Communication

Enantioselective Cycloaddition of Styrenes with Aldimines Catalyzed by a Chiral Magnesium Potassium Binaphthyldisulfonate Cluster as a Chiral Brønsted Acid Catalyst

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Enantioselective Cycloaddition of Styrenes with Aldimines Catalyzed by a Chiral Magnesium Potassium Binaphthyldisulfonate Cluster as a Chiral Brønsted Acid Catalyst

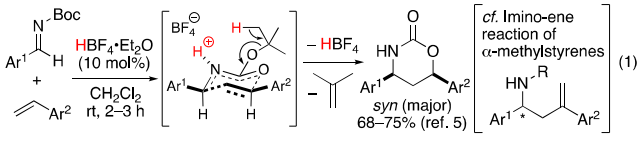
Manabu Hatano, Keisuke Nishikawa, Kazuaki Ishihara*

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

Supporting Information Placeholder

ABSTRACT: A chiral magnesium potassium binaphthyldisulfonate cluster, as a chiral Brønsted acid catalyst, was shown to catalyze an enantioselective cycloaddition of styrenes with aldimines for the first time. The strong Brønsted acidity of the unoptimized catalyst-precursors, which might dissolve drying agents and take up the leached Mg^{2+} and K^{+}, led to serendipitous results. Mechanistic aspects were supported by X-ray and ESI-MS analysis of the catalyst and a kinetics study of the reaction. Useful transformations to optically active 1,3-amino alcohols on a gram scale were also demonstrated.

In modern asymmetric catalysis, chiral Brønsted acid catalysts with (*R*)- or (*S*)-binaphthyl skeletons have been used as practical organocatalysts.[1] Since the suitable Brønsted acidity of the catalysts is different for each substrate and reagent to promote the desired reactions, fine tuning of the acidity as well as fine stereo-tuning of the catalysts are very important. In this regard, we have recently developed a practical synthesis of chiral 3,3'-Ar_2-BINSA (1,1'-binaphthalene-2,2'-disulfonic acid) **1**,[2] which might have both strong Brønsted acidity[3] and sufficient bulkiness for asymmetric induction. Here, we report for the first time an asymmetric catalysis that uses chiral 3,3'-Ar_2-BINSAs **1** in the presence of magnesium and potassium sources through a somewhat interesting scenario.[4,5] In particular, we focused on the enantioselective cycloaddition of styrenes with *N*-Boc aldimines, which has been originally developed by Hossain in an achiral manner using $HBF_4 \cdot Et_2O$ (Eq. 1).[6] Indeed, chiral oxazinanones sometimes have biological activities,[7] and are useful as chiral auxiliaries and precursors of chiral 1,3-amino alcohols.[8] Nevertheless, while catalytic enantioselective oxazinanone synthesis has not been reported,[9] a few examples of a catalytic enantioselective imino-ene reaction of α-methylstyrenes have been

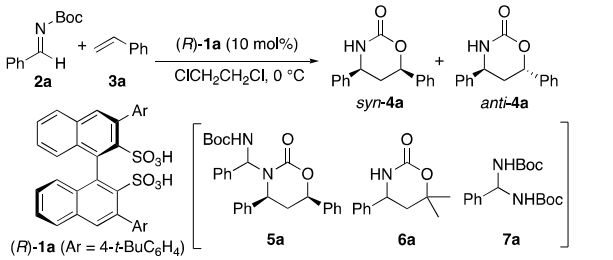


(1)

reported (Eq. 1).[10] We envisioned that, to promote the reaction of interest, chiral strong Brønsted acids should be effective, since (1) simple styrenes, which are regarded as relatively weak nucleophiles,[11] could be used without direct activation by the catalysts and (2) fragmentation of the *t*-Bu moiety is involved.

We initially examined the reaction of styrene **3a** with *N*-Boc aldimine **2a** through the use of (*R*)-3,3'-(4-*t*-$BuC_6H_4)_2$-BINSA **1a** (5 mol%) in 1,2-dichloroethane at 0 °C for 5 h (Table 1, also see the SI). With the use of (*R*)-**1a** alone, the reaction was slow and *syn*-**4a** was obtained with poor enantioselectivity along with *anti*-**4a**, double adduct **5a**, and hydrolyzed **7a** (entry 1). When we used $MgSO_4$ to prevent the hydrolysis to **7a** by adventitious water, the enantioselectivity of *syn*-**4a** was temporarily improved, although reproducibility was not observed and **6a** and **7a** were still obtained by overreaction and hydrolysis, respectively (entry 2). We then suspected that Mg^{2+} was being leached from $MgSO_4$ due to the strong acidity of (*R*)-**1a**. Therefore, we used a

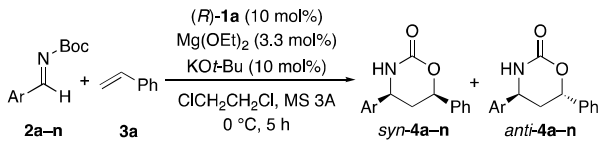
Table 1. Optimization of the catalysts[a]



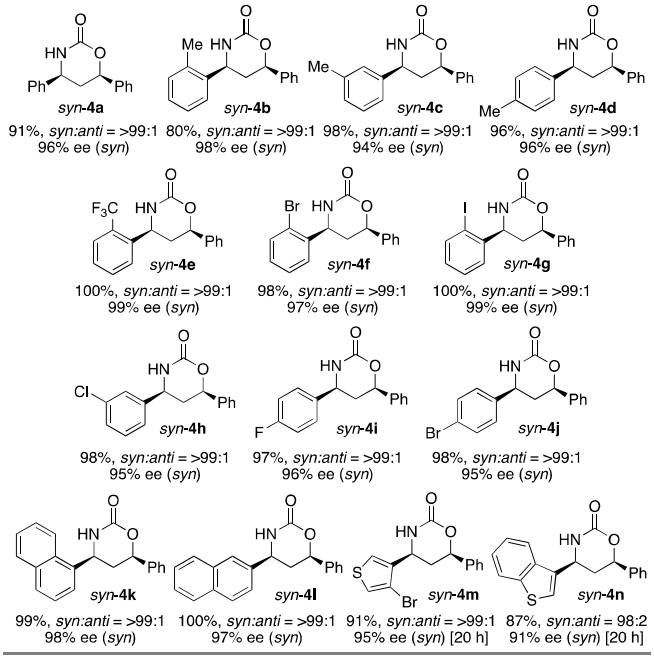
entry	additive (mol%)	yield of **4** (%)	*syn*:*anti* of **4a**	ee of *syn*-**4a** (%)	yield of **5** (%)	yield of **6** (%)	yield of **7** (%)
1	–	52	76:24	–4	4	0	13
2	$MgSO_4$	38~59	89:11~93:7	28~70	5~10	5~10	15~20
3	$Mg(OEt)_2$ (5)	73	92:8	48	0	0	0
4	$Mg(OEt)_2$ (5) MS 3A	90	94:6	78	4	0	0
5	$Mg(OEt)_2$ (3.3) KO*t*-Bu (10)	56	>99:<1	95	0	0	20
6	**$Mg(OEt)_2$ (3.3) KO*t*-Bu (10) MS 3A**	**91**	**>99:<1**	**96**	**4**	**0**	**0**

[a] The reaction was carried out with (*R*)-**1a** (10 mol%), **2a** (0.2 mmol), **3a** (4 mmol), and additives in 1,2-dichloroethane at 0 °C for 5 h.

Scheme 1. Reactions of simple styrene **3a** with a variety of *N*-Boc aldimines **2**.[a]



Products *syn*-**4**, yield, ratio of *syn:anti*, and enantioselectivity of *syn*-**4**.

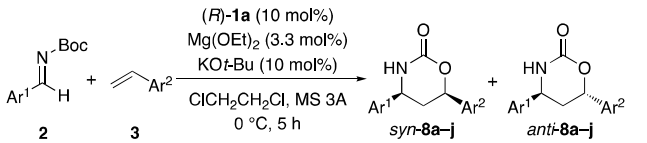


[a] The reaction was carried out with (*R*)-**1a** (10 mol%), **2** (0.2 mmol), and **3a** (4 mmol) in 1,2-dichloroethane with MS 3A at 0 °C for 5 h.

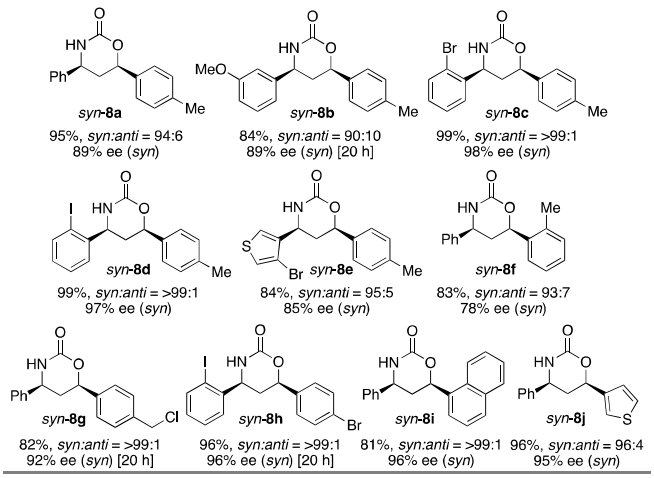
catalyst, which was prepared from (*R*)-**1a** (10 mol%) and $Mg(OEt)_2$ (5 mol%). As a result, *syn*-**4a** was obtained reproducibly in moderate yield with 48% ee (entry 3). Interestingly, the addition of MS 3A to the catalyst provided *syn*-**4a** with 78% ee (entry 4). Again, we suspected that K^+ was being leached due to the strong acidity of the (*R*)-**1a**–Mg complex, since MS 3A is $K_9Na_3[(AlO_2)_{12}(SiO_2)_{12}]$ (see the SI). Therefore, we used a catalyst prepared from (*R*)-**1a** (10 mol%), $Mg(OEt)_2$ (3.3 mol%), and KO*t*-Bu (10 mol%). As a result, *syn*-**4a** was obtained in 56% yield with 95% ee without the generation of *anti*-**4a** (entry 5). Finally, the use of MS 3A prevented the generation of undesired **7** (see the SI including ICP-OES analysis), *syn*-**4a** was exclusively obtained in 91% yield with 96% ee (entry 6). Overall, strong acids may trigger unexpected excellent results or invalidate the evaluations in the presence of common drying agents.[4,12]

We next examined the scope of *N*-Boc aldimines **2b**–**n** in the presence of the optimized 3:1:3 complex of (*R*)-**1a**/Mg/K (Scheme 1). As a result, **2b**–**j** with a variety of *ortho*-, *meta*-, or *para*-substituted aryl moieties, **2k** with a 1-napththyl moiety, **2l** with a 2-naphthyl moiety, and **2k** and **2l** with a heteroaryl moiety could be used, and the corresponding *syn*-**4a**–**n** were exclusively obtained with excellent enantioselectivities (91–99% ee) in high

Scheme 2. Reactions of a variety of styrene derivatives **3b**–**g** with *N*-Boc aldimines **2**.

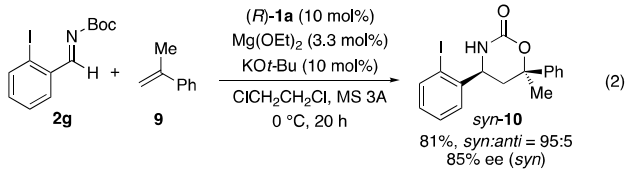


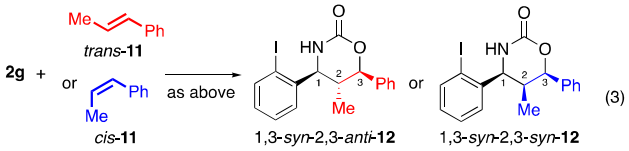
Products **8**, reaction time, yield, and enantioselectivity.



yields (80–100%). In particular, the tolerance of sterically hindered *ortho*-substituted compounds such as **2e** (*o*-$CF_3C_6H_5$), **2f** (*o*-BrC_6H_5), **2g** (*o*-IC_6H_5), **2k** (1-naphthyl), and **2n** (3-benzothienyl) was remarkable. Moreover, we examined the scope of styrene derivatives **3b**–**g** (Scheme 2). As a result, not only simple 4-methylstyrene (**3b**) and sterically hindered 2-methylstyrene (**3c**), but also 4-(chloromethyl)styrene (**3d**) and less nucleophilic 4-bromostyrene (**3e**) could be used. The steric effect of 1-vinylnaphthalene (**3f**) did not affect the yield, *syn*/*anti*-ratio, or enantioselectivity. Moreover, heteroaromatic 3-vinylthiophene (**3g**) could also be used successfully.

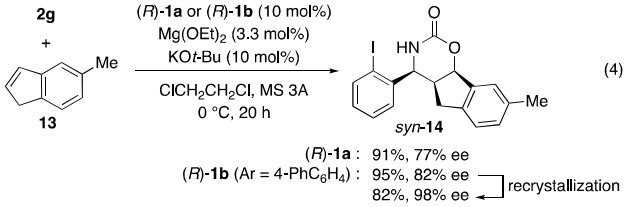
Next, the α- or β-Me-substituent effect on the vinyl moiety of styrene was examined (also see the SI). The reaction of α-methylstyrene **9** with aldimine **2g** provided the corresponding cycloadduct **10** in 81% yield (*syn:anti* = 95:5) with 85% ee for *syn*-**10** (Eq. 2). Moreover, *trans*-β-methylstyrene (*trans*-**11**) and *cis*-β-methylstyrene (*cis*-**11**) were examined (Eq. 3). As a result, from *trans*-**11**, 1,3-*syn*-2,3-*anti*-**12** was obtained exclusively in 62% yield with 99% ee. In contrast, the





reaction of *cis*-**11** with **2g** was sluggish, and 1,3-*syn*-2,3-*syn*-**12** was obtained as a sole product, although enantioselectivity was not induced. These *trans/cis*-retention results strongly indicated that the reaction might proceed *via* a concerted pathway as seen Eq. 1, and a stepwise pathway involving a benzyl cation is unlikely.

As another application of styrene derivatives, indene **13** was examined (Eq. 4). As a result, the corresponding product *syn*-**14** was obtained with good enantioselectivity in the presence of the (*R*)-**1a**-derived catalyst (77% ee). The use of (*R*)-**1b**-derived catalyst (Ar = 4-PhC_6H_4) improved the enantioselectivity (82% ee). Fortunately, recrystallization of *syn*-**14** increased the enantio-purities to 98% ee without any serious loss of yield.



(4)

Next, we performed some transformations to synthetically useful 1,3-amino alcohols[8b] to validate our catalytic system (Scheme 3, Eqs. 5–7). First, transformations to *syn*- and *anti*-1,3-amino alcohols **15** were demonstrated. Hydrolysis of *syn*-**4a** afforded corresponding *syn*-**15** in 98% yield without a loss of optical purity (Eq. 5). On the other hand, transformation to *anti*-**15** was also achieved in five steps in good yields (Eq. 6). A key step is the Mitsunobu reaction, in which di-2-methoxyethyl azodicarboxylate (DMEAD)[13] and *N*-hydroxyphthalimide were carefully selected to suppress an undesired spontaneous elimination reaction that would give undesired β,γ-unsaturated amide. Moreover, we performed a formal total synthesis of bioactive 1,3-amino alcohol **21**,[14] which is a drug candidate for neuropathic pain due to its NMDA receptor antagonistic activity (Eq. 7).[15] Actually, a 1.5 g-scale cycloaddition of **3b**, which used only 2 molar equivalents to **2g**, was conducted with a reduced amount of catalyst (5 mol%). As a result, the desired *syn*-**8d** was obtained with 96% ee. Consequently, Manabe's palladium-catalyzed carbocyclization[16] of *syn*-**8d** provided tricyclic amide **18** quantitatively. After the hydrolysis of **18**, the Mitsunobu reaction of **19** followed by N–O bond cleavage afforded 0.70 g of the key compound **20** with 98% ee.

Finally, we turn our attention to mechanistic aspects. We tried to crystallize the optimized 3:1:3 complex of (*R*)-**1a**/Mg/K for X-ray structural analysis.[5] As a result, we instead obtained a 3:1:4 aqua complex of (*R*)-**1a**/Mg/K (**22**) (Figure 1, also see the SI). The obtained cluster **22** could be formally assembled by 2:2:1 and 1:0:2 complexes of (*R*)-**1a**/Mg/K and adventitious water. As expected, due to the lack of a Brønsted acid part (i.e., SO_3H), the cluster **22** itself (or the use of (*R*)-**1a** (10 mol%), $Mg(OEt)_2$ (3.3 mol%), and KO*t*-Bu (13.3mol%)) showed no catalytic activity in a probe reaction (Eq. 8). However, addition of TfOH (see the SI) restored the catalytic activity through H^+-exchange, and *syn*-**4a** was obtained in 58% yield with 90% ee (Eq. 9). Actually, the Brønsted acid part of the optimized 3:1:3 complex of (*R*)-**1a**/Mg/K might be essential, since the addition of methallyltrimethylsilane or sterically hindered 2,6-*t*-Bu_2-pyridine, both of which would selectively react on H^+, completely deactivated the catalytic activity in the probe reaction (Eq. 10). In contrast, the use of (*R*)-**1a** (10 mol%), $Mg(OEt)_2$ (3.3 mol%), and KO*t*-Bu (6.6 mol%) which would lead to the corresponding 3:1:2 complex of (*R*)-**1a**/Mg/K with two Brønsted acid parts, still showed high catalytic activity (85% yield and 89% ee of *syn*-**4a**) (Eq. 11), although the result was slightly inferior to that with the optimized catalyst. Overall, the X-ray-analyzed cluster **22** might be an inactive species, and a similar structural cluster with active H^+ in place of inactive K^+ might be considered to be an active catalyst *in situ*.

Scheme 3. Transformations to 1,3-amino alcohols.

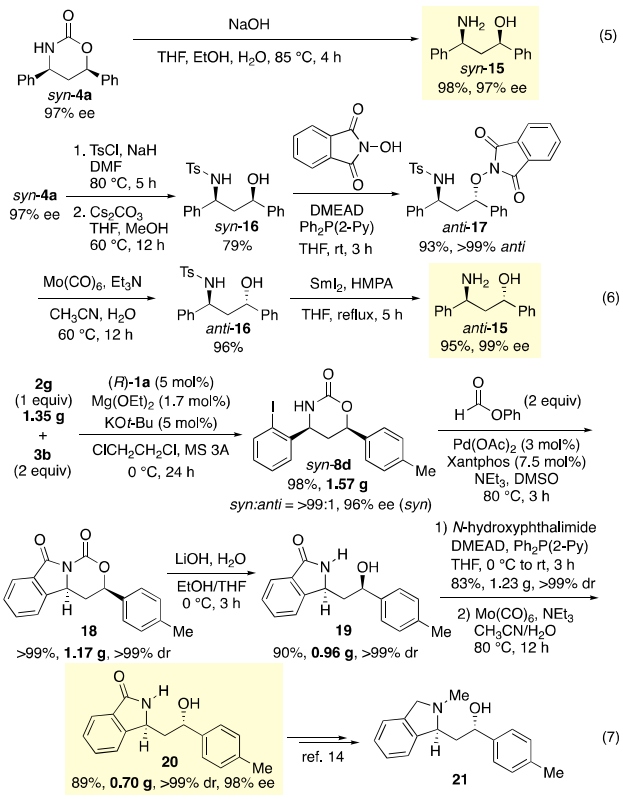
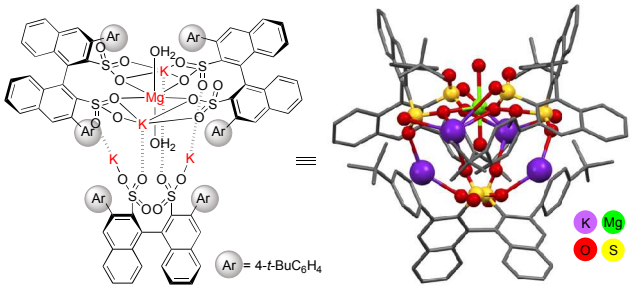
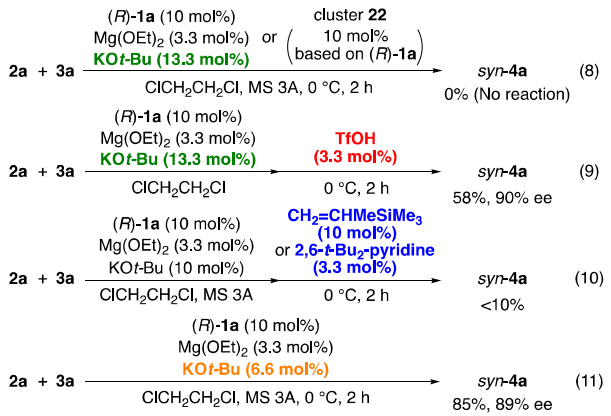


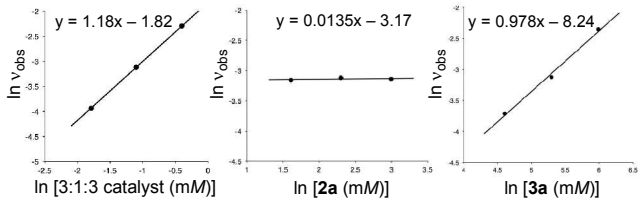
Figure 1. X-ray analysis of a 3:1:4 complex of (*R*)-**1a**/Mg/K **22**.





To consider the active species *in situ*, ESI-MS analysis of the catalyst was carried out. As a result, a variety of BINSA trimers [*m/z* = 2150–2230], possibly with cluster structures, were exclusively observed (see the SI). Moreover, a kinetics study was conducted for a 3:1:3 complex of (*R*)-**1a**/Mg/K, **2a**, and **3a**. The results showed first-order dependency for the catalyst as well as zero-order dependency for **2a** and first-order dependency for **3a** (Figure 2, also see the SI). This may support the presence of a 3:1:3 complex of (*R*)-**1a**/Mg/K, and the rate-determining step might be the addition of **3a** to activated **2a**. At this preliminary stage, possible transition states cannot be considered, since the position of the active site (H^+) has not been specified, although the Brønsted acid center itself should be essential.

Figure 2. Kinetics study for the catalyst, **2a**, and **3a**.



In summary, we have developed for the first time a chiral magnesium potassium binaphthyldisulfonate cluster, which can catalyze a highly enantioselective cycloaddition of styrenes with aldimines. We serendipitously discovered that the strong Brønsted acidity of unoptimized catalysts dissolved drying agents and took up leached Mg^{2+} and K^+. Mechanistic insights were supported by X-ray, ESI-MS and ICP-OES analyses of the clusters, a kinetics study, and control experiments. Moreover, synthetically useful transformations to optically active 1,3-amino alcohols on a gram scale were demonstrated.

ASSOCIATED CONTENT

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ishihara@cc.nagoya-u.ac.jp

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The authors declare no competing financial interest.

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REFERENCES

(1) For reviews on chiral Brønsted acids. (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Synthesis* **2010**, *2010*, 1929. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (e) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277.

(2) (a) Hatano, M.; Sugiura, Y.; Ishihara, K. *Tetrahedron: Asymmetry* **2010**, *21*, 1311. (b) Hatano, M.; Ozaki, T.; Nishikawa, K.; Ishihara, K. *J. Org. Chem.* **2013**, *78*, 10405. (c) Hatano, M.; Ishihara, K. *Asian J. Org. Chem.* **2014**, *3*, 352. Also see our original paper of 3,3'-unsubstituted BINSA. (d) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (e) Hatano, M.; Sugiura, Y.; Akakura, M.; Ishihara, K. *Synlett* **2011**, *2011*, 1247. (f) Hatano, M.; Ozaki, T.; Sugiura, Y.; Ishihara, K. *Chem. Commun.* **2012**, *48*, 4986.

(3) pK_a (DMSO) of (*R*)-3,3'-unsubstituted BINSA is –9.06. Yang, C.; Xue, X.-S.; Li, X.; J.-P. Cheng, *J. Org. Chem.* **2014**, *79*, 4340.

(4) We had a similar experience during the development of chiral calcium phosphates (a) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823. Also see, (b) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, *2010*, 2189. (c) Terada, M.; Kanomata, K. *Synlett* **2011**, *2011*, 1255. (d) Akiyama, T. *Synlett* **2016**, *27*, 542.

(5) Shibasaki pioneeringly developed chiral heterobimetallic M_3[Ln(binol)$_3$] catalysts for a variety of asymmetric reactions. See a review, Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.

(6) Uddin, N.; Ulicki, J. S.; Foersterling, F. H.; Hossain, M. M. *Tetrahedron Lett.* **2011**, *52*, 4353.

(7) For reviews: (a) Wang, G. Anti-Infect. *Agents Med. Chem.* **2008**, *7*, 32. (b) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1.

(8) (a) Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2753. (b) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

(9) Diastereoselective cycloaddition. (a) Richter, H.; Fröhlich, R.; Daniliuc, C.-G.; Mancheño, O. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 8656. (b) Spreider, P. A.; Haydl, A. M.; Heinrich, M.; Breit, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 15569.

(10) (a) Drury, III, W. J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (b) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547. (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, III, W. J.; Ryzhkov, L.; Taggi, A. W.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (d) Caplan, N. A.; Hancock, F. E.; Page P. C. B.; Hutchings, G. H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1685. (e) Momiyama, N.; Okamoto, H.; Shimizu, M.; Terada, M. *Chirality* **2015**, *27*, 464. (f) Momiyama, N.; Okamoto, H.; Kikuchi, J.; Korenaga, T.; Terada, M. *ACS Catal.* **2016**, *6*, 1198.

(11) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

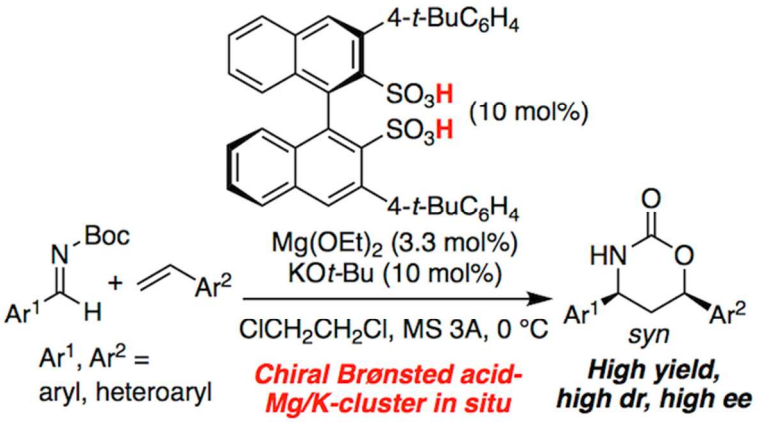
(12) We investigated chiral BINSA-catalyses in our previous reports (refs. 2d–f). However, no leaching effect was observed. See the SI.

(13) Hagiya, K.; Muramoto, N.; Misaki, T.; Sugimura, T. *Tetrahedron* **2009**, *65*, 6109.

(14) Müller, A.; Höfner, G.; Renukappa-Gutke, T.; Parsons, C. G.; Wanner, K. T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5795.

(15) (a) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø., Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609. (b) Stawski, P.; Janovjak, H.; Trauner, D. *Bioorg. Med. Chem.* **2010**, *18*, 7759.

(16) Konishi, H.; Nagase, H.; Manabe, K. *Chem. Commun.* **2015**, *51*, 1854.


4-t-BuC6H4
SO3H
SO3H
(10 mol%)
4-t-BuC6H4
N
Boc
Ar1
H
+
Ar2
Mg(OEt)2 (3.3 mol%)
KOt-Bu (10 mol%)
ClCH2CH2Cl, MS 3A, 0 °C
Ar1, Ar2 =
aryl, heteroaryl
Chiral Brønsted acid-
Mg/K-cluster in situ
HN
O
O
Ar1
Ar2
syn
High yield,
high dr, high ee