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Synthesis of 1,5-Substituted Iminodibenzo[*b*,*f*][1,5]diazocine, an Analogue of Tröger's Base

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A method for the synthesis of 1,5-disubstituted iminodibenzo[*b*,*f*][1,5]diazocines is presented. The synthesis is achieved by the metal-free cyclization of 2-aminophenyl ketimines using the corresponding 2-aminophenyl ketone as the catalyst. The synthesis gives new insight into the mechanism of formation of this class of compounds. The presence of potential sites for hydrogen-bond formation and two aromatic bromine atoms available for functionalization make these targets attractive for further development in supramolecular chemistry. The structure of the complex derived from the iminodibenzo[*b*,*f*][1,5]diazocine and $PdCl_2$ was determined by X-ray crystallography.

In recent years a great deal of attention has been directed towards the synthesis of original building blocks for the development of novel supramolecular structures, and particular interest has been focused on derivatives of Tröger's base (Figure 1).[1] The rigidity and curvature of the molecule allow new architectures to be built, such as the Wilcox molecular torsion balance, molecular clefts, or self-replicating systems.[2] More recently, this interest has been extended towards analogous scaffolds and particularly to iminodibenzodiazocines (IDBDs; Figure 2).[3–7]

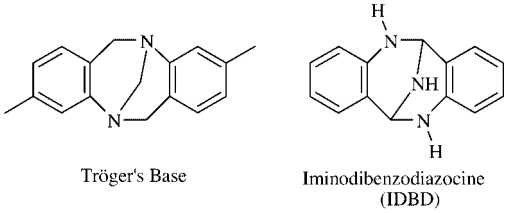
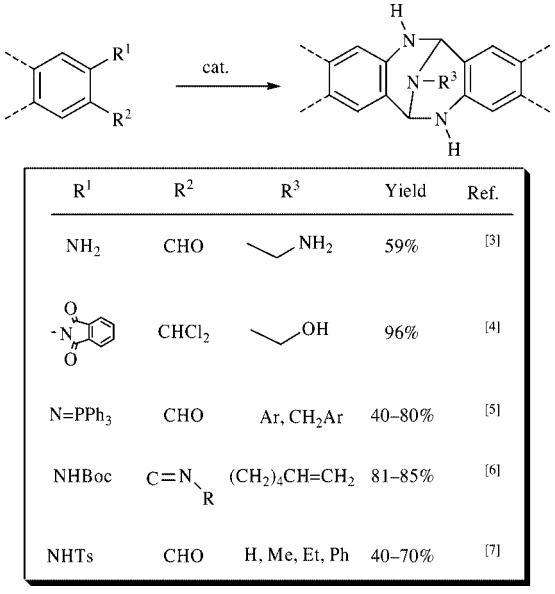


Figure 1. Structures of Tröger's base and iminodibenzodiazocine.

These systems present the same structural features as Tröger's base, with the added possibility of exploiting the covalent (reactivity) and non-covalent (hydrogen-bonding) capabilities offered by the three secondary amines. Additionally, the two aromatic rings create a chiral cleft suitable for molecular recognition. IDBDs were first synthesized in good yields by treating 2-aminobenzaldehydes with a primary amine under acidic conditions.[3] IDBDs are usually referred to as "anhydrous dimers" of the corresponding aminobenzaldehyde. More recently, new synthetic methods based on the cyclization of synthetic equivalents of 2-aminobenzaldehydes have been developed (Figure 2). Masking both the amine and aldehyde functionalities resulted in increased yields of the final product and led to the synthesis of products with a higher degree of complexity, such as extended substitution at the apical nitrogen atom and at the aromatic rings.



R^1	R^2	R^3	Yield	Ref.
NH_2	CHO	NH_2	59%	[3]
	$CHCl_2$	OH	96%	[4]
$N=PPh_3$	CHO	Ar, CH_2Ar	40–80%	[5]
NHBoc	$C=N_R$	$(CH_2)_4CH=CH_2$	81–85%	[6]
NHTs	CHO	H, Me, Et, Ph	40–70%	[7]

Figure 2. Reported strategies for the synthesis of variously substituted iminodibenzodiazocines.

The IDBD structure came to our attention in the course of the synthesis of the bromazepam and nitrazepam build-

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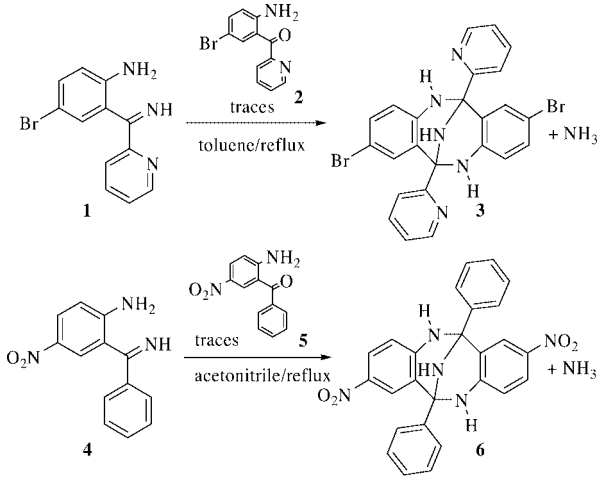
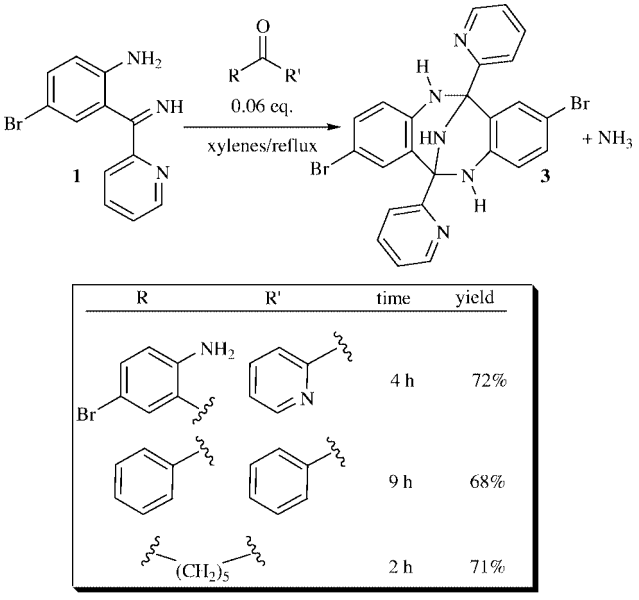
ing blocks. We noticed that in the preparation of ketimines **1** and **4**, the products were always contaminated by small quantities of the corresponding diazocines **3** and **6** (Scheme 1).[8] A more detailed investigation revealed that, during the recrystallization procedure, the presence of traces of the corresponding ketones **2** and **5** in the reaction mixture was responsible for the formation of the dimer. Both dimers were isolated and characterized. However, difficulties encountered in the synthesis and isolation of ketimine **4** led us to focus our attention on ketimine **1**. Ketimine **1** was synthesized from the corresponding carbonitrile by Grignard addition and purified by recrystallization.[9] After refluxing in toluene for 6 h in the presence of 1 equiv. of **2**, **1** was completely converted into IDBD **3**, which was isolated in 76% overall yield.



Scheme 1.

The process was associated with ammonia evolution and benzophenone **2** was recovered unchanged. Subsequent optimization allowed the synthesis of **3** using only a catalytic amount of bromobenzophenone **2** (0.06 equiv.). In order to obtain complete conversion, the mixture of reagents was refluxed either in toluene for 8 h or in xylenes for 4 h. The analysis of the reaction mixture by LC-MS showed complete conversion of ketimine **1** and regeneration of the catalyst **2**, which was recovered unaltered at the end of the reaction in any run. IDBD **3** was readily isolated as colorless needles after filtration of the product mixture at 40 °C.

More information about the process was obtained by using other ketones as catalysts. Interestingly, benzophenone displayed catalytic activity as well. However, this ketone displays a lower activity than the original compound **2**. In order to achieve the same conversion, the reaction mixture was refluxed for 9 h. In contrast, cyclohexanone was able to catalyze the reaction within 2 h under the same conditions (Scheme 2). This observation suggests a definite role of the ketone in the catalysis, that any ketone can be used to catalyze the reaction and also that carbonyl compounds are not generated during the reaction. Indeed, the reaction does not proceed in a biphasic toluene/water mixture (i.e. water does not hydrolyse **1** to **2** under the reaction conditions).

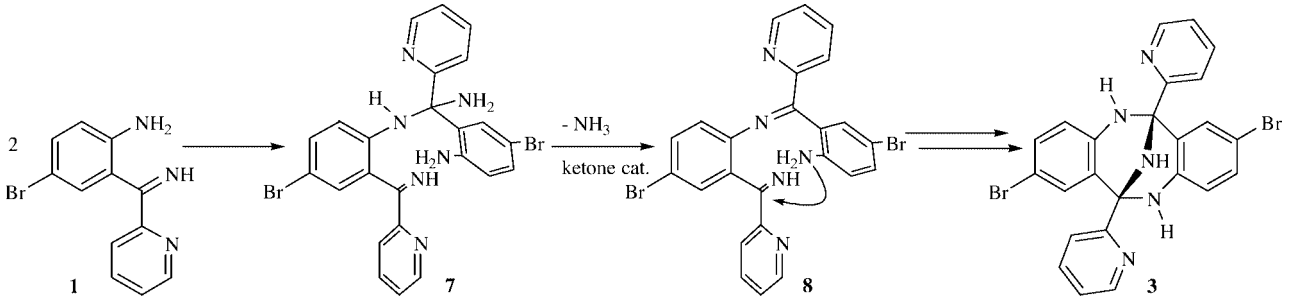


R	R'	time	yield
		4 h	72%
		9 h	68%
$(CH_2)_5$		2 h	71%

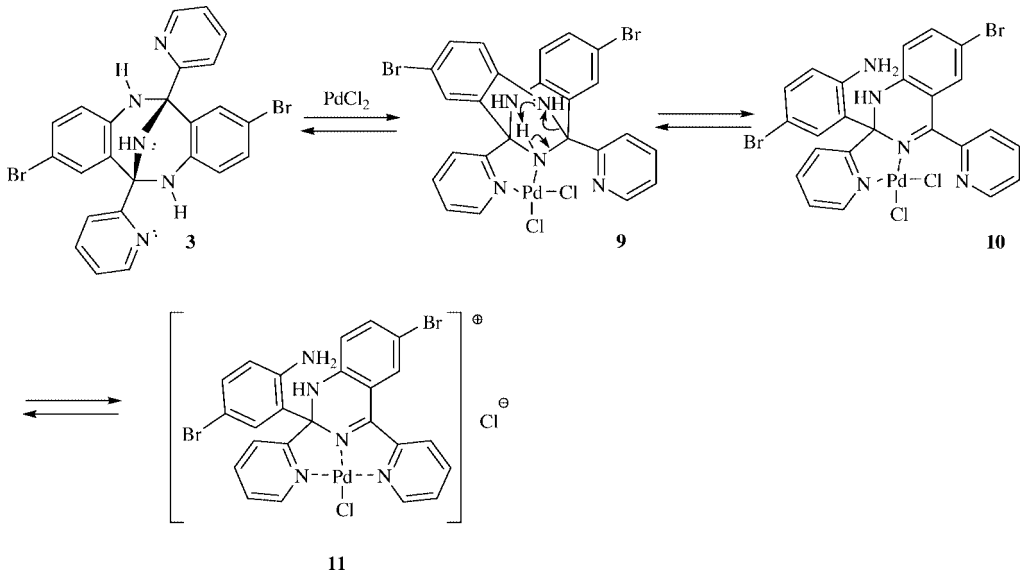
Scheme 2.

The role of the ketone in the catalytic process may be related to the ability of the carbonyl group to act as an ammonia scavenger by forming the corresponding hemiaminal (Scheme 3). This would also explain the different reactivities of the ketones. As illustrated in Scheme 4, a plausible mechanism involves the formation of dimer **7**, which evolves to the products by a mechanism proposed by Molina for similar systems.[5]

The reactivity of the benzodiazocine **3** was then studied. Treatment of **3** with benzyl bromide in THF selectively benzylates the apical position, while camphorsulfonic and methanesulfonic acid readily transform **3** into the ammonium salt. As expected, heating of **3** in concentrated HCl at



Scheme 3.



Scheme 4.

90 °C for 1 h led to complete conversion to benzophenone **2**. Attempts to resolve **3** by derivatization with (–)-menthyl chloroformate failed to give the corresponding compound.

Benzodiazocine **3** was also refluxed in toluene with $PdCl_2$ and red crystals precipitated from the solution at room temperature. The crystals were submitted to an X-ray crystal structure analysis, which revealed the presence of the tridentate ligand as its complex with Pd^{II} (**11**; Figure 3). The formation of **11** can be explained as follows. The metal atom coordinates the pyridine moiety and the apical amino group of **3**; the resulting chelate **9** enhances the acidity of the apical NH group, which is in an antiperiplanar arrangement with respect to one aminal bond (Scheme 4). This arrangement favors ketimine formation and opening of the ring with concomitant formation of the free aniline **10**. The diminished strain allows for coordination of the second pyridine N atom to the Pd atom to afford the monovalent chloropalladium(II) complex cation **11**. When the complex is dissolved in DMSO, it reverts completely to **3**.

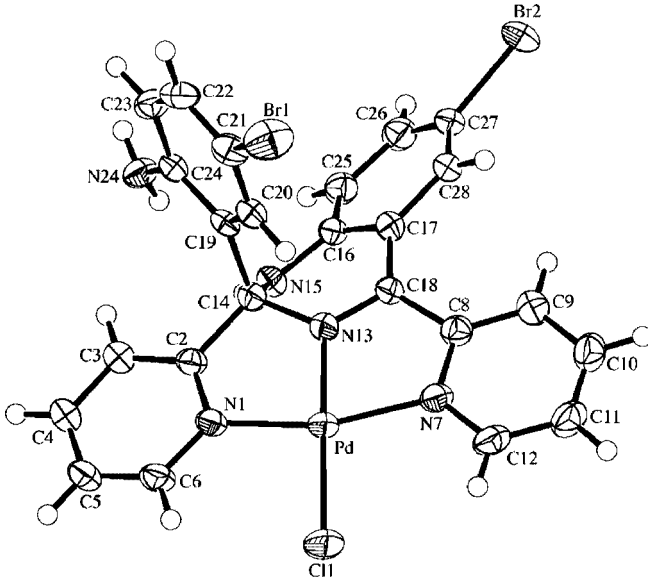


Figure 3. ORTEP representation of the cation in **11** (50% probability ellipsoids). The chloride counterion and toluene of crystallization have been omitted for clarity.

Compound **3** represents the first example of an IDBD functionalized at the 1- and 5-positions. The other important feature is the presence of the bromine atoms on the aromatic rings, which permits further synthetic and supramolecular developments, such as the development of new fused Tröger's base analogues.[10]

In conclusion, compound **3** represents an interesting starting point for supramolecular and synthetic applications. The functionalization at the bridge and the new method of synthesis of IDBD structures will allow for further development.

Experimental Section

General: Melting points are not corrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance-300. Commercial high-purity reagents and solvents were employed without further purification. Microanalyses were performed with a Perkin–Elmer 2400 CHN elemental analyser.

Synthesis of 1: *i*PrMgCl (20 mmol) was added to 2-bromopyridine (3.16 g, 20 mmol) in THF (30 mL) at room temp. After 2 h, 2-amino-5-bromobenzonitrile (3.9 g, 20 mmol) was added. After 18 h at room temp., water (50 mL) was added. Extraction with dichloromethane (3×20 mL), drying with $MgSO_4$ and recrystallization from dichloromethane/diethyl ether afforded **1** (3.9 g, 14 mmol, 71%), m.p. 96.5–100 °C. IR (KBr): $\tilde{\nu}$ = 3364, 3072 (Ph), 1612 (Py and Ph), 1481 (Py and Ph) cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 10.87 (s, 1 H), 8.68 (ddd, J = 4.5, 1.5 and 0.9 Hz, 1 H), 7.92 (dt, J = 7.5 and 2.1 Hz, 1 H), 7.51–7.43 (m, 2 H), 7.34 (br. s, 2 H), 7.26 (dd, J = 9.0 and 2.4 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H), 6.82 (d, J = 9.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): δ = 175.0, 156.2, 149.3, 149.2, 137.3, 133.7, 133.3, 124.4, 122.7 (2C), 118.2, 104.2 ppm. ESI-MS: m/z = 276 $[M+H]^+$.

$C_{12}H_{10}BrN_3$ (275.01): calcd. C 52.20, H 3.65, N 15.22; found C 52.16, H 3.63, N 15.28.

Synthesis of 3: A solution of ketimine **1** (5.0 g, 18.1 mmol) and ketone **2** (0.3 g, 1.0 mmol, 0.06 equiv.) in xylenes (50 mL) was refluxed for 4 h. The mixture was cooled to 40 °C and filtered. The filtrate was washed with toluene (4 × 5 mL) and the compound was dried in an oven at 50 °C to give **3** as colorless needles (3.5 g, 6.1 mmol, 72%), m.p. 235–237 °C. IR (KBr): $\tilde{\nu}$ = 3384, 3047 (Ph), 1591 (Py and Ph), 1498 (Py and Ph) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 8.66 (d, J = 4.8 Hz, 2 H), 7.94–7.84 (m, 4 H), 7.64 (s, 2 H), 7.43 (m, 2 H), 7.05 (dd, J = 8.4 and 2.4 Hz, 2 H), 6.84 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 2.4 Hz, 2 H) 3.89 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 160.2, 148.3, 142.7, 137.4, 130.1, 130.0, 129.0, 123.4, 120.9, 118.3, 107.6, 69.0 ppm. ESI-MS: m/z = 534 $[M+H]^+$. $C_{24}H_{17}Br_2N_5$ (534.98): calcd. C 53.86, H 3.20, N 13.08; found C 53.96, H 3.22, N 12.99.

Synthesis of 6: A solution of ketimine **4** (3.2 g, 13.3 mmol) and ketone **5** (0.3 g, 1.3 mmol, 0.1 equiv.) in acetonitrile (250 mL) was refluxed to complete dissolution. The mixture was cooled to 0 °C and filtered. The filtrate was washed with cold acetonitrile (4 × 5 mL) and the compound was dried in an oven at 50 °C to give **6** as a yellow powder (0.78 g, 1.6 mmol, 12%), m.p. 201–202 °C. IR (KBr): $\tilde{\nu}$ = 3312, 1611, 1590, 1468, 1322, 1253, 1093, 1024, 701 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 8.91 (s, 2 H), 7.92 (d, J = 9.0 Hz, 2 H), 7.71 (d, J = 6.6 Hz, 4 H), 7.44 (m, 8 H), 6.88 (d, J = 9.0 Hz, 2 H) 4.29 (s, 1 H) ppm ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 151.0, 140.9, 136.1, 128.4, 128.0, 127.8, 127.3, 124.5, 123.5, 115.0, 69.9 ppm. ESI-MS: m/z = 466 $[M+H]^+$. $C_{26}H_{19}N_5O_4$ (465.14): calcd. C 67.09, H 4.11, N 15.05; found C 66.89, H 4.09, N 14.99.

Synthesis of Palladium(II) Complex 11: A solution of **3** (0.5 g, 9.3 mmol) and $PdCl_2$ (0.1 g, 0.6 mmol) in toluene (3 mL) was refluxed for 5 min. The mixture was filtered and cooled. The filtered solution was left to concentrate slowly, yielding **11** as red, crystalline prisms (35 mg, 0.02 mmol).

Crystal Data for 11·1.5toluene: $C_{34.5}H_{29}Br_2Cl_2N_5Pd$, M_r = 850.76, monoclinic, space group $C2/c$, a = 24.6800(4), b = 17.4701(3), c = 17.4364(3) Å, β = 116.632(1)°, V = 6736.1(2) $Å^{-3}$, Z = 8, D_X = 1.678 $g\,cm^{-3}$, crystal dimensions: 0.15 × 0.18 × 0.23 mm, T = –113 °C, Nonius KappaCCD area-detector diffractometer, Mo-K_α radiation, λ = 0.71073 Å, μ = 3.122 mm^{-1}, absorption correction based on analysis of equivalent reflections (SORTAV), transmission factors (min./max.) 0.531/0.611, $2\theta_{max}$ = 52°, 52974 measured reflections, 6633 symmetry-independent reflections, 5301 reflections with $I > 2\sigma(I)$, refinement on F^2 with SHELXL-97, 451 parameters, 111 restraints, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.035, $wR(F^2)$ (all reflections) = 0.091, $S(F^2)$ = 1.063, $\Delta\rho_{max}$ = 0.58 $e\,Å^{-3}$. The asymmetric unit contains one monovalent Pd complex cation, one chloride anion and 1.5 disordered toluene molecules distributed over two sites. One of the symmetry-independent toluene molecules is in a general position, while another is in a center of inversion. Both toluene molecules are disordered and the disordered model was established with the aid of suitable geometric and atomic displacement parameter constraints and restraints. CCDC-277072 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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[1] a) J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225–245; b) M. Demeunynck, A. Tatibouet, "Recent Developments in Tröger's Base Chemistry", in *Progress in Heterocyclic Chemistry* (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, UK, **1999**; c) B. G. Bag, *Curr. Sci.* **1995**, *68*, 279–288; d) T. Mas, C. Pardo, F. Salort, J. Elguero, M. R. Torres, *Eur. J. Org. Chem.* **2004**, *5*, 1097–1104; e) A. Hansson, J. Jensen, O. F. Wendt, K. Wärnmark, *Eur. J. Org. Chem.* **2003**, *4*, 3179–3188; f) C. Solano, D. Svensson, Z. Olomi, J. Jensen, O. F. Wendt, K. Wärnmark, *Eur. J. Org. Chem.* **2005**, *6*, 3510–3517.

[2] a) S. Stončius, E. Butkus, A. Žilinskas, K. Larsson, L. Öhrström, U. Berg, K. Wärnmark, *J. Org. Chem.* **2004**, *69*, 5196–5203; b) B. Dolenský, M. Valík, D. Sýkora, V. Král, *Org. Lett.* **2005**, *7*, 67–70; c) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498; d) B. G. Bag, G. von Kiedrowski, *Angew. Chem. Int. Ed.* **1999**, *38*, 3713–3714.

[3] A. Albert, H. Yamamoto, *J. Chem. Soc. C* **1968**, 1944–1949.

[4] H. Hagen, R.-D. Kohler, **1987**, US 4667035.

[5] a) P. Molina, A. Arques, I. Cartagena, R. Obón, *Tetrahedron Lett.* **1991**, *32*, 2521–2524; b) P. Molina, A. Arques, A. Tárraga, M. d. R. Obón, C. Foces-Foces, N. Jagerovic, J. Elguero, *Tetrahedron* **1998**, *54*, 997–1004.

[6] a) K. E. Frank, J. Aubè, *Tetrahedron Lett.* **1998**, *39*, 7239–7242; b) K. E. Frank, J. Aubè, *J. Org. Chem.* **2000**, *65*, 655–666.

[7] a) L. Y. Ukhin, Z. I. Orlova, V. N. Khrustalev, *Russ. Chem. Bull.* **2004**, *46*, 1931–1935; b) L. Y. Ukhin, L. G. Kuz'mina, *Russ. Chem. Bull.* **2004**, *53*, 2262–2268.

[8] Synthesis of **4**: R. I. Fryer, L. H. Sternbach, **1969**, US 3440281.

[9] F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, G. Quéguiner, *Tetrahedron* **2000**, *56*, 1349–1360.

[10] a) J. Jensen, J. Tejler, K. Wärnmark, *J. Org. Chem.* **2002**, *67*, 6008–6014; b) A. Hansson, T. Wixe, K.-E. Bergquist, K. Wärnmark, *Org. Lett.* **2005**, *7*, 2019–2022.

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