

# Asymmetric Binary-Acid Catalysis with Chiral Phosphoric Acid and $\text{MgF}_2$ : Catalytic Enantioselective Friedel–Crafts Reactions of $\beta,\gamma$ -Unsaturated $\alpha$ -Ketoesters

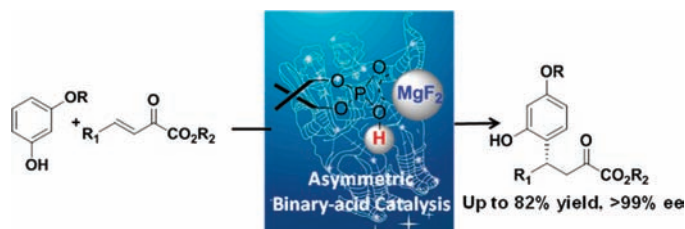
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## ABSTRACT



A unique binary chiral phosphoric acid  $1/\text{MgF}_2$  catalyst that enables effective catalysis of asymmetric Friedel–Crafts reactions of phenols with up to 82% yield and >99% ee is presented. A dramatic synergistic effect has been observed in the combinations of two types of acids, wherein a highly active binary-acid catalyst can be generated from two individually inert acids.

In the context of the extraordinary pace in exploring chiral acid catalysis, the development of new catalysts, particularly those with enhanced efficiency to address difficult substrates and transformations, remains a challenging task.<sup>1</sup> For example, although a number of chiral acid catalysts for the asymmetric Friedel–Crafts reaction of activated aromatics, such as indoles and pyrroles, have been reported,<sup>2</sup> the reactions with less active aromatic substrates (e.g., parent phenols) have only been explored with very limited success.<sup>3</sup> One conceivable way to address this problem is to design chiral acids with sufficient acidity, since it is known that strong acids can promote this and similar types of Friedel–Crafts reactions.<sup>4</sup> Previous efforts in this regard by

Yamamoto,<sup>5</sup> Ishihara,<sup>6</sup> and List<sup>7</sup> have shown that chiral Brønsted acids with stronger acidity could indeed enable activations of less active substrates such as simple aldehydes, leading to asymmetric catalysis beyond the

(1) (a) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Chem. Commun.* **2008**, 4097. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

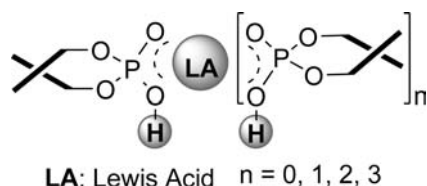
(2) For reviews, see: (a) Poulsen, T.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. For recent examples with chiral Lewis acid catalysis, see: (c) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.–Eur. J.* **2008**, *14*, 3630. (d) Liu, Y.; Shang, D.; Zhou, X.; Zhu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 180. For recent examples with Brønsted acid, see: (e) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. (f) Kang, Q.; Zhang, X.-J.; You, S.-L. *Chem.–Eur. J.* **2008**, *14*, 3539. (g) Rowland, G. B.; Rowland, E. G.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (h) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016.

(3) For an example on reactions of 2-naphthol with nitrostyrenes, see: Liu, T.; Cui, H.; Chai, Q.; Long, J.; Li, B.; Wu, Y.; Ding, L.; Chen, Y. C. *Chem. Commun.* **2007**, 2228.

(4) Olah, G. A.; Krishnamurit, R.; Prakash *Friedel–Crafts Alkylation in Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, 293.

reach of weak acids. Nevertheless, a new strategy and catalyst design to achieve asymmetric strong acid catalysis is still highly desirable.

In the present work, we propose a combinatorial approach for asymmetric strong acid catalysis by simply combining known chiral Brønsted acids with classical Lewis acids. In this binary-acid strategy, enhanced acidity of either the Brønsted acid, Lewis acid, or both would be expected according to Yamamoto's combined acid principles.<sup>8</sup> Most importantly, the resulting multiacidic centers may induce a synergistic effect for catalysis by judicious selection of each acid component and their combinations (Figure 1).<sup>9</sup> Our



**Figure 1.** Asymmetric binary-acid catalysts.

current study indicates that such binary-acid catalysis is indeed possible and a successful example combining chiral phosphoric acid and  $\text{MgF}_2$  is presented herein.

Preliminary studies started with the examination of binary-acids catalyzed addition of 3-methoxyphenol **2a** to the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester **3a**, for which asymmetric catalysis has not been achieved.<sup>10</sup> While no reactions were observed when weak Brønsted acids, such as thioureas, BINOL, and BINOL-derived phosphoric acids (e.g., **1a**, Table 1, entry 2), were used, the joint use of **1a** and catalytic amounts of  $\text{Mg}(\text{OTf})_2$ , which is a quite active catalyst itself (Table 1, entry 1), led to chemo- and regioselective formation of adduct **4a** with 70% yield and 88% ee (Table 1, entry 3). It is noted that the reaction could not proceed with phosphoric acid salts of **1a** such as sodium salt **1e** and pyridinium salt **1f** (Table 1, entries 7 and 8), suggesting that the use of free acid is essential for effective catalysis and that the role played by the acid may be very likely beyond simply as chiral counteranions<sup>11</sup> or phosphate ligands<sup>12</sup> as previously observed in phosphoric acid–metal combined catalysis.<sup>13</sup>

(5) (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175.

(6) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858.

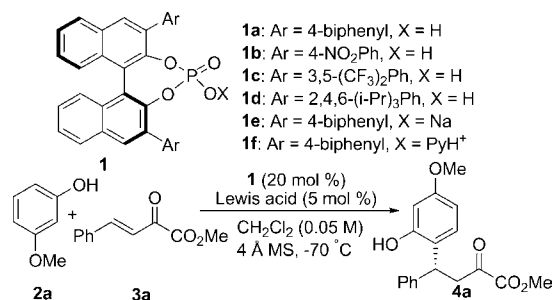
(7) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363.

(8) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

(9) The combination of chiral Brønsted acid and boron Lewis acid has recently been reported as a new Brønsted acid of singular structure: (a) Gao, L.; Hwang, G.-S.; Lee, M. Y.; Ryu, D. H. *Chem. Commun.* **2009**, 5460. (b) Hu, G.; Huang, L.; Huang, R.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615.

(10) For examples with 1,3-dimethoxybenzene, see: (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Ling, H. L.; Zhuang, W.; Hansen, T.; Rutjes, P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953.

**Table 1.** Selected Screening and Optimization Results<sup>a</sup>



entry	Brønsted acid	Lewis acid	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	none	$\text{Mg}(\text{OTf})_2$	trace/90% <sup>g</sup>	
2	<b>1a</b>	none	no reaction	
3	<b>1a</b>	$\text{Mg}(\text{OTf})_2$	70	88
4	<b>1b</b>	$\text{Mg}(\text{OTf})_2$	92	70
5	<b>1c</b>	$\text{Mg}(\text{OTf})_2$	40	38
6	<b>1d</b>	$\text{Mg}(\text{OTf})_2$	trace	
7	<b>1e</b>	$\text{Mg}(\text{OTf})_2$	no reaction	
8	<b>1f</b>	$\text{Mg}(\text{OTf})_2$	no reaction	
9	<b>1a</b>	$\text{Mg}(\text{ClO}_4)_2$	71	88
10	<b>1a</b>	$\text{MgSO}_4$	74	90
<b>11</b>	<b>1a</b>	<b><math>\text{MgF}_2</math></b>	<b>79</b>	<b>95</b>
12	<b>1a</b>	$\text{MgI}_2$	75	80
13	<b>1a</b>	$\text{Cu}(\text{OTf})_2$	78	30
14	<b>1a</b>	$\text{InBr}_3$	72	46
15	<b>1a</b>	$\text{Zn}(\text{OTf})_2$	75	70
16	<b>1a</b>	$\text{Bi}(\text{OTf})_3$	95	40
17	<b>1a</b>	$\text{Ni}(\text{OTf})_2$	68	86
18	none	$\text{MgF}_2$	no reaction <sup>h</sup>	
19 <sup>d</sup>	<b>1a</b>	$\text{MgF}_2$	61	92
20 <sup>e</sup>	<b>1a</b>	$\text{MgF}_2$	40	91
21 <sup>f</sup>	<b>1a</b>	$\text{MgF}_2$	21	90

<sup>a</sup> General conditions: **2a** (0.12 mmol), **3a** (0.10 mmol), **1** (20 mol %), Lewis acid (5 mol %), and 4 Å MS (40 mg) at  $-70^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$ , 36 h; for entries 13–17, 24 h. <sup>b</sup> Isolated yield. <sup>c</sup> Enantioselectivities were determined by HPLC analysis. <sup>d</sup> **1a** (15 mol %). <sup>e</sup> **1a** (10 mol %). <sup>f</sup> **1a** (5 mol %). <sup>g</sup> Yield at rt. <sup>h</sup> Both at rt and  $-70^\circ\text{C}$ .

A quick survey of different phosphoric acids such as **1a–d** was then followed and the best results were obtained in the presence of **1a** (Table 1, entries 3–6), whereas others resulted in either low activity or poor enantioselectivity. With phosphoric acid **1a**, the use of different Lewis acids was next

(11) For examples, see: (a) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (c) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (d) Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 14450.

(12) For examples, see: (a) Suzuki, S.; Furono, H.; Yokoyama, Y.; Inanaga, J. *Tetrahedron: Asymmetry* **2006**, *17*, 504. (b) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 8396. (c) After our original submission, Xia and Huang reported the enantioselective addition of indole nucleophiles to unsaturated  $\alpha$ -hydroxy ketones using a chiral phosphoric acid–iron(III) system. The phosphoric acid is also a phosphate ligand for the metal according to this study: Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia, C.; Huang, H. *Chem.—Eur. J.* **2010**, *16*, 1638.

(13) For other recent examples using the combined chiral Brønsted acid and transition metal, see: (a) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (b) Xu, X.; Zhou, J.; Yang, L.; Hu, W. *Chem. Commun.* **2008**, 6564. (c) Guo, Z.; Shi, T.; Jiang, J.; Yang, L.; Hu, W. *Org. Biomol. Chem.* **2009**, 5028. (d) Tetrade, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354. (e) Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284.

probed and some selected results were listed in Table 1. In all the cases, the reactions proceeded very well in the presence of binary-acids while the activity and enantioselectivity varied significantly with different Lewis acid such as Mg<sup>II</sup>, Cu<sup>II</sup>, In<sup>III</sup>, Zn<sup>II</sup>, Bi<sup>III</sup>, and Ni<sup>II</sup> salts (Table 1, entries 9–17). To our delight, Group IIA metal Mg<sup>II</sup> Lewis acids generally exhibited superior performance in terms of both activity and stereoselectivity. Among a myriad of Mg<sup>II</sup> salts examined, MgF<sub>2</sub> was identified to be the optimal Lewis acid, giving 79% yield and 95% ee (Table 1, entry 11). This result is quite beyond our expectation since there has been no report on the use of MgF<sub>2</sub> as homogeneous Lewis acid in asymmetric catalysis.<sup>14,15</sup> More surprisingly, MgF<sub>2</sub><sup>16</sup> itself turned out to be an inert catalyst for the reaction in the absence of chiral phosphoric acid **1a** even at rt (Table 1, entry 18). These intriguing findings further prove the synergistic function of chiral Brønsted acids and Lewis acids, causing a concerted complex formation for effective catalysis. The impact of the ratio of two acids was also examined. While the enantioselectivity was maintained at a similar level by increasing the ratio of **1a**/MgF<sub>2</sub> from 1:1 to 4:1, the activity was considerably improved with higher ratio (Table 1, entries 19–21). Further increasing the ratio did not lead to much improvement. An optimal 4:1 ratio of **1a**/MgF<sub>2</sub> was used in our subsequent experiments.<sup>17</sup>

With optimal conditions established, the scope of an asymmetric binary-acid-catalyzed enantioselective Friedel–Crafts alkylation reaction was next explored with **1a**/MgF<sub>2</sub> in dichloromethane at –70 °C. The results are presented in Table 2. A variety of β,γ-unsaturated-α-ketoesters can be applied in the reactions with free phenols **2a** and **2b** to give the desired Friedel–Crafts alkylation products **4a–j** in good yields and with up to 99% ee (Table 2). Interestingly, no reaction was observed when 1,3-dimethoxybenzene was used.

Not only free phenols but also the asymmetric binary-acid catalytic system **1a**/MgF<sub>2</sub> could also be successfully applied in similar Friedel–Crafts reactions of indoles. Remarkably, 0.5 mol % of MgF<sub>2</sub> suffices for effective catalysis and the reactions work well with a range of indole derivatives and β,γ-unsaturated-α-ketoesters, affording the desired 1,4-addition adducts in good yields with 82–94% ee (Table 3).<sup>18</sup> Previously, simple phosphoric acids have been shown to be unable to catalyze similar reactions and therefore a specially designed *N*-triflylphosphoramidate acid with strong

**Table 2.** Friedel–Crafts Alkylation Reactions of **2a,b** and β,γ-Unsaturated α-Ketoesters<sup>a</sup>

entry	product	R	R <sub>1</sub>	R <sub>2</sub>	yield (%) <sup>b</sup>	ee (%) <sup>c,d</sup>
1	<b>4a</b>	Me	Ph	Me	79	95
2	<b>4b</b>	Et	Ph	Me	80	90
3	<b>4c</b>	Me	4-ClC <sub>6</sub> H <sub>4</sub>	Me	70	96
4	<b>4d</b>	Et	4-ClC <sub>6</sub> H <sub>4</sub>	Me	65	95
5	<b>4e</b>	Me	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Me	81	>99
6	<b>4f</b>	Me	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Et	76	86
7	<b>4g</b>	Me	2-FC <sub>6</sub> H <sub>4</sub>	Me	82	97
8	<b>4h</b>	Me	4-MeC <sub>6</sub> H <sub>4</sub>	Me	57	82
9	<b>4i</b>	Me	3-MeC <sub>6</sub> H <sub>4</sub>	Me	75	84
10	<b>4j</b>	Me	4-PhC <sub>6</sub> H <sub>4</sub>	Me	59	79

<sup>a</sup> General conditions: **2a** (0.12 mmol), **3a** (0.10 mmol), **1** (20 mol %), MgF<sub>2</sub> (5 mol %) and 4 Å MS (40 mg) at –70 °C in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Isolated yield. <sup>c</sup> Enantioselectivities were determined by HPLC analysis. <sup>d</sup> The absolute configurations were assigned by analogy with the known indole adducts.<sup>10a,20</sup>

**Table 3.** Friedel–Crafts Alkylation Reactions of Different Indoles **2c–e** and β,γ-Unsaturated α-Ketoesters<sup>a</sup>

entry	product	R	R <sub>1</sub>	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>4k</b>	H	Ph	82	90 (R) <sup>d</sup>
2	<b>4l</b>	H	2-FC <sub>6</sub> H <sub>4</sub>	87	94
3	<b>4m</b>	H	4-ClC <sub>6</sub> H <sub>4</sub>	82	83
4	<b>4n</b>	H	3,4-ClC <sub>6</sub> H <sub>4</sub>	80	88
5	<b>4o</b>	H	4-MeC <sub>6</sub> H <sub>4</sub>	78	87
6	<b>4p</b>	H	4-PhC <sub>6</sub> H <sub>4</sub>	81	82
7	<b>4q</b>	5-MeO	Ph	90	92
8 <sup>e</sup>	<b>4q</b>	5-MeO	Ph	81	84
9	<b>4r</b>	6-Cl	Ph	83	92
10 <sup>f</sup>	<b>4s</b>	6-Cl	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	64	91

<sup>a</sup> General conditions: **2c** (0.10 mmol), **3a** (0.12 mmol), **1a** (2 mol %), MgF<sub>2</sub> (0.5 mol %) and 4 Å MS (40 mg) at –70 °C in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Isolated yield. <sup>c</sup> Enantioselectivities were determined by HPLC analysis. <sup>d</sup> The absolute configuration was determined by comparing the optical rotation with that reported in ref 10a. <sup>e</sup> MgF<sub>2</sub> was not used. <sup>f</sup> For 72 h.

acidity was required for such catalysis.<sup>19</sup> From our studies, it was found that phosphoric acid **1a** was actually a viable catalyst for this reaction<sup>20</sup> (Table 3, entry 8) and the combination of **1a** with MgF<sub>2</sub> could further improve the catalysis with better activity and stereocontrol (Table 3, entry

(14) For a review on magnesium Lewis acid, see: Zhang, X.; Li, W. *Chin. J. Org. Chem.* **2003**, *23*, 1185.

(15) For a review on metal fluoride complexes in asymmetric catalysis, see: Pagenkopf, B. L.; Carreira, E. M. *Chem.—Eur. J.* **1999**, *5*, 3437. For one recent example, see: Hamada, T.; Manabe, K.; Kobayashi, S. *Chem.—Eur. J.* **2006**, *12*, 1205.

(16) Solubility of MgF<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> was determined to be around 10 mg/100 mL at room temperature. Therefore, solubility would not be the major reason for inertness of MgF<sub>2</sub> (0.31 mg/2 mL of CH<sub>2</sub>Cl<sub>2</sub>) in the control reaction at rt. On the other hand, the binary-acid **1a**/MgF<sub>2</sub> is very soluble under the reaction conditions and homogeneous reactions were generally observed in our experiments.

(17) The real active catalytic species remains unclear and awaits further study.

(18) *N*-Methylindole has also been examined. Instead of the desired 1,4-addition product, this reaction gave regioselectively 1,2-addition product. Further exploration along this line is underway.

(19) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593.

7 vs 8), thus highlighting again the beneficial features of this binary-acid catalytic system.

In summary, we have developed a combinatorial approach for chiral strong acid catalysis by simply combining the known chiral Brønsted acids with typical Lewis acids. A unique binary-acid **1a**/MgF<sub>2</sub> was identified via this approach and the catalyst was found to enable effective catalysis of asymmetric Friedel–Crafts reactions of phenols and indoles with good activity and high to excellent enantioselectivity. A dramatic synergistic effect has been observed in the combinations of two types of acids, demonstrating that a

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(20) Compared with inertness in the reaction of phenol, the activity of phosphoric acid **1a** in this case may be a result of high reactivity of indoles. In a control reaction, 3-methoxyphenol **2a** and indole were treated with **3g** in one pot in the presence of **1a** (20 mol %)/MgF<sub>2</sub> (5 mol %). The reaction afforded the desired products **4g** and **4l** with 94% and 94% ee, respectively, almost the same as listed in Table 2 (entry 7) and Table 3 (entry 2), suggesting a common stereocontrol mode in these two reactions. In this instance, indole was consumed in less than 1 h, but there was only ca. 10% conversion for phenol **2a**.

highly active binary-acid catalyst can be generated from two individually inert acids. This beneficial feature together with the modular and combinatorial flexibility promise wide application of such asymmetric binary-acid catalysis in many other strong acid-catalyzed reactions. A detailed mechanism study and further investigations in this field of catalysis are ongoing and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectral data for compound **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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