hartwig, *ibid*, p. 969. P. Fey, *ibid*, p. 1030.

2 W. Oppolzer, C. Darcel, P. Rochet, S. Rosset and J. De Brabander, *Helv. Chim. Acta*, 1997, **80**, 1319.

3 P. Duhamel, in *Stereoselective Synthesis* (Houben-Weyl), ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme Verlag: New York, 1996, p. 1101.

4 C. Fehr and J. Galindo, *J. Am. Chem. Soc.*, 1988, **110**, 6909.

5 K. Ishibara, H. Nakamura and H. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 7720.

6 For examples: Ref. 4; J. Pracejus and H. Mätje, *J. Prakt. Chem.*, 1964, **24**, 195; Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida and K. Mikami, *Tetrahedron*, 1999, **55**, 4595.

7 C. Fehr and J. Galindo, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1888.

8 Y. Nakamura, S. Takeuchi, A. Ohira and Y. Ohgo, *Tetrahedron Lett.*, 1996, **37**, 2805; S. Takeuchi, Y. Nakamura, Y. Ohgo and D. P. Curran, *Tetrahedron Lett.*, 1998, **39**, 8691; B. L. Hodous, J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 2637.

9 C. Fehr, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2566.

10 F. Hénin, S. Létinois and J. Muzart, *Tetrahedron: Asymmetry*, 2000, **11**, 2037 and references cited therein.

11 F. Hénin, J. Muzart, M. Nedjma and H. Rau, *Monatsh. Chem.*, 1997, **128**, 1181.

12 H. Brunner, J. Müller and J. Spitzer, *Monatsh. Chem.*, 1996, **127**, 845.

13 H. Brunner and P. Schmidt, *Eur. J. Org. Chem.*, 2000, 2119.

14 H. Brunner and P. Schmidt, *Z. Naturforsch.*, 2000, **55b**, 369.

15 J. Muzart, F. Hénin and S. Jamal Aboulhoda, *Tetrahedron: Asymmetry*, 1997, **8**, 381; S. Jamal Aboulhoda, I. Reiners, J. Wilken, F. Hénin, J. Martens and J. Muzart, *Tetrahedron: Asymmetry*, 1998, **9**, 1847.

16 A *syn* relative configuration has been determined for the diastereomer in slight excess (around 55±3%) which could be compared with analogous values observed for **3a** resulting of the hydride reduction of **2a**: C. Alvarez Ibarra, F. Fernandez Gonzalez, M. L. Quiroga Feijoo and J. Santoro, *An. Quim.*, 1978, **74**, 449; C. Alvarez Ibarra, R. Pérez-Ossorio, M. L. Quiroga, M. S. Arias Pérez and M J. Fernandez Dominguez, *J. Chem. Soc., Perkin Trans. 2*, 1988, 101.

17 T. Izawa, Y. Terao and K. Suzuki, *Tetrahedron: Asymmetry*, 1997, **8**, 2645.

18 A. I. Meyers, D. R. Williams, S. White and G. W. Erickson, *J. Am. Chem. Soc.*, 1981, **103**, 3088.