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ASYMMETRIC SYNTHESIS BY COPPER-CATALYZED DECARBOXYLATION OF PHENYLMALONIC DIACIDS AND HEMIESTERS

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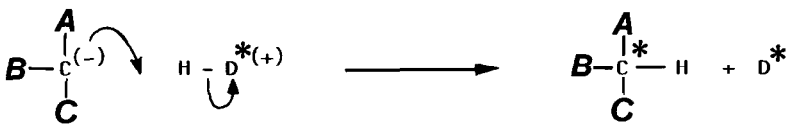
Abstract : The first asymmetric decarboxylation of monoalkyl phenylmalonates (Z = CO_2Et) and a novel asymmetric decarboxylation of malonic diacids (Z = CO_2H) have been achieved by a very mild catalysis with Cu^I and a chiral alkaloid.

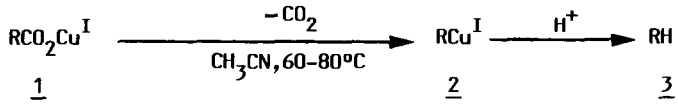
In a recent review dealing with asymmetric protonation [1], Duhamel *et al.* state that only a few reactions involving the protonation of a prochiral carbanion are known :



(D^* : chiral inductor ; $D^{*(+)}$: protonated chiral inductor)

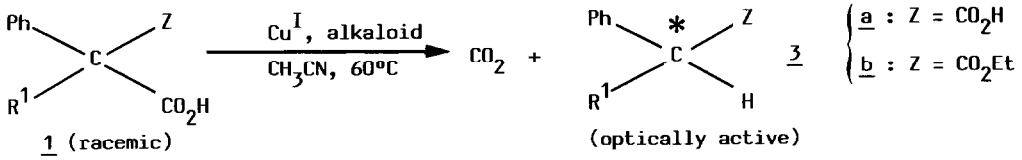
These enantioface differentiating protonations are applied, for example, to deracemization of carbonyl compounds and α-aminoacids[1].

We have previously studied the copper(I) catalyzed decarboxylation of carboxylic acids[2] and established that a carbanion (R^-, in RCu^I) is formed during the evolution of appropriate cuprous carboxylates in acetonitrile.



Different types of carboxylic acids undergo this reaction[2,3], including malonic diacids 1a and their hemiesters 1b. Protonation of the intermediate carbanion 2 is effected by the acid 1 itself in the usual procedure and, thus, racemic product 3 is obtained[2,3].

Now, if the carbanion 2 is no more protonated by the acid 1, but by a chiral proton donor, optically active monoacids 3a or esters 3b are effectively obtained in good chemical yields (85-95 %) :



1 (racemic)

(optically active)

We report here our results about the asymmetric decarboxylation of some phenylmalonic acids 1a and of their hemiesters 1b. As chiral inductors (D^*), alkaloids gave the best results : table summarizes typical results :

1		D^*	configuration of 3	$[\alpha]_D^{25}$	optical purity (o.p.)
R^1	Z				
CH_3	CO_2Et	cinchonidine	R-(-)	-12°2 [a]	17 %
CH_3	CO_2Et	quinine	R-(-)	-3° [a]	4 %
CH_3	CO_2Et	cinchonidine 9-acetate	S-(+)	+10°4 [a]	14.5 %
CH_3	CO_2Et	quinine 9-acetate	S-(+)	+2°2 [a]	3 %
CH_3	CO_2Et	brucine	R-(-)	-7°2 [a]	10 %
$CH(CH_3)_2$	CO_2Et	cinchonidine	R-(-)	-16°2 [b]	31 %
CH_3	CO_2H	cinchonidine	R-(-)	-29°5 [c]	27 %
$CH(CH_3)_2$	CO_2H	cinchonidine	R-(-)	-13°3 [d]	24 %

[a] c=10, toluene ; lit.[10] : $[\alpha]_D$ max=+72°, c=10, toluene, for S-(+) enantiomer.

[b] c=10, CH_3OH ; lit.[11] : $[\alpha]_D$ = -52°3, c=6.8, CH_3OH.

[c] Methyl ester (after esterification with CH_2N_2), c=10, toluene ; lit.[10] : $[\alpha]_D$ = +109°2, c=6.2, toluene, for S-(+) methyl hydratropate.

[d] Ethyl ester (after esterification with $EtOH/H_2SO_4$), c=10, CH_3OH ; lit.[11] : $[\alpha]_D$ = -52°3, c=6.8, CH_3OH.

Table : Asymmetric decarboxylations of phenylmalonic acids 1a and hemiesters 1b.

The procedure is rather simple in principle : the malonic derivative (diacid or hemiester) is slowly added to a stirred mixture of copper(I) chloride and alkaloid in acetonitrile. As shown on figure 1, when the initial product is a hemiester 1b of a malonic diacid, catalytic amounts of alkaloid are sufficient[4].

First, the acidic proton of 1b is trapped by the alkaloid D^* ; after the decarboxylation step, the prochiral center (carbanion 2b) is protonated by the inductor $D^{*(+)}$-H to give the optically active product 3b, which is not racemized under these conditions.

To our knowledge, this is the first example of asymmetric synthesis by decarboxylation of hemiesters of malonic diacids.

In the decarboxylation of malonic diacids, the presence of an acidic proton in 3a requires one equivalent of alkaloid to trap it. So, if the mechanism is not actually different, remaining catalytic with regard to decarboxylation-protonation process, stoichiometric amounts of basic chiral inductor become necessary in addition to the aforementioned catalytic quantity[5].

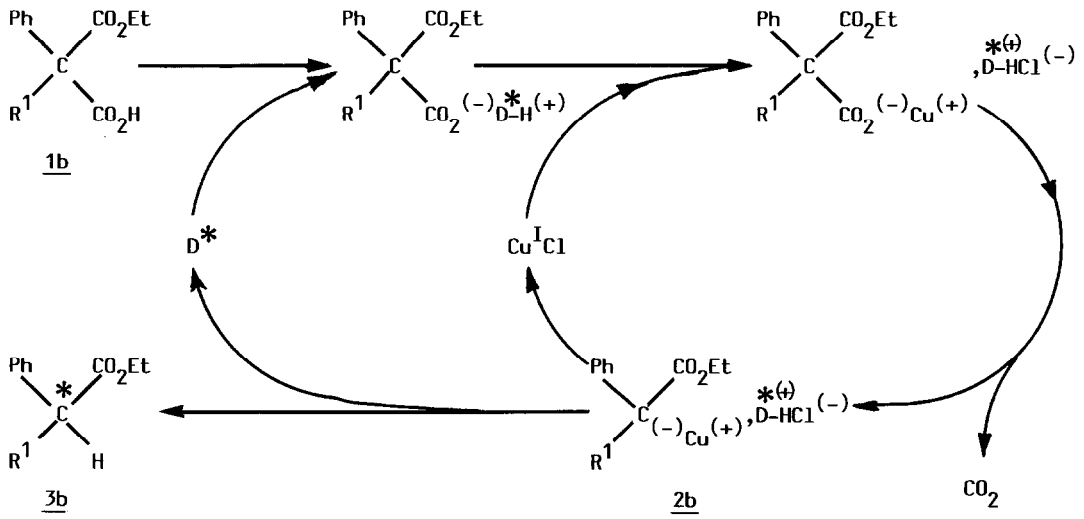
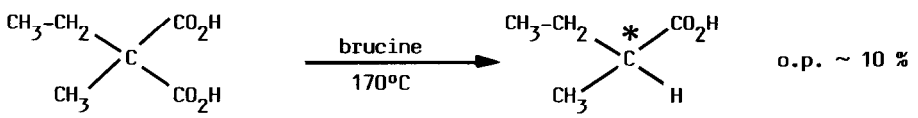


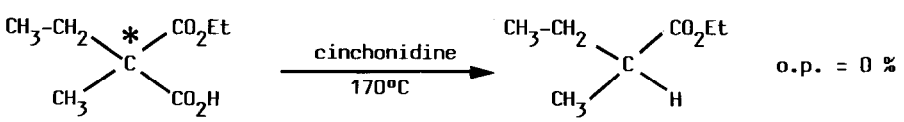
Figure 1

This asymmetric decarboxylation of malonic hemiesters is a new reaction ; asymmetric decarboxylation of malonic diacids was first reported by Marckwald[6] but the experimental conditions are very different :



Moreover, it is well established that an optically active solvent as cholesteryl benzoate does not induce asymmetric synthesis by thermal decarboxylation of ethyl phenyl malonic acid[7].

Kenyon and Ross[8] re-examined Marckwald's reaction and also reported that the corresponding optically active hemiester decarboxylates to racemic product :



In the same paper[8], Kenyon and Ross state that methyl phenyl malonic acid, under Marckwald's conditions, gives hydratropic acid with 0.2 % - 1.6 % optical purity, to be compared to our results (o.p. = 27 %).

The table shows that the optical purity is strongly dependent on apparently slight modifications of the alkaloid, e.g. cinchonidine (o.p. = 17 %), quinine (o.p. = 4 %) : the

mere difference is the presence of a methoxy group on the quinolein moiety of quinine. Furthermore, inversion of the configuration obtained in 3b when alkaloids (9-OH such as quinine or cinchonidine) are acetylated (9-OAc) is noteworthy ; optical purities are of the same magnitude (cinchonidine : 17 % [R-(-)] ; 9-acetoxy cinchonidine : 14.5 % [S-(+)]).The possibility to obtain in excess R or S enantiomers may be useful.

Different structural modifications of alkaloids are under investigation in order to distinguish between electronic and steric factors in the chiral induction step.

We have also observed that substitution of copper (I) by silver (I) gives the same chemical yield for decarboxylation but with a lower optical yield.

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4. Hemiester decarboxylations : the hemiester (1.5 mmol) 1b in 40 ml. of anhydrous acetonitrile is slowly added (6 hours) under argon to a stirred mixture of 0.6 mmol. of the alkaloid and 0.3 mmol. of Cu(I)Cl in 70 ml of acetonitrile at 60°C. The solution is further stirred for 2 h, solvent removed *in vacuo* and the residue taken up with ether and 5 % HCl. Purification of monoesters are achieved by thin layer chromatography. Chemical yields : 85-95 %. Purity confirmed by HPLC and ^{1}H NMR.
5. Phenylmalonic acid decarboxylations : the aforementioned procedure[4] is employed with 2.1 mmol. (0.6 + 1.5 mmol.) of alkaloid , 1.05 mmol. Cu(I)Cl and 1.5 mmol. of diacid 1a. Optical purity is determined after esterification and chromatography (TLC) of the ester.
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