Asymmetric Catalysis

Oxazaborolidine-Derived Lewis Acid Assisted Lewis Acid as a Moisture-Tolerant Catalyst for Enantioselective Diels–Alder Reactions**

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The Diels–Alder reaction is one of the most powerful construction processes in organic synthesis, especially for the formation of molecules containing quaternary carbon stereocenters.[1] For this reason there has been much research on the development of enantioselective versions using chiral Lewis acid catalysis.[2] While various kinds of chiral Lewis acid promoted reactions have been developed, these reactions must be carried out under strictly anhydrous conditions. The presence of even a small amount of water stops the reaction because most Lewis acids react immediately with water rather than with the substrate, and decompose or are deactivated.[3] This turns out to be a serious problem when using chiral Lewis acid catalyst in organic synthesis since a large quantity of optically active product is expected to be obtained with a very small amount (>1 mol %) of enantiopure catalyst.

Among the most useful and reactive enantioselective Diels–Alder catalysts are those reported by Corey that employ an oxazaborolidine catalyst in the presence of a Brønsted acid[4]: this is an excellent example of a Brønsted acid assisted Lewis acid catalyst (BLA).[5] Since we have been interested in combined acid catalysis systems for several years,[5–7] the activity of the corresponding Lewis acid assisted Lewis acid catalyst (LLA) system[6]—an L-proline derived oxazaborolidine as a precatalyst combined with a Lewis acid as an activator—was examined for Diels–Alder reactions. However, the resulting LLA was much less efficient (62 % *ee*) than the original BLA catalyst. Surprisingly, a simple monocyclic oxazaborolidine **1** derived from L-valine (Scheme 1) was found to be a promising chiral precatalyst for the LLA system.[8] The resulting LLA was not only found to be a highly potent and stable chiral catalyst for the Diels–Alder reaction but it is also unusually resistant to moisture, oxygen, and Lewis bases,[9,10] which we believe has wide implications for versatile catalyst designs in the future.

Our study commenced with a search for the most effective Lewis acid activator for the Diels–Alder reaction of 1,3-cyclopentadiene and methacrolein with the oxazaborolidine **1a** as precatalyst. LLA catalysts were typically prepared by

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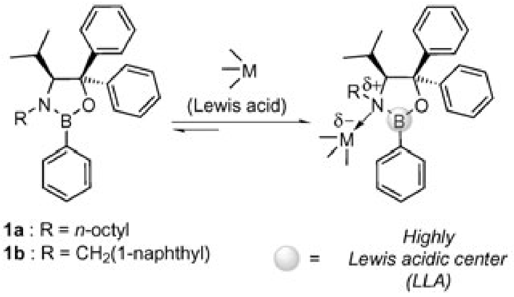
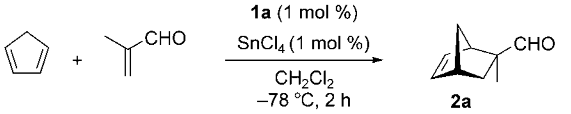


Scheme 1. Plausible reactive species (LLA) generated from **1** and a Lewis acid.

addition of the Lewis acid (6 mol %) to a solution of the chiral oxazaborolidine (7.2 mol %) at −78 °C, followed by stirring for 15 min. Among various kinds of Lewis acids examined, $AlCl_3$, Et_2AlCl, $FeCl_3$, $Sc(OTf)_3$, $SnCl_4$, $[CpTiCl_3]$, and $TiCl_4$ were found to be effective activators for this reaction, and the cycloadducts were obtained in good yield (69–94 % yield, *exo*/*endo* = 73:27 to 77:23) at −78 °C within 2 h with high enantioselectivities (80–87 % *ee* for the *exo* adduct and 95–97 % *ee* for the *endo* adduct).[11] With these activators, both the enantioselectivity and diastereoselectivity (*exo*/*endo* ratio) were uniformly in the same range, and the reactivity was found to be optimal with $SnCl_4$. In contrast, the use of a strong Brønsted acid, bis(trifluoromethanesulfonyl)imide gave the cycloadduct with lower enantioselectivity (67 % *ee* (*exo*), 85 % *ee* (*endo*)). Remarkably, only 1 mol % of **1a** and $SnCl_4$ gave the same high reactivity and enantioselectivity [Eq. (1)].[12]



(1)

95% yield (*exo*/*endo* = 75:25)
84% *ee* (*exo*), 96% *ee* (*endo*)

The potent reactivity of the present catalyst system was further demonstrated by changing the ratio of $SnCl_4$ to chiral oxazaborolidine **1a**. Surprisingly, only a slight loss of enantioselectivity was observed even in the presence of a large excess of $SnCl_4$ (Figure 1). This observation indicates the much higher reactivity of LLA in the Diels–Alder reaction than that of $SnCl_4$. An even more attractive finding is that only a small amount of $SnCl_4$ (0.5 mol %) is needed to promote the reaction (86 % yield (*exo*/*endo* = 75:25), 85 % *ee* (*exo*), 96 % *ee* (*endo*) using 0.5 mol % $SnCl_4$ and 2 mol % **1a**).

These unusual features led us to assume that such a reactive catalyst might be able to survive the presence of a small amount of a Lewis base such as water if a slight excess of $SnCl_4$, which might act as both an activator of the chiral oxazaborolidine and a scavenger of Lewis basic impurities, is utilized in this combined acid system (Scheme 2).

Pursuing this hypothesis, Diels–Alder reactions were conducted with **1a** and $SnCl_4$ in the presence of possible deactivators for the reactive Lewis acid (Figure 2). Indeed,

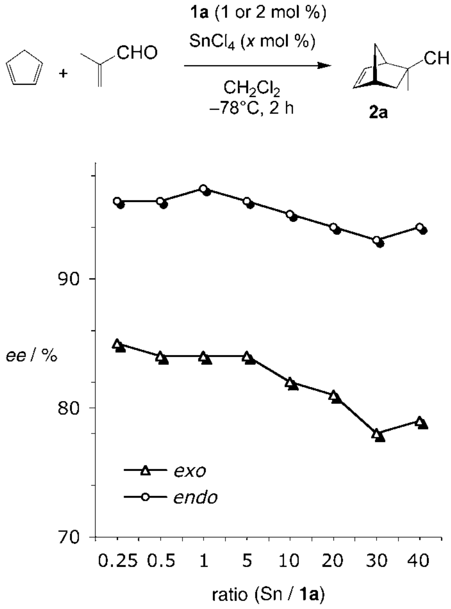
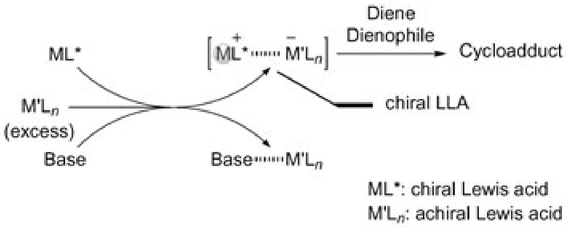


Figure 1. The effect of the amount of $SnCl_4$ on the enantioselectivity.



Scheme 2. Proposed working model for chiral LLA in the presence of Lewis bases.

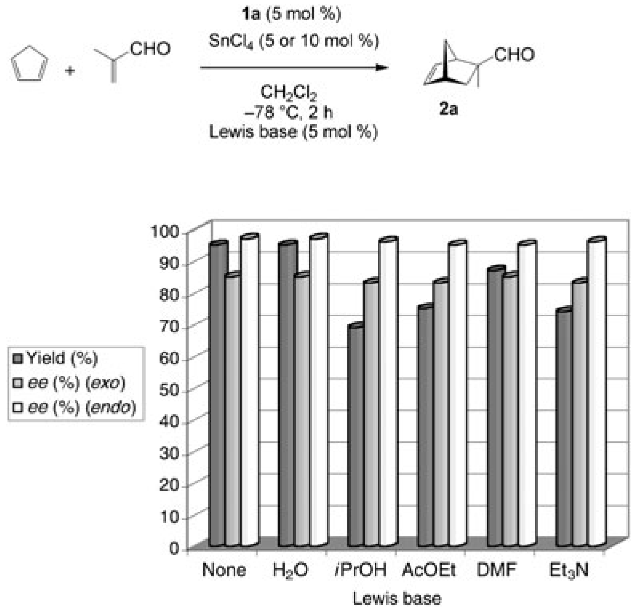
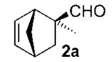
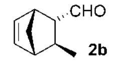
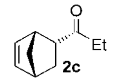
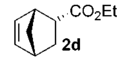
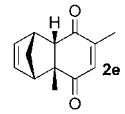
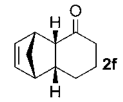
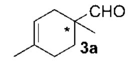
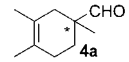


Figure 2. Diels–Alder reactions in the presence of various Lewis bases.

the LLA catalyst maintained its reactivity even in the presence of an equal amount of water to **1a** and $SnCl_4$ without any loss in enantioselectivity.[13] As expected, this LLA could be utilized in nonpurified, reagent-grade dichloromethane as a reaction solvent, in air, with **1a** (5 mol%) and $SnCl_4$ (10 mol%). Similarly, this LLA system was found to function in the presence of a small amount of other Lewis bases (Figure 2). No significant loss of enantioselectivities was observed in any case, although the presence of these Lewis bases led to a slight diminution of the reaction rate.

Finally, a simple modification of the alkyl substituent on the nitrogen of the chiral oxazaborolidine **1a** led to a more enantioselective precatalyst **1b** (entry 1, Table 1). With this chiral unit in hand, the scope of this Diels–Alder reaction was investigated (Table 1). In every case the cycloadducts[14] were obtained in high yield using less than 10 mol% of **1b** and $SnCl_4$ at −78 °C, except for the reaction between 2-cyclohexen-1-one and 1,3-cyclopentadiene. The level and the sense of asymmetric induction were found to be compatible with Corey's proline-derived BLA catalyst in most cases.

Table 1: Diels–Alder reactions catalyzed by **1b** and $SnCl_4$.[a]

1b/ $SnCl_4$ [mol%]	*T* [°C]	*t* [h]	Product[b]	Yield [%][c]	*exo*/*endo*[d]	*ee* [%][e]
1:1	−78	2	 **2a**	> 99	68:32	95 (98)[f]
10:10	−78	13	 **2b**	73	18:82	88 (34)[f]
10:10	−78	2	 **2c**	90	1:99	96
10:10	−78	16	 **2d**	96	1:99	95
10:10	−78	1.5	 **2e**	94	< 1:99	99
20:20	−20	14	 **2f**	93	8:92	95
5:10	−78	16	 **3a**	> 99		90[g]
5:5	−78	16	 **4a**	80		93[g]

[a] Unless otherwise specified, reactions were carried out with diene (5 equiv.), dienophile, **1b** (1–20 mol%), and $SnCl_4$ (1–20 mol%) in dichloromethane under the conditions indicated. [b] Major diastereomers are shown. For the determination of the absolute configuration, see reference [15] and Supporting Information. [c] Yield of the mixture of diastereomers isolated. [d] Determined by GC analysis or ^1H NMR analysis of the crude mixture. [e] Enantioselectivities given for the major diastereomers. For the determination of enantioselectivities, see ref. [16] and Supporting Information. [f] Enantioselectivities for the minor diastereomers. [g] The absolute configuration was not determined.

In conclusion, we have demonstrated that the combination of a chiral oxazaborolidine **1** and $SnCl_4$ leads to an extremely reactive chiral LLA as a promising catalyst for enantioselective Diels–Alder reactions. The unique characteristics of this LLA system are as follows: 1) the enantioselectivity can be preserved even in the presence of a large amount of *achiral* Lewis acid activator, which implicates the generation of highly reactive species; 2) only 0.5 mol% of $SnCl_4$ is necessary to promote the reaction; 3) its inherent reactivity and asymmetric induction ability can be maintained even in the presence of a small amount of water as well as other Lewis bases by adding a slightly larger amount of $SnCl_4$; 4) a simple modification of the oxazaborolidine structure is possible by using commercially available chiral amino alcohols. Other applications of this LLA system are currently underway in our laboratory.

Experimental Section

The synthesis of **2e** catalyzed by **1b** and $SnCl_4$ is given as an example. CH_2Cl_2 (35 mL) and a 1.0 M solution of oxazaborolidine **1b** in CH_2Cl_2 (1 mL, 1 mmol) were added to a dried, three-necked flask under argon. After being cooled to −78 °C, a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (1 mL, 1 mmol) was added dropwise. The resulting pale-yellow solution was stirred for 15 min at this temperature. A solution of 2,5-dimethyl-1,4-benzoquinone (1.4 g, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise to this mixture, and after 1–2 min a solution of cyclopentadiene (4.1 mL, 50 mmol) in CH_2Cl_2 (4.1 mL; pre-cooled to −78 °C) was added dropwise over 10 min from a syringe. The reaction mixture was stirred for 90 min at −78 °C and then quenched by addition of Et_3N (700 μL). The reaction mixture was then allowed to warm to room temperature slowly, and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 10:1) to give **2e** in 98% yield with > 99% *ee*. The physical and spectroscopic data of **2e** were identical to the literature values.[4c,14e] No signals for the *exo* adduct were detected in the NMR spectrum of the crude product. The enantioselectivity was determined by HPLC analysis (Daicel OD-H, hexane (99.4%)/*i*PrOH (0.6%), flow rate = 0.5 mL min^{-1}); t_R = 28.2 min (major), 30.4 min (minor).

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[1] For reviews on the construction of chiral quaternary carbon stereocenters, see: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; b) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146.

[2] For recent reviews on enantioselective Diels–Alder reactions, see: a) L. C. Diaz, *J. Braz. Chem. Soc.* **1997**, *8*, 289–332; b) ref. [1]; c) D. A. Evans, J. S. Johnson, in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1177–1235; d) K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **1999**, 527–538; E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724–1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; e) Y. Hayashi, in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, pp. 5–55.

[3] a) *Lewis Acids in Organic Synthesis, Vols. 1 and 2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**; b) *Lewis Acid

Reagents: A Practical Approach (Ed.: H. Yamamoto), Oxford University Press, Oxford, **1999**.

[4] a) E. J. Corey, T. Shibata, T. W. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808 – 3809; b) D. H. Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992 – 9993; c) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388 – 6390; d) G. Zhou, Q.-Y. Hu, E. J. Corey, *Org. Lett.* **2003**, *5*, 3979 – 3982; e) D. H. Ryu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 4800 – 4802; f) Q.-Y. Hu, P. D. Rege, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 5984 – 5986; g) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8106 – 8107; h) Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708 – 13712.

[5] a) K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 1561 – 1562; b) K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 10520 – 10524; c) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 3049 – 3050; d) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920 – 6930.

[6] a) M. Oishi, S. Aratake, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 8271 – 8272; b) K. Ishihara, J. Kobayashi, K. Inanaga, H. Yamamoto, *Synlett* **2001**, 394 – 396; c) G. Xia, K. Shibatomi, H. Yamamoto, *Synlett* **2004**, 2437 – 2439; for a similar activation of a chiral boron Lewis acid by another Lewis acid, see: d) H. Lachance, X. Lu, M. Gravel, D. G. Hall, *J. Am. Chem. Soc.* **2003**, *125*, 10160 – 10161; e) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518 – 4519; f) M. Gravel, H. Lachance, X. Lu, D. G. Hall, *Synthesis* **2004**, 1290 – 1302.

[7] Lewis acid assisted Brønsted acid (LBA): a) K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179 – 11180; b) K. Ishihara, S. Nakamura, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854 – 12855; c) K. Ishihara, H. Nakamura, S. Nakamura, H. Yamamoto, *J. Org. Chem.* **1998**, *63*, 6444 – 6445; d) K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906 – 4907; e) S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120 – 8130; f) S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8131 – 8140; g) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 1505 – 1506; h) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 3647 – 3655; i) K. Ishihara, D. Nakashima, Y. Hiraiwa, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 24 – 25; j) K. Kumazawa, K. Ishihara, H. Yamamoto, *Org. Lett.* **2004**, *6*, 2551 – 2554; k) H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 11122 – 11123.

[8] This mode of activation was speculated from the plausible active species for CBS reduction. In this process, the coordination of the electrophilic BH_3 to the nitrogen atom of the oxazaborolidine serves to increase the Lewis acidity of the endocyclic boron atom strongly. For recent reviews, see: a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 – 2012; b) S. Itsuno in *Comprehensive Asymmetric Catalysis*, *Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 290 – 315.

[9] Some chiral Lewis acid catalysts have been reported to be air-stable, and even storable, see: a) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani, Y. Yamashita, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5476 – 5481; b) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506 – 6507;

[10] For a chiral Lewis acid catalyzed Diels–Alder reaction in water, see: a) S. Otto, G. Boccaletti, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1998**, *120*, 4238 – 4239; b) S. Otto, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1999**, *121*, 6798 – 6806.

[11] The use of other Lewis acids ($BF_3{\cdot}Et_2O$, tris(pentafluorophenyl)boron, $[Cp_2TiCl_2]$, $ZnCl_2$) resulted in either poor reactivity or lower enantioselectivity.

[12] For other highly enantioselective Diels–Alder reactions with less than 1 mol% of chiral Lewis acid catalyst for the same substrates, see: a) J. Bao, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **1998**, *120*, 8271 – 8272; b) ref. [4c].

[13] The addition of more than one equivalent of water to **1a** resulted in a decrease in both reactivity and enantioselectivity. This obstacle could be overcome by use of a larger amount of $SnCl_4$ without dramatic loss of enantioselectivity.

[14] The physical and spectroscopic data for all cycloadducts were identical to those reported previously for these compounds. **2a**: a) Y. Hayashi, J. J. Rohde, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502 – 5503; **2b**: b) S. Hashimoto, N. Komeshima, K. Koga, *J. Chem. Soc. Chem. Commun.* **1979**, 437 – 438 and ref. [5d]; **2c**: c) R. Kumareswaran, P. S. Vankar, M. V. R. Reddy, S. V. Pitre, R. Roy, Y. D. Vankar, *Tetrahedron* **1999**, *55*, 1099 – 1110 and ref. [4b]; **2d**: d) M. E. Jung, W. D. Vaccaro, K. R. Buszek, *Tetrahedron Lett.* **1989**, *30*, 1893 – 1896 and ref. [4b]; **2e**: e) G. Mehta, A. Srikrishna, A. V. Reddy, M. S. Nair, *Tetrahedron* **1981**, *37*, 4543 – 4559 and ref. [4c]; **2f**: f) S. Takano, T. Kamikubo, M. Morita, K. Ogasawara, *Synthesis* **1994**, 601 – 604, g) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458 – 2459, and ref. [4b]; **3a**: h) Z. Zhu, J. H. Espenson, *J. Am. Chem. Soc.* **1997**, *119*, 3507 – 3512 and i) J. E. Baldwin, M. J. Lusch, *J. Org. Chem.* **1979**, *44*, 1923 – 1927; **4a**: ref. [14i].

[15] The absolute configurations of **2a**,[14b] **2c**,[4b] **2e**,[4c] and **2f**[4b] were assigned by comparison with optical rotation values reported in the literature. For **2b**, the absolute configuration was assigned by comparison with an authentic sample prepared separately, see a) D. Sartor, J. Saffrich, G. Helmchen, *Synlett* **1990**, 197 – 198. The absolute configuration of **2d** was assigned by comparison with the optical rotation value of the corresponding alcohol, see: b) O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, T. Taguchi, *J. Org. Chem.* **1998**, *63*, 2634 – 2640.

[16] The enantioselectivities of the cycloadducts were determined as follows. **2a**: a) K. Furuta, S. Shimizu, Y. Miwa, H. Yamamoto, *J. Org. Chem.* **1989**, *54*, 1481 – 1483. For a general procedure for the acetalization of Diels–Alder adducts with (−)-(2*R*,4*R*)-2,4-pentanediol, see: b) K. Furuta, Q. Gao, H. Yamamoto, *Org. Synth.* **1995**, *72*, 86 – 94; **2b**: ref. [5d]; for **2c–f**, see Supporting Information; **3a**: ref. [5d]; **4a**: refs. [5d] and [16b].