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An Easy and Fast Way to Determine the Enantiomeric purity of Substituted Cyclanones

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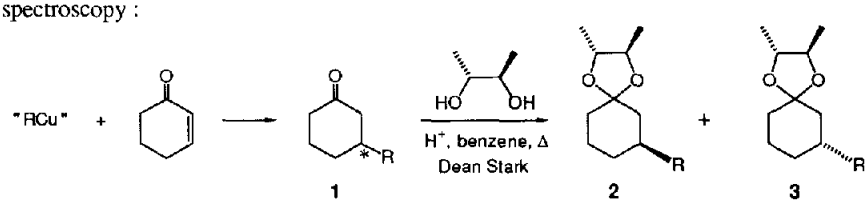
Abstract *: The determination of the enantiomeric purity of 2 or 3-substituted cyclanones, particularly cyclohexanones, is conveniently achieved by derivatisation into cyclic aminals with commercially available (R, R)-1,2-diphenylethylenediamine. The derivatisation procedure is directly done into the NMR tube, instantaneously, and* ^{13}C *NMR allows an accurate measure of the ee.*

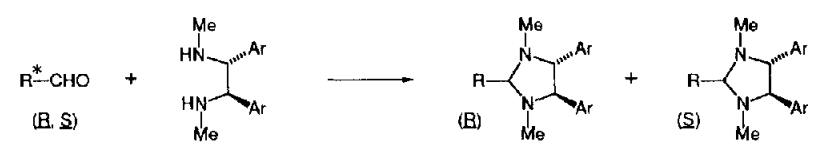
In the course of our studies on the asymmetric conjugate addition of organocopper reagents to cycloalkenone,[1] we needed a tool to determine the enantiomeric purity of the final adduct. As most chemists working in this field,[2] we relied on Wynberg's method,[3] where a 3-substituted cyclohexanone, for example **1**, is derivatized as diastereomeric ketals **2** and **3** with optically pure 2,3-butanediol. These ketals are then analyzed by ^{13}C NMR spectroscopy :



1 **2** **3**

By analogy, this method was also used with chiral aldehydes by formation of acetals.[4] Although very efficient, as a reliable way to know the ee of such ketones, the formation of ketals needs a Dean Stark apparatus to trap azeotropically the formed water and the reaction takes a few hours to be completed. For our part, we needed a less time consuming way to obtain the same result.

We described, recently, that the diastereomeric aminals **5** and **6** obtained by reaction of an optically pure diamine **4** and a chiral aldehyde is a very efficient and fast method to determine the enantiomeric purity of aldehydes : [5]

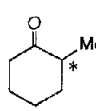


4 **5** **6**

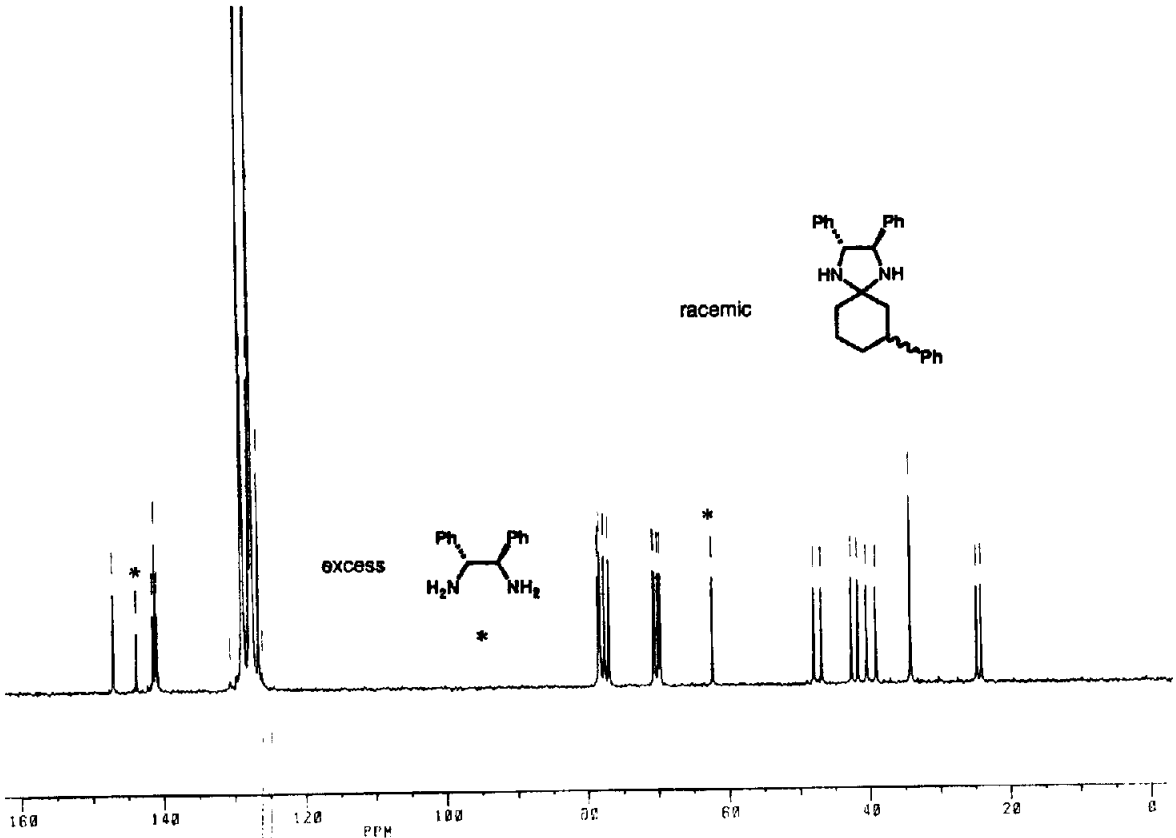
However, N,N' dialkylated diamines such as **4** do not form aminals of ketones.[6] In contrast, primary diamines were reported to form aminals with certain ketones, particularly with substituted cyclohexanones.[7] Only, under forcing conditions the bis-imine is isolated.[8]

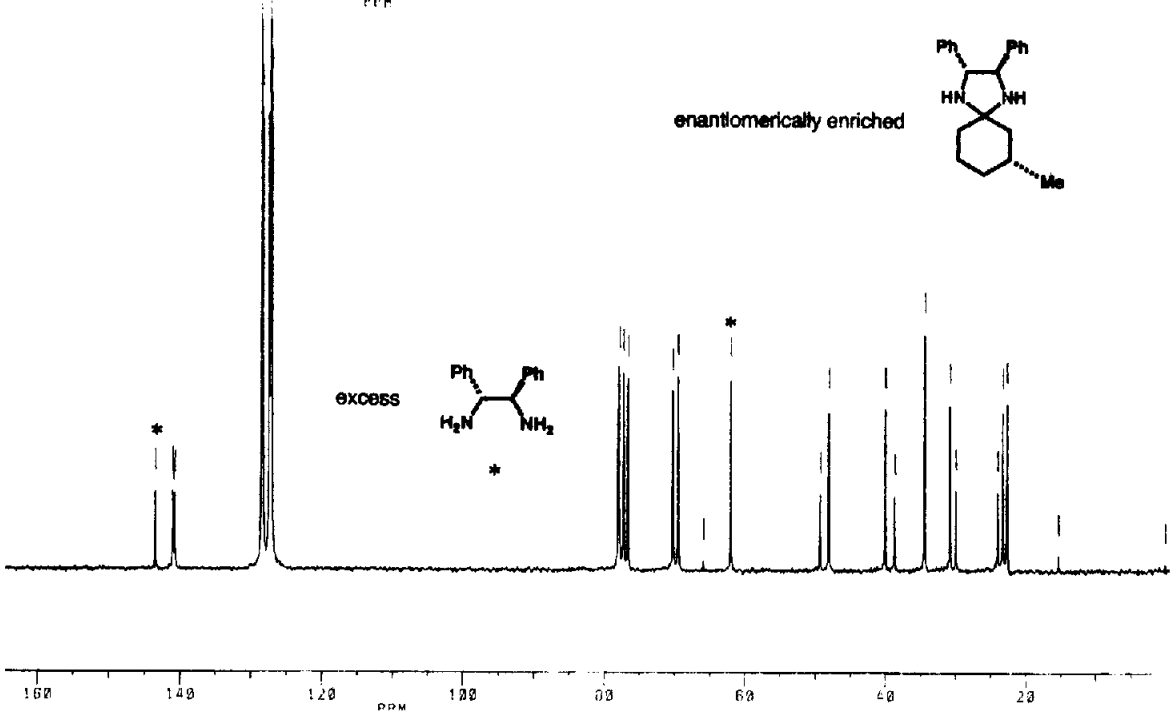
7 8 9

TABLE

Aminal		C1	C2	C3	C4	C5	C6	C7	Comments [a]
diastereomeric **ketals**	**2a**	108.49	45.91	30.12	23.44	35.82			taken from ref 3b
n=1	**3a**	108.49	44.98	30.61	23.05	36.89			
R=Me	Δδ	-	*(0.93)*	*(0.49)*	*(0.39)*	*(1.07)*			
n=1	**8a**	77.86	49.15	29.88	23.89	38.58	70.05	69.36	see NMR spectrum
R=Me	**9a**	77.86	47.93	30.70	23.16	39.92	70.14	69.36	on next page
	Δδ	-	*(1.22)*	*(0.82)*	*(0.73)*	*(1.34)*	*(0.09)*	-	
n=1	**8b**	77.82	46.78	36.57	31.93	39.09	70.07	69.38	
R=Et	**9b**	77.62	45.93	37.37	31.78	40.31	70.11	69.32	
	Δδ	*(0.20)*	*(0.85)*	*(0.80)*	*(0.15)*	*(1.22)*	*(0.04)*	*(0.06)*	
n=1	**8c**	77.99	47.36	35.01	32.61	39.26	70.30	69.60	
R=nBu	**9c**	77.99	46.49	35.91	32.44	40.48	70.30	69.53	
	Δδ	-	*(0.87)*	*(0.90)*	*(0.17)*	*(1.22)*	-	*(0.07)*	
n=1	**8d**	78.38	47.76	38.93	24.54	41.49	70.37	69.63	see NMR spectrum
R=Ph	**9d**	78.24	46.67	40.26	23.69	42.43	70.52	69.53	on next page
	Δδ	*(0.14)*	*(1.09)*	*(1.33)*	*(0.85)*	*(0.94)*	*(0.15)*	*(0.10)*	
n=1	**8e**	77.99	47.40	35.04	32.52	39.33	70.27	69.56	
R=-$(CH_2)_4$-OtBu	**9e**	77.82	46.51	35.93	32.40	40.51	70.27	69.56	
	Δδ	*(0.17)*	*(0.89)*	*(0.89)*	*(0.12)*	*(1.18)*	-	-	
n=1	**8f**	78.06	47.27	35.07	32.51	39.25	70.31	69.61	
R= -$(CH_2)_3$- 	**9f**	78.06	46.31	35.93	32.39	40.48	70.50	69.56	
	Δδ	-	*(0.96)*	*(0.86)*	*(0.12)*	*(1.23)*	*(0.19)*	*(0.05)*	
"	**8f**	77.01	47.13	35.04	32.66	39.72	70.39	69.55	
	9f	76.77	46.86	36.03	32.50	40.47	70.47	69.46	b
	Δδ	*(0.24)*	*(0.27)*	*(0.99)*	*(0.16)*	*(0.75)*	*(0.08)*	*(0.09)*	
n=0	**8g**	87.21	49.68	32.78	32.93	40.99	70.52	70.22	derivatization
R=Me	**9g**	87.12	50.40	33.30	33.38	41.83	70.52	70.39	completed after 3h
	Δδ	*(0.09)*	*(0.72)*	*(0.52)*	*(0.45)*	*(0.84)*	-	*(0.17)*	
n=0	**8h**	86.72	47.85	not	not	40.52	70.18	70.18	derivatization
R=nBu	**9h**	86.72	48.57	determined	determined	41.42	70.46	70.37	completed after 3h
	Δδ	-	*(0.72)*			*(0.90)*	*(0.28)*	*(0.19)*	
n=2	**8i**	80.55	49.95	38.58	36.03	43.92	70.00	69.78	derivatization
R=-$(CH_2)_4$-OtBu	**9i**	80.95	50.28	38.78	36.87	43.42	69.61	69.56	completed after 3h
	Δδ	*(0.40)*	*(0.33)*	*(0.20)*	*(0.84)*	*(0.50)*	*(0.39)*	*(0.22)*	
	**8j**	78.90	42.10	31.93	23.66	39.67	70.60	76.44	
	9j	78.90	40.49	32.52	24.82	40.95	71.23	77.08	
	Δδ	-	*(1.61)*	*(0.59)*	*(1.16)*	*(1.28)*	*(0.63)*	*(0.64)*	

a. All spectra are recorded on a Brucker AC 200 or a Jeol GSX 400 instrument. Unless otherwise noted, the solvent is $CDCl_3$.
b. Solvent C_6D_6.


racemic
Ph
Ph
HN
NH
Ph
excess
Ph
Ph
H2N
NH2
*
*
*
160
140
120
100
80
60
40
20
0
PPM


enantiomerically enriched
Ph
Ph
HN
NH
Me
excess
Ph
Ph
H2N
NH2
*
*
*
160
140
120
100
80
60
40
20
PPM

We found that optically pure (R, R)-1,2-diphenyl ethylene diamine **7** (now commercially available) reacts immediately with 3-substituted cyclohexanones to form the diastereomeric aminals **8** and **9**. Analysis by ^{13}C NMR either in $CDCl_3$ or C_6D_6 solvent shows a slightly larger separation of signals than do diastereomeric ketals. However, the main advantage of this new method lies in the ease of manipulation. *The ketone and the diamine (in slight excess) are mixed directly into the NMR tube. The reaction is over in a few seconds and the formation of water is indicated by the turbidity of the content of the NMR tube. Addition of a single piece of 4Å molecular sieve gives again a clear homogeneous solution.*

In the case of 3-substituted cyclopentanones and cycloheptanones, the derivatization reaction with diamine **7** is slower, taking a few minutes or 2-3 hours. Acyclic ketones and enones do not react. This result is in complete agreement with the previous observations on the kinetics of such cyclizations.[7]

In the figure (previous page) are represented the ^{13}C NMR spectra of the aminals of racemic 3-phenyl cyclohexanone **8d** and **9d** and enantiomerically enriched (R)3-methyl cyclohexanone **8a** and **9a**. The general shape of the spectrum of aminals is in close analogy to the spectrum of the corresponding ketals[3a] and the measure of ee is done on the same carbons. In addition, more signals are clearly distinguished, giving a more accurate value of the enantiomeric excess. Some representative examples are shown in the Table. In all the cases where enantiomerically enriched cyclanones were available, the corresponding diastereomeric ketals were also formed, and the ee values were in complete agreement with those determined via aminal formation. Moreover, the assignement of the absolute stereochemistry seems to follow the same rules as those described for diastereomeric ketals.[3b]

In summary, we described a very practical way to determine the enantiomeric excess of substituted cyclanones, which is particularly fast for cyclohexanones.

Copies of the ^{13}C NMR spectra are available upon request

References and notes.

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