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Replacement of HMPA in Samarium Diiodide Promoted Cyclizations and Reactions of Organolithium Compounds

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Dedicated to Professor Dr. Gerhard Erker on the occasion of his 65th birthday

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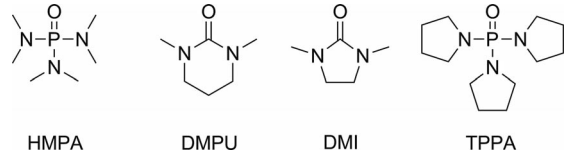
Tripyrrolidinophosphoric acid triamide (TPPA) can replace carcinogenic HMPA as a Lewis basic additive in many reactions involving samarium ketyls. In most cases, yields and selectivities of cyclizations of (het)aryl, alkenyl, and alkynyl ketones are similar. TPPA is also a good substitute of HMPA in the *O*-silylation of an ester enolate and in reactions of lithiated 1,3-dithiane. All these results clearly demonstrate that in many cases the use of HMPA can be avoided.

Introduction

Hexamethylphosphoric acid triamide (HMPA) is known to be an excellent polar aprotic solvent (E_T = 40.9).[1] Its high Lewis basicity is also exploited in organocatalysis.[2] HMPA is frequently employed as a powerful ligand for organolithium compounds,[3] but more recently it was mainly applied in reactions promoted by samarium diiodide, also known as Kagan's reagent.[4] This electron-transfer reagent has been used for many interesting selective transformations,[5] including the syntheses of complex natural products.[6] It has been demonstrated that in THF as solvent, four equivalents of HMPA[7] provide a species $[Sm(HMPA)_4(THF)_2]^{2+}$ $2I^-$ which is much more reactive than SmI_2 itself.[8] The standard potential of ca. –1.3 V in the absence of ligands is shifted to ca. –2.1 V in the presence of four HMPA ligands, hence leading to a strongly increased reducing power. Unfortunately, HMPA is known as a carcinogenic, antispermatogenic, and mutagenic compound and its use has thus been banned in many laboratories.[9] Very severe safety rules have strictly to be followed when HMPA is employed. It has been demonstrated that the *N*-methyl groups of HMPA are responsible for these deleterious biological activities, as they are metabolized to provide formaldehyde, which then undergoes subsequent reactions.[10] As a consequence, compounds without the dimethylamino groups may serve as potential HMPA substitutes.

Due to the positive chemical effects of HMPA in the above-mentioned transformations, a search for substitutes of this useful additive started long ago. For the chemistry of organolithium compounds, including enolates, DMPU (Scheme 1) was found to be a good replacement in many cases,[3] but there are still reactions where HMPA is superior. In samarium diiodide promoted processes alternative solvent systems often provided good results, sometimes even with surprising chemoselectivities. The growing use of alcohols, water, or water/amine mixtures as Lewis basic and protic activators for carbonyl reductions with SmI_2 should be emphasized.[5i,11] Curran also reported on DMPU as an HMPA substitute, but the scope of this system is limited.[12] When samarium ketyls are involved, strong Lewis bases seem to be unavoidable. Recently, McDonald et al. reported on the use of the commercially available pyrrolidino analogue of HMPA, tripyrrolidinophosphoric acid triamide (TPPA), and carefully characterized the complexes with SmI_2 by electrochemical measurements.[13] Similar to HMPA, four equivalents of TPPA are required to take full advantage of reactivity enhancement. The McDonald group also performed a few typical samarium diiodide induced reactions: the reductions of 1-bromodecane and of 2-octanone as well as an intermolecular and an intramolec-



Scheme 1. HMPA and possible substitutes such as DMPU, DMI, or TPPA.

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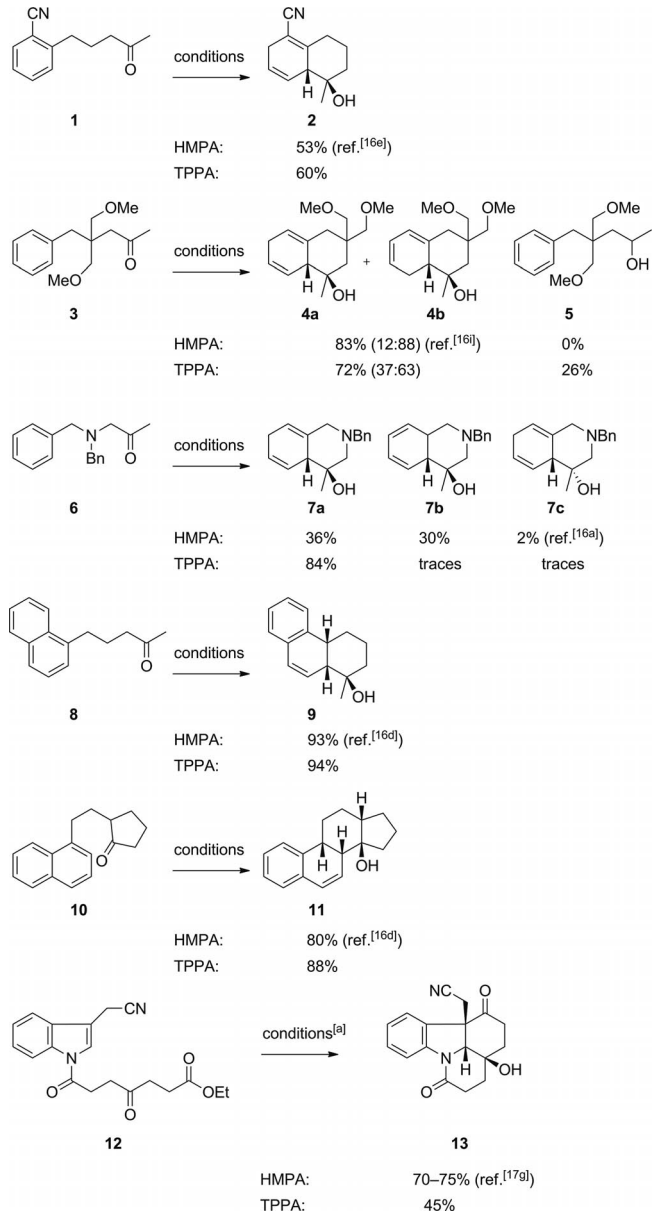
ular samarium ketyl olefin addition. These reactions proceeded equally well when compared to the HMPA-promoted transformations.

Our long-standing interest in intramolecular couplings of samarium ketyls to alkenes,[14] alkynes,[15] and (het)arenes[16,17] also caused us to search for a replacement of HMPA during the last 10 years. In singular examples, a mixture of DMI and lithium bromide served as a good substitute for HMPA,[16f,16g] but in most cases it was observed that this method of samarium diiodide activation failed. Actually, we also studied TPPA some time ago,[18] as it is to be expected that a pyrrolidino moiety is an even slightly stronger donor substituent[19] at the phosphorus than the dimethylamino group. We found that TPPA can replace HMPA often with good success, but there were also limitations. Here we present typical results of samarium diiodide induced coupling reactions comparing the use of TPPA with HMPA. We also include two transformations demonstrating that TPPA may probably replace HMPA in many reactions of lithium enolates or other organolithium species.

Results and Discussion

As typical samarium diiodide promoted transformations, the reductive cyclizations of several γ-aryl ketones to bi- or polycyclic products were studied (Scheme 2). This novel reductive dearomatizing process was discovered by our group in 1998 and subsequently investigated in many variations.[16,17] A strong Lewis base such as HMPA is required to generate a sufficiently reactive samarium ketyl which is able to undergo the addition to the aromatic moiety. Model substrate **1** was converted into bicyclic product **2**[16e] in moderate yield in the presence of HMPA, whereas the use of TPPA even slightly increased the yield. Substrate **3** with geminal dialkyl groups underwent cyclization to regioisomers **4a/4b**[16i] in good yield under standard conditions, whereas with TPPA the regioselectivity and the yield were moderate; secondary alcohol **5** was isolated in 26% yield as a byproduct. In contrast, the transformation of tertiary amine **6** proceeded with higher yield and selectivity by employing TPPA as ligand. Isoquinoline derivative **7a**[16a] was formed almost exclusively. The reductive cyclizations of naphthalene derivatives **8** and **10** furnished expected tri- and tetracyclic compounds **9** and **11**,[16d] respectively, in excellent yields with both additives. The conversion of indole derivative **12** into tetracyclic product **13** – the crucial intermediate in our short strychnine synthesis[17g] – was much less efficient in the presence of TPPA, providing the product only in 45% yield. The separation of relatively polar **13** from TPPA was fairly difficult.

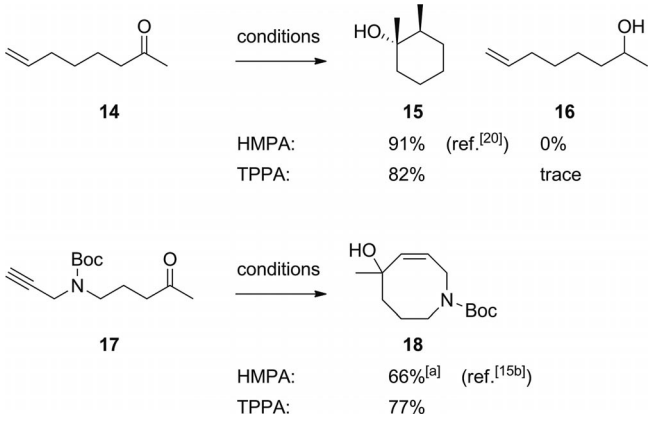
We also compared the efficacy of the two Lewis bases HMPA and TPPA in typical intramolecular couplings of samarium ketyls to alkene or alkyne moieties (Scheme 3). The first example shows that the yield for the TPPA-supported cyclization of **14** to **15** is almost as high as that of the HMPA-promoted reaction;[20] traces of secondary alcohol **16** were isolated by using TPPA. The cyclization



Scheme 2. Samarium diiodide induced cyclizations of γ-(het)aryl ketones to bi- and polycyclic compounds in the presence of HMPA or TPPA as additive. Conditions: SmI_2 (2.2–3.0 equiv.), *t*BuOH (2 equiv.), additive (18 equiv.). [a] Reaction in the absence of *t*BuOH; after decoloration of the solution, bromoacetonitrile (1.0–3.0 equiv.) was added.

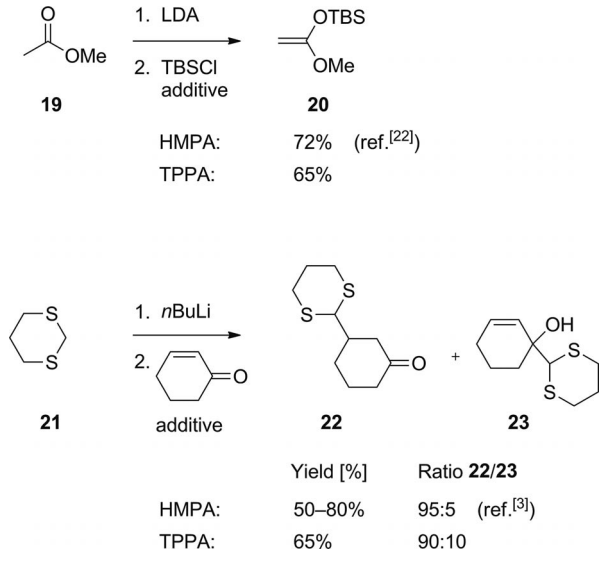
of propargylamine derivative **17** leading to eight-membered heterocycle **18**[15b] is even more efficient with TPPA. With HMPA, 9% of starting material **17** was recovered. These two experiments and those in Scheme 2 indicate that it is difficult to decide which additive is actually more efficient. Because samarium diiodide is a fairly sensitive reagent (trace amounts of oxygen or other impurities can interfere), single experiments for one substrate may not be sufficient for a final statement about the influence of an additive.

HMPA is also an important additive that strongly influences the structure and reactivity of organolithium compounds.[21] It converts lithium enolates into solvent-sepa-



Scheme 3. Samarium diiodide induced cyclizations of alkenyl ketone **14** and propargylamine derivative **17** in the presence of HMPA or TPPA as additive. Conditions: SmI_2 (2.2–2.5 equiv.), *t*BuOH (2–3 equiv.), additive (18–20 equiv.). [a] Substrate was recovered in 9%.

rated ion pairs and thus considerably increases its reactivity as nucleophiles, often connected with a change in selectivity. In Scheme 4 we present an example demonstrating that TPPA can substitute HMPA in lithium enolate chemistry (or related carbanions). By treatment with LDA, methyl acetate **19** was converted into the corresponding ester enolate which was trapped with *tert*-butyldimethylsilyl chloride to give desired ketene silyl acetal **20**. Without additive this process is slow and also provides the C-silylated compound. The literature-reported method employed HMPA as additive and furnished **20** in 72% yield.[22] We used TPPA in a similar procedure and isolated product **20** in 65% yield without formation of the C-silylated methyl acetate. As a second example, we investigated the influence of additives on the 1,2- vs. 1,4-addition selectivity of lithiated 1,3-dithiane. Two equivalents of HMPA[3] or TPPA provided al-



Scheme 4. Synthesis of ketene silyl acetal **20** and addition of lithiated 1,3-dithiane **21** to cyclohexenone in the presence of HMPA or TPPA as additives.

most identical ratios of **22/23** with the first additive being only slightly more selective in favor of 1,4-addition product **23**. These preliminary results indicate that TPPA may replace HMPA also in reactions of other organolithium compounds.[23]

Conclusions

The examples presented in this communication reveal that TPPA is indeed a very good substitute of HMPA in many samarium diiodide induced cyclization reactions and in representative transformations of organolithium compounds. Nevertheless, it cannot be regarded as a general substitute, as it was considerably less efficient than HMPA in several reactions for unknown reasons. In a few cases examined, larger amounts of samarium diiodide could increase the conversion to the products, but this was not always the case. Differences in the regioselectivities have also to be considered. It should be mentioned that TPPA is more viscous and higher boiling than HMPA and hence its transfer by syringe is less convenient. TPPA is also less polar and often needs higher efforts to remove this additive required in fairly high amounts. This may have led to lower yields in singular cases due to the more difficult separation of products from TPPA. Nevertheless, the first reagent of choice should be TPPA in reactions such as those reported here, and if it fails, the second choice may be HMPA.

Experimental Section

SmI_2-Induced Cyclization of 4-Benzyl-5-methoxy-4-(methoxymethyl)pentan-2-one: Degassed TPPA (726 μL, 3.16 mmol) was added to a solution of SmI_2 in THF (0.1 M, 5.27 mL, 0.53 mmol), and the solution was stirred for 15 min. In a second flask, ketone **3** (44 mg, 0.18 mmol) and *t*BuOH (26 mg, 0.35 mmol) were dissolved in THF (5 mL) and argon was bubbled through the solution for 20 min. Then, the substrate solution was transferred to the SmI_2 solution at room temperature by syringe. After stirring overnight, sat. aq. $NaHCO_3$ solution was added, the organic phase was separated, and the aqueous phase was extracted with diethyl ether (4×). The combined ether extracts were washed once with brine, dried with $MgSO_4$, and filtered. After evaporation of the solvent, the residue was filtered through a short silica gel plug with hexane/EtOAc (1:1) for removal of TPPA. The solvent was evaporated, and the residue was purified by column chromatography on aluminum oxide (activity III; hexane/EtOAc, 4:1) to afford 32 mg (72%) of a 37:63 mixture of (1*S**,8a*S**)-3,3-bis(methoxymethyl)-1-methyl-1,2,3,4,6,8a-hexahydronaphthalen-1-ol (**4a**) and (1*S**,8a*S**)-3,3-bis(methoxymethyl)-1-methyl-1,2,3,4,8,8a-hexahydronaphthalen-1-ol (**4b**). In addition, 4-benzyl-5-methoxy-4-(methoxymethyl)pentan-2-ol (**5**; 12 mg, 26%) was isolated. Analytical data of **4b**: ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.52, 1.63 (2 d, J = 14.3 Hz, 1 H each, 2-H), 1.70 (br. s, 1 H, OH), 1.98 (d, J = 13.6 Hz, 1 H, 4-H^1), 2.06 (tdd, J = 2.8, 12.8, 17.4 Hz, 1 H, 8-H^1), 2.26 (dddd, J = 1.3, 4.9, 9.7, 17.4 Hz, 1 H, 8-H^2), 2.32–2.37 (m, 1 H, 8a-H), 2.54 (br. d, $J \approx$ 13.6 Hz, 1 H, 4-H^2), 3.14, 3.17 (AB system, J_{AB} = 9.6 Hz, 1 H each, OCH_2), 3.26 (m_c, 2 H, OCH_2), 3.29, 3.38 (2 s, 3 H each, OCH_3), 5.64 (m_c, 1 H, 5-H), 5.69 (td, J = 4.1, 9.1 Hz, 1 H, 7-H), 5.80 (m_c, 1 H, 6-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.4 (t, C-8), 26.0 (q, CH_3), 36.0 (t, C-4), 39.9 (s, C-3), 42.2 (t,

C-2), 45.7 (d, C-8a), 59.1, 59.2 (2 q, OCH_3), 73.0 (s, C-1), 76.1, 79.1 (2 t, OCH_2), 120.4, 123.8, 124.4 (3 d, C-5, C-6, C-7), 137.5 (s, C-4a) ppm. The following signals were assigned to **4a**: ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, CH_3), 5.48 (m_c, 1 H, 5-H), 5.83–5.86 (m, 2 H, 7-H, 8-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.7 (q, CH_3), 120.8 (d, C-5), 124.2, 125.5 (2 d, C-6, C-7) ppm. IR (ATR): $\tilde{\nu}$ = 3410 (O–H), 3035–2825 (=C–H, C–H), 1660 (C=C), 1105 (C–O) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{24}O_3$ [M + Na]$^+$ 275.1623; found 275.1625.

1-Methoxy-1-[*tert*-butyl(dimethyl)silyloxy]ethene (20): A solution of diisopropylamine (1.92 g, 19.0 mmol) in THF (20 mL) was treated with *n*BuLi (2.3 M in hexanes; 7.9 mL, 18.1 mmol) at –78 °C. After 15 min, ethyl acetate (1.27 g, 17.1 mmol) was slowly added whilst stirring. The mixture was further stirred for 50 min at the same temperature before TPPA (2.80 g, 10.9 mmol) was added. After an additional 10 min, a solution of TBSCl (2.73 g, 18.1 mmol) in hexane (5 mL) was added, and the mixture was stirred for 1 h at –78 °C. The mixture was quenched with water (10 mL), the phases were separated, and the aqueous layer was extracted with hexane (3 × 30 mL). The combined organic layers were washed with brine (1 × 10 mL), dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by kugelrohr distillation (70 °C, 6–10 mbar) to yield ketene silyl acetal **20** (2.07 g, 65%) as a colorless liquid. The NMR spectroscopic data are identical with those reported in the literature.[22]

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[1] C. Reichardt, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2010**.
[2] S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432–440 and references cited therein.
[3] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385–391 and references cited therein.
[4] a) J.-L. Namy, H. B. Kagan, *Nouv. J. Chim.* **1977**, *1*, 5–7; b) P. Girard, J.-L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
[5] For selected reviews on samarium diiodide promoted reactions, see: a) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307–338; b) F. A. Khan, R. Zimmer, *J. Prakt. Chem.* **1997**, *339*, 101–104; c) G. A. Molander, C. R. Harris, *Tetrahedron* **1998**, *54*, 3321–3354; d) A. Krief, A.-M. Laval, *Chem. Rev.* **1999**, *99*, 745–777; e) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351–10372; f) M. Berndt, S. Gross, A. Hölemann, H.-U. Reissig, *Synlett* **2004**, 422–438; g) K. Gopalaiah, H. Kagan, *New J. Chem.* **2008**, *32*, 607–637; h) I. M. Rudkin, L. C. Miller, D. J. Procter, *Organomet. Chem.* **2008**, *34*, 19–45; i) D. J. Procter, R. A. Flowers II., T. Skrydstrup, *Organic Synthesis Using Samarium Diiodide*, Royal Society of Chemistry, Cambridge, **2009**; j) C. Beemelmanns, H.-U. Reissig, *Chem. Soc. Rev.* **2011**, *40*, 2199–2210.
[6] For reviews dealing with SmI_2-induced reactions in natural product synthesis, see: a) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371–3404; b) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem.* **2009**, *121*, 7276–7301; *Angew. Chem. Int. Ed.* **2009**, *48*, 7140–7165; c) M. Szostak, D. J. Procter, *Angew. Chem.* **2011**, *123*, 7881–7883; *Angew. Chem. Int. Ed.* **2011**, *50*, 7737–7739.
[7] a) K. Otsububo, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 5763–5764; b) J. Inanaga, M. Ishikawa, M. Yamaguchi, *Chem. Lett.* **1987**, 1485–1486.
[8] a) M. Shabangi, R. A. Flowers II, *Tetrahedron Lett.* **1997**, *38*, 1137–1140; b) M. Shabangi, J. M. Sealy, J. R. Fuchs, R. A. Flowers II, *Tetrahedron Lett.* **1998**, *39*, 4429–4432.
[9] a) J. A. Zapp Jr., *Am. Ind. Hyg. Assoc. J.* **1975**, *36*, 916; b) K. P. Lee, H. J. Trochimowicz, *J. Natl. Cancer Inst.* **1982**, *68*, 157–171; c) C. P. Mihal Jr., *Am. Ind. Hyg. Assoc. J.* **1987**, *48*, 997–1000.
[10] Hexa*ethyl* phosphoric acid triamide is reported to be non-carcinogenic: J. A. Zilstra, *Proefschrift*, Rijks-Universiteit Leiden, **1987** and references cited therein.
[11] Reviews: a) A. Dahlen, G. Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3393–3403; b) R. A. Flowers II, *Synlett* **2008**, 1427–1439; c) M. Szostak, M. Spain, D. Parmar, D. J. Procter, *Chem. Commun.* **2012**, *48*, 330–346.
[12] E. Hasegawa, D. P. Curran, *J. Org. Chem.* **1993**, *58*, 5008–5010.
[13] C. McDonald, J. D. Ramsey, D. G. Sampsell, J. A. Butler, M. R. Cecchini, *Org. Lett.* **2010**, *12*, 5178–5181.
[14] a) F. A. Khan, R. Czerwonka, R. Zimmer, H.-U. Reissig, *Synlett* **1997**, 995–997; b) H.-U. Reissig, F. A. Khan, R. Czerwonka, C. U. Dinesh, A. L. Shaikh, R. Zimmer, *Eur. J. Org. Chem.* **2006**, 4419–4428; c) J. Saadi, D. Lentz, H.-U. Reissig, *Org. Lett.* **2009**, *11*, 3334–3337; d) J. Saadi, H.-U. Reissig, *Synlett* **2009**, 2089–2092; e) J. Saadi, H.-U. Reissig, *Beilstein J. Org. Chem.* **2010**, *6*, 1229–1245.
[15] a) E. Nandanan, C. U. Dinesh, H.-U. Reissig, *Tetrahedron* **2000**, *56*, 4267–4277; b) A. Hölemann, H.-U. Reissig, *Synlett* **2004**, 2732–2735.
[16] a) C. U. Dinesh, H.-U. Reissig, *Angew. Chem.* **1999**, *111*, 874–876; *Angew. Chem. Int. Ed.* **1999**, *38*, 789–791; b) S. Gross, H.-U. Reissig, *Synlett* **2002**, 2027–2030; c) M. Berndt, I. Hlobilová, H.-U. Reissig, *Org. Lett.* **2004**, *6*, 957–960; d) F. Aulenta, M. Berndt, I. Brüdgam, H. Hartl, S. Sörgel, H.-U. Reissig, *Chem. Eur. J.* **2007**, *13*, 6047–6062; e) U. K. Wefelscheid, M. Berndt, H.-U. Reissig, *Eur. J. Org. Chem.* **2008**, 3635–3646; f) U. K. Wefelscheid, H.-U. Reissig, *Adv. Synth. Catal.* **2008**, *350*, 65–69; g) R. S. Kumaran, I. Brüdgam, H.-U. Reissig, *Synlett* **2008**, 991–994; h) U. K. Wefelscheid, H.-U. Reissig, *Tetrahedron: Asymmetry* **2010**, *21*, 1601–1610; i) A. Niermann, H.-U. Reissig, *Synlett* **2011**, 525–528.
[17] a) S. Gross, H.-U. Reissig, *Org. Lett.* **2003**, *5*, 4305–4307; b) V. Blot, H.-U. Reissig, *Eur. J. Org. Chem.* **2006**, 4989–4992; c) V. Blot, H.-U. Reissig, *Synlett* **2006**, 2763–2766; d) C. Beemelmanns, H.-U. Reissig, *Org. Biomol. Chem.* **2009**, *7*, 4475–4480; e) F. Aulenta, U. K. Wefelscheid, I. Brüdgam, H.-U. Reissig, *Eur. J. Org. Chem.* **2008**, 2325–2335; f) C. Beemelmanns, V. Blot, S. Gross, D. Lentz, H.-U. Reissig, *Eur. J. Org. Chem.* **2010**, 2716–2732; g) C. Beemelmanns, H.-U. Reissig, *Angew. Chem.* **2010**, *122*, 8195–8199; *Angew. Chem. Int. Ed.* **2010**, *49*, 8021–8025; h) C. Beemelmanns, D. Lentz, H.-U. Reissig, *Chem. Eur. J.* **2011**, *17*, 9720–9730.
[18] a) M. Berndt, Dissertation, Freie Universität Berlin, **2003**; b) A. Hölemann, Dissertation, Freie Universität Berlin, **2004**.
[19] Y. Ozari, J. Jagur-Grodzinski, *J. Chem. Soc., Chem. Commun.* **1974**, 295–296.
[20] G. A. Molander, J. A. McKie, *J. Org. Chem.* **1992**, *57*, 3132–3139.
[21] D. Seebach, *Angew. Chem.* **1988**, *100*, 1685–1715; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624–1654.
[22] Y. Kita, J. Segawa, J.-i. Haruta, H. Yasuda, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1099–1104.
[23] For a singular example where HMPA was successfully replaced by TPPA, see: J. M. Wright, G. B. Jones, *Tetrahedron Lett.* **1999**, *40*, 7605–7608.

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