Asymmetric Catalysis

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Enantioselective Synthesis of 4-Hydroxytetrahydropyridine Derivatives by Intramolecular Addition of Tertiary Enamides to Aldehydes**

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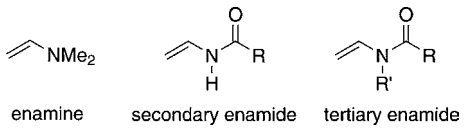
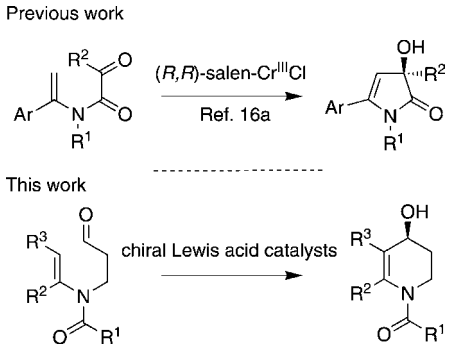
Chiral 4-hydroxypiperidine rings constitute the core structures of natural products[1–5] such as dendrobate alkaloid 241D,[1] lasubine I,[2] and 13α-hydroxy-4-oxasparteine.[3] Furthermore, a large number of 4-hydroxypiperidine derivatives have interesting bioactivity,[6–9] ranging from activation of 5-hydroxytryptamine (5-HT_{1F}) receptors[6] to inhibition of γ-secretase[7] and the mammalian target of rapamycin.[8] Despite their importance in varied disciplines, general synthetic methods for producing 4-hydroxypiperidine derivatives have remained scarcely explored.[2,6–10]

Enamides are enamine variants that contain an electron-withdrawing carbonyl group on the nitrogen atom (Scheme 1). As a result of the electronic effect of the carbonyl group, the delocalization of the lone pair of electrons from the



Scheme 1. Structure of an enamine as well as secondary and tertiary enamides.

nitrogen atom into the C=C bond is reduced, which decreases the electron density and the nucleophilicity of the enaminic carbon atom.[11] Whereas secondary enamides, which contain an N–H moiety, are aza-ene components that undergo reactions with active electrophiles,[11,12] tertiary enamides are known as stable species in nucleophilic reactions.[11,13] The notion of tertiary enamides as inert chemical entities, however, has been challenged recently after the discovery of intramolecular nucleophilic addition of tertiary enamides to an oxirane in the biomimetic synthesis of clausena alkaloids.[14] The nucleophilicity of tertiary enamides has been exploited in the (*R*,*R*)-salen-Cr^{III}Cl-catalyzed intramolecular addition to activated ketones, which produces (*S*)-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives in excellent yields and with high enantioselectivity (Scheme 2).[15] We envisioned that tertiary enamides would act as general and unique nucleophilic reagents. Moreover, the nucelophilicity of enamides is amenable to regulation by the nature of the substituent R (Scheme 1). Changes in the electronic and steric effects of the substituent, for instance, would control the conjugation of the enamine segment and tune the reactivity of enamides. Herein, we present the efficient synthesis of highly enantiopure 4-hydroxy-1,2,3,4-tetrahydropyridine derivatives from the intramolecular nucleophilic addition of tertiary enamides to aldehydes catalyzed by a chiral Lewis acid (Scheme 2). Mechanistic insight into the asymmetric catalysis by the chiral binol–Ti complex that was used in this reaction was also obtained. Reduction of the resulting addition products completes preparation of chiral 4-hydroxypiperidine compounds.



Scheme 2. Catalytic asymmetric reactions of tertiary enamides.

We examined the transformation of enamides into 4-hydroxy-1,2,3,4-tetrahydropyridines (Table 1) by using Jacobsen's salen-metal complexes (10 mol%) as chiral catalysts[16] (Scheme 3). Whereas (*R*,*R*)-salen-FeCl (**Cat-2**), -Co (**Cat-3**) and -MnCl (**Cat-4**) complexes had virtually no catalytic activity (Table 1, entries 2–4), (*R*,*R*)-salen-CrCl (**Cat-1**) (Table 1, entry 1) and -AlCl (**Cat-5**) (Table 1, entry 5) complexes catalyzed the conversion of **1d** effectively at room temperature in dichloromethane. However, asymmetric

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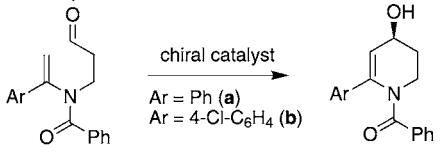
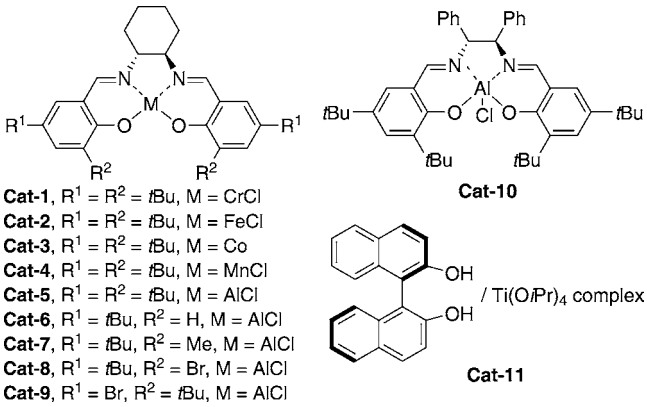
Table 1: Reaction optimization.



Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	**2** (Yield [%])[a]	*ee* [%][b]
1	**Cat-1** (10)	RT	5	**2a** (92)	3.3
2	**Cat-2** (10)	RT	120	**2a** (15)	2.1
3	**Cat-3** (10)	RT	120	**2a** (0)	-
4	**Cat-4** (10)	RT	120	**2a** (0)	-
5	**Cat-5** (10)	RT	72	**2a** (81)	35.4
6	**Cat-5** (10)	−30	120	**2a** (75)	52.1
7	**Cat-6** (10)	RT	13.5	**2a** (89)	69.3
8	**Cat-7** (10)	RT	9	**2a** (93)	59.4
9	**Cat-8** (10)	RT	12	**2a** (91)	31.8
10	**Cat-8** (10)	−40	36	**2a** (51)	72.6
11	**Cat-9** (10)	RT	12	**2a** (90)	28.0
12	**Cat-9** (10)	−10	36	**2a** (42)	60.0
13	**Cat-10** (10)	RT	19	**2a** (93)	60.6
14	**Cat-11** (5)	5	1	**2b** (96)	72.0
15	**Cat-11** (5)	−10	3	**2b** (96)	90.1
16	**Cat-11** (5)	−20	6	**2b** (96)	93.0
17	**Cat-11** (5)	−30	13.5	**2b** (98)	97.0
18	**Cat-11** (5)	−35	35	**2b** (92)	97.6
19	**Cat-11** (5)	−40	>96	**2b** (trace)	n.d.
21	**Cat-11** (2.5)	−35	>96	**2b** (27)	89.7
22	**Cat-11** (10)	−35	12	**2b** (96)	97.4

[a] Yield of isolated product. [b] Determined by HPLC analysis. n.d. = not determined.



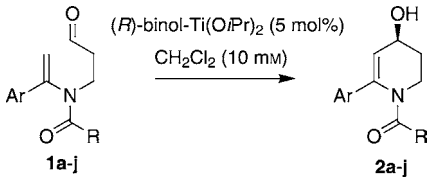
Scheme 3. Chiral catalysts used in this study.

induction was very low, with the *ee* values for the product **2d** of 3.3% and 35.4%, respectively. When the reaction catalyzed by **Cat-1** was performed at −30°C, which led to a sluggish transformation, only a slight improvement in enantioselectivity to 52.1% was obtained (Table 1, entry 6). Screening of salen-AlCl catalysts **Cat-6** to **Cat-10**, which are derived from the modified chiral salen ligands (Table 1, entries 7–13), indicated that **Cat-6** was a promising hit in terms of catalytic efficiency and enantioselectivity, as product **2d** was obtained in 89% yield with an *ee* value of 69.3% within 13.5 h (Table 1 entry 7). Further optimization of the **Cat-6**-catalyzed reaction of **1d** by using either different solvents, including acetonitrile, benzene, or toluene, or adding additives, such as molecular sieve (4 Å), Na_2SO_4, AgOTf, or LiCl, led to the *ee* values not exceeding 80%, albeit high conversion was achieved in some cases (see Table S1 in the Supporting Information).

We then turned our attention to binol–metal complexes.[17] To our delight, the complex formed in situ between (*R*)-binol and Ti(O*i*Pr)$_4$ (2:1, **Cat-11**) was a highly active and enantioselective catalyst. With a 5 mol% catalyst loading, complete conversion of **1b** into **2b** was effected within 1 h at 5°C, to afford a 96% yield of isolated product in 72.0% *ee* (Table 1, entry 14). Decreasing the reaction temperature from 5°C to −35°C gave rise to the dramatic improvement in *ee* value from 72.0% to 97.6% (Table 1, entries 14–18). The reaction became extremely slow when temperature was further reduced to −40°C (Table 1, entry 19). It is also interesting to note that other solvents, including acetonitrile, benzene, toluene, and carbon tetrachloride had a detrimental effect on the asymmetric catalysis, which resulted in either low conversion even over an elongated reaction period at room temperature, or diminished enantioselectivity (see Table S1 in the Supporting Information). A higher loading of catalyst (10 mol%) gave the same level of enantiocontrol (Table 1, entry 22), whereas a lower loading caused a decrease in the reaction velocity and selectivity (Table 1, entry 21).

Catalyzed by (*R*)-binol–Ti complex **Cat-11** under optimized conditions, a range of enamides underwent efficient intramolecular nucleophilic addition to an aldehyde group to afford (*S*)-4-hydroxy-1,2,3,4-tetrahydropyridine products **2** in excellent yields and high *ee* values. As shown in Table 2, phenyl-substituted enamide **1a** and its analogues **1b–f**, which contain electron-withdrawing halogen atoms at different

Table 2: Synthesis of chiral 4-hydroxy-1,2,3,4-tetrahydropyridine derivatives **2**.

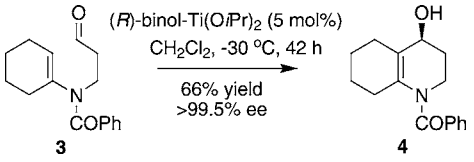


Entry	**1**	R	Ar	*T* [°C]	*t* [h]	(*S*)-**2** (Yield [%])[a]	*ee* [%][b]
1	**1a**	Ph	Ph	−30	24	**2a** (89)	92.8
2	**1b**	Ph	4-Cl-C_6H_4	−35	35	**2b** (92)	97.6
3	**1c**	Ph	4-F-C_6H_4	−20	6	**2c** (97)	92.6
4	**1d**	Ph	4-Br-C_6H_4	−30	40	**2d** (99)	97.6
5	**1e**	Ph	2-Cl-C_6H_4	−30	14	**2e** (96)	>99.5
6	**1f**	Ph	2,4-$Cl_2C_6H_3$	−30	20	**2f** (97)	>99.5
7	**1g**	Ph	3,4-$(OCH_2O)C_6H_3$	−20	4	**2g** (94)	91.4
8	**1h**	Ph	4-Me-C_6H_4	−20	42	**2h** (77)	>99.5
9	**1i**	Me	Ph	−10	5	**2i** (90)	80.0
10	**1i**	Me	Ph	−20	50	**2i** (82)	88.6
11	**1i**	Me	Ph	−30	96	**2i** (trace)	n.d.
12	**1j**	BnO	Ph	−30	42	**2j** (69)	93.5
13[c]	**1a**	Ph	Ph	−30	22	(*R*)-**2a** (91)	95.9

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] (*S*)-binol–Ti complex was used. n.d. = not determined.

positions on the benzene ring, were transformed into the corresponding heterocyclic products in 89–99% yields with *ee* values ranging from 92.6% to more than 99.5% (Table 2, entries 1 to 6). A high conversion and good enantioselectivity was also obtained from the reaction of **1g**, which has an electron-rich phenyl moiety (Table 2, entry 7). In the case of enamide **1h**, which contains a 4-tolyl group, the highly enantioselective cyclization proceeded slowly at −20 °C, and **2h** was obtained in 77% yield after 42 h with an *ee* value of more than 99.5% (Table 2, entry 8). It is noteworthy that *N*-acetyl substituted enamide **1i** and enecarbamate **1j** were also tolerated by the (*R*)-binol–Ti catalytic system, and these reactions proceeded analogously to yield products **2i** and **2j**, respectively (Table 2, entries 10 and 12). The comparable *ee* values of the products reflect the consistent level of enantiocontrol of the chiral catalyst. The different reaction rates for substrates **1a**, **1l**, and **1j**, however, indicate the tuning effect of the electron-withdrawing group on the nitrogen atom on the nucleophilic reactivity of the enamides. The absolute configuration of the products (*S*)-**2** was determined by X-ray crystallographic analysis of (*S*)-**2e** and (*S*)-**2h** (Figure S1 in the Supporting Information).[18] When the (*S*)-binol–Ti complex was applied as a chiral catalyst, the reaction gave (*R*)-**2a**, the enantiomer of (*S*)-**2a**, in excellent yield and enantioselectivity (Table 2, entry 13).

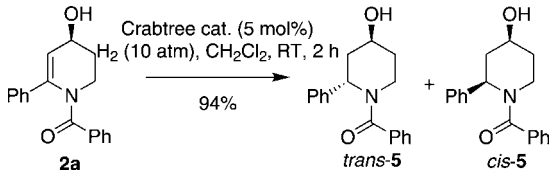
The asymmetric catalysis was readily extended to alkyl-substituted enamides. For example, the reaction of enamide **3**, which contains a cyclohexenyl substituent is shown in Scheme 4. The bicyclic product, 1-benzoyl-4-hydroxy-octahydroquinoline (**4**), was conveniently obtained in 66% yield in more than 99.5% *ee*.



Scheme 4. Synthesis of enantiopure bicyclic compound **4**.

Although combinations of binol and $Ti(OiPr)_4$ have been used widely as chiral Lewis acid catalysts in asymmetric syntheses, an understanding of the reaction mechanisms still remains elusive, with different catalytic species being proposed depending upon the reactions and reaction conditions.[18] To provide mechanistic insight into the reaction of enamides, we examined the transformation of **1d** into **2d** as a model reaction. Almost identical, positive nonlinear effects[19] were obtained with different catalyst concentrations (0.5 mM and 0.25 mM, Figure S2 in the Supporting Information). However, a higher catalyst loading (5 mol%) led to a faster conversion than a lower catalyst loading (2.5 mol%). These results are contrary to the (*R*)-binol–Ti complex-catalyzed enantioselective glyoxylate-ene reaction reported by Mikami and co-workers.[20] These results clearly indicate that the monomeric (*R*)-binol–Ti complex is not responsible for the asymmetric catalysis of enamides. To shed light on the catalytic species, ^{1}H NMR spectroscopy and diffusion-ordered spectroscopy (DOSY) were used. Except for free (*R*)-binol protons, additional proton signals were detected downfield in the ^{1}H NMR spectrum (Figure S3–S5 in the Supporting Information) in a mixture of the chiral ligand and $Ti(OiPr)_4$ at a 2:1 ratio, which indicates a slow exchange of ligand and ligand–Ti complexes on the NMR time scale. The high intensity of proton signals of the free (*R*)-binol ligand also suggests a low conversion of the ligand into (*R*)-binol–Ti complexes. The diffusion coefficients of the (*R*)-binol–Ti complex ($7.81\times10^{-10}\,m^2s^{-1}$) and free (*R*)-binol ($1.33\times10^{-9}\,m^2s^{-1}$) were then measured in CD_2Cl_2 by using the DOSY technique (Figure S6 and S7 in the Supporting Information). On the assumption that the molecules are spherical, the ratio of the molecular weights of two species $M_{complex}/M_{binol}$ calculated from $(D_{binol}/D_{complex})^3$ is 4.9:1.[21] This calculation suggests that the complex has an approximate structure of $[(R)\text{-binol–Ti}(OiPr)_2]_3$, which co-exists in equilibrium with free (*R*)-binol in solution. Computer simulation shows that the nonlinear effect fits well to a trimeric $(ML)_3$ model[19a] (Figure S8–S10 in the Supporting Information). Although the exact mechanism awaits further study, the aforementioned outcomes support the involvement of $[(R)\text{-binol–Ti}(OiPr)_2]_3$ as the most probable catalytic species.

The chiral hydroxylated 1,2,3,4-tetrahydropyridines **2** are conceivably invaluable building blocks in organic synthesis. As a demonstration, the hydrogenation of **2a** in the presence of the Crabtree catalyst[22] produced 4-hydroxypiperidine derivatives *trans*-**5** and *cis*-**5** almost quantitatively in a 5:1 ratio (Scheme 5).



Scheme 5. Catalytic hydrogenation of **2a**.

In summary, we have demonstrated a general and efficient method for the synthesis of highly enantiopure 4-hydroxy-1,2,3,4-tetrahydropyridine derivatives from the intramolecular nucleophilic addition of tertiary enamides to aldehydes catalyzed by a chiral binol–Ti complex. The outcomes, along with our previous discoveries, show convincingly that tertiary enamides are stable and versatile nucleophiles that are useful in organic synthesis. The study of various enaminic reactions of tertiary enamides in synthesis is being actively pursued and the results will be reported in due course.

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[1] M. W. Edwards, J. W. Daly, *J. Nat. Prod.* **1988**, *51*, 1188.
[2] a) H. Iida, M. Tanaka, C. Kibayashi, *J. Chem. Soc. Chem. Commun.* **1983**, 1143; b) H. Iida, M. Tanaka, C. Kibayashi, *J. Org. Chem.* **1984**, *49*, 1909.

[3] M. H. Mohamed, K. M. Mohamed, H. A. Hassanean, S. E. El-Moghazy, *Pharmazie* **1999**, *54*, 778.
[4] a) D. W. Hughes, I. D. Spenser, J. T. Wrobel, *Magn. Reson. Chem.* **2000**, *38*, 707; b) H. J. Kim, I. S. Lee, U. Youn, Q. C. Chen, T. M. Ngoc, D. T. Ha, H. Liu, B. S. Min, J. Y. Lee, R. S. Seong, K. Bae, *J. Nat. Prod.* **2009**, *72*, 749.
[5] A.-L. Sagen, J. Gertsch, R. Becker, J. Heilmann, O. Sticher, *Phytochemistry* **2002**, *61*, 975.
[6] M.-J. Blanco-Pillado, D. R. Benesh, S. A. Filla, K. J. Hudziak, B. M. Mathes, D. T. Kohlman, B.-P. Ying, D. Zhang, Y.-C. Xu, PCT WO 094380A1, **2004**.
[7] H. Li, T. Asberom, T. A. Bara, J. W. Clader, W. J. Greenlee, H. B. Josien, M. D. McBriar, A. Nomeir, D. A. Pissarnitski, M. Rajagopalan, R. Xu, Z. Zhao, L. Song, L. Zhang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6290.
[8] N. Aay, C. M. Blazey, O. J. Bowles, J. Bussenius, J. K. Curtis, S. C. Defina, L. Dubenko, J. R. Harris, E. E. Jackson-Ugueto, A. I. Kim, J.-c. L. Manalo, M. Pack, C. J. Peto, K. D. Rice, T. H. Tsang, L. Wang, PCT WO 138490A1, **2010**.
[9] I. Hamamoto, J. Takahashi, M. Yano, D. Hanai, T. Iwasa, EP 1731518A1, **2006**.
[10] For selected examples: a) F. A. Davis, H. Xu, J. Zhang, *J. Org. Chem.* **2007**, *72*, 2046; b) F. A. Davis, A. Rao, P. J. Carroll, *Org. Lett.* **2003**, *5*, 3855; c) D. Ma, H. Sun, *Org. Lett.* **2000**, *2*, 2503; d) R. Weis, A. J. Kungl, W. Seebacher, *Tetrahedron* **2003**, *59*, 1403; e) D. L. Comins, D. H. LaMunyon, *J. Org. Chem.* **1992**, *57*, 5807; f) R. S. C. Kumar, G. V. Reddy, G. Shankaraiah, K. S. Babu, J. M. Rao, *Tetrahedron Lett.* **2010**, *51*, 1114; g) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774.
[11] For reviews: a) D. R. Carbery, *Org. Biomol. Chem.* **2008**, *6*, 3455; b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599.
[12] a) R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292, and references therein; b) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; c) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336; d) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598; e) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804.
[13] For examples of enaminic reactions with very strong electrophiles: a) T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S.-i. Yamane, T. Kanazawa, T. Aoki, *J. Am. Chem. Soc.* **1982**, *104*, 6697; b) L. Eberson, M. Malmberg, K. Nyberg, *Acta Chem. Scand.* **1984**, *38*, 391; c) O. Meth-Cohn, K. T. Westwood, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1173; d) M. G. Nilson, R. L. Funk, *Org. Lett.* **2006**, *8*, 3833.
[14] a) L. Yang, Q.-Y. Zheng, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Org. Lett.* **2008**, *10*, 2461; b) L. Yang, G. Deng, D.-X. Wang, Z.-T. Huang, J. Zhu, M.-X. Wang, *Org. Lett.* **2007**, *9*, 1387; c) L. Yang, D.-X. Wang, Q.-Y. Zheng, J. Pan, Z.-T. Huang, M.-X. Wang, *Org. Biomol. Chem.* **2009**, *7*, 2628; d) L. Yang, S. Tong, D.-X. Wang, Z.-T. Huang, J. Zhu, M.-X. Wang, *Synlett* **2010**, 927.
[15] a) L. Yang, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *J. Am. Chem. Soc.* **2009**, *131*, 10390; b) L. Yang, C.-H. Lei, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Org. Lett.* **2010**, *12*, 3918.
[16] a) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691; b) P. G. Cozzi, *Chem. Soc. Rev.* **2004**, *33*, 410; c) C. Baleizão, H. Garcia, *Chem. Rev.* **2006**, *106*, 3987.
[17] a) M. Shibasaki, S. Matsunaga, *binol* in *Privileged Chiral Ligands and Catalysts* (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**, pp. 295 – 332; b) J. Balsells, T. J. Davis, P. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10336.
[18] CCDC 862898 (**2e**) and 862899 (**2h**) contain 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.
[19] a) D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430; b) For a recent review on the nonlinear effect: T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456.
[20] a) M. Terada, K. Mikami, T. Nakai, *J. Chem. Soc. Chem. Commun.* **1990**, 1623; b) K. Mikami, M. Terada, *Tetrahedron* **1992**, *48*, 5671.
[21] C. Schalley, *Analytical Methods in Supramolecular Chemistry*, Wiley-VCH, Weinheim, **2007**, p. 193.
[22] G. Stork, D. E. Kahne, *J. Am. Chem. Soc.* **1983**, *105*, 1072.

