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Remarkably Slow Rotation about a Single Bond between an sp^3-Hybridised Carbon Atom and an Aromatic Ring without *ortho* Substituents

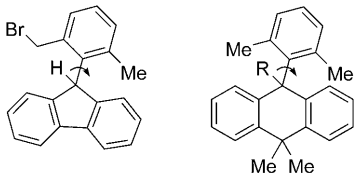
Sarah Murrison,[a] David Glowacki,[a] Christian Einzinger,[b] James Titchmarsh,[a] Stephen Bartlett,[a] Ben McKeever-Abbas,[c] Stuart Warriner,*[a] and Adam Nelson*[a]

Abstract: A series of polycycles was prepared by using a three-component Joullié–Ugi reaction. The rate of rotation about the bond between a highly hindered bridgehead and a phenyl ring with no *ortho* substituents was measured by using, in general, variable-temperature HPLC. The rate of rotation was highly dependent on substitution and rotamer half-lives of up to 21 h at 298 K were observed. Insights into the effect of substitution on the rate of rotation were gleaned through electronic structure calculations on closely related derivatives. Rotamers resulting from restricted rotation about a bond between an sp^3-hybridised carbon atom and a phenyl ring with no *ortho* substituents were isolated for the first time, and the equilibration of the separated rotamers was followed by using analytical HPLC. It was demonstrated, for the first time, that a highly hindered environment for the sp^3-hybridised atom is sufficient for slow bond rotation about a single bond between sp^3- and sp^2-hybridised carbon atoms.

Keywords: amides · atropisomerism · electronic structure · multicomponent reactions · polycycles

Introduction

Barriers to rotation about single bonds between sp^2- and sp^3-hybridised carbon atoms are, in general, so small that isomers arising from restricted rotation cannot be isolated at room temperature.[1] However, in some highly hindered systems, such as 9-arylfluorene **1**, bond rotation is sufficiently slow that two rotamers may be isolated.[2] Here, the slow rate of bond rotation may be ascribed to the hindered environment of the sp^3 carbon atom and the 2,6-substitution pattern of the phenyl ring. In some cases, such as 9-aryl-9,10-dihydroanthracenes **2**, the barrier to bond rotation may be increased through selective destabilisation of the TS.[3]



1 **2**

Herein, we describe some compounds that exhibit slow rotation about a bond between sp^2- and sp^3-hybridised carbon atoms. In each compound, the sp^2-hybridised carbon is part of a phenyl ring *without* any *ortho* substituents. Remarkably, however, in some cases the rate of bond rotation is sufficiently slow that the individual rotamers may, nonetheless, be isolated.

Results and Discussion

Polycyclic compounds **9**–**12** were each prepared by using two three-component reactions (Scheme 1). Triazines **3** and **4** were prepared by Suzuki reactions involving the appropriate boronic acids. Condensation of a triazine (**3** or **4**) with

[a] S. Murrison, Dr. D. Glowacki, J. Titchmarsh, Dr. S. Bartlett, Dr. S. Warriner, Prof. A. Nelson
School of Chemistry, University of Leeds
Leeds, LS2 9 JT (UK)
Fax: (+44) 113-343-6565
E-mail: a.s.nelson@leeds.ac.uk
s.l.warriner@leeds.ac.uk

[b] Dr. C. Einzinger
Institute of Applied Synthetic Chemistry, Getreidemarkt 9/163
1060 Vienna (Austria)

[c] Dr. B. McKeever-Abbas
AstraZeneca, Hurdsfield Industrial Estate
Macclesfield, SK10 2NA (UK)

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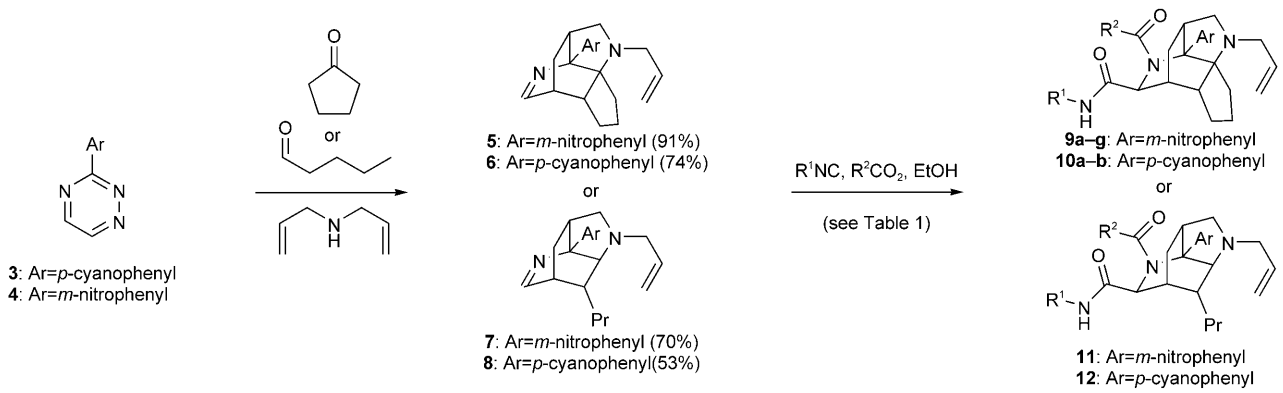


Scheme 1. Preparation of polycyclic compounds **9**–**12**.

diallylamine and either cyclopentanone or valeraldehyde gave polycyclic imines **5**–**8** in good to excellent yield.[4] A Joullié–Ugi reaction[5] involving an imine (**5**–**8**), an isocyanide and a carboxylic acid was then used to prepare polycyclic compounds **9**–**12** (see Table 1). In each case the reaction

Table 1. Preparation of polycyclic compounds **9**–**12** by using a three component Joullié–Ugi reaction.

Imine	Product	Ar	R^1	R^2	Yield [%]
5	**9a**	*m*-nitrophenyl	*c*Hex	Ph	92
	9b	*m*-nitrophenyl	*c*Hex	Me	82
	9c	*m*-nitrophenyl	*c*Hex	*i*Pr	76
	9d	*m*-nitrophenyl	*c*Hex	*t*Bu	64
	9e	*m*-nitrophenyl	*c*Hex	*p*-$MeOC_6H_4$-	53
	9f	*m*-nitrophenyl	*c*Hex	*p*-$O_2NC_6H_4$-	71
	9g	*m*-nitrophenyl	Bu	Ph	58
6	**10a**	*p*-cyanophenyl	*c*Hex	Ph	73
	10b	*p*-cyanophenyl	*c*Hex	*i*Pr	70
7	**11**	*m*-nitrophenyl	*c*Hex	Ph	72
8	**12**	*p*-cyanophenyl	*c*Hex	Ph	94

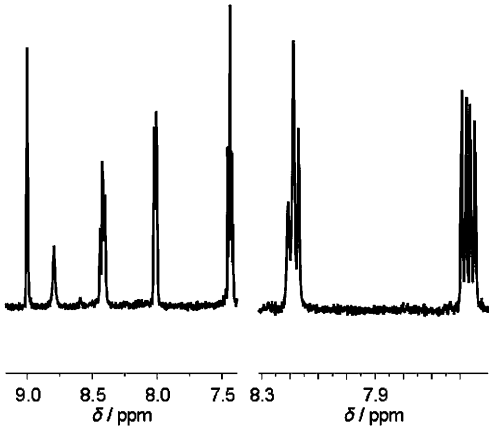
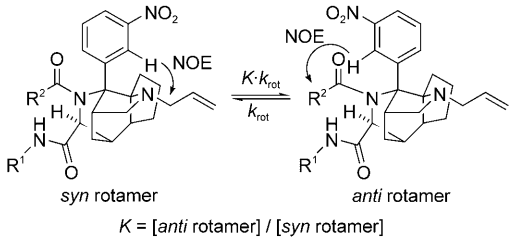


Figure 1. Expansion of regions of the 500 MHz ^{1}H NMR spectra of the polycycles **9a** (left) and **10a** (right). For polycycle **9a**, signals for two rotamers are present, whereas for **10a**, the sides of the *p*-cyanophenyl ring are diastereotopic. On the NMR timescale, rotation about the single bond between the sp^3-hybridised bridgehead carbon and the substituted phenyl ring is slow.

was $>98:<2$ diasteroselective, with the isocyanide attacking the less hindered face of the polycyclic imine. The relative configurations of **10a** and **10b** were determined by X-ray crystallography (see the Supporting Information), and that of **9g** was established by observing diagnostic NOE interactions.

For polycyclic compounds **9**–**12**, slow rotation about the single bond between the sp^3-hybridised bridgehead carbon and the substituted phenyl ring was immediately apparent. The 500 MHz ^{1}H NMR spectra of *m*-nitrophenyl-substituted polycycles **9a**–**g** and **11** indicated that two rotamers were present (see Figure 1 and Scheme 2). Similarly, for analogues **10a**–**b** and **12**, two pairs of diastereotopic protons (H2/H6 and H3/H5) were observed on the *p*-cyanophenyl ring. These observations both implicate slow rotation about the bond between the sp^3-hybridised bridgehead carbon and the substituted phenyl ring.

The rate of interconversion of the rotamers of polycyclic compounds **9a**–**g** (Scheme 2) was studied by using variable-temperature HPLC[6] (vt-HPLC) at 5 K intervals. In each



Scheme 2. Interconversion of the *syn* and *anti* rotamers of polycyclic compounds **9** and **11**. The configurations of the rotamers of **9g** were determined through observation of diagnostic NOE interactions.

case, peaks for each of the rotamers were observed at low temperature (Figure 2). However, coalescence of the peaks was observed as the rate of equilibration increased with temperature. Forward and reverse rate constants were determined by analysis of the chromatograms, which were acquired in triplicate. Our results are summarised in Tables 2 and 3.

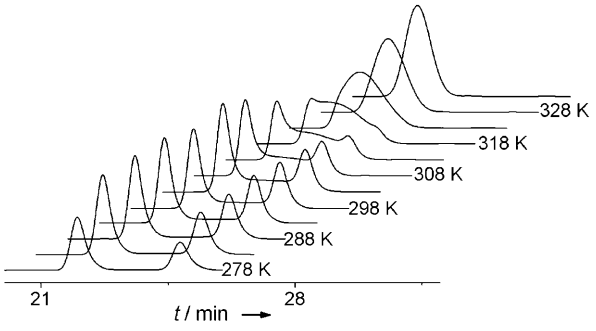


Figure 2. Chromatograms for polycycle **9a** determined by using variable-temperature analytical HPLC in acetonitrile/water.

Table 2. Populations of the *syn* and *anti* rotamers of polycyclic compounds **9** and **11** (in which Ar = *m*-nitrophenyl). Unless otherwise indicated, the populations were determined in water/acetonitrile.[a]

	syn:*anti*[b]	K[b,c]	$\Delta H°$[d] [kJmol^{-1}]	$\Delta S°$[d] [Jmol^{-1}K^{-1}]	$\Delta G°$[b] [kJmol^{-1}]
9a	65:35	0.53±0.05	−1.7±1.6	−11±7	1.6±0.2
9b	67:33	0.50±0.01	−2.8±0.4	−15±1	1.70±0.05
9c	62:38	0.61±0.01	−1.8±0.4	−10±1	1.24±0.04
9d	66:34	0.53±0.05	−3.1±0.5	−16±2	1.6±0.1
9e	70:30	0.37±0.01	−6.9±1.2	−29±4	2.43±0.03
9f	66:34	0.53±0.05	−2.5±0.8	−13±3	1.61±0.06
9g	68:32	0.47±0.01	−4.3±0.3	−20±1	1.84±0.05
11	56:44	0.79±0.07[e]	–[f]	–[f]	0.6±0.2

[a] See Table 1 for the substitution of each compound. [b] At 298 K. [c] For the definition of *K*, see Scheme 2. [d] Unless otherwise indicated, derived from the populations of the rotamers, determined by HPLC, in the slow and intermediate exchange regimes. [e] Determined by 500 MHz ^{1}H NMR spectroscopy in [D$_6$]DMSO by integrating the signals corresponding to each rotamer in the slow exchange regime. [f] Not determined.

Table 3. Kinetic data for rotation about the single bond between the sp^3-hybridised bridgehead carbon and the *m*-nitrophenyl ring.[a]

	Solvent	Method[b]	k_{rot}[c] [×10^{-6} s^{-1}]	$\Delta G_f^{\ddagger}$[c,d] [kJmol^{-1}]	$t_{1/2}$[c,e] [h]
9a	H$_2$O/MeCN	vt-HPLC	250±6	94.7±0.8	0.77
9a	H$_2$O/MeCN	HPLC[f]	87±6[g]	93±1[g]	2.2[g]
9b	H$_2$O/MeCN	vt-HPLC	9±7	101±4	21
9c	H$_2$O/MeCN	vt-HPLC	94±6	97±1	2.0
9d	H$_2$O/MeCN	vt-HPLC	84±5	97.5±0.8	2.3
9e	H$_2$O/MeCN	vt-HPLC	720±80	92.1±0.5	0.26
9f	H$_2$O/MeCN	vt-HPLC	180±10	95±1	1.1
9g	H$_2$O/MeCN	vt-HPLC	310±5	94±1	0.6
11	[D$_6$]DMSO	vt-NMR	200 000[h]	77[i]	0.0008

[a] See Table 1 for the substitution of the polycyclic compounds. [b] See the Supporting Information for the temperature ranges used in the vt-HPLC studies. [c] At 298 K unless otherwise specified. [d] For the forward direction, that is, conversion of the *syn* into the *anti* rotamer. [e] Half-life of the *anti* rotamer. [f] The rotamers were separated by preparative HPLC at 278 K; the equilibration of both rotamers at 288 K was followed by analytical HPLC. [g] At 288 K. [h] Extrapolated to 298 K on the assumption that $\Delta S_f^{\ddagger}$ is small. [i] At the coalescence temperature.

To validate the results obtained by using vt-HPLC, we also studied the re-equilibration of the rotamers of **9a**. For this compound, the rotamers were separated by HPLC at 278 K. The rate of equilibration of both rotamers was determined at 288 K in water/acetonitrile by using analytical HPLC (see Figure 3). The rate constant at 288 K determined by this method compared extremely well with that determined by using vt-HPLC (equilibration: $k_{rot} = 8.7 \pm 0.6 \times 10^{-5}$ s^{-1}; vt-HPLC: $k_{rot} = 8.4 \pm 0.2 \times 10^{-5}$ s^{-1}).

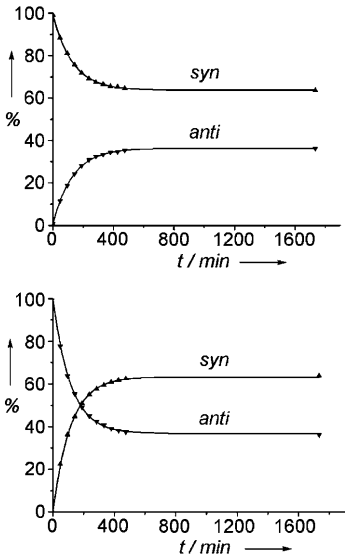
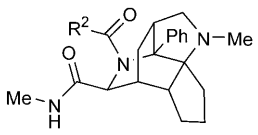
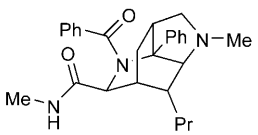


Figure 3. Equilibration of the *syn* (top) and *anti* (bottom) rotamers of polycycle **9a** at 288 K in acetonitrile/water.

The interconversion of the rotamers of **11** was much faster than those of polycycles **9a**–**g** (Table 3). The rotamers of **11** interconverted rapidly on the HPLC timescale, and only one peak was, therefore, observed by analytical HPLC; thus, variable-temperature NMR experiments were used to study the interconversion process. The half-life of the *syn* rotamer of **11**, extrapolated to 298 K, was about 3 s (compared with 0.77 h for its constrained analogue **9a**).



13a: R^2=Ph
13b: R^2=Me
13c: R^2=*i*Pr
13d: R^2=*t*Bu
13e: R^2=*p*-MeOC$_6$H$_4$
13f: R^2=*p*-O$_2$NC$_6$H$_4$



14

We quantified the distortion of the amide with the R^2 substituent by using independent parameters[7] that have been developed. These parameters describe the pyramidalisation at the nitrogen (χ_N) and carbon atoms (χ_C) and the torsion about the C–N bond (τ).The crystal structures of **10a** (R^2 = Ph) and **10b** (R^2 = *i*Pr) provide experimental evidence for

amide distortion (Table 4), although the observed distortion was smaller than in the minimised structures (Table 5) of similarly substituted compounds (compare compounds **13a** and **10a**, R^2 = Ph, with compounds **13c** and **10b**, R^2 = *i*Pr).

Table 4. Analysis of the amide groups with the R^2 substituent in the crystal structures of polycyclic compounds **10a** and **10b**.[a]

	Bond lengths [Å]		Distortion parameters [°]		
	N–C(O)	C=O	χ_N	χ_C	τ
10a	1.372	1.232	−19.4	−0.8	6.6
10b[b]	1.371	1.239	−10.8	3.6	7.6
	1.363	1.240	10.3	−2.7	−9.6
	1.368	1.238	−10.6	3.3	11.0

[a] See Table 1 for the substitution of the polycyclic compounds. [b] The asymmetric unit contains two molecules from one enantiomeric series and one molecule from the other; these molecules populate significantly different conformations in the crystal.

Table 5. Distortion of the amide group with the R^2 substituent and barrier heights for bond rotation for polycyclic compounds **13a–f** and **14** determined by using the B3LYP hybrid functional and a 6-31G* basis set.[a]

	Distortion parameters[b] [°]			Free-energy barrier [kJmol^{-1}]
	χ_N	χ_C	τ	
13a	−23.9	0.3	16.7	93.4
13b	−17.5	1.2	14.9	104.2
13c	−18.0	3.4	18.1	105.0
13d	−22.5	−0.1	17.1	105.9
13e	−24.7	0.1	18.1	89.5
13f	−22.8	0.6	16.1	93.9
14	−35.9	1.3	26.1	83.9

[a] See Table 1 for the substitution of the polycyclic compounds. [b] Calculated for the minimised structure.

The fusion of a cyclopentane ring onto the nucleus of the polycycles had a remarkable effect on the rate of bond rotation: k_{rot} was about 1000 times larger for **11** than for its more constrained analogue **9a**. The electronic structure theory results similarly show a reduced barrier height for **14** compared with **13a**, and permit a structural explanation for its origin. Inspection of the transition-state (TS) structures of **13a–f** shows that there are three significant steric interactions that contribute to the barrier heights (see Figure 4). As the phenyl ring rotates, the most significant interactions are between hydrogen atoms Ha and Hc, and between hydrogen Hb and carbonyl oxygen O. During the rotation of the phenyl ring, the carbonyl group rotates out of conjugation, which leads to increased steric interaction between carbonyl oxygen O and hydrogen Hd. The removal of the fused cyclopentane ring (as in **14**) means that the carbonyl oxygen encounters less steric repulsion, which results in a smaller barrier.

The electronic nature of an aromatic R^2 substituent had a small but significant influence on k_{rot} (compare **9a**, R^2 = Ph, with **9e**, R^2 = *p*-$MeOC_6H_5$, and **9f**, R^2 = *p*-$O_2NC_6H_5$; Table 3). Bond rotation was significantly faster with an electron-rich aryl substituent, R^2, (Hammett[8] parameter $\rho \approx$ −0.5), which implies that its conjugation with the carbonyl group was greater in the TS than in the ground state. The calculated barrier heights for polycycles **13a** (R^2 = Ph), **13e** (R^2 = *p*-$MeOC_6H_5$) and **13f** (R^2 = *p*-$O_2NC_6H_5$) reproduced this trend, with lower barriers with a more electron-rich R^2 aryl group (Table 5). Furthermore, the calculations supported the view that the R^2 aryl ring was more conjugated with the carbonyl group in the TS (the dihedral angles were 15, 12 and 33° for **13a**, **13e** and **13f**, respectively) than in the minimised structures (the dihedral angles were 48, 44 and 50° for **13a**, **13e** and **13f**, respectively).

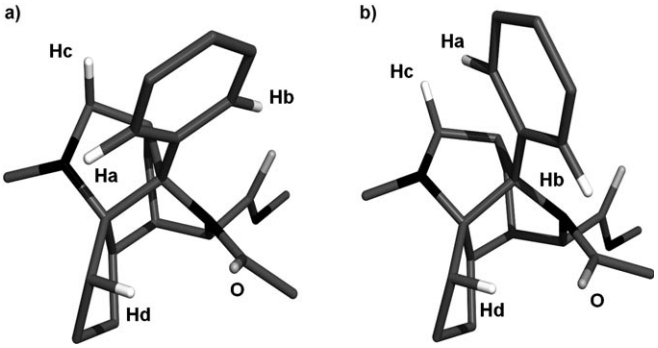


Figure 4. Minimised structure (a) and TS structure (b) for polycycle **13b**. An animation for the bond-rotation process is provided in the Supporting Information.

The steric influence of R^2 was also important, with slower bond rotation with smaller groups (compare **9b**, R^2 = Me, with **9c**, R^2 = *i*Pr, and **9d**, R^2 = *t*Bu; Table 3). However, all of our DFT calculations, which also used alternative functionals and basis sets (see the Supporting Information), predict **13b–d** to have very similar free-energy barriers. Analysis of the origins of this discrepancy is complicated given the very small differences in the free-energy barrier for these compounds. However, a comparison of the minimised structures of polycycles **13a–d** revealed that the amide distortion is greater with the larger R^2 groups (Ph, *i*Pr and *t*Bu) than with R^2 = Me (compare **13a**, **13c** and **13d** with **13b**; Table 5). Because bond rotation requires the amide to distort dramatically (see Figure 4 and the Supporting Information), the compounds with larger R^2 groups may have more destabilised ground states, which result in a faster rate of bond rotation.

Conclusions

Previously, rotamers arising from restricted rotation about bonds between sp^2- and sp^3-hybridised carbon atoms have only been isolated when the sp^2-hybridised atom is part of an aryl ring with *ortho* substituents. The rate of equilibration between the rotamers of polycycles **9** is remarkable because the *m*-nitrophenyl ring does not have any such substituents. We have therefore shown for the first time that a highly hindered environment for the sp^3-hybridised carbon is sufficient for slow bond rotation. The sp^3-hybridised bridgehead

carbon atoms in polycycles **9** are exceptionally hindered, being both fully substituted and flanked by three highly substituted atoms. Indeed, our ability to study the dynamic properties of highly hindered polycycles **9** at all probably stemmed from the intramolecular nature of the final step of the Joullié–Ugi reaction;[9] we had previously been unable to prepare similar compounds by reduction of the imines **5** and acylation under forcing reaction conditions.

Experimental Section

Variable-temperature HPLC: Samples of the polycycles were analysed by using vt-HPLC with a Phenomenex Hyperclone column [ODS (C18), 250×4.6 mm) and a Dionex analytical HPLC system equipped with a diode array detector. 20 μL samples of the polycycles (ca. 2 mM in methanol) were analysed at 5 K intervals in triplicate (see the Supporting Information for the ratio of acetonitrile/water used in each case). At each temperature, K and k_{rot} were extracted by analysing chromatograms with DCXplorer.[10] The results in Tables 2 and 3 were obtained by weighted fitting of the data to appropriate equations (see the Supporting Information).

Separation and re-equilibration of the rotamers of 9a: The rotamers of polycycle **9a** were separated by semi-preparative HPLC at 278 K [Phenomenex Hyperclone column ODS (C18); 250×10 mm; gradient elution 74:26→79:21, acetonitrile/water, 5 °C]. Samples of the rotamers were collected in vials cooled to 278 K. The re-equilibration process was followed over 21 h by HPLC analysis of aliquots of the rotamers stored at 288 K [Phenomenex Hyperclone column ODS (C18); 250×4.6 mm]. The results in Table 3 were obtained by fitting the data to appropriate equations (see the Supporting Information).

Computational methods: TS structures were determined by performing constrained potential-energy surface (PES) scans about the torsional coordinate and then initiating TS optimizations in the region of the energy maximum. Frequency calculations were performed for all stationary points and confirmed whether they were minima or TSs. The frequency calculations were also used to obtain $\Delta S_f^{\ddagger}$, which was significant to an accurate calculation of $\Delta G_f^{\ddagger}$. It has been shown that gas-phase PESs may be subject to considerable error when investigating solution-phase systems if there is substantial zwitterionic character associated with the TS dynamics.[11] However, as this is not the case for the molecules investigated in this study, we did not implement solvent continuum models. Details of comparisons with calculations using other basis sets and functionals are described in the Supporting Information.

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[1] M. Ŏki in *Topics in Stereochemistry, Vol. 14* (Eds: N. L. Allinger, E. L. Eliel, S. H. Wilen), Wiley, New York, **1983**, pp. 1–81.
[2] a) M. Nakamura, M. Ŏki, *Tetrahedron Lett.* **1974**, *15*, 505–508; b) M. T. Ford, T. B. Thompson, K. A. J. Snoble, J. M. Timko, *J. Am. Chem. Soc.* **1975**, *97*, 95–101.
[3] M. Nakamura, M. Ŏki, *Bull. Chem. Soc., Jpn.* **1980**, *53*, 2977–2980.
[4] a) W. J. Bromley, M. Gibson, S. Lang, S. A. Raw, A. C. Whitwood, R. J. K. Taylor, *Tetrahedron* **2007**, *63*, 6004–6014; b) S. A. Raw, R. J. K. Taylor, *J. Am. Chem. Soc.* **2004**, *126*, 12260–12261.
[5] a) M. M. Bowers, P. Carroll, M. M. Joullié, *J. Chem. Soc. Perkin Trans. 1* **1989**, 857–865; b) T. M. Chapman, I. G. Davies, B. Gu, T. M. Block, D. I. C. Scopes, P. A. Hay, S. M. Courtney, L. A. McNeill, C. J. Schofield, B. G. Davis, *J. Am. Chem. Soc.* **2005**, *127*, 506–507.
[6] a) J. Veciana, M. I. Crespo, *Angew. Chem.* **1991**, *103*, 85–88; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 74–76; b) A. C. Spivey, P. Charbonneau, T. Fekner, D. H. Hochmuth, A. Maddaford, C. Malardier-Jugroot, A. J. Redgrave, M. A. Whitehead, *J. Org. Chem.* **2001**, *66*, 7394–7401.
[7] J. D. Dunitz, F. K. Winkler, *Acta Crystallogr. Sect. B* **1975**, *31*, 251–263.
[8] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96–103.
[9] a) I. Ugi, G. Kaufhold, *Just. Liebigs Ann. Chem.* **1967**, *709*, 11–28; b) S. Marcaccini, T. Torroba, *Nat. Prot. Nat. Toxicants Food* **2007**, *2*, 632–639.
[10] a) O. Trapp, *Anal. Chem.* **2008**, *80*, 189–198; b) O. Trapp, *J. Chromatogr. B* **2008**, *875*, 42–47.
[11] V. K. Aggarwal, J. N. Harvey, J. Richardson, *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756.

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