Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of Spirooxindoles by a Mannich-Type Reaction of Isothiocyanato Oxindoles**

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Spirooxindoles are privileged structural motifs found in many alkaloids and unnatural biologically active compounds.[1] Inspired by these important scaffolds, various synthetic methods for producing chiral spirooxindoles, especially applications to natural product synthesis, have been investigated over the last decade.[2] As a state-of-the-art method, catalytic asymmetric one-step construction of spirooxindoles has also been intensively studied.[3–5] However, most of the studies reported to date have focused on the catalytic asymmetric synthesis of spirooxindoles bearing an all-carbon quaternary stereocenter at the C3' position of the oxindole, such as in a spirocycloalkaneoxindole core[4] and a spiro[pyrrolidin-3,3′-oxindole] core.[5] On the other hand, catalytic asymmetric methods for spirooxindoles bearing a nitrogen atom at the C3′ position of the oxindole unit are still limited,[6,7] despite their importance for the design of medicinally important compounds (Figure 1), such as a CRTH2 antagonist with good oral bioavailability,[8] a selective inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B,[9] a potent antimalarial agent,[10] and an inhibitor of the interaction between the tumor suppressor p53 and its negative regulator Hdm2.[11] Thus, expansion of the scope of available chiral spirooxindole cores is in high demand. Herein, we report a highly diastereo- and enantioselective synthesis of a spiro[imidazolidine-4,3′-oxindole] core by an asymmetric Mannich-type reaction of isothiocyanato oxindoles catalyzed by a strontium/Schiff base complex **1** (Figure 2). The transformation of a Mannich adduct into a spiro[imidazoline-4,3′-oxindole] core is also described.

As part of our ongoing investigation of the synthesis of chiral oxindoles[12] and asymmetric reactions with isothiocyanato esters as donors[13,14] under bifunctional metal/Schiff base catalysis,[15] we studied the reaction of imine **2a** and 3-isothiocyanato oxindole **3a**. Initial screenings of various metal/Schiff base catalysts developed in our group showed promising results, in particular with group 2 metal/Schiff base **1a** (Figure 2). The optimization studies are summarized in Table 1. Bu_2Mg/Schiff base **1a**, which was suitable for reactions using isothiocyanato esters as donors,[13a] promoted the reaction with high diastereoselectivity (Table 1, entry 1, 98:2 d.r.), but with only poor enantioselectivity (5% *ee*). Among the group 2 metals screened (Table 1, entries 1–4), $Sr(OiPr)_2$ afforded the best enantioselectivity (93% *ee*; entry 3). Enantioselectivity was much poorer when using

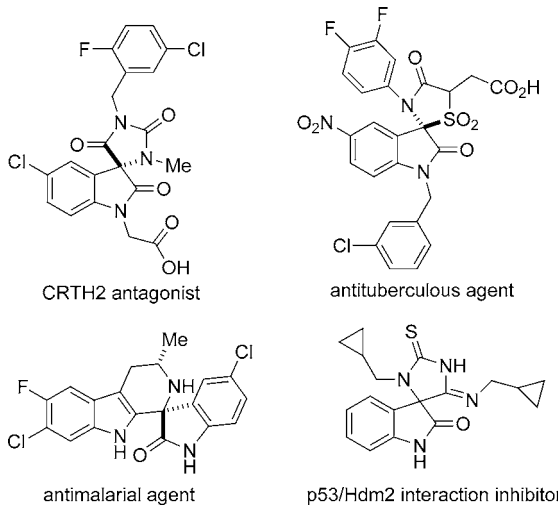
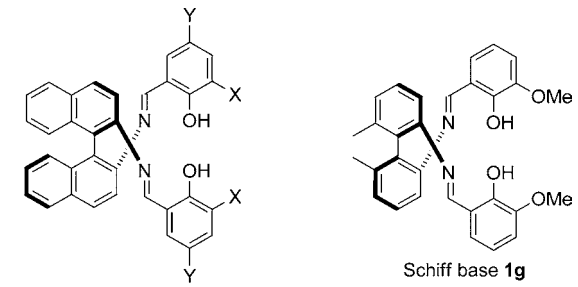


Figure 1. Spirooxindoles bearing a nitrogen atom at the C3′ position of the oxindole unit; a CRTH2 antagonist with good oral bioavailability, an antituberculous agent, an antimalarial agent, and an inhibitor of p53/Hdm2 interaction.



1a: X = OMe, Y = H **1d**: X = OBn, Y = H
1b: X = H, Y = H **1e**: X = OMe, Y = OMe
1c: X = *t*Bu, Y = H **1f**: X = OMe, Y = Br

Figure 2. Structures of Schiff bases (*R*)-**1a–g**. Bn = benzyl.

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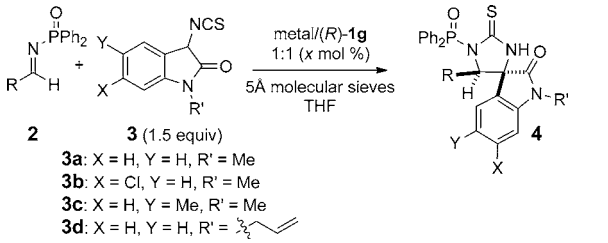
Table 1: Optimization of the catalytic asymmetric Mannich-type reaction.

Entry	Metal source	1	T [°C]	Yield [%][a]	d.r.[a]	*ee* [%][b]
1	Bu_2Mg	**1a**	−40	60	98:2	5
2	$Ca(OiPr)_2$	**1a**	−40	96	87:13	1
3	$Sr(OiPr)_2$	**1a**	−40	95	91:9	93
4	$Ba(OiPr)_2$	**1a**	−40	62	91:9	9
5	$Al(OiPr)_3$	**1a**	−40	92	55:45	30
6	$Ni(OAc)_2$	**1a**	−40	99	91:9	10
7	$Sr(OiPr)_2$	**1b**	−40	68	76:24	1
8	$Sr(OiPr)_2$	**1c**	−40	90	76:24	3
9	$Sr(OiPr)_2$	**1d**	−40	91	71:29	5
10	$Sr(OiPr)_2$	**1e**	−40	92	89:11	76
11	$Sr(OiPr)_2$	**1f**	−40	87	84:16	89
12	$Sr(OiPr)_2$	**1g**	−40	95	97:3	95
13[c]	$Sr(OiPr)_2$	**1g**	−60	88[d]	98:2	97

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [b] Determined by chiral stationary phase HPLC analysis. [c] Reaction was run for 12 h. [d] Yield of isolated **4aa** after purification by silica gel column chromatography.

Table 2: Sr-catalyzed asymmetric Mannich-type reaction of isothiocyanato oxindoles.[a]



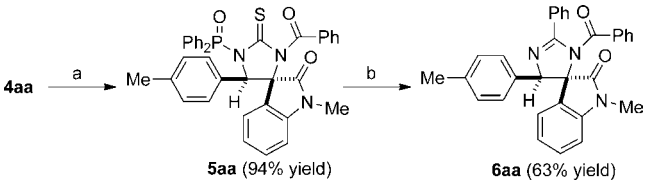
	R	2	3	x[b]	4	T [°C]	t [h]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	4-Me-C_6H_4	**2a**	**3a**	10	**4aa**	−60	12	88	98:2	97
2[f]	3-Me-C_6H_4	**2b**	**3a**	10	**4ba**	−60	9	98	92:8	97
3[f]	2-Me-C_6H_4	**2c**	**3a**	10	**4ca**	−60	9	95	94:6	96
4[g]	4-MeO-C_6H_4	**2d**	**3a**	10	**4da**	−20	12	92	81:19	93
5[f]	Ph	**2e**	**3a**	10	**4ea**	−60	9	99	96:4	98
6	Ph	**2e**	**3a**	5	**4ea**	−60	24	96	95:5	97
7	Ph	**2e**	**3a**	2.5	**4ea**	−60	48	96	95:5	95
8[f]	4-F-C_6H_4	**2f**	**3a**	10	**4fa**	−60	8	95	87:13	99
9	3-F-C_6H_4	**2g**	**3a**	10	**4ga**	−60	12	98	98:2	99
10	4-Cl-C_6H_4	**2h**	**3b**	10	**4hb**	−60	11	87	97:3	97
11	4-Cl-C_6H_4	**2h**	**3c**	10	**4hc**	−60	9	93	97:3	97
12	4-Br-C_6H_4	**2i**	**3a**	10	**4ia**	−60	9	99	97:3	98
13[f]	3-thienyl	**2j**	**3a**	10	**4ja**	−60	9	98	83:17	94
14[g]	2-furyl	**2k**	**3d**	10	**4kd**	−40	9	88	89:11	98
15[g]	4-Me-C_6H_4	**2a**	**3d**	10	**4ad**	−40	12	90	98:2	94

[a] Unless otherwise noted, reactions were run in THF (0.17 M) using imine **2** (0.20 mmol), isothiocyanato oxindole **3** (1.5 equiv), $Sr(OiPr)_2$ (10 mol%), and (*R*)-**1g** with 5 Å molecular sieves (40 mg). [b] *x* = mol% of catalyst used. [c] Yield of isolated **4** after purification by silica gel column chromatography. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [e] Determined by chiral stationary phase HPLC analysis. [f] Schiff base (*S*)-**1g** was used instead of (*R*)-**1g**, and *ent*-**4** was obtained as the major product. [g] Schiff base (*S*)-**1a** was used instead of (*R*)-**1g**, and *ent*-**4** was obtained as the major product.

other metal sources, such as $Al(OiPr)_3$ and $Ni(OAc)_2$ (entries 5 and 6). To improve the diastereoselectivity with $Sr(OiPr)_2$, several Schiff bases were investigated (entries 7–12). Schiff bases **1b**–**1d**, which lack an *ortho*-MeO substituent, resulted in poor diastereo- and enantioselectivity, thus suggesting the importance of the MeO-group. Electronic tuning of the ligands using **1e** and **1f** resulted in less satisfactory selectivity (entries 10 and 11). Modification of the diamine backbone was effective, and Schiff base **1g**, which bears a 2,2′-biphenyldiamine backbone, gave product **4aa** in 97:3 d.r. and 95% *ee* at −40°C (entry 12). After further optimization of the reaction temperature and the reaction time with Schiff base **1g**, product **4aa** was isolated in 88% yield, 98:2 d.r., and 97% *ee* after 12 h at −60°C (entry 13).

The substrate scope of the Mannich-type reaction under optimized reaction conditions is summarized in Table 2.[16] Substituents at the *para*-, *meta*-, and even the sterically hindered *ortho*-positions on the aromatic ring of imines **2a**–**2c** were compatible, and the products were obtained in 97–96% *ee* and 98:2–92:8 d.r. (Table 2, entries 1–3). In the case of the less reactive 4-MeO-substituted imine **2d**, Schiff base **1a** with the binaphthyl backbone showed better reactivity, and product **4da** was obtained in 92% yield and 93% *ee* at −20°C, albeit with only moderate diastereoselectivity (81:19 d.r.; entry 4). Catalyst loading was successfully reduced to 5 mol% and then to 2.5 mol% with imine **2e**. Although a longer reaction time was required with reduced catalyst loading, high diastereoselectivity and enantioselectivity were observed (entries 6 and 7). Imines **2f**–**2I**, which bear electron-withdrawing substituents, also resulted in high selectivity, 99–97% *ee* and 98:2–87:13 d.r. (entries 8–12). Aside from **3a**, the oxindole donors Cl-substituted oxindole **3b** and Me-substituted oxindole **3c** also gave the respective products in excellent diastereo- and enantioselectivity (entries 10 and 11). For *N*-allyl protected oxindole donor **3d**, Schiff base **1a** had better reactivity and stereoselectivity, and the Mannich adducts were obtained in comparably good yield, diastereoselectivity, and enantioselectivity with *N*-Me oxindole donors **3a**–**3c** (entries 14 and 15). These results with a removable *N*-protecting group on the oxindole unit are important for future synthetic applications using the present method.

To demonstrate the synthetic utility of the products, we transformed the spiro[imidazolidine-4,3′-oxindole] core in **4aa** into a spiro[imidazoline-4,3′-oxindole] core (Scheme 1). After benzoylation of **4aa** (94% yield), **5aa** was subjected to Pd-catalyzed desulfurative cross-coupling conditions.[17] Removal of a diphenylphosphinoyl group and cross-coupling with $PhB(OH)_2$ proceeded simultaneously at 50°C in THF, and the spiro[imidazoline-4,3′-oxindole] product **6aa** was obtained in 63% yield. Product **6aa** has a *cis*-diaryl relationship, and can be regarded as a hybrid of two species: 1) Nutlin,[18] an imidozoline-based inhibitor of p53/E3-ubiquitin ligase Mdm2 interaction, and 2) MI-219,[19] a spiro[pyrrolidin-3,3′-oxindole]-based p53/Mdm2 inhibitor. Because of this, the present method would be useful in the field of



Scheme 1. Transformation of Mannich adduct **4aa** into spiro(imidazoline-4,3′-oxindole) **6aa**. Reagents and conditions: a) Benzoyl chloride (1.5 equiv), Et_3N (1.5 equiv), DMAP (10 mol%), CH_2Cl_2, RT, 4 h. b) $PhB(OH)_2$ (2 equiv), CuTC (3 equiv), $Pd(PPh_3)_4$ (10 mol%), THF, 50°C, 1 h. DMAP = *N*,*N*-dimethyl-4-aminopyridine, TC = thiophen-2-carboxylate.

medicinal chemistry for the design and synthesis of new potent anti-tumor agents.[20]

In summary, we have developed an asymmetric Mannich-type reaction of isothiocyanato oxindoles catalyzed by a Sr/Schiff base complex, which provides concise access to enantiomerically enriched spiro[imidazolidine-4,3′-oxindole] compounds, as well as a spiro[imidazoline-4,3′-oxindole] through a two-step conversion from the Mannich adduct. In an effort to develop a new anti-tumor agent, library syntheses of divergent spiro[imidazoline-4,3′-oxindole] compounds is ongoing and will be reported together with the biological activity of the products in due course.

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[1] For a review, see: C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748.

[2] For reviews, see: a) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; b) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem. Int. Ed.* **2003**, *42*, 36; c) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127; d) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209.

[3] For a general review on the enantioselective synthesis of tetrasubstituted oxindoles, see: F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381.

[4] For selected leading examples of catalytic asymmetric synthesis of spirooxindoles bearing a carbocyclic ring, see: a) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396; b) B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2764; c) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200; d) K. Jiang, Z.-J. Jia, S. Chen, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852; e) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735; f) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672; g) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473; h) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem.* **2011**, *123*, 7983; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; i) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; j) J. Peng, X. Huang, L. Jiang, H.-L. Cui, Y.-C. Chen, *Org. Lett.* **2011**, *13*, 4584; k) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212.

[5] For selected examples of the catalytic asymmetric synthesis of a spiro[pyrrolidin-3,3′-oxindole] core, see: a) L. E. Overman, M. D. Rosen, *Angew. Chem.* **2000**, *112*, 4768; *Angew. Chem. Int. Ed.* **2000**, *39*, 4596; b) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670; c) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; d) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 9290; *Angew. Chem. Int. Ed.* **2011**, *50*, 9124.

[6] For the catalytic asymmetric synthesis of spirooxindoles with a nitrogen atom at the C3′ position of the oxindole unit, see: a) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 15786; b) S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Chem. Commun.* **2009**, 6264; c) W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2011**, *13*, 2472; d) S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli, G. Bencivenni, *Adv. Synth. Catal.* **2011**, *353*, 860.

[7] For related works on spirooxindoles with an oxygen atom at C3′ position of the oxindole unit, see: a) D. Hojo, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2008**, *120*, 5904; *Angew. Chem. Int. Ed.* **2008**, *47*, 5820; b) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328; c) L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 1943; d) G. Bergonzini, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 995; *Angew. Chem. Int. Ed.* **2012**, *51*, 971.

[8] The introduction of a heteroatom at the C3′ position of an oxindole unit played a key role in improving the stability of human plasma and the oral bioavailability of a CRTH2 antagonist; see: S. Crosignani, C. Jorand-Lebrun, P. Page, G. Campbell, V. Colovray, M. Missotten, Y. Humbert, C. Cleva, J.-F. Arrighi, M. Gaudet, Z. Johnson, P. Ferro, A. Chollet, *ACS Med. Chem. Lett.* **2011**, *2*, 644.

[9] M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science* **2010**, *329*, 1175.

[10] V. V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hübel, D. Rauh, H. Waldmann, *Angew. Chem.* **2010**, *122*, 6038; *Angew. Chem. Int. Ed.* **2010**, *49*, 5902.

[11] A. Czarna, B. Beck, S. Srivastava, G. M. Popowicz, S. Wolf, Y. Huang, M. Bista, T. A. Holak, A. Dömling, *Angew. Chem.* **2010**, *122*, 5480; *Angew. Chem. Int. Ed.* **2010**, *49*, 5352.

[12] a) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; b) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 1255; c) H. Mitsunuma, S. Matsunaga, *Chem. Commun.* **2011**, *47*, 469; d) H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem.* **2012**, *124*, 5307; *Angew. Chem. Int. Ed.* **2012**, *51*, 5217.

[13] a) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082; b) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4474; *Angew. Chem. Int. Ed.* **2011**, *50*, 4382.

[14] For related reports on a Mannich-type reaction with α-isothiocyanato imides for the synthesis of α,β-diamino acids, see: a) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632; b) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648; c) Z. Shi, P. Yu, P. J. Chua, G. Zhong, *Adv. Synth. Catal.* **2009**, *351*, 2797; d) X. Chen, S. Dong, Z. Qiao, Y. Zhu, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 2583; for the use of isothiocyanato oxindoles **3** in the asymmetric aldol reaction, see Ref. [6c].

[15] For selected recent representative examples, see: a) H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384; b) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666; c) Y. Xu, L. Lin, M. Kanai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5791.

[16] The relative and absolute configuration of the Mannich adduct was unequivocally determined by X-ray crystallographic analysis of **5aa**. CCDC 876876 (**5aa**) 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.

[17] a) R. S. Bon, N. E. Sprenkels, M. M. Koningstein, R. F. Schmitz, F. J. J. de Kanter, A. Dömling, M. B. Groen, R. V. A. Orru, *Org. Biomol. Chem.* **2008**, *6*, 130; b) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983; c) A. Lengar, C. O. Kappe, *Org. Lett.* **2004**, *6*, 771.

[18] a) L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi, E. A. Liu, *Science* **2004**, *303*, 844; b) C. Tovar, J. Rosinski, Z. Filipovic, B. Higgins, K. Kolinsky, H. Hilton, X. Zhao, B. T. Vu, W. Qing, K. Packman, O. Myklebost, D. C. Heimbrook, L. T. Vassilev, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1888.

[19] S. Shangary, D. Qin, D. McEachern, M. Liu, R. S. Miller, S. Qiu, Z. Nikolovska-Coleska, K. Ding, G. Wang, J. Chen, D. Bernard, J. Zhang, Y. Lu, Q. Gu, R. B. Shah, K. J. Pienta, X. Ling, S. Kang, M. Guo, Y. Sun, D. Yang, S. Wang, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3933.

[20] For reviews, see: a) G. M. Popowicz, A. Dömling, T. A. Holak, *Angew. Chem.* **2011**, *123*, 2732; *Angew. Chem. Int. Ed.* **2011**, *50*, 2680; b) L. Römer, C. Klein, A. Dehner, H. Kessler, J. Buchner, *Angew. Chem.* **2006**, *118*, 6590; *Angew. Chem. Int. Ed.* **2006**, *45*, 6440.

