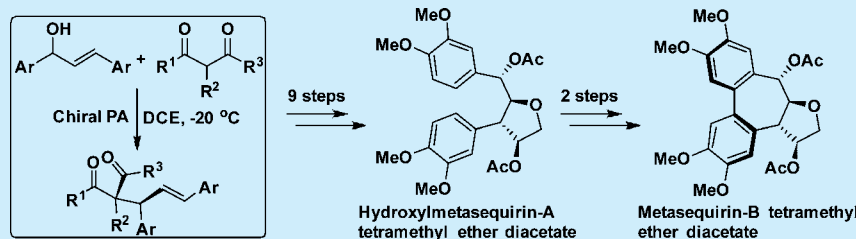


# An Organocatalytic Asymmetric Allylic Alkylation Allows Enantioselective Total Synthesis of Hydroxymetasequirin-A and Metasequirin-B Tetramethyl Ether Diacetates

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**S** Supporting Information

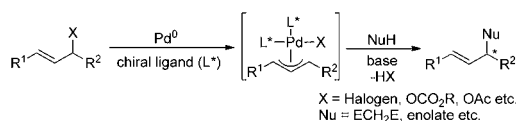


**ABSTRACT:** The first highly stereoselective organocatalytic intermolecular allylic alkylation of allylic alcohols with 1,3-dicarbonyls has been developed to allow the first enantioselective total synthesis of hydroxymetasequirin-A and metasequirin-B tetramethyl ether diacetates.

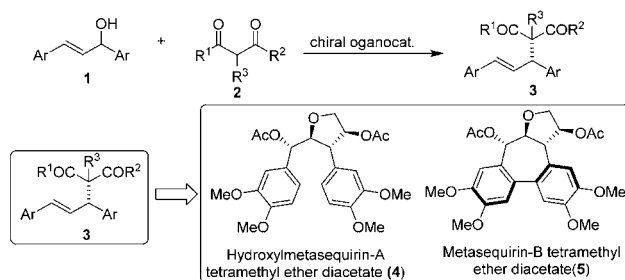
Since the seminal reports by Tsuji and Trost on the palladium-catalyzed allylic alkylation (Scheme 1a),<sup>1</sup> this

## Scheme 1. Asymmetric Allylic Alkylation Reactions

(a) Classical palladium catalyzed asymmetric allylic alkylation.



(b) Asymmetric organocatalytic asymmetric allylic alkylation for enantioselective total synthesis of natural products



transformation has been accepted as one of the most significant carbon–carbon or carbon–heteroatom bond forming reactions. In particular, the asymmetric version (AAA) has been a long-term hot project receiving worldwide attention.<sup>2</sup> This reaction has eventually prompted the explosive development of chiral ligands and also led to the emergence of synthetically important protocols, which have enabled the concise enantioselective synthesis of structurally complicated bioactive molecules.<sup>3</sup> In

recent decades, asymmetric organocatalysis has received tremendous research interest and turned out to be an indispensable alternative to access chiral substances.<sup>4</sup> However, organocatalytic asymmetric allylic alkylations are truly elusive and therefore remain a formidable challenge. Herein, we document the first highly enantioselective organocatalytic allylic alkylation reaction of allylic alcohols with 1,3-dicarbonyls. More importantly, this new protocol allows a concise enantioselective total synthesis of hydroxymetasequirin-A and metasequirin-B tetramethyl ether diacetates (Scheme 1b).

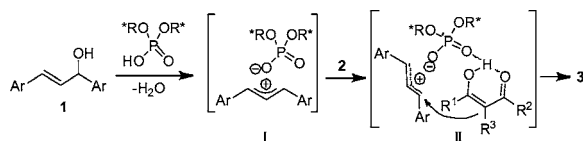
The greatest challenge that needs to circumvent in the allylic alkylation is undoubtedly the activation of allylic substrates by the organocatalysts. Basically, the allylic substrates exploited in the traditional AAA reactions are those installed with relatively more active leaving groups, such as halides, carbonates, or acetates (Scheme 1a).<sup>2,3</sup> Previous explorations have indicated that Brønsted acids or Lewis acids are able to facilitate the conversion of allylic alcohols to π-allyl cationic species either in combination with transition metals<sup>5</sup> or alone<sup>6</sup> and, therefore, allow the reality of organocatalytic allylic alkylation reactions. In particular, Rueping and co-workers described the first *N*-triflylphosphoramidate-catalyzed intramolecular enantioselective allylic alkoxylation of phenol derivatives,<sup>7</sup> implying that chiral Brønsted acids might be able to activate some allylic alcohols to accomplish more complex transformations. Thus, we envisaged that the chiral phosphoric acids, which were capable of catalyzing a range of interesting processes,<sup>8</sup> might also be able to protonate the allylic alcohol to generate a chiral ion pair

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(intermediate I),<sup>9</sup> and then the resultant conjugate base, a chiral phosphate, would activate 1,3-dicarbonyl compounds **2** by hydrogen bonding interaction,<sup>8b</sup> leading to an intermolecular organocatalytic asymmetric allylic alkylation via intermediate II (Scheme 2).

**Scheme 2. General Principle for the Chiral Brønsted Acid Catalyzed Intermolecular Asymmetric Allylic Alkylation**



Our investigation started with a benchmark allylic alkylation reaction between (*E*)-1,3-bis(3,4-dimethoxyphenyl)prop-2-en-1-ol (**1a**) and acetylacetone (**2a**) at 35 °C in the presence of BINOL derived phosphoric acids<sup>8</sup> (Table 1). To our delight,

**Table 1. Evaluation of Brønsted Acid Catalysts and Optimization of Reaction Conditions<sup>a</sup>**

**1a**: Ar = 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**2a**: Acetylacetone

**3a**: Ar = 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**A1**: R = 1-Naphthyl

**A2**: R = 2-Naphthyl

**A3**: R = 9-Anthracenyl

**A4**: R = Ph<sub>3</sub>Si

**A5**: R = 2,4,6-(*i*-Pr)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>

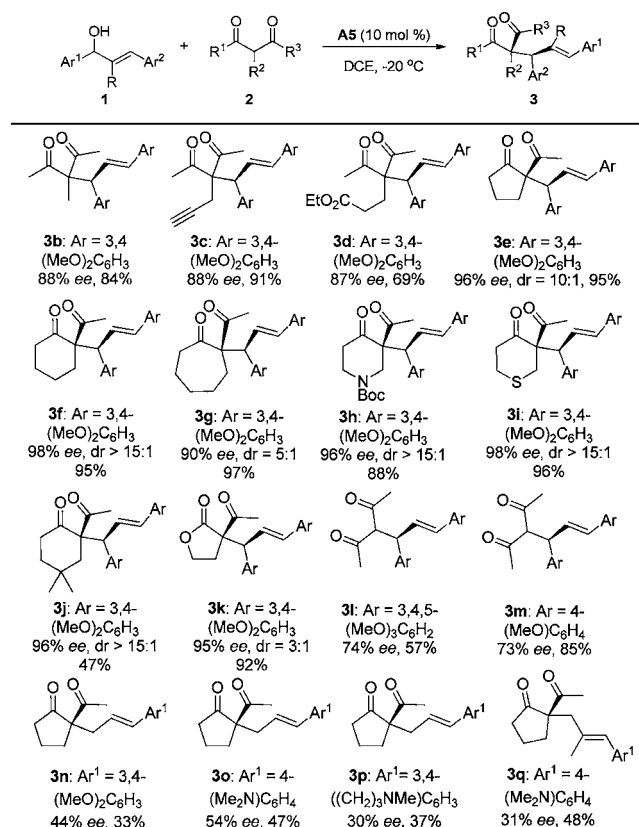
entry	B*–H	solvent	temp (°C)	time (h)	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	A1	toluene	35	12	89	22
2	A2	toluene	35	12	97	18
3	A3	toluene	35	12	96	61
4	A4	toluene	35	12	99	38
5	A5	toluene	35	12	98	76
6	A5	THF	35	36	95	76
7	A5	MeCN	35	1	89	81
8	A5	DCM	35	1.5	97	83
9	A5	DCE	35	1.5	98	85
10	A5	DCE	0	12	97	91
11	A5	DCE	–10	24	96	94
12	A5	DCE	–20	36	92	96
13	A5	DCE	–35	72	79	97

<sup>a</sup>Unless indicated otherwise, reactions performed with 0.05 mmol of **1a**, 0.1 mmol of **2a** at 0.05 M. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by HPLC analysis.

the reaction catalyzed by **A1** proceeded cleanly to give rise to the desired alkylation product **3a** in 89% yield, albeit with a moderate enantiomeric excess (entry 1). Various structurally different chiral phosphoric acids (**A2**–**A5**), derived from 3,3'-disubstituted 1,1'-bi-2-naphthols (BINOLs), were evaluated and found that they were all able to accelerate the reaction (entries 2–5). Among them, the phosphoric acid **A5** turned out to be the optimal catalyst, capable of offering a nearly quantitative yield and the highest levels of enantioselectivity (76% ee, entry 5). An examination of solvents suggested that halogenated and ether-based solvents were beneficial to the stereochemical control and led to a considerable improvement in the reaction performance (entries 6–9). Basically, lowering the temperature resulted in an enhanced enantioselectivity, but

the prolonged reaction time was required to ensure a complete conversion (entries 10–13). In particular, the reaction still proceeded even at –35 °C and was able to give 97% ee, but with a dramatic erosion of the yield (entry 13). In terms of the yield and stereochemical outcome, the best results were obtained by conducting the reaction at –20 °C (92% yield, 96% ee, entry 12).

Under the optimized conditions, a variety of substrates, including electro- and nucleophiles, were then explored (Figure 1). Significantly, this asymmetric allylic alkylation reaction was



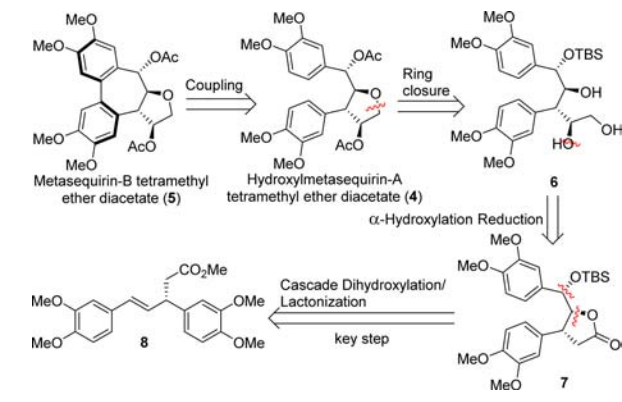
**Figure 1. Substrate scope.** Unless indicated otherwise, the reaction of **1** (0.05 mmol) and **2** (0.1 mmol) was carried out at –20 °C in the presence of **A5** (10 mol %) for 36 h. Specially, the reactions of **3n** and **3q** were carried out at 40 °C in toluene for 24 h while the reactions of **3o** and **3p** were conducted at 0 °C in toluene for 24 h.

able to tolerate a wide spectrum of 1,3-dicarbonyl compounds bearing either a branch chain (**3b**–**3d**) or cyclic moiety (**3e**–**3k**), giving rise to the desired product with a quaternary stereogenic carbon in high yields (up to 97%) and with excellent enantioselectivities (up to 98% ee) and synthetically useful diastereoselectivities (up to >15/1). More interestingly, the compound **3i**, which was usually unable to be accessed by virtue of the transition metal catalyzed reaction, could also be obtained from the current organocatalytic allylic alkylation reaction in 96% yield and with >15/1 dr and 98% ee. The configuration of **3i** was determined by X-ray crystallography analysis of its monoketoxime derivative (see Supporting Information). Notably, the aromatic substituent of 1,3-diaryl allylic alcohol had an obvious impact on the reaction. For instance, although both (*E*)-1,3-bis(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (**1b**) and (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-ol (**1c**) underwent the asymmetric allylic alkylation, the

corresponding products **3l** and **3m** were generated in much lower enantiomeric excesses in comparison with their structural analogue (Table 1, entry 12). Simple allylic alcohols were also able to participate in the organocatalytic allylic alkylation to give rise to the desired products in moderate yields and enantioselectivities (**3n–3q**).

The current enantioselective allylic alkylation holds great synthetic importance and could be applicable to the synthesis of natural products, for example, hydroxymetasequirin-A and metasequirin-B (Scheme 3). These two compounds were

**Scheme 3. Retrosynthetic analysis of Hydroxymetasequirin-A and Metasequirin-B Tetramethyl Ether Diacetates**

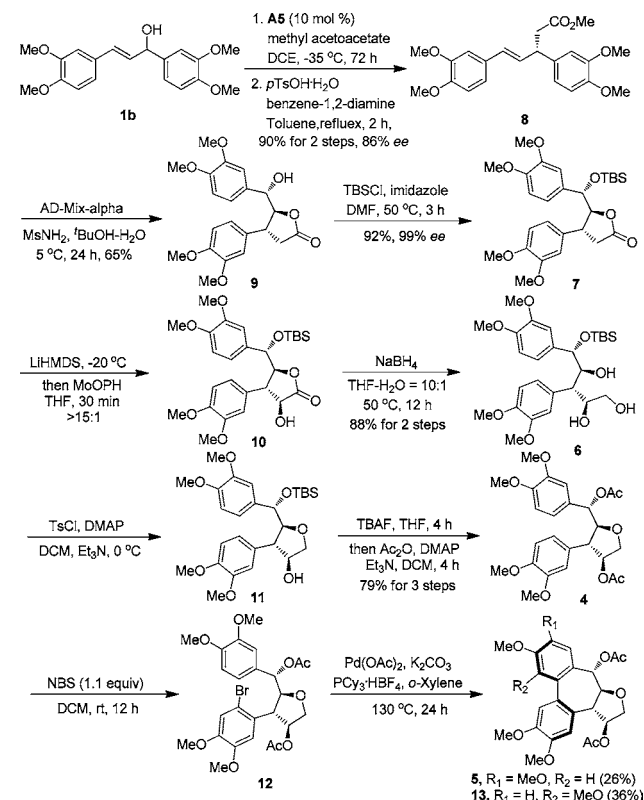


isolated from the heartwood of *M. glyptostroboides* by A. Enoki and co-workers in 1977.<sup>10</sup> Due to the high polarity, the two natural products were identified after their phenol and hydroxyl groups were entirely methylated and acetylated, respectively. The metasequirin-B, presumably formed from hydroxymetasequirin-A, represents a structurally unique norlignan bearing a dibenzocycloheptene skeleton fused with a tetrahydrofuran (THF) system. Over the past several decades, a number of endeavors have been directed toward the synthesis of metasequirin-B.<sup>11</sup> However, the total synthesis of metasequirin-B has not been accomplished, yet.

Retrosynthetic analysis of metasequirin-B tetramethyl ether diacetate (**5**) indicated that the dibenzocycloheptene skeleton could be disconnected at the aryl–aryl bond, which would be assembled by an intramolecular aryl–aryl coupling reaction. The tetrahydrofuran moiety is principally able to be prepared by a ring-closing ether formation protocol from 1,2,4-triol **6**, which could be accessed from a sequential procedure consisting of an  $\alpha$ -hydroxylation of  $\gamma$ -lactone **7** and reduction. The key intermediate **7** was proposed to be synthesized by cascade Sharpless asymmetric dihydroxylation<sup>12</sup> and lactonization of chiral building block **8**, which could be obtained from the current organocatalytic asymmetric allylic alkylation reaction.

The synthetic route to approach metasequirin-B is shown in Scheme 4. Under the optimized conditions, the asymmetric allylic alkylation between (*E*)-1,3-bis(3,4-dimethoxyphenyl)-prop-2-en-1-ol (**1a**) and methyl acetoacetate gave rise to the desired product as a 1:1 mixture of two isomers. The exposure of the diastereomeric mixture to benzene-1,2-diamine and *p*-toluenesulfonic acid (*p*-TsOH) led to the deacetylation reaction and furnished **8** in an overall 90% yield in two steps and with 86% *ee*. The intermediate **8** was directly transformed into **9** in a 65% yield and with 99% *ee* by a sequential Sharpless asymmetric dihydroxylation and lactonization. The protection of the hydroxyl group of **9** with *tert*-butyldimethylsilyl chloride

**Scheme 4. Total Synthesis of Hydroxymetasequirin-A and Metasequirin-B Tetramethyl Ether Diacetates**



led to the formation of compound **7** in a 92% yield. An oxidative hydroxylation of the lactone **7** with LiHMDS/MoOPH<sup>13</sup> completely generated **10** with >15:1 *dr*. At this stage, a direct reduction of the crude  $\alpha$ -hydroxy lactone **10** with NaBH<sub>4</sub> furnished the triol **6** in an overall 88% yield in two steps from **7**. The treatment of the triol **6** with TsCl/DMAP at 0 °C gave rise to the tetrahydrofuran-type intermediate **11**, followed by a deprotection of the TBS group and an acetylation of both hydroxyl groups to provide hydroxymetasequirin-A tetramethyl ether diacetate **4** in a 79% yield from the triol **6**. Then, we screened a variety of reaction conditions to directly convert **4** to metasequirin-B tetramethyl ether diacetate (**5**),<sup>14</sup> but failed. Ultimately, a two-step reaction sequence, including monobromination of one of two aryl substituents and a palladium catalyzed intramolecular C–H/C–X biaryl coupling,<sup>15</sup> was able to furnish metasequirin-B tetramethyl ether diacetate (**5**) in an overall 26% yield in two steps without observation of the other atropisomer, but regioisomer **13** was isolated in 36% yield. All of the spectroscopic data of the synthetic hydroxymetasequirin-A tetramethyl ether diacetate and metasequirin-B tetramethyl ether diacetate are in agreement with those reported previously.<sup>16</sup>

In conclusion, we have developed the first highly enantioselective organocatalytic intermolecular allylic alkylation of allylic alcohols with 1,3-dicarbonyls. More importantly, this reaction allowed the first enantioselective total synthesis of hydroxymetasequirin-A tetramethyl ether diacetate (9 steps, 37% overall yield) and metasequirin-B tetramethyl ether diacetate (11 steps, 10% overall yield). Moreover, the finding that chiral Brønsted acids were able to efficiently control the stereoselection of the allylic alkylation involving 1,3-dicarbonyls actually points out that the related organocatalytic alkylation

reactions of other soft nucleophiles would be accessed by virtue of such a strategy.

## ■ ASSOCIATED CONTENT

### Supporting Information

Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) For the first allylic alkylation, see: (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. For the first asymmetric allylic alkylation, see: (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.
- (2) For general reviews of asymmetric allylic alkylation, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (d) Falcioni, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765. (e) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (f) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185.
- (3) For general reviews of development of chiral ligands for AAA and its application, see: (a) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59. (d) Rios, I. G.; Rosas-Hernandez, A.; Martin, E. *Molecules* **2011**, *16*, 970. (e) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.
- (4) For general reviews of organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (f) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
- (5) For selected examples of transition metal-catalyzed asymmetric allylic alkylations with allyl alcohols, see: (a) Stary, I.; Stará, G.; Kocovsky, P. *Tetrahedron Lett.* **1993**, *34*, 179. (b) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (c) García-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459. (d) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (e) Trost, B. M.; Quancard, J. J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (f) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (g) Usui, I.; Schmidt, S.; Breit, B. *Org. Lett.* **2009**, *11*, 1453. (h) Jiang, G. X.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (i) Yasuda, S.; Kumagai, N.; Shibasaki, M. *Heterocycles* **2012**, *86*, 745. (j) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (k) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994. (l) Tao, Z. L.; Zhang, W. Q.; Chen, D. F.; Adele, A.; Gong, L. Z. *J. Am. Chem. Soc.* **2013**, *135*, 9255.
- (6) For reviews of direct nucleophilic  $S_N1$ -type allylic alkylations with allyl alcohols, see: (a) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 1. (b) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzzello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647.
- (7) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.
- (8) For pioneering work in the field of chiral BINOL-phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uruguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. Reviews on BINOL-phosphoric acids: (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Terada, M. *Chem. Commun.* **2008**, 4097. (e) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31. (f) Terada, M. *Synthesis* **2010**, 1929. (g) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *101*. (h) Yu, J.; Shi, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156.
- (9) For recent reviews about asymmetric ion-pairing catalysis, see: (a) Avila, E. P.; Amarante, G. W. *ChemCatChem* **2012**, *4*, 1713. (b) Brière, J. F.; Oudeyer, S.; Dallab, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696. (c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (d) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (e) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518.
- (10) Enoki, A.; Takahama, S.; Kitao, K. *Mokuzai Gakkaishi* **1977**, *23*, 587.
- (11) (a) Sancéau, J. Y.; Dhal, R.; Brown, E. *Tetrahedron* **1994**, *50*, 3363. (b) Kramer, B.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 2446. (c) Hackelöer, K.; Schnakenburg, G.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2011**, 6314. (d) Hackelöer, K.; Schnakenburg, G.; Waldvogel, S. R. *Org. Lett.* **2011**, *13*, 916. (e) Hackelöer, K.; Waldvogel, S. R. *Tetrahedron Lett.* **2012**, *53*, 1579.
- (12) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
- (13) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Taschner, M. J.; Aminbhavi, A. S. *Tetrahedron Lett.* **1989**, *30*, 1029.
- (14) The classical oxidants for direct Aryl–Aryl coupling including  $\text{FeCl}_3/\text{SiO}_2$ ,  $\text{PhI}(\text{OTFA})_2/\text{BF}_3\cdot\text{OEt}_2$ , and DDQ/ $\text{MsOH}$  failed to be applicable for the coupling reaction of 4.
- (15) (a) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (d) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 7865.
- (16) See the Supporting Information.