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The influence of steric hindrance on the lithiation of ferrocenylalkylamines *

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Abstract

1-{*N*,*N*-Dimethylamino[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-(*R*)-methyl}-ferrocene and 1-{*N*,*N*-dimethylamino[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-(*S*)-methyl}ferrocene have been prepared from (−)-menthone and ferrocene, and their conformation in solution elucidated by NMR spectroscopy. Upon lithiation, neither amine shows the high regio- and diastereo-selectivity observed in the case of the simple (*N*,*N*-dimethylamino-1-ethyl)ferrocene. Reasons for this behaviour are discussed. Reaction of the mixture of lithiation products with chlorodiphenylphosphine leads to mixtures of phosphine derivatives, which have been used as chiral chelating ligands in rhodium-catalyzed asymmetric hydrogenation of *N*-acetyl-2-aminocinnamic acid.

Introduction

Current interest in the synthesis of enantiomerically pure (or, at least, enriched) compounds, especially natural products, has led to the development of efficient and sophisticated synthetic techniques. The most elegant among them use chiral catalysts to generate enantiomerically enriched products from achiral starting materials, and industrial applications are of growing importance [1]. Most of the research has been carried out in the field of rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids, and many chelating phosphine ligands have been developed for this purpose [2–4]. The application of these ligands is not limited to hydrogenation reactions; carbon–carbon bond formation by cross-coupling of halides with Grignard reagents and hydrosilylation of carbonyl compounds are other prominent examples of asymmetric catalysis [5]. The combination of central and planar

* Dedicated to Prof. Dr. Karl Schlögl on the occasion of his 65th birthday.

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chirality in ferrocene derivatives allows the construction of a variety of chiral ligands, which have been used with remarkable success in many catalytic processes [6,7]. However, all the ligands are derived from (*N*,*N*-dimethylamino-1-ethyl)ferrocene, and their preparation involves a time-consuming resolution of the racemate [8]. A synthesis of this type of a chiral chelating 1,2-disubstituted ferrocene derivative, starting from a cheap enantiomerically pure compound from the natural chiral pool, would therefore represent an important step forward.

We have recently demonstrated that some terpenes, such as camphor, α- and β-pinene [9], and menthone [10,11], can be readily introduced as substituents in ferrocene. We show below how tertiary amines suitable for further introduction of phosphine substituents in the ferrocenyl moiety can be obtained from (−)-menthone and ferrocene. Their behaviour towards lithiation and the potential of their phosphine derivatives in asymmetric hydrogenation are discussed.

Results and discussion

(−)-Menthone **1** is readily converted into the enol ether **2** by a Wittig reaction with methoxymethylenephosphorane. Under strongly acidic conditions, ferrocene reacts with the enol ether to form the carbocation **3** [11]. If trapped immediately by a nucleophile, in this case dimethylamine, the amine **5** is obtained as the main product. The cation **3** rearranges in solution within 3 h to the cation **4** by rotation around the ferrocene–cationic carbon bond [11]. Trapping of **4** leads to the amine **6**, which is also a byproduct (about 10%) in the preparation of the amine **5**. The amines are readily purified by chromatography. Attempts to prepare the amine **9**, with axial orientation of the ferrocenylmethyl substituent at the cyclohexane ring, by the reaction of the cation **8** (obtained by protonation of the alkene **7** [10]) with dimethylamine, failed; only the starting alkene **7** could be isolated. Obviously, dimethylamine is too weak a nucleophile to bring about a substitution reaction, in contrast with the azide ion which gives the corresponding azide derivative [10] (see Fig. 1).

Since the feasibility of introducing additional substituents into the cyclopentadienyl rings will probably depend on the conformation of the bulky menthyl moiety, we decided to conduct a systematic NMR spectroscopic study on the amines **5** and **6** in order to determine their conformations. First, we achieved the complete assignment of the carbon and hydrogen resonances by first determining the carbon skeleton using DEPT and C–C correlation (INADEQUATE) [12,13], and then assigning the proton signals using C–H-correlation (inverse measurement [14,15]), and COSY for confirmation. The numbering of the carbons and attached hydrogens is given in Fig. 2, and the NMR data are listed in Table 1. The C–C correlation was necessary for unequivocal assignment of the carbons C(9) and C(10), which could not be made by other techniques.

A notable feature of the proton spectrum of **6** is the unusual chemical shift of the equatorial proton of the CH_2 group at C(12) (δ 0.05 ppm vs. δ 1.48 ppm for its axial counterpart). It is coupled to its three neighbouring protons with the same coupling constant (10.3 Hz). This enhanced shielding can be accounted for by the close vicinity of the equatorial hydrogen to the ferrocene, where it experiences a strong shielding by the aromatic ring current. No such effect is observed in the amine **5**, which indicates that it probably has a completely different conformation.

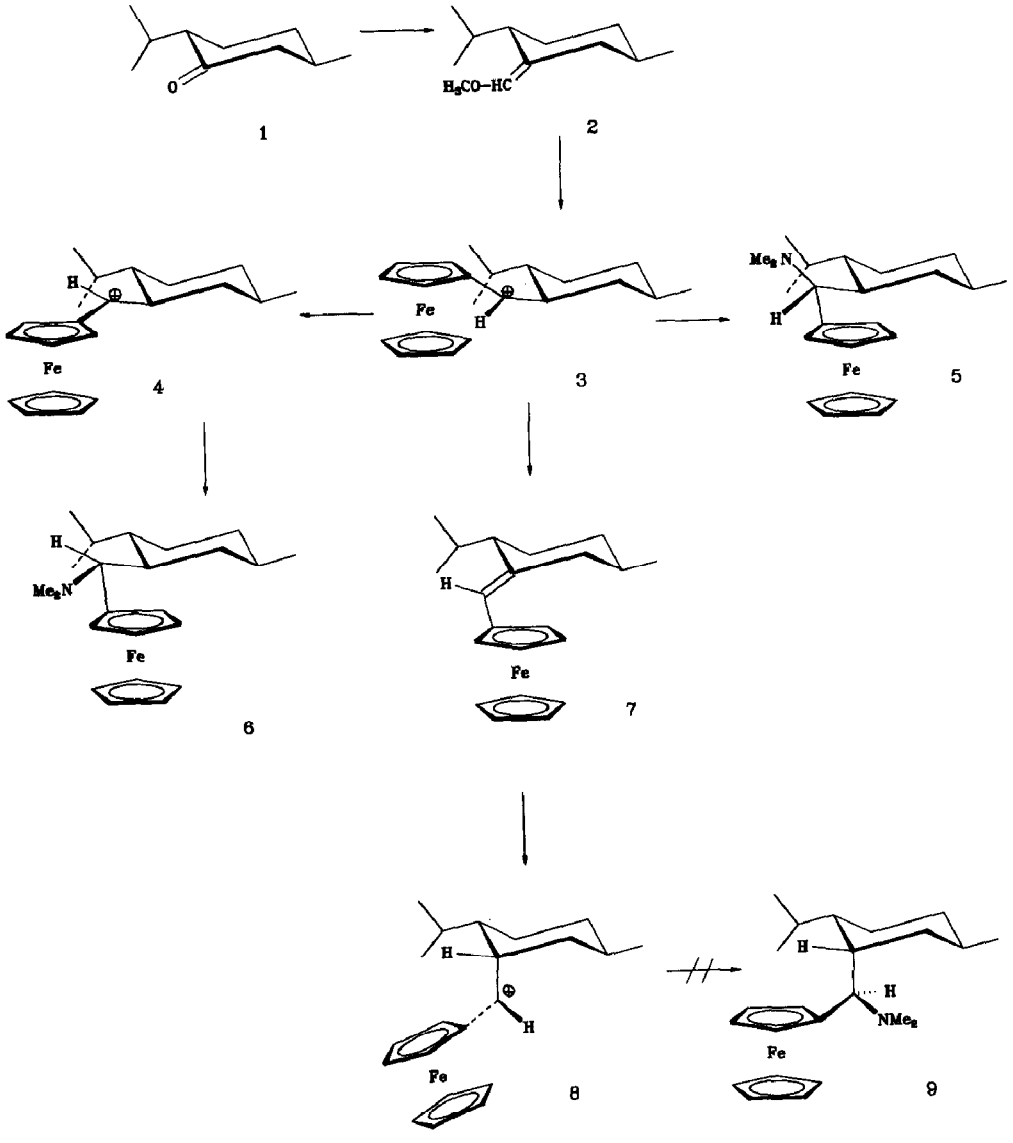

Fig. 1. Synthesis of the amines **5** and **6**.

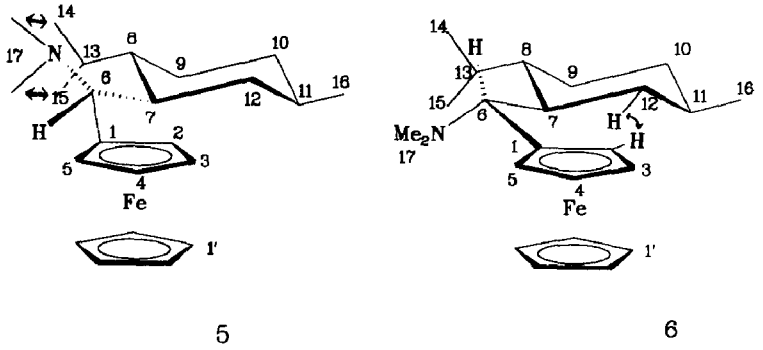

Fig. 2. NMR numbering and most relevant NOE effects in the amines **5** and **6**.

Table 1

NMR spectra of the amines 5 and 6 in $CDCl_3$.

Group		5	6
1′	^{1}H NMR	4.08	4.09
	^{13}C NMR	68.6	69.1
2–5	^{1}H NMR	4.08 (3H), 4.12 (1H)	3.99, 4.08, 4.14, 4.17
1–5	^{13}C NMR	87.4, 66.6, 67.1, 68.2, 69.8	89.4, 65.9, 66.0, 66.3, 68.8
6	^{1}H NMR	3.82 (<1 Hz)	3.25 (2.3 Hz)
	^{13}C NMR	61.5	63.4
7	^{1}H NMR	1.92 (m)	1.70 (m)
	^{13}C NMR	45.9	40.8
8	^{1}H NMR	1.47 ("tr", 10.3 Hz)	1.10 (trtr, 3.3 Hz, 12.3 Hz)
	^{13}C NMR	43.7	45.4
9	^{1}H NMR	1.09 (m), 1.73 (m, 11.3 Hz)	0.90 (m), 1.60 (m)
	^{13}C NMR	24.7	24.5
10	^{1}H NMR	0.95 (m), 1.73 (d, br 11.3 Hz)	0.60 (dqu, 4.0 Hz, 11.3 Hz), 1.59 (m)
	^{13}C NMR	35.4	35.1
11	^{1}H NMR	1.36 (m)	1.23 (m)
	^{13}C NMR	33.5	32.6
12	^{1}H NMR	1.09 (m) 1.96 (m, 13.3 Hz)	0.05 (eq, qu, 10.3 Hz), 1.48 (ax, m, 10.3 Hz)
	^{13}C NMR	38.0	36.6
13	^{1}H NMR	2.16 (m)	2.14 (m)
	^{13}C NMR	26.7	26.2
14, 15	^{1}H NMR	0.88 (6.2 Hz), 1.00 (5.5 Hz)	0.72 (6.7 Hz), 0.82 (7.2 Hz)
	^{13}C NMR	14.2, 22.0	15.2, 21.3
16	^{1}H NMR	0.90 (6.2 Hz)	0.96 (6.8 Hz)
	^{13}C NMR	23.3	22.7
17	^{1}H NMR	2.13	2.57
	^{13}C NMR	44.8	45.4

To gain further insight in the conformation in solution, we observed the NOE effects by the rotating frame technique (ROESY [16–19]). For each amine the strongest and most significant interaction for the conformational assignment is indicated by arrows in Fig. 2. In **5**, the dimethylamino group comes very close to the isopropyl substituent of the cyclohexane ring; the corresponding cross-peak in the ROESY spectrum of **6** is much weaker. In contrast, the extremely shielded hydrogen at C(12) in the amine **6** (δ 0.05 ppm) has a very strong cross-peak with an α-hydrogen of the ferrocene ring at C(2). Taken together with other, less pronounced, cross-peaks, these characteristic NOE effects allow the assignment of the probable conformations of **5** and **6** shown in Fig. 2.

As for the consequences in the lithiation by alkyllithium reagents, an inspection of molecular models shows that the 2-position of the ferrocene ring is still accessible in the compounds **5** and **6**. The general lithiation reaction of such ferrocenyl amines is depicted in Fig. 3. Its stereochemistry is mainly governed by the stabilization of

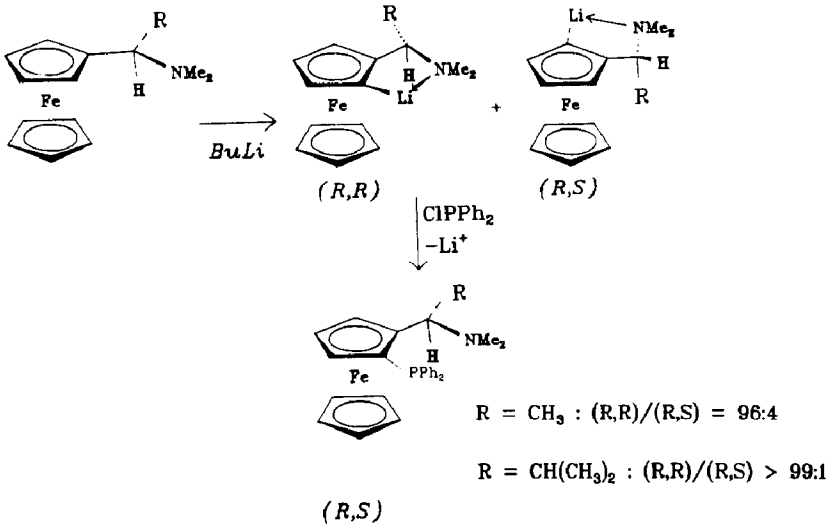

Fig. 3. Stereoselective lithiation of ferrocenylalkylamines and preparation of their phosphine derivatives.

the lithio derivative and of the transition state which leads to its formation by a chelating effect involving the nitrogen lone pair. For R = methyl, the diastereoselectivity is 96/4 for lithiation at the 2-position relative to that at the 5-position [20,21], which leads to the (*R*,*R*) and the (*R*,*S*) isomers, respectively. The difference in energy between the two diastereoisomeric transition states results from the interaction between the group at the C(6) carbon that points down ("*endo*") to the iron, and the substituted cyclopentadienyl ring; in the (*R*,*R*) isomer, this group is a hydrogen atom, whereas in the (*R*,*S*) isomer the bulkier R group introduces severe steric repulsion at this position. Increasing the steric bulk of the substituent R should therefore lead to higher energy differences and thus to even better diastereoselectivity. This is indeed so for replacement of methyl by isopropyl; in this case, no product of substitution at the 5-position could be detected [22]. In the absence of additional chelating amines such as *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminoethane (TMEDA), lithiation in other positions does not occur. The extremely bulky and asymmetric menthyl substituent in the amines **5** and **6**, however, introduces so much steric hindrance that lithiation in the 2-position of the ferrocene is slowed down considerably. Complete blocking of the reaction is not expected, because in the conformations of the amines, as determined by NOE measurements, there is still enough space left for the approach of an alkyllithium molecule. But the gain in energy by stabilization of the transition state by the chelating nitrogen will be smaller, and the directing effect of the lone pair less pronounced.

The reaction of the lithiated amines **5** and **6** with chlorodiphenylphosphine under a variety of conditions always gave mixtures of products with an ill-defined distribution of phosphine substituents in the ferrocene ring, showing that the directing effect of the nitrogen is indeed greatly diminished in these amines. The ^{31}P NMR data for the mixtures obtained under various conditions are listed in Table 2; consistent assignments to definite compounds were not possible. A low (15°) flip angle and a long relaxation delay (10 s) between the pulses allowed a reliable integration of the signals. According to their ^{1}H NMR spectra the mixtures contain monophosphines and heteroannular diphosphines, generally with more diphos-

Table 2

Reaction conditions for the preparation of the phosphine derivatives of **5** and **6**, and composition of the product mixtures according to ^{31}P NMR ($CDCl_3$)

Amine	Conditions	^{31}P NMR (δ, relative to 85% H_3PO_4)					Remarks
5	refl., 20 h	−16.7 (21%)	−20.4 (7%)	−25.7 (42%)	−25.9 (30%)		[a]
5	r.t., 5 h TMEDA	−16.7 (13%)	−17.6 (23%)	−17.5 (26%)	−25.8 (12%)	−26.2 (26%)	[b]
5	r.t., 30 h TMEDA	−17.5 (16%)	−17.6 (21%)	−17.7 (25%)	−18.0 (17%)	−18.1 (21%)	[c]
5	refl., 20 h TMEDA	−19.2 (15%)	−20.0 (18%)	−20.4 (20%)	−26.8 (13%)	−28.3 (34%)	[c]
6	r.t., 30 h	−16.6 (26%)	−17.7 (31%)	−24.1 (43%)			[a]
6	refl., 20 h TMEDA	−16.7 (15%)	−18.5 (22%)	−20.2 (18%)	−24.1 (29%)	−24.3 (16%)	[d]

[a] Mainly monosubstituted products. [b] Mainly disubstituted products. [c] No unsubstituted Cp. [d] Only small quantity of unsubstituted Cp.

phines in the reactions in the presence of added TMEDA, as estimated from the integration of the characteristic singlets of unsubstituted cyclopentadienyl rings. Because of signal overlap, this integration can be used only as qualitative indication. Statistically, 5 monophosphines and 4 diphosphines might be expected as products, and these should give rise to 13 phosphorus signals. Since only 3 to 5 signals are observed, there is still some selectivity. Despite many attempts to separate the mixtures by chromatography and crystallization, no pure compounds could be isolated.

The initial aim of the experiments, to find an easier route to ligands for asymmetric catalysts from the chiral pool was therefore not achieved. However, inspired by the work of Wilke, who used a "mixtura mirabilis" [23] of diastereoisomeric phosphines derived from pinene for catalytic purposes with remarkable success, we performed asymmetric catalytic hydrogenations with rhodium and our mixture of phosphines. Surprisingly, the catalyst turned out to be quite efficient, producing *N*-acetylphenylalanine from *N*-acetyl-2-aminocinammic acid in up to 84% enantiomeric excess. Efforts to separate the mixture of phosphines are therefore being continued.

Experimental

NMR spectra were recorded on a Bruker AM 360 instrument (^1H NMR: 360.1 MHz, ^{13}C NMR: 90.56 MHz, 31 P NMR: 145.8 MHz). Mass spectra were obtained with Varian CH 5 instrument, and optical rotations were measured with a Roussel–Jouan Digital 71 polarimeter. The enol ether **2** was prepared as previously described [10].

1-{N,N-Dimethylamino[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(R)-methyl}-ferrocene (5) and 1-{N,N-dimethylamino[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(S)-methyl}-ferrocene (6)

To a solution of 1.86 g (10 mmol) ferrocene in a mixture of 10.0 g of trichloroacetic acid and 4 ml of dichloromethane were added, at −10 °C under nitrogen

with very efficient stirring, 12 mmol (2.2 g) of the enol ether **2** and 1.0 ml of fluorosulfonic acid. The mixture was stirred at −10 °C for 20 min to give the carbocation **3**, or 3 h at 0 °C to give carbocation **5**. The solution of the cation was diluted with 50 ml of dichloromethane and added dropwise with very efficient stirring to a solution of dimethylamine (22.5 g) in isopropanol (60 ml). The mixture was allowed to come to room temperature. Water (100 ml) and dichloromethane (100 ml) were added and the organic layer was washed twice with water (100 ml). The solution was dried over sodium sulfate and the solvent then evaporated. The residue was purified by column chromatography (silica gel, hexane/ether 10/1).

Amine **5** was obtained as an oil; yield 1.52 g (40%). MS: 381 (M^+), 242 (100%). $[\alpha]_D^{22}$ −8.1° (*c* 0.4, ethanol). Found: C, 72.6; H, 9.6; N, 3.5. $C_{23}H_{35}FeN$ (381.38) calcd.: C, 72.4; H, 9.3; N, 3.7%.

Amine **6** was obtained as an oil; yield 1.71 g (45%). MS: 381 (M^+), 242 (100%). $[\alpha]_D^{22}$ +28.6° (*c* 0.6, ethanol). Found: C, 72.7; H, 9.5; N, 3.6. $C_{23}H_{35}FeN$ (381.38) calcd.: C, 72.4; h, 9.3; N, 3.7%.

Preparation of phosphine derivatives

To a solution of 3.81 g (10 mmol) of amine **5** or **6** in 50 ml of dry ether under nitrogen was added a solution of n-butyllithium (1.5 *M*) in hexane (18 mmol, 12.0 ml). Freshly distilled *N,N,N′,N′*-tetramethyl-1,2-diaminoethane (TMEDA) (20 mmol, 2.32 g) was added in some experiments (see Table 2) and stirring was continued for the time indicated in Table 2. A solution of chlorodiphenylphosphine (4.0 g, 18 mmol) in 50 ml of dry ether was added dropwise and the mixture stirred for 5 h under reflux. Water (100 ml) was then added and the organic layer washed with water (100 ml) then dried over sodium sulfate. Evaporation of the solvent (and TMEDA, if present) left a residue, which was purified by column chromatography (silica gel, hexane). The fractions containing phosphines (yields between 40 and 70%) could not be resolved. They were oils of varying composition; their ^{31}P NMR spectra showed three to five signals which could be attributed to mixtures of mono- and di-phosphines (Table 2); this was confirmed by microanalyses.

The catalytic asymmetric hydrogenation of *N*-acetyl-2-amino-cinnamic acid was performed in methanol as previously described [24,25]; 10 h was required for complete reaction. Work up [25] gave a 96% yield of N-acetylphenylalanine, e.e. 84% (determined by polarimetry).

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References

1 H.B. Kagan, Bull. Soc. Chim. France, (1988) 846.
2 L. Horner, Pure Appl. Chem., 52 (1980) 843.
3 B. Bosnich and M.D. Fryzuk, Top. Stereochem., 12 (1981) 119.
4 W.S. Knowles, Acc. Chem. Res., 16 (1983) 106.
5 H. Brunner, J. Organomet. Chem., 300 (1986) 39.
6 T. Hayashi and M. Kumada, Acc. Chem. Res., 15 (1982) 395.

7 T. Hayashi and M. Kumada, in J.D. Morrison (Ed.), Asymmetric Synthesis, Vol. 5, Academic Press, Orlando, 1985, p. 147.
8 G. Gokel and I. Ugi, J. Chem. Educ., 49 (1972) 294.
9 F. Siglmüller, R. Herrmann, and I. Ugi, Liebigs Ann. Chem., (1989) 623.
10 A. Gieren, C.-P. Kaerlein, T. Hübner, R. Herrmann, F. Siglmüller, and I. Ugi, Tetrahedron, 42 (1986) 427.
11 F. Siglmüller, R. Herrmann, and I. Ugi, Tetrahedron, 42 (1986) 5931.
12 D.L. Turner, J. Magn. Res., 49 (1982) 175.
13 T.H. Mareci and R. Freeman, J. Magn. Res., 48 (1982) 158.
14 R.A. Byrd, F. Summers, G. Zon, C.S. Fouts, and L.G. Marzili, J. Am. Chem. Soc., 108 (1986) 504.
15 W. Bermel, C. Griesinger, H. Kessler, and K. Wagner, Magn. Res. Chem., 25 (1987) 325.
16 A.A. Bothner-By, R.L. Stephens, J. Lee, C.D. Warren, and R.W. Jeanloz, J. Am. Chem. Soc., 106 (1984) 811.
17 A. Bax and D.G. Davis, J. Magn. Res., 63 (1985) 207.
18 C. Griesinger and R.R. Ernst, J. Magn. Res., 75 (1987) 261.
19 H. Kessler, C. Griesinger, R. Kerrsebaum, K. Wagner, and R.R. Ernst, J. Am. Chem. Soc., 109 (1987) 607.
20 D. Marquarding, H. Klusacek, G. Gokel, P. Hofmann, and I. Ugi, J. Am. Chem. Soc., 92 (1970) 5389.
21 L.F. Battelle, R. Bau, G.W. Gokel, R.T. Oyakawa, and I.K. Ugi, J. Am. Chem. Soc., 95 (1973) 482.
22 D. Marquarding, H. Burghard, I. Ugi, R. Urban, and H. Klusacek, J. Chem. Res., (S) (1977) 82; (M) (1977) 0915–0958.
23 G. Wilke, Angew. Chem., 100 (1988) 190.
24 W.S. Knowles, H.J. Sabacky, and B.D. Vineyard, J. Chem. Soc., Chem. Commun., (1972) 10.
25 M.D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 99 (1977) 6262.