

# Catalytic Asymmetric Thioacetalization of Aldehydes

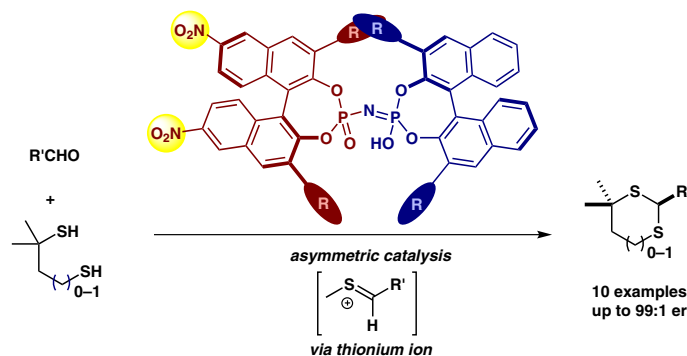
Ji Hye Kim

Aurélien Tap

Luping Liu

Benjamin List\*

Max-Planck-Institut für Kohlenforschung,  
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an  
der Ruhr, Germany  
list@kofo.mpg.de



Received: 05.09.2016

Accepted after revision: 04.10.2016

Published online: 25.10.2016

DOI: 10.1055/s-0036-1588083; Art ID: st-2016-d0587-l

**Abstract** A catalytic enantioselective thioacetalization reaction has been developed. Various aldehydes react with unsymmetrical 1,3- or 1,2-dithiols to furnish chiral, enantioenriched thioacetals in excellent enantioselectivities upon treatment with a nitrated imidodiphosphoric acid catalyst. The transformation is assumed to proceed via a thionium ion intermediate.

**Key words** thioacetals, imidodiphosphates, Brønsted acid catalysis

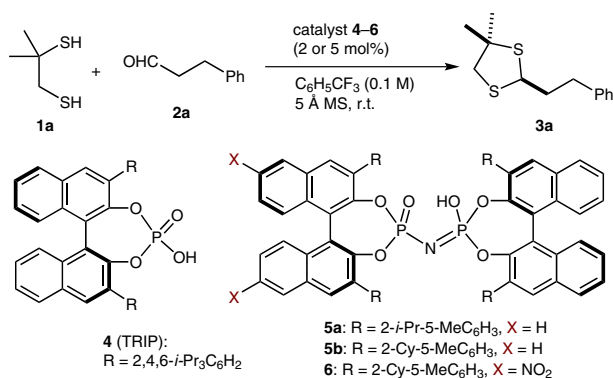
The synthesis of optically active organic sulfur compounds is of interest because of their high abundance in natural products and pharmaceuticals.<sup>1</sup> Sulfur-based scaffolds are also widely used as chiral ligands, auxiliaries, catalysts, and intermediates in chemical synthesis.<sup>2</sup> However, despite the high synthetic utility of (achiral) dithioacetals,<sup>3</sup> little attention has been given to the development of asymmetric methods for the synthesis of their chiral, enantiopure analogues, which may have interesting biological properties.<sup>4</sup> We now report highly enantioselective direct thioacetalization reactions of aldehydes with dithiols catalyzed by a nitrated imidodiphosphoric acid.<sup>5</sup>

Previous approaches towards enantioenriched dithioacetals involve either Diels–Alder reactions of dithioesters with dienes or electrophilic sulfenylations of sulfur-substituted active methines.<sup>6</sup> In contrast, the conceptually straightforward direct dithioacetalization of carbonyl compounds with dithiols has long remained unknown. Inspired by recent studies on chiral Brønsted acid catalyzed direct asymmetric acetalization reactions and related transformation, proceeding via oxocarbenium-<sup>7</sup> and iminium ions,<sup>8</sup> we became curious if an asymmetric thioacetalization, which would proceed via a thionium ion as the critical intermedi-

ate, would also be realizable. Remarkably though, while catalytic asymmetric reaction that proceed via iminium ions are well established, and those involving oxocarbenium ions are currently being developed,<sup>7,9</sup> thionium ions, to our knowledge, have not previously been invoked as critical intermediate in a catalytic enantioselective transformation. Success in developing a catalytic asymmetric thioacetalization of aldehydes would therefore also constitute a proof-of-principle of the general utility of thionium ions in asymmetric catalysis.

We began our investigations by reacting 2-methylpropane-1,2-dithiol (**1a**) with hydrocinnamaldehyde (**2a**) to give dithiolane **3a** in trifluorotoluene in the presence of 5 Å molecular sieves at room temperature (Table 1). A catalytic amount of TRIP (**4**) was tested for the thioacetalization reaction, but did not lead to any conversion after 10 days (entry 1). Based on our previous studies regarding asymmetric spiroacetalizations,<sup>7c</sup> O,O-acetalizations,<sup>7d,e</sup> sulfoxidations,<sup>10a</sup> and carbonyl-ene cyclizations,<sup>10b</sup> we set to explore the ability of our chiral confined imidodiphosphoric acid catalysts to perform an asymmetric thioacetalization reaction. Indeed, both imidodiphosphoric acids **5a** and **5b** afforded the expected thioacetal **3a** with an excellent 98:2 er (entries 2 and 3). However, the reactivity at room temperature turned to be moderate and full conversion was obtained after 3 days.

We have recently designed more active imidodiphosphoric acid catalysts by increasing their acidity either via backbone nitration or by replacing a P=O group with a P=NTf group.<sup>9f,g</sup> Gratifyingly, the use of 5 mol% of unsymmetrical catalyst **6** led to significantly increased reactivity and product **3a** was obtained with full conversion after only 2 hours with an er of 98:2 (entry 4). Lowering the catalyst loading to 2 mol% gave full conversion within 24 hours while retaining the excellent enantioselectivity (entry 5).

Table 1 Reaction Development<sup>a</sup>

Entry	Catalyst (mol%)	Time	Conv. <sup>b</sup>	er <sup>c</sup>
1	<b>4</b> (5)	10 d	0%	–
2	<b>5a</b> (5)	3 d	full	98:2
3	<b>5b</b> (5)	3 d	full	98:2
4	<b>6</b> (5)	2 h	full	98:2
5	<b>6</b> (2)	24 h	full	98:2

<sup>a</sup> Reactions were run on a 0.05 mmol scale.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis.

<sup>c</sup> Determined by HPLC analysis.

The aldehyde scope of the enantioselective thioacetalization reaction was investigated next (Table 2). Reacting aldehyde **2a** with dithiol **1a** furnished product **3a** in 90% isolated yield and with an er of 98:2 (entry 1).<sup>11</sup> The use of pentanal led to the formation of product **3b** with 84% yield and an excellent er of 98:2 (entry 2). Isovaleraldehyde and the  $\alpha$ -branched aldehyde **2d** gave access to the corresponding dithiolanes **3c** and **3d** with good yields and excellent enantioselectivities (entries 3 and 4). A significantly lower er of 74:26 of product **3e** was obtained when benzaldehyde was subjected to the reaction conditions (entry 5). Our method can also be applied to acetalizations with a 1,3-dithiol to access six-membered thioacetals.<sup>12</sup> 1,3-Dithiane **3f** was obtained with slightly lower er (90:10) compared to the corresponding dithiolane (entry 6 vs. entry 1). In addition, lower yield was obtained due to the non-negligible formation of the corresponding enethiol ether (see Supporting Information). Thioacetalization of (*E*)-cinnamaldehyde with 4,4-dimethyl-2-phenethyl-1,3-dithiane (**1b**) proceeded with good enantioselectivity giving product **3g** with an er of 92:8 (entry 7). Pentanal and isovaleraldehyde could be employed in the reaction to give product **3h** and **3i** with enantiomeric ratios of 89:11 and 91.5:8.5, respectively (entries 8 and 9). Replacing isovaleraldehyde with  $\alpha$ -branched aldehyde **2d** resulted in lower enantioselectivity (er = 85.5:14.5) and reactivity (51% yield, entry 10).

Table 2 Reaction Scope<sup>a</sup>

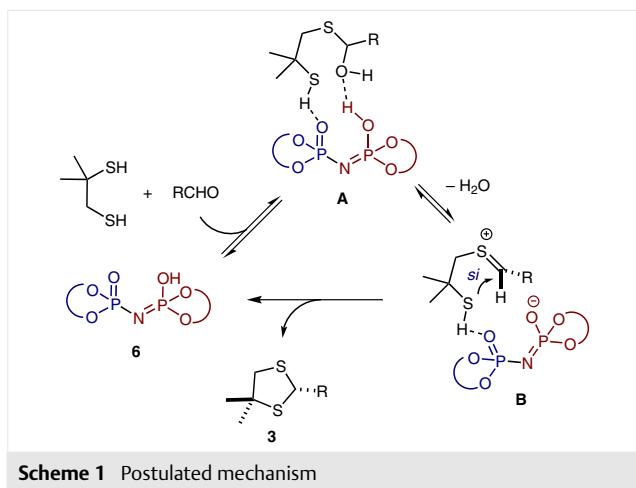
Entry	Temp	Time	Product	Yield (%)	er <sup>b</sup>
1	r.t.	24 h	<b>3a</b>	90	98:2
2	r.t.	24 h	<b>3b</b>	84	98:2
3	r.t.	24 h	<b>3c</b>	82	98.5:1.5
4	r.t.	24 h	<b>3d</b>	86	99:1
5	r.t.	38 h	<b>3e</b>	88	74:26
6 <sup>c</sup>	0 °C	24 h	<b>3f</b>	73	90:10
7 <sup>c</sup>	–20 °C	2 d	<b>3g</b>	80	92:8
8 <sup>c</sup>	0 °C	24 h	<b>3h</b>	46	89:11
9 <sup>c</sup>	0 °C	2 d	<b>3i</b>	73	91.5:8.5
10 <sup>c</sup>	0 °C	6 d	<b>3j</b>	51	85.5:14.5

<sup>a</sup> Reactions were run on a 0.2 mmol scale in trifluorotoluene with 40 mg of 5 Å MS.

<sup>b</sup> Determined by HPLC analysis or GC analysis.

<sup>c</sup> 5 mol% of catalyst were used.

Based on our previous studies on the O,O-acetalization reaction of aldehydes,<sup>7d</sup> we suggest the following mechanism (Scheme 1). Nitrated imidodiphosphate catalyst **6** activates both the aldehyde and the dithiol simultaneously to lead to the formation of S,O-hemiacetal-imidodiphosphoric acid complex **A**. Protonative dehydration of complex **A** results in the formation of the crucial thionium ion intermediate **B**. Cyclization directed by the chiral imidodiphosphate anion leads to enantioenriched product **3** with regeneration of the catalyst.



Scheme 1 Postulated mechanism

In summary, we have developed an enantioselective direct thioacetalization reaction of aldehydes with dithiols. Various enantioenriched dithiolanes and dithianes have been obtained with excellent enantioselectivities and in high yields.

## Acknowledgment

Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant 'High Performance Lewis Acid Organocatalysis, HIPOCAT') is gratefully acknowledged. We thank our technician team and the members of our NMR, MS, GC and HPLC departments for their excellent service.

## Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0036-1588083>.

## References and Notes

- (1) (a) Damini, L. A. *Sulphur-Containing Drugs and Related Organic Compounds*; Wiley: New York, **1989**. (b) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147. (c) Christophersen, C.; Anthoni, U. *Sulfur Rep.* **1986**, *4*, 365.
- (2) (a) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: New York, **1995**. (b) Toru, T.; Bolm, C. *Organosulfur Chemistry in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2008**.
- (3) (a) Kociejowski, P. J. *Protecting Groups*; Thieme: Stuttgart, **2005**. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, **1999**. (c) Page, P. C. B.; van Niel, M. B.; Procter, J. C. *Tetrahedron* **1989**, *45*, 7643. (d) Luh, T.-Y. *J. Organomet. Chem.* **2002**, *653*, 209. (e) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (f) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807.
- (4) (a) Rutenber, E.; Fauman, E. B.; Keenan, R. J.; Fong, S.; Furth, P. S.; de Montellano, P. R. O.; Meng, E.; Kuntz, I. D.; DeCamp, D. L.; Salto, R.; Rosé, J. R.; Craik, C. S.; Stroud, R. M. *J. Biol. Chem.* **1993**, *268*, 15343. (b) Smith, E. M.; Swiss, G. F.; Neustadt, B. R.; McNamara, P.; Gold, E. H.; Sybertz, E. J.; Baum, T. *J. Med. Chem.* **1989**, *32*, 1600.
- (5) This work has first been described in the PhD thesis of JHK ('Brønsted acid catalyzed asymmetric acetalizations', University of Cologne, published online in November 2015, <http://kups.uni-koeln.de/6422/>). After the completion of our studies and during the preparation of this manuscript, Zhou et al. reported a chiral phosphoric acid catalyzed thioacetalization of salicylaldehydes: Yu, J.-S.; Wu, W.-M.; Zhou, F. *Org. Biomol. Chem.* **2016**, *14*, 2205.
- (6) (a) Dentel, H.; Chataigner, I.; Le Cavalier, F.; Gulea, M. *Tetrahedron Lett.* **2010**, *51*, 6014. (b) Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200. (c) Liao, K.; Zhou, F.; Yu, J.-S.; Gao, W.-M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255.
- (7) (a) Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536. (b) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (c) Čorić, I.; List, B. *Nature* **2012**, *483*, 315. (d) Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 4474. (e) Kim, J. H.; Čorić, I.; Palumbo, C.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 1778. (f) Čorić, I.; Vellalath, S.; Müller, S.; Cheng, X.; List, B. *Top. Organomet. Chem.* **2013**, *44*, 165. (g) Sun, Z. K.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074. (h) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 12932. (i) Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc.* **2016**, *138*, 444. (j) Chen, Z.; Sun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 13593.
- (8) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (c) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (d) Ingle, G. K.; Mormino, M. G.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4822. (e) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (f) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 9749. (g) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 908.
- (9) (a) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (b) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430. (c) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8572. (d) Brak, E. N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534. (e) Tsui, G. C.; Liu, L.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 7703. (f) Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B. *J. Am. Chem. Soc.* **2016**, *138*, 9429.

- (g) Liu, L.; Kaib, P.; Tap, A.; List, B. *J. Am. Chem. Soc.* **2016**, *138*, 10822. (h) Zhao, C.; Chen, B. S.; Seidel, D. *J. Am. Chem. Soc.* **2016**, *138*, 9053. (i) Gheewala, C. D.; Collins, B. E.; Lambert, T. H. *Science* **2016**, *351*, 961.
- (10) (a) Liao, S.; Čorić, I.; Wang, Q.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 10765. (b) Liu, L.; Leutzsch, M.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 13268.
- (11) **Representative Procedure for the Synthesis of a Dithiolanes**  
Freshly distilled hydrocinnamaldehyde (**2a**, 26.0  $\mu$ L, 0.2 mmol, 1 equiv) was added to a mixture of 2-methylpropane-1,2-dithiol (**1a**, 29  $\mu$ L, 0.24 mmol, 1.2 equiv), catalyst **6** (5.8 mg, 4  $\mu$ mol, 2 mol%), and 5 Å MS (40 mg) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (2 mL). The mixture was stirred vigorously at r.t. for 24 h and then treated with an aqueous saturated solution of NaHCO<sub>3</sub>. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification was performed by column chromatography on silica gel using 2% EtOAc in hexane as the eluents to obtain product **3a** as a colorless oil (43 mg, 90% yield); er = 98:2. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.31–7.26 (m, 2 H), 7.22–7.17 (m, 3 H), 4.52 (t,  $J$  = 7.0 Hz, 1 H), 3.09 (d,  $J$  = 11.5 Hz, 1 H), 2.96 (d,  $J$  = 11.5 Hz, 1 H), 2.75 (m, 2 H), 2.19–2.15 (m, 2 H), 1.59 (s, 3 H), 1.55 (s, 3 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 141.0, 128.6, 128.5, 126.1, 77.4, 77.2, 76.9, 60.3, 53.2, 50.9, 40.7, 35.4, 29.7, 29.4. HRMS (APPI pos.):  $m/z$  calcd for C<sub>13</sub>H<sub>19</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 239.0928; found: 239.0924. [ $\alpha$ ]<sub>D</sub><sup>25</sup> –20.2 (c 1.00, CHCl<sub>3</sub>).
- HPLC (Chiralpak OJ-H, *n*-heptane–*i*-PrOH = 99:1, flow rate: 0.5 mL/min,  $\lambda$  = 254 nm):  $t_R$  (minor) = 14.76 min,  $t_R$  (major) = 16.89 min.
- (12) **Representative Procedure for the Synthesis of Dithianes**  
Freshly distilled hydrocinnamaldehyde (26.0  $\mu$ L, 0.2 mmol, 1 equiv) was added to a mixture of 2-methylpropane-1,3-dithiol (**1b**, 29  $\mu$ L, 0.4 mmol, 1.2 equiv), catalyst **6** (14.6 mg, 10  $\mu$ mol, 5 mol%), and 5 Å MS (40 mg) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (2 mL). The mixture was stirred vigorously at 0 °C for 24 h and then quenched with an aqueous saturated solution of NaHCO<sub>3</sub>. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. Purification was performed by column chromatography on silica gel using 30% CH<sub>2</sub>Cl<sub>2</sub> in hexane as the eluents to get product **3f** as a colorless oil (37 mg, 73% yield); er = 90:10. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.30–7.27 (m, 2 H), 7.21–7.18 (m, 3 H), 4.16 (t,  $J$  = 7.2 Hz, 1 H), 3.09 (ddd,  $J$  = 15.4, 12.6, 3.1 Hz, 1 H), 2.86 (m, 2 H), 2.74 (ddd,  $J$  = 15.4, 4.5, 3.1 Hz, 1 H), 2.05 (m, 2 H), 1.88–1.77 (m, 2 H), 1.34 (s, 3 H), 1.28 (s, 3 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 140.9, 128.5, 128.4, 126.0, 43.1, 41.5, 39.5, 36.5, 32.5, 32.0, 26.7, 26.5. HRMS (EI, FE):  $m/z$  calcd for C<sub>14</sub>H<sub>20</sub>S<sub>2</sub> [M]: 252.1006; found: 252.1006. [ $\alpha$ ]<sub>D</sub><sup>25</sup> –54.9 (c 0.85, CHCl<sub>3</sub>). HPLC (Chiralpak Cellucoat RP, MeCN–H<sub>2</sub>O = 60:40, flow rate: 1 mL/min,  $\lambda$  = 207 nm):  $t_R$  (minor) = 9.90 min,  $t_R$  (major) = 10.84 min.