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1-4 ADDITION OF CHIRAL HETEROCUPRATES TO CHALCONE

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Summary : Heterocuprates prepared from chiral aminoalcools, iminoalcohols and iminophenols react with chalcone. The best optical yield is 34%.

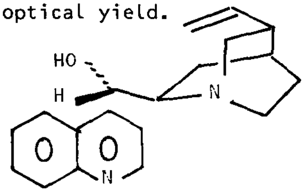
The addition of chiral cuprates to enones has been reported (1,2). However if we except a 68% enantiomeric excess obtained by using a very large excess of both organometallic and chiral agent (2) the optical yields are generally low and do not excess 16%.

Optically active hydroxylic compounds could be very useful agents for the generation of chiral heterocuprates $(R^{*}O\text{-}Cu\text{-}R')Li$ as Posner (3) had first described the transfer of the R' group to α-enones when R = t C_4H_9 or C_6H_5.

Unfortunately many easily available chiral alcohols are either primary or secondaryones and it is known that their copper^{I} derivatives are less stable than those derived from phenols or tertiary alcohols (4,5).

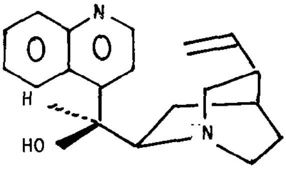
This prompted us to investigate the reaction of some alkoxy or phenoxy cuprates prepared from commercial (or direct derivative of) products I-IX where the copper species can be stabilized by internal complexation.

Moreover this chelation should lead to a more rigid transition state and thus to a better optical yield.



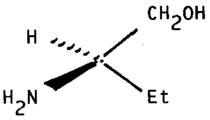
I cinchonidine

$[\alpha]_D$=-109,3°



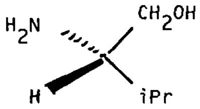
II cinchonine

$[\alpha_D]$ = 228°



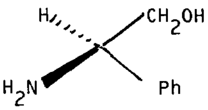
III R(-) 2-amino butanol

$[\alpha]_D$ = -10°



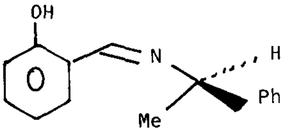
IV S(+) valinol

$[\alpha]_D$ = 14,6°

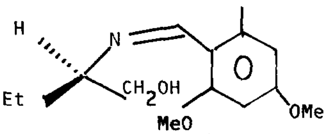


V R(-) α-phenyl glycinol

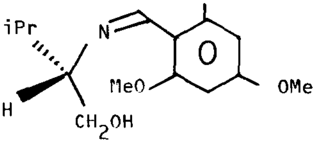
$[\alpha]_D$= -31,7°



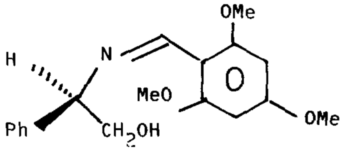
VI R(-) $[\alpha]_D$= -188° (6)



VII R(-) $[\alpha]_D$=-30,7°



VIII S(+) $[\alpha]_D$=38,8°



IX R(-) $[\alpha]_D$ = -12,9°

(VII-IX have been synthesized as in (6) and recrystallized in hexane or carbon tetrachloride).

Hetero-cuprates have been prepared as illustrated in scheme 1

$$CuI \xrightarrow[(M= Li,\ MgBr)]{2\ CH_3M} (CH_3)_2\ Cu\ M \xrightarrow{R^*OH} (R^*O\text{-}Cu\text{-}CH_3)M \quad \underline{1}$$

Scheme 1

This procedure, recently proposed by Mukaiyama (2) should be preferred to the more classical one, illustrated in scheme 2, which leads with the same reagents to poor chemical yields and very low enantiomeric excess (7)

$$R^*OH \longrightarrow R^*O^- \xrightarrow{CuI} R^*OCu \xrightarrow{CH_3M} \underset{\underline{1}}{(R^*\text{-}O\text{-}Cu\text{-}CH_3)M}$$

Scheme 2

By reaction with chalcone, <u>1</u> leads after usual work up to 1,3-diphenyl 1-butanone - the results are summarized in the following table.

Table:yields and enantiomeric excess

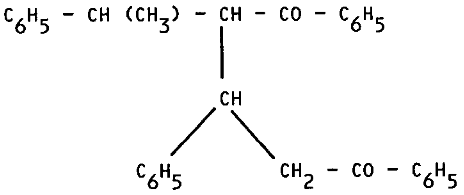
Entry	Inductor	Organo-metallic	Solvent	$[\alpha]_D$ CCl_4 (a)	%e e	yield %	configuration
1	I	MeLi	ether	5	34	21	S
2	II	MeLi	ether	0	0	8	-
3	II (b)	MeLi	ether	-2.5	17	29	R
4	III	MeLi	ether	0.41	3	44	S
5	IV	MeLi	ether	0.30	2	59	S
6	V	MeLi	ether	0	0	35	-
7	VI	MeLi	ether	-1.7	12	75	R
8	VII	MeMgBr	THF	-0.64	4	35	R
9	VIII (c)	MeLi	ether	2.15	15	59	S
10	VIII	MeMgBr	THF	3.6	25	23	S
11	IX	MeLi	ether	4.5	31	17	S
12	IX	MeMgBr	THF	0	0	30	-

(a) pure 1,3-diphényl 1-butanone has an optical rotation $[\alpha]_D^{25} = -14{,}6°$ (CCl_4) for its R isomer (8)

(b) cinchonine and chalcone are introduced together at -80°C in ethereous solution of Me_2CuLi and the mixture is allowed to warm slowly up to 25°C.Therefore it is likely that the true ee is largely higher than the 17% observed, due to the competitive reaction of the Me_2CuLi with chalcone.

(c) heterocuprate/chalcone ratio is : 4/1

The chemical yields are generally low although no starting chalcone (or in some cases only small traces) is recovered at the end of the reaction. The main reason lies in the fact the intermediate organometallic species can react with a second molecule of enone to give, after hydrolysis :



3

3 has been isolated in run 1 32% yield $[\alpha]^{20}_{D} = 5°$ (CCl_4)

In all cases heavy products resulting most probably from analogous polycondensations are obtained.

From the study of molecular models it is obvious that the heterocuprate obtained with cinchonine can hardly be chelated (severe steric hindrance).
Indeed this organometallic species is much less stable than its isomer (resulting from cinchonidine) and optical yield is much lower (compare entries 1 and 2,3).

In conclusion the 1-4 addition has been successfully performed with heterocuprates derived from accessible chiral agents.

In some cases the optical yields obtained with an inductor/chalcone ratio 1/1 (except in run 9) are fairly higher than those already reported.

These results encourage us to investigate further this promising area of asymmetric synthesis.

Experimental : The reactions were carried out under argon atmosphere at -20°C. In a typical procedure 2 mmol of CH_3Li (or CH_3MgBr) are added to 1 mmol of CuI in 5ml of solvent. After 15^{mn}, 1mmol of solid chiral agent is added and the mixture stirred for 15mn. Chalcone (1 mmol in 5ml of the same solvent) is then added and after 5mn the reaction is quenched with a 10% aqueous solution of KCN. The organic layer is washed by dilute HCl solution and the product isolated by preparative tlc (SiO_2, ethylacetate/hexane 20/80).

References and notes :

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