Attempts to Carry Out Enantioselective Reactions in a Static Magnetic Field

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In a recent article in this journal Zadel, Eisenbraun, Wolff, and Breitmaier reported enantioselective reactions in a static magnetic field.[1] The results were dramatic: prochiral aldehydes were treated with aliphatic Grignard reagents to produce (chiral) alcohols with enantiomeric excesses (*ee*) of 57–98%, and reductions of some aryl alkyl ketones with lithium aluminum hydride (LAH) proceeded with 11–68% *ee*.

These results have produced excitement in the chemical community. At an informal meeting during the recent Bürgenstock Stereochemical Conference in Switzerland Dr. Zadel reported on these remarkable experiments to a large group of highly interested stereochemists. The interest stems first from the fact that these results seem to contradict straightforward theory from which one concludes that static magnetic fields are not chiral.[2] Previous claims of enantioselective syntheses in magnetic fields have been shown to be spurious; a recent example not cited in reference [1] involves the electrochemical reduction of α-keto acids in magnetic fields.[3, 4] Circumventing these theoretical barriers might be possible; we mention, for example, the concept of "true" and "false" chirality as introduced by Barron.[5] Another possibility is that a small stereochemical bias might be amplified by a large nonlinear effect[6] or asymmetric autocatalysis.[7]

From the practical side these claims of enantioselective reactions could have profound implications for the manner in which asymmetric synthesis is carried out in academic and industrial laboratories. In an extreme scenario the painstakingly developed methods relying on chiral auxiliaries and optically active catalysts could be supplanted by simply conducting reactions in large magnets.

Independent confirmation of these important experiments is clearly of great importance to the chemical community.

We have repeated the Breitmaier experiments in our own laboratories with magnets having flux densities of 0.3 and 1.2 Tesla. In addition our colleague Prof. Bert Meijer in Eindhoven has also carried out these experiments in magnets available to him and has obtained results fully analogous to ours as described below. We have also contacted Prof. Breitmaier and have carried out experiments in his laboratories in Bonn with the same magnets used in his original work. Glassware and chemicals were brought from our laboratories, and the enantiomeric excesses were determined in Groningen.

We take this opportunity to express our sincere appreciation to Prof. Breitmaier and his co-workers for their hospitality, as well as openness and cooperativity in helping us to reproduce these experiments. The results of our experiments are summarized in Tables 1 and 2.

Table 1. Reduction of acetophenone [a] by addition to LAH.

Run	B_o [T]	LAH [mg]	Solvent	Aceto-phenone [a]	t [d] [min]	Con-version [%]	Isolated yield [%]
1 [b]	0.3	90	2 mL THF/ 2 mL C_6H_6	200 mg in 200 μL C_6H_6	30	100	86
2 [b]	0.3	80	2 mL THF/ 2 mL C_6H_6	204 mg in 1 mL C_6H_6	60	100	91
3 [b]	0.3	122	2 mL THF/ 2 mL C_6H_6	300 mg in 3 mL C_6H_6	60	100	86
4 [b]	0.3	80	2 mL THF/ 4 mL C_6H_6	206 mg in 200 μL C_6H_6	75	100	82
5–8 [b]	0.3	Runs 1–4 repeated in C_6H_6; comparable conversions					
9–12 [b]	0.3	Runs 1–4 repeated with twice the concentrations; yields ca. 70–75%					
13–15 [b]	0.3	Runs 1, 3, and 4 repeated in 1.5 mL THF and 0.5 mL C_6H_6; comparable conversions					
16–18 [b]	0.3	Runs 1, 3, and 4 repeated in 0.5 mL THF and 1.5 mL C_6H_6; comparable conversions					
19 [b]	0.3	Run 1 repeated in THF; comparable conversion					
20 [b]	0.3	130	1 mL THF	359 mg in 2.5 mL C_6H_6 [a]	40	100	> 75
21 [b]	0.3	25	0.6 mL THF/ 1.3 mL C_6H_6	90 mg in 2 mL C_6H_6 [a]	45	100	95
22 [c]	0.3	80	2 mL THF/ 4 mL C_6H_6	289 mg [a] in 6 mL C_6H_6	60	90	69
23–26 [b]	1.2	Runs 1–4 repeated; comparable conversions					
27–43 [b]	1.2	Runs 5–21 repeated; comparable conversions					
44 [c]	2.3	80	2 mL THF/ 4 mL C_6H_6	228 mg [a] in 6 mL C_6H_6	60	90	69

[a] Acetonaphthone was used in runs 20–22, propionaphthone in run 44. [b] Experiments conducted in Groningen. [c] Experiments conducted in Bonn in the Breitmaier laboratory. [d] Addition time.

All experiments were performed using Schlenck techniques except for the experiments conducted in Bonn, which were carried out without special precautions. Solvents were dried over Na/K. The solutions were added through a Teflon tube attached to a stainless steel needle that was kept 2–3 mm above the surface of the solution. Alternatively, the Teflon tube without an attached stainless steel needle was kept 2–3 mm above the surface of the solution. The experiments were performed at room temperature.

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Table 2. Reaction of benzaldehyde with CH_3MgI in a magnetic field flux of 0.3 T.

Run	CH_3MgI	Benzaldehyde	Addition time [min]	Conversion [%]	Isolated yield [%]
1 [a]	1.4 mmol in 1 mL Et_2O	100 µL in 0.2 mL C_6H_6/ 1 mL Et_2O	60	100	80
2	Run 1 repeated; addition over 90 min; comparable conversion				
3 [b]	2.7 mmol in 3 mL Et_2O	300 µL in 0.2 mL C_6H_6/ 1 mL Et_2O	90	100	80

[a] The solution of benzaldehyde was added to the Grignard reagent. [b] The Grignard reagent was added to the solution of benzaldehyde.

Two magnets were used in Groningen: a 0.3 T permanent horseshoe magnet with a homogeneous magnetic field between the poles, dimensions: 4 cm (diameter) × 3 cm (separation); and an electromagnet (Bruker B-E 20 C 8) adjusted to 1.2 T with a homogeneous field between the poles, dimensions: diameter 7.8 cm (diameter) × 3 cm (separation). The field strengths were checked with a Gaussian meter. The magnets used in Bonn were like those described in reference [1]; the Bruker magnet was adjusted to 2.3 T. The field strengths were not checked.

The reaction mixtures were quenched with an excess of water and extracted with ether. Conversions were determined by ^1H NMR spectroscopy (300 MHz, recorded in $CDCl_3$) or gas chromatography (GC). Optical rotations were measured in methanol or toluene, and the enantiomeric excesses were determined by GC using a chiral column (WCOT fused silica, CP-cyclodextrine-β-2,3,6-M-19, 0.25 mm × 50 m, 7501 Chrompack). Baseline separations were obtained in all cases. The experimental error in the *ee* determination is estimated to be 1%. In no case did we observe a distribution of enantiomers that deviated within experimental error from a 50:50 ratio.

At this time on the basis of the experiments that have been carried out, we must conclude that we have been unsuccessful in reproducing the Breitmaier results. At the request of the editor of *Angewandte Chemie* we make these initial results available.

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Absolute asymmetrische Synthese allein durch ein statisches homogenes Magnetfeld?

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Die absolute asymmetrische Synthese ist von größter Bedeutung für das Entstehen von Chiralität auf der Erde. Die physikalischen und chemischen Grundlagen für die Erzeugung von Chiralität ohne chirale Hilfsstoffe sind wohlbekannt[1]. Von daher überraschte eine Veröffentlichung von Breitmaier et al.[2], wonach aus homogener Lösung allein durch Anlegen eines statischen homogenen Magnetfelds (0.2–2.1 T) eine effiziente (*Re*)/(*Si*)-Differenzierung prochiraler aromatischer Aldehyde und Ketone bei Reduktion bzw. Grignard-Reaktion (Schema 1) eintreten soll, wobei die gebildeten Alkoholate gallertartig ausfallen. Die *ee*-Werte der isolierten Alkohole sollen sehr hoch (bis 98%) und leicht reproduzierbar sein[2]. Regellos sollen die (*R*)- und (*S*)-Produkte mit jeweils gleichem *ee*-Wert entstehen[2]. Entgegen wissenschaftlichem Brauch verzichtete die Darstellung völlig auf Erklärungsversuche oder Erläuterungen zur Frage, wie durch ein homogenes Magnetfeld ohne weitere Vorkehrungen Seitendifferenzierungen erreicht werden könnten, obwohl dabei grundlegende Prinzipien verletzt würden. Dies hätte die Veröffentlichung der Arbeit aufhalten müssen, nicht aber ihre schnelle Verbreitung in der Sekundärliteratur[3] nach dem Erscheinen. Eine Klärung der Sachverhalte hinsichtlich der absoluten asymmetrischen Synthese[1] ist auch aus förderungspolitischen Gründen erforderlich, denn dieses wichtige Forschungsgebiet darf bei Drittmittelgebern und deren Gutachtern nicht in den Verdacht der unnötigen Kompliziertheit geraten.

$$ArCRO + LiAlH_4 \longrightarrow ArCHR(OH) \longleftarrow RMgX + ArCHO$$

Schema 1.

Die *theoretische Analyse* führt zu schwerwiegenden inneren Widersprüchen in der Arbeit von Breitmaier et al.[2]. Ein statisches Magnetfeld im homogenen Bereich ist gerichtet, aber keinesfalls chiral. Es kann also für sich allein keine Chiralität in Form von *ee*-Werten bei der Reaktion achiraler Moleküle erzeugen, etwa nach dem vom magnetischen Circulardichroismus

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