# Stereoselective synthesis of enones from the reaction of aldehydes with sterically hindered dimethylaluminum enolates

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## Abstract

The equimolar reaction between $Me_3Al$ and the methyl ketones $(2,4,6-R_3–C_6H_2)C(O)CH_3$, where R = Me or $^iPr$, results in exclusive formation of the enolization products $[\{Me_2AlOC(2,4,6-R_3–C_6H_2)=CH_2\}_2]$, **1** and **2**, upon heating to reflux temperature in toluene solution. The property of $Me_3Al$ acting as a base rather than a nucleophile in these reactions is due to the sterically hindered nature of the ketones. Crystallographic analysis of **2** revealed a dimeric complex where the metal centers are bridged by the enolate anions, consistent with the previous studies of **1**. Addition of a series of aldehydes to hexane solutions of **1** and **2**, followed by heating to reflux for several hours gave enone products in generally high conversions. The presumed aluminum aldolate intermediates were not detected by in situ monitoring studies and are presumably short-lived under the reaction conditions. The enone products from the addition reactions were formed predominantly as the *E*-isomers with good to excellent stereoselectivities.
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## 1. Introduction

The reaction between triorganoaluminum compounds and ketones commonly results in four outcomes: acid-base complex formation, reduction via β-hydride elimination, direct alkylation across the carbonyl, and enolization [1]. The product distribution is influenced by all the expected factors including the nature of the organic anions, the size and electronics of the ketone, the temperature of the reaction and the solvent media used [2,3]. In general, these reactions produce a mixture of products and hence their utility in synthesis has remained limited [4,5]. We previously reported that the reaction between $Me_3Al$ and 2,4,6-trimethylacetophenone in toluene under ambient temperature resulted in formation of the complex $[Me_3Al \cdot O=C(2,4,6-Me_3–C_6H_2)Me]$, which cleanly converted to the enolate $[\{Me_2AlOC(2,4,6-Me_3–C_6H_2)=CH_2\}_2]$, **1** upon heating to reflux for several

hours [6,7]. The behavior of $Me_3Al$ as a base rather than a nucleophile to give exclusive enolization was somewhat unexpected considering the small size of the organic moiety [8,9]. The key to this selectivity was found to be dependant on the steric encumbrance of the aromatic ketone, where disubstitution at the *ortho* positions of the ring by methyl groups was required for enolization to be the dominant reaction pathway. We now report an extension to this work, investigating the reaction chemistry of two aluminum enolates derived by this direct enolization route with a series of aldehydes. In addition, the crystal structure of a new dimethylaluminum enolate intermediate has been elucidated.
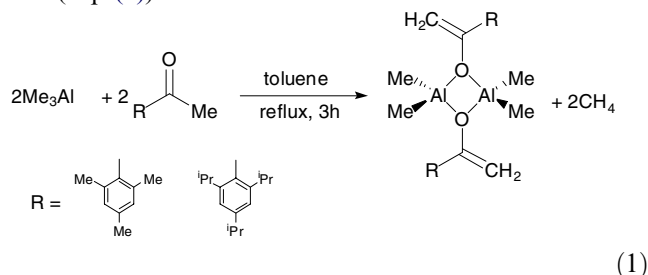
## 2. Results and discussion

### 2.1. Syntheses and structural characterization

The enolate complex $[\{Me_2AlOC(2,4,6-Me_3–C_6H_2)=CH_2\}_2]$, **1**, was prepared as previously described [6]. For

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comparative purposes, the enolate [{Me₂AlO-C(2,4,6-$^i$Pr₃–C₆H₂)=CH₂}₂], **2**, was targeted and successfully prepared as the sole product from the equimolar reaction of Me₃Al with 2,4,6-triisopropylacetophenone in toluene solution after heating to reflux for 3 h (Eq. (1)).

$$2Me_3Al + 2 \underset{R}{\overset{O}{\parallel}}\!\!C\!\!-\!\!Me \xrightarrow[\text{reflux, 3h}]{\text{toluene}} \text{(product)} + 2CH_4$$

R =  (structures shown)

(1)

Removal of the solvent in vacuo and replacement by hexane followed by cooling the solution to −45 °C resulted in the precipitation of high quality crystals of **2**. In turn, this allowed the characterization of **2** by ¹H and ¹³C NMR spectroscopy, and also by single-crystal X-ray diffraction. The ¹H NMR spectrum of **2** in C₆D₆ shows a single set of signals for the aromatic *meta*-Hs and also for the methyl groups attached to the aluminum, consistent with the expected composition. A pair of doublets due to the olefinic protons are present and two independent sets of $^i$Pr groups in a 2:1 ratio arising from the *ortho*- and *para*-units, respectively, complete the spectrum. A somewhat different pattern is found in the ¹³C NMR spectrum of **2**. Three independent methyl resonances at δ 23.35, 24.48 and 27.07 are found, along with two methine signals at δ 31.23 and 35.15. This pattern suggests that the methyl carbons of the *ortho*-isopropyl groups are inequivalent. Indeed, the recent characterization by Kunicki of the closely related complex [Ph₂AlOC(2,4,6-$^i$Pr₃–C₆H₂)=CH₂}₂], **3**, displays a very similar ¹³C NMR spectrum [10]. This pattern of signals can be explained by restricted rotation of the aromatic groups locking the isopropyl units into asymmetrical environments [11]. Interestingly, the ¹H NMR spectrum of **3** also displays this behavior whereas that of **2** shows only a single set of resonances for the *ortho*-units. This suggests greater flexibility in **2** due to smaller methyl groups being attached to the metal compared with phenyl groups in **3**. These studies are also consistent with the expected dimeric aggregation remaining intact in solution.

X-ray crystallographic studies of **2** revealed the expected dimeric arrangement, with a central Al₂O₂ ring (Fig. 1). This structure is in accord with those previously reported for **1** and **3** [6,10]. Two almost identical but independent dimers are formed within the unit cell of **2** and their key bond lengths and angles are given in Table 1. In general, the geometric parameters in **2** are similar to those reported for related Al₂O₂ ring systems [12]. For example, the mean Al–O distance of 1.870 Å (range 1.863–1.878 Å), and the mean Al–C distance of 1.950 Å
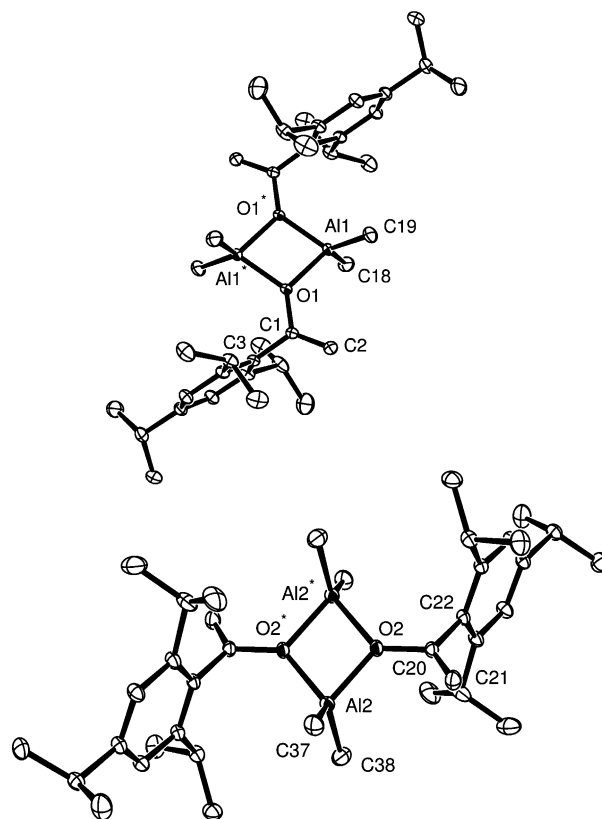


Fig. 1. Crystal structure of the two independent molecules of **2**, showing two alternative views of the dimers. Hydrogen atoms are removed for clarity.

(range 1.949–1.952 Å) are within the ranges of those found in **1** and **3**. Also the mean Al–O–Al and O–Al–O angles of 100.75° and 79.25° in **2** are within 1.5° of those in **1** and **3**. In all three complexes **1**–**3** the enolate group sits approximately in the same plane as the Al₂O₂ ring, with Al–O–C=CH₂ dihedral angles of 23.3 and 22.0° in **1** and **3**, whereas the two independent dimers of **2** have these angles at 28.1° and 31.8°. The overall similarity of **1**–**3** indicates that the increase in steric hindrance at the *ortho*-positions of the aromatic ring in **2** and **3** compared to **1**, or the increased size of the organic anion of **3** compared to that in **1** and **2** has little notable effect on the structures adopted. Nevertheless, the structural characterization of **2** represents an addition to the small handful of crystal structures that have been successfully completed for aluminum enolates derived from simple ketones [13].

### 2.2. Reaction of enolates 1 and 2 with aldehydes

We were interested in determining the reactivity of the aluminum enolates **1** and **2** with aldehydes. From our perspective the most desirable reaction was aldol addition, due to the importance of this transformation in the stereoselective formation of new carbon–carbon

Table 1
Selected bond lengths (Å) and angles (°) for **2**[a]

| | |
|---|---|
| Al(1)–O(1) | 1.8721(10) |
| Al(1)–C(19) | 1.9487(15) |
| O(1)–C(1) | 1.3918(13) |
| Al(2)–O(2)#2 | 1.8648(11) |
| Al(2)–C(37) | 1.9490(14) |
| O(2)–C(20) | 1.3919(14) |
| Al(1)–O(1)#1 | 1.8626(10) |
| Al(1)–C(18) | 1.9516(16) |
| C(1)–C(2) | 1.3305(16) |
| Al(2)–O(2) | 1.8783(10) |
| Al(2)–C(38) | 1.9505(15) |
| C(20)–C(21) | 1.3286(17) |
| | |
| O(1)#1–Al(1)–O(1) | 79.17(5) |
| O(1)–Al(1)–C(19) | 112.36(6) |
| O(1)–Al(1)–C(18) | 109.32(6) |
| Al(1)#1–O(1)–Al(1) | 100.83(4) |
| C(1)–O(1)–Al(1) | 127.35(7) |
| O(2)#2–Al(2)–O(2) | 79.33(5) |
| O(2)–Al(2)–C(37) | 114.40(6) |
| O(2)–Al(2)–C(38) | 107.81(6) |
| Al(2)#2–O(2)–Al(2) | 100.67(5) |
| C(20)–O(2)–Al(2) | 126.93(7) |
| O(1)#1–Al(1)–C(19) | 114.46(6) |
| O(1)#1–Al(1)–C(18) | 112.10(6) |
| C(19)–Al(1)–C(18) | 121.54(7) |
| C(1)–O(1)–Al(1)#1 | 131.81(7) |
| C(2)–C(1)–O(1) | 120.47(10) |
| O(2)#2–Al(2)–C(37) | 114.24(6) |
| O(2)#2–Al(2)–C(38) | 112.12(6) |
| C(37)–Al(2)–C(38) | 121.25(6) |
| C(20)–O(2)–Al(2)#2 | 132.40(7) |
| C(21)–C(20)–O(2) | 120.28(10) |

[a] Symmetry transformations used to generate equivalent atoms: #1 $-x + 1, -y + 2, -z + 1$, #2 $-x + 1, -y + 2, -z + 2$.

bonds [14]. However, potentially problematic alternative reaction pathways include nucleophilic addition of the methyl groups across the highly reactive carbonyl groups and also for the complexes to act as bases to produce bisenolate species [15,16]. Initially, a test reaction between **1** and pivaldehyde in $d_6$-benzene solution was monitored by $^1$H NMR spectroscopy. No reaction was observed over several hours at ambient temperature and the chemical shift positions indicated no discernable interaction between the species present in solution. NMR analysis of the mixture following heating to reflux temperature for 3 h revealed remarkably clean conversion to an enone product along with traces of unreacted enolate **1** (Eq. (2)).

$$(2)$$
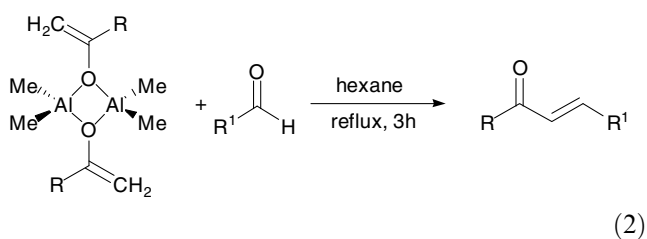
Encouraged by these results a series of reactions using **1** and **2** as enolate synthons and pivaldehyde, benzaldehyde, mesitylaldehyde, isobutyraldehyde and isovaleraldehyde as electrophiles were performed. In each instance the reactions were conducted on a 1-mmol scale in hexane solution and the products were determined by GCMS and $^1$H NMR spectroscopy after aqueous work-up. The results of the reactions are outlined in Tables 2 and 3, and in all the cases the major product was determined to be the $E$-enone derivatives by their characteristic NMR spectra. In most instances the enolates were converted to the enones in high yields, with only the reactions using the bulky mesitylaldehyde requiring extended reaction times (entries 3 in Tables 2 and 3). No alkylation products were detected from GCMS analyses of the crude reaction mixtures. Similarly, no β-hydroxyketones were found, presumably due to the instability of the aluminum aldolate intermediates under the reaction conditions. In comparison, Barron has reported that the bulky alkoxide EtAl(2,6-$^t$Bu$_2$-4-Me–C$_6$H$_2$O)$_2$ reacts with a variety of ketones to yield stable aluminum aldolates [17]. In Barron's system no intermediate enolates could be identified and hydrolysis resulted in non-selective fragmentation of the aldolate backbone.

Finally, in all cases, the dominant stereoisomer formed in the reactions was the $E$-enone. This outcome is in accord with the $E$-enones being the thermodynamically favored isomers [14]. Indeed, using **1** as enolate resulted in exclusive formation of the $E$-isomer when pivaldehyde and mesitylaldehyde were used as electrophile. Moreover, all of the reactions using **2** as enolate gave exclusive $E$-enone, with the exception of isovaleraldehyde (97:3 $E/Z$, entry 5, Table 3). Clearly, the
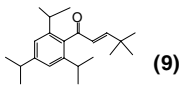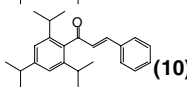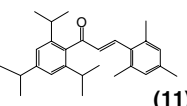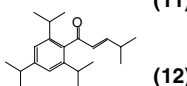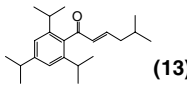
Table 2
Products from the reaction of **1** with a series of aldehydes

| Entry | Aldehyde | Major Product | Conv.[a] | (E):(Z) |
|---|---|---|---|---|
| 1 | | **(4)** | 84.3% | 100:0 |
| 2 | | **(5)** | >99.0% | 92:8 |
| 3 | | **(6)** | 64.1%[b] | 100:0 |
| 4 | | **(7)** | 85.8% | 90:10 |
| 5 | | **(8)** | 67.8% | 89:11 |

[a] Conversion after 3 h reflux.
[b] After 22 h reflux, 80.8%.

Table 3
Products from the reaction of **2** with a series of aldehydes

| Entry | Aldehyde | Major Product | Conv.[a] | (E):(Z) |
|-------|----------|---------------|----------|---------|
| 1 | | **(9)** | 90.0% | 100:0 |
| 2 | | **(10)** | 93.1% | 100:0 |
| 3 | | **(11)** | 10.8%[b] | 100:0 |
| 4 | | **(12)** | 90.3% | 100:0 |
| 5 | | **(13)** | 88.1% | 97:3 |

[a] Conversion after 3 h reflux.
[b] After 42 h reflux, 74.8%.

stereoselectivity of the reaction is promoted by increasing the steric bulk of both the enolate and the aldehyde.

## 3. Conclusions

Trimethylaluminum can act as a selective base in the enolization of sterically hindered ketones. In particular, aromatic ketones substituted at the 2- and 6-positions with methyl or isopropyl groups, react with Me$_3$Al upon heating to exclusively yield the respective dimethylaluminum enolates. The enolates adopt dimeric structures featuring central Al$_2$O$_2$ rings in the solid state and also in solution. Reaction of these enolates with a series of simple aldehydes at elevated temperatures results in enone formation presumably via an aldol addition reaction followed by an elimination step. The enones are produced in high yields and as predominantly the *E*-isomers.

## 4. Experimental

### 4.1. General

All experiments were carried out under a dry nitrogen atmosphere and scrupulously anhydrous conditions using standard Schlenk techniques [18]. Toluene and hexane were purified by passage through a solvent purification system (Innovative Technology). The Me$_3$Al was supplied by Aldrich as 1.6 M solutions in hexane and used as received. The NMR experiments were recorded on Varian-300 and -500 spectrometers. $^1$H and $^{13}$C NMR spectra were referenced internally to the deuterated solvents. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

### 4.2. Syntheses

The enone compounds were prepared in a similar manner and the synthesis of **4** is given as a representative example. Once prepared, the enone compounds were purified after aqueous workup by crystallization from either hexane or ether, or alternatively by column chromatography using a solvent system of 90% methylene chloride and 10% hexane. Compound **1** was prepared as reported previously [6].

### 4.3. Synthesis of [Me$_2$AlOC(2,4,6-(CH(CH$_3$)$_2$)$_3$–C$_6$H$_2$)=CH$_2$] (**2**)

2,4,6-Triisopropylacetophenone (1.05 g, 4.2 mmol) was added dropwise to a −78 °C cooled solution of Me$_3$Al (6.4 mmol) in 12 ml of toluene. The reaction mixture was allowed to warm to ambient temperature with constant stirring and subsequently heated to reflux for 3 h. Solvents were removed in vacuo, the residue dissolved in 12 ml of hexane and a solid was obtained upon cooling the mixture to −45 °C for 24 h. Isolated yield 80.2%. $^1$H NMR spectrum, $\delta$ −0.52 (s, 6H, AlC$H_3$), 1.17 (d, $J$ = 6.9 Hz, 12H, o-C(C$H_3$)$_2$), 1.42 (d, $J$ = 6.6 Hz, 6H, p-C(C$H_3$)$_2$), 2.73 (sept, $J$ = 6.9 Hz, 1H, p-C$H$(CH$_3$)$_2$), 3.38 (sept, $J$ = 6.9 Hz, 2H, o-C$H$(CH$_3$)$_2$), 4.32 (d, $J$ = 2.1 Hz, 1H, C=C$H_2$), 5.01 (d, $J$ = 2.1 Hz, 1H, C=C$H_2$), 7.09 (s, 2H, m-C$_6$H$_2$). $^{13}$C NMR spectrum, $\delta$ −9.13 (Al$C$H$_3$), 23.35 ($C$H$_3$), 24.48 ($C$H$_3$), 27.07 ($C$H$_3$), 31.23 ($C$H), 35.15 ($C$H), 98.76 (C=$C$H$_2$), 121.46, 132.02, 147.94, 151.27 (Ar–$C$), 153.07 (O$C$=CH$_2$). Theoretical elemental analysis for C$_{38}$H$_{62}$-O$_2$Al$_2$: C, 75.46; H, 10.33. Found C, 73.70; H, 10.05%.

### 4.4. Synthesis of E-[(2,4,6-Me$_3$–C$_6$H$_2$)C(O)CH=CHC-(CH$_3$)$_3$] (**4**)

2,4,6-Trimethylacetaldehyde (0.207 g, 2.3 mmol) was added dropwise to a solution of 12 ml hexane and **1** (0.500 g, 1.15 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and then heated at reflux for 3 h. The solution was quenched with deionized water, extracted into ether (3 × 15 mL) and purified using column chromatography (9:1 methylene chloride/hexane).

### 4.5. X-ray crystallography

Table 4 contains information on the data collection for **2**. A crystalline sample of **2** was placed in inert oil, mounted on a glass pin, and transferred to the cold

Table 4
Crystallographic parameters for **2**

| | |
|---|---|
| Chemical formula | $C_{38}H_{62}Al_2O_2$ |
| Formula weight | 604.84 |
| Crystal size (mm) | 0.36 0.28 0.25 |
| Crystal system | Triclinic |
| Space group | $P\bar{1}$ |
| Unit cell dimensions | |
|   $a$ (Å) | 8.0860(16) |
|   $b$ (Å) | 14.768(3) |
|   $c$ (Å) | 17.659(4) |
|   $\alpha$ (°) | 66.62(3) |
|   $\beta$ (°) | 86.19(3) |
|   $\delta$ (°) | 82.43(3) |
| $V$ (Å$^3$) | 1918.5(7) |
| $Z$ | 2 |
| No. reflections collected | 17200 |
| No. independent reflections | 13673 |
| $R_{int}$ | 1.047 |
| $D_{calc}$ (g cm$^{-3}$) | 0.104 |
| $\mu$ mm$^{-1}$ | 0.104 |
| $R$ | 0.0564 |
| $wR2$ | 0.1465 |

gas stream of the diffractometer. Crystal data were collected and integrated using a Bruker Apex system, with graphite monochromated Mo K$\alpha$ ($\lambda = 0.71073$ Å) radiation at 100 K. The structure was solved by direct methods using SHELXS-97 and refined using SHELXL-97 [19,20]. Non-hydrogen atoms and hydrogen atoms that are bound to carbanions were found by successive full matrix least squares refinement on $F^2$ and refined with anisotropic thermal parameters.

## 5. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Structural Data Centre, CCDC No. 268686, for compound **2**. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccds. cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

## References

[1] J.R. Zietz, G.C. Robinson, K.L. Lindsay, in: G. Wilkinson, F.G.A. Stone, E.W. Abel (Eds.), Comprehensive Organometallic Chemistry, vol. 7, Pergamon, Oxford, 1982 (Chapter 46).
[2] S. Pasynkiewicz, E. Silwa, J. Organomet. Chem. 3 (1965) 121.
[3] E.A. Jeffery, A. Meisters, T. Mole, J. Organomet. Chem. 74 (1974) 365.
[4] A. Itoh, S. Ozawa, K. Oshima, H. Nozaki, Tetrahedron Lett. 21 (1980) 361.
[5] K. Biswas, O. Prieto, P.J. Goldsmith, S. Woodward, Angew. Chem. Int. Ed. 44 (2005) 2232.
[6] J.F. Allan, W. Clegg, M.R.J. Elsegood, K.W. Henderson, A.E. McKeown, P.H. Moran, I.M. Rakov, J. Organomet. Chem. 602 (2000) 25.
[7] W. Clegg, K.W. Henderson, I.M. Rakov, Acta Cryst. Sect. E E57 (2001) 387.
[8] E.A. Jeffery, A. Meisters, T. Mole, J. Organomet. Chem. 74 (1974) 373.
[9] E.A. Jeffery, A. Meisters, J. Organomet. Chem. 82 (1974) 307.
[10] A.R. Kunicki, A. Chojecki, J. Zachara, M. Glinski, J. Organomet. Chem. 664 (2002) 136.
[11] D. Casarini, L. Lunazzi, R. Verbeek, Tetrahedron 52 (1996) 2471.
[12] J.P. Oliver, R. Kumar, Polyhedron 9 (1990) 409.
[13] F.H. van der Steen, G.P.M. van Mier, A.L. Spek, J. Kroon, G. van Koten, J. Am. Chem. Soc. 113 (1991) 5742.
[14] R. MahrwaldModern Aldol Reactions, vol. 1–2, Wiley-VCH, Weinheim, 2004.
[15] J.J. Eisch, in: G. Wilkinson, F.G.A. Stone, E.W. Abel (Eds.), Comprehensive Organometallic Chemistry, vol. 1, Pergamon Press, Oxford, 1982 (Chapter 6).
[16] G.H. Robinson, Coordination Chemistry of Aluminum, VCH, New York, 1993.
[17] M.B. Power, A.W. Apblett, S.G. Bott, J.L. Atwood, A.R. Barron, Organometallics 9 (1990) 2529.
[18] D.F. Schriver, M.A. Drezdon, The Manipulation of Air-sensitive Compounds, Wiley, New York, 1986.
[19] G.M. Sheldrick, Acta Crystallogr. Sect. A 46 (1990) 467.
[20] G.M. Sheldrick, SHELXL-97: Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997.