USE OF ALKALOIDS AND AMINOALCOHOLS IN CATALYTIC ASYMMETRIC INDUCTION: TEMPERATURE EFFECT ON THE ADDITION OF DIETHYLZING TO BENZALDEHYDE

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Abstract:

A surprising effect of temperature on enantiomeric excess in the stereospecific addition of diethylzinc to benzaldehyde with alkaloids as catalysts is reported, as well as the induction of chirality by some commercial aminoalcohols as catalysts in the same reaction.

The recent scientific interest in the highly enantioselective catalytic addition of dialkylzinc to carbonyl compounds (1 - 4) shows the importance of this type of reaction. In our aim to investigate the influence of temperature and the behaviour of the catalytic species on this reaction, we tried some commercial aminoalcohols as well as several alkaloids and their corresponding derivatives in the reaction of benzaldehyde with diethylzinc:

> PhCHO + Et₂Zn <u>chiral</u> PhCH→ Et catalyst(3%) OH

Our preliminary investigations showed that for this reaction - especially in respect to the introduction of chirality - the effect of temperature changes seems rather low for the aminoalcohols. Thus, the e.e. of 83% obtained with Chirald at room temperature was only raised by four percent at $-10^{\circ}C$. With (-)-N-methylephedrine, an increase in e.e. of only six percent was observed, namely to 81%, by lowering the temperature to $-10^{\circ}C(Table I)$.

Catalyst	Time[h]	T[°C] ^a	b Yield[%]	e.e.[%]	Config.
(S)-(+)-Prolinol ^d	38	- 10	66	7	(R)
	40	r.t.	89	19	(R)
l,4-bis(dimethylamino) e -2,3-butanediol	38 16	- 10 r.t.	88 99	61 45	(R) (R)
(-)-N-Methylephedrine	38	- 10	81	81	(R)
	16	r.t.	98	75	(R)
Chirald ^f	38	- 10	66	87	(R)
	16	r.t.	98	83	(R)

<u>Table I:</u> Aminoalcohol's Influence on Chemical and Optical Yield in Dependence of Temperature (6):

(a): r.t. means room temperature

(b): Measured as &-conversion into the product by GC, column CPSIL 5, (25m).

- (c): Determined on GC after derivatization with isopropylisocyanate on chiral phase XE-60 S-Valine, (50m) (7).
- (e): Derived from (S,S)-(+)-3,4-isopropylidenedioxy-N,N,N'N'-tetramethyl-1,4butanediamine 1 (8), through acid hydrolysis: 0,01 mole of 1 were dissolved in 10 ml methanol. Under continuous stirring, 10 ml of 15% HCl were added and the reaction mixture was heated to reflux during 2 h. On cooling, solid NaOH was added to basic reaction. The solvents were flashed off and the residue was distilled on a Büchi Kugelrohr oven (b.p.~115°C/1.2 mm Hg). The diol was fully characterized by IR-, H- and 13 and C-spectroscopy (9).
- (d): Result in accordance with ref. (1) .
- (f): Chirald : (2S,3R)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol.

On the other hand, at room-temperature all reactions except for one were practically terminated after 16 h, whilst at -10° C the conversion after 38 h was usually in the order of 90%. The applied aminoalcohols only led to the (R)-configuration in the product.

An interesting feature is revealed with the alkaloids: in short reaction times (15 min.), the best e.e. (73%) was obtained at elevated temperature and not, as could be expected, at a lower temperature(5). Through the appropriate choice of the alkaloid, it is possible to obtain either product enantiomer in excess (Table II):

Catalyst	Time[h]	T[°C] ^a	b Yield[%]	e.e.[%]	Config.
Quinine	38	- 10	90	48	(R)
	16	r.t.	97	64	(R)
	3	43	97	68	(R)
	0.5	70	95(3) ^a	69	(R)
	0.25	100	95(4)	73	(R)
Cinchonidine	38	- 10	92	38	(R)
	16	r.t.	98	57	(R)
	3	43	99	62	(R)
	0.5	70	98(2)	67	(R)
	0.25	100	94(5)	71	(R)
Cinchonine	38	- 10	91	46	(\$)
	16	r.t.	98	46	(S)
	3	43	98	55	(S)
	0.5	70	98(2)	61	(S)
	0.25	100	94(4)	66	(S)
Quinidine	38	- 10	92	45	(S)
	16	r.t.	98	51	(S)
	3	43	98	57	(S)
	0.5	70	97(3)	66	(S)
	0.25	100	96(4)	69	(S)

<u>Table II:</u> Influence of Selected Alkaloids on Chemical and Optical Yield in Dependence of Temperature (6) :

(+): Footnotes refer to Table I.

(d): Numbers in brackets indicate percentage benzyl alcohol generated.

It is well established that chiral aminoalcohols are effective catalysts for the reaction of dialkylzinc reagents on aromatic aldehydes (4b), though the reaction mechanism is still unclear. It seems apparent, however, that the aminoalcohol undergoes quantitative conversion with the dialkylzinc to form a Lewis acid (10,11), which in turn activates the carbonyl function of the reacting aldehyde. On the other hand, the amine part of the active species changes the state of hybridisation of the dialkylzincs, which then attacks the carbonyl group. At this stage, a final description of the mechanistic pathway of the reaction cannot yet been given, unless further work on the subject gives rise to new perspectives for the action of dialkylzinc reagents also on other reactions.

References and Notes:

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(6) Addition of benzaldehyde (9.4 mmol) in dry toluene (5 ml) to a mixture prepared from diethylzinc (11.75 mmol) and the catalyst (1.28 mmol) in dry toluene (5 ml) at reaction temperature under a shielding atmosphere of

nitrogen. See also Ref.(2), also for the work-up of the reaction mixture.

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- (9) <u>IR</u>(cm⁻): 3400(broad), 2942 (s), 2817 (s), 2772 (s), 1455 (s), 1285 (s), 1037 (s), 849 (s). <u>H (ppm):</u> 2.04 (singlet, 12 H), 2.23-2.74 (multiplet, 4 H), 3.72 (triplet, 2H), ~4.4 (broad peak, 2H). <u>C (ppm):</u> 45.9 (Methyl), 62.8 (CH₂), 69.5 (CHOH).
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