

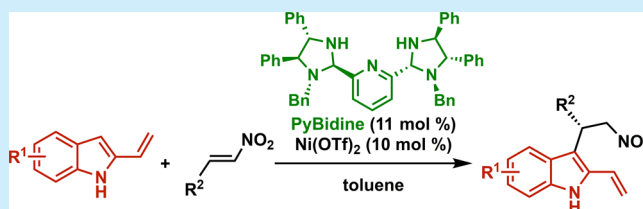
## Catalytic Asymmetric Synthesis of Chiral 2-Vinylindole Scaffolds by Friedel–Crafts Reaction

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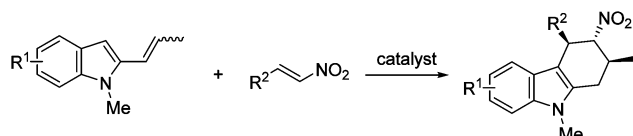
## Supporting Information

**ABSTRACT:** A chiral bis(imidazolidine)pyridine (PyBidine)–Ni(OTf)<sub>2</sub> complex smoothly catalyzed an asymmetric Friedel–Crafts reaction of 2-vinylindoles with nitroalkenes to give chiral indoles in a highly enantioselective manner while maintaining the 2-vinyl functionality. The chiral 2-vinylindoles offer unique chiral scaffolds for diverse transformations.

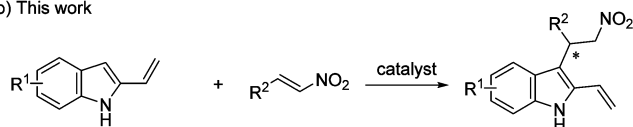


Various chiral indoles have been isolated from naturally occurring alkaloids, and their structural complexity is strongly related to their biological activity.<sup>1</sup> Studies on the total synthesis of indole alkaloids and on the preparation of a chemical library of diversified indoles have been conducted on the indole skeleton. During the past five years in particular, novel synthetic methodologies have been rapidly developed for the construction of highly substituted chiral indoles.<sup>2</sup> Among these, alkenyl indoles have been widely utilized as reactive substrates. Xiao reported an organocatalyzed double Michael addition/aromatization reaction using 2-propenylindoles and nitroalkenes to construct tetrahydrocarbazoles (Scheme 1a).<sup>3a</sup>

## Scheme 1. Classification of 2-Vinylindoles by Reactivity

a) Xiao's cycloaddition<sup>3a</sup>

b) This work



Not only 2-alkenylindoles<sup>3,4</sup> but also indoles with alkenyl substituents at the other positions underwent a series of cycloaddition reactions.<sup>5–8</sup> Although these pioneering works have been fruitful in the production of an array of polycyclic indoles, the cycloaddition reactions have all resulted in loss of the vinyl functionality from the indole products.<sup>9</sup> Here, we report a catalytic asymmetric Friedel–Crafts reaction using 2-vinylindoles and nitroalkenes to produce chiral indoles while retaining the 2-vinyl functionality (Scheme 1b).

Inspired by Xiao's pioneering work,<sup>3a</sup> this study began by targeting the cycloaddition reaction of 2-vinylindoles with

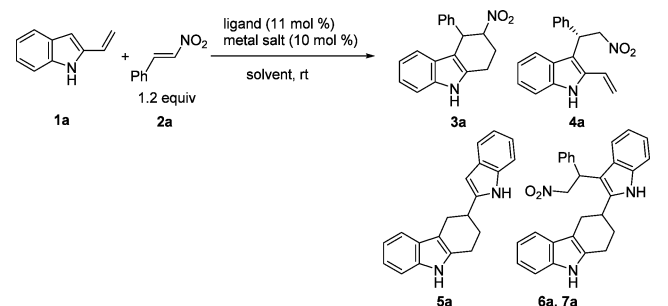
nitroalkenes. Because we had previously succeeded in the development of several chiral metal catalysts for asymmetric Friedel–Crafts reactions of indoles with nitroalkenes,<sup>10</sup> the catalyst system was simply applied to the reaction of the 2-vinylindole **1a** with nitrostyrene **2a**.<sup>11,12</sup> When an imidazoline–aminophenol (IAP)–CuOTf catalyst was used,<sup>10a</sup> the desired reaction was not promoted, and the only products isolated were dimerized adducts of 2-vinylindole (Table 1, entries 1, 2). The use of a valinol-derived bis(oxazolidine)pyridine (PyBodine)–Cu(OTf)<sub>2</sub> complex<sup>10f</sup> also gave a mixture of dimerized adducts of 2-vinylindole, accompanied by the Friedel–Crafts products in 16% yield (entry 3). Changing the ligand of the catalyst to bis(imidazolidine)pyridine (PyBidine)<sup>13</sup> to give the PyBidine–Cu(OTf)<sub>2</sub> catalyst resulted in a dramatically improved yield of **4a** (93%), although the enantioselectivity was only 10% ee. Among the first-row transition metal salts we examined, metal complexes prepared from Zn(OTf)<sub>2</sub> and Ni(OTf)<sub>2</sub> gave better stereoselectivity for **4a**, with 36% ee and 45% ee, respectively, while the PyBidine–Ni(OTf)<sub>2</sub> catalyst in toluene gave an 83% yield of **4a** with 84% ee (entry 9). In all cases in Table 1, the cycloadduct **3a** was not detected.

Under the optimized conditions, the general application of the catalytic asymmetric Friedel–Crafts reaction was examined, and the results are shown in Scheme 2.

Both electron-donating and -withdrawing substituents on the nitrostyrenes were successfully employed in the enantioselective Friedel–Crafts reaction to give a series of chiral 2-vinylindoles. From 1 mmol of nitrostyrene (**2a**) with 1.2 equiv of 2-vinylindole (**1a**), the chiral 2-vinylindole **4a** was obtained in 81% yield with 84% ee. A furan-derived nitroalkene was also compatible with the reaction, giving **4g** with 79% ee. Although the reactions using aliphatic nitroalkenes, unfortunately, resulted in low yields, the vinyl indole products **4i–4k** were obtained in all cases. The 5-methyl 2-vinylindole adduct **4f** was obtained with 85% ee

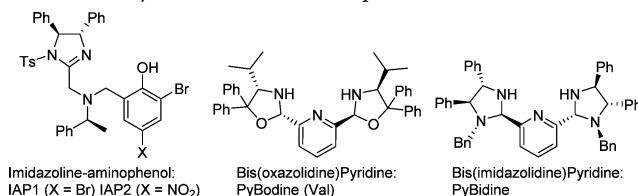
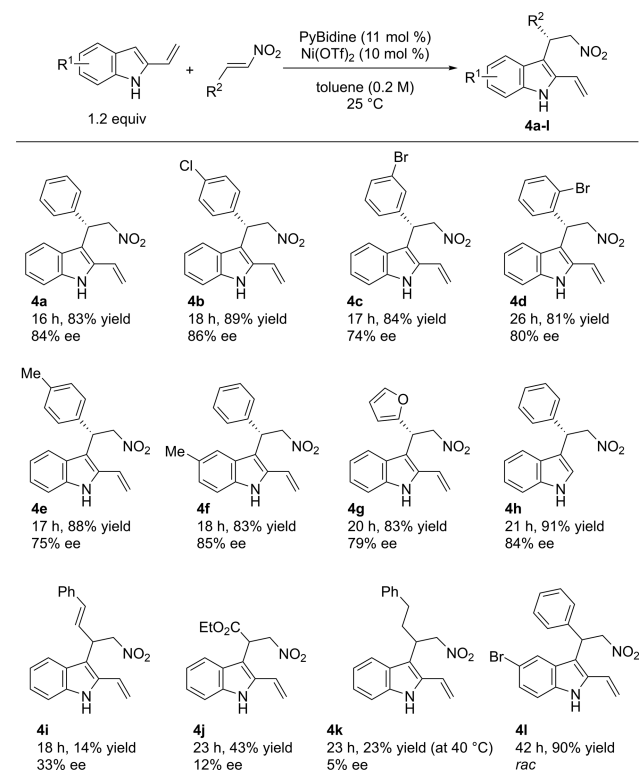
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Table 1. Catalyst Screening for the Reaction of 2-Vinylindole (1a) with Nitrostyrene (2a)



| entry          | ligand   | metal salt                        | solvent                         | time (h) | yield (%) <sup>a</sup> |       |             | ee of 4a (%) |
|----------------|----------|-----------------------------------|---------------------------------|----------|------------------------|-------|-------------|--------------|
|                |          |                                   |                                 |          | 3a                     | 4a    | 5a/6a/7a    |              |
| 1              | IAP1     | CuOTf <sup>b</sup>                | CH <sub>2</sub> Cl <sub>2</sub> | 4        | trace                  | 4     | 28/4/4      | 33           |
| 2              | IAP2     | CuOTf <sup>b</sup>                | CH <sub>2</sub> Cl <sub>2</sub> | 2        | trace                  | trace | 8/12/17     | –            |
| 3              | PyBodine | Cu(OTf) <sub>2</sub>              | CH <sub>2</sub> Cl <sub>2</sub> | 3        | trace                  | 16    | trace/22/35 | –47          |
| 4              | PyBidine | Cu(OTf) <sub>2</sub>              | CH <sub>2</sub> Cl <sub>2</sub> | 40       | trace                  | 93    | trace       | 10           |
| 5              | PyBidine | Zn(OTf) <sub>2</sub>              | CH <sub>2</sub> Cl <sub>2</sub> | 4        | –                      | 81    | –           | 36           |
| 6              | PyBidine | Ni(OTf) <sub>2</sub>              | CH <sub>2</sub> Cl <sub>2</sub> | 7        | –                      | 68    | –           | 45           |
| 7              | PyBidine | Ni(OAc) <sub>2</sub> <sup>c</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 17       | –                      | trace | –           | –            |
| 8              | PyBidine | Ni(OTf) <sub>2</sub>              | toluene                         | 6        | –                      | 73    | –           | 83           |
| 9 <sup>d</sup> | PyBidine | Ni(OTf) <sub>2</sub>              | toluene                         | 16       | –                      | 83    | –           | 84           |

<sup>a</sup>Isolated yield. <sup>b</sup>(CuOTf)<sub>2</sub>–C<sub>6</sub>H<sub>6</sub> was used. <sup>c</sup>Tetrahydrate was used. <sup>d</sup>1.2 equiv of 1a was added to 2a at 25 °C.

Scheme 2. General Application of Friedel–Crafts Reaction Catalyzed by PyBidine–Ni(OTf)<sub>2</sub>

in 83% yield, and the racemic 5-bromo 2-vinylindole adduct **4l** was obtained in 90% yield under the same catalyst system.

The stereochemistry of the (*R*)-enriched formation of **4d** using (*S,S*)-PyBidine–Ni(OTf)<sub>2</sub> was unequivocally determined by X-ray crystallographic analysis, as shown in Figure 1.

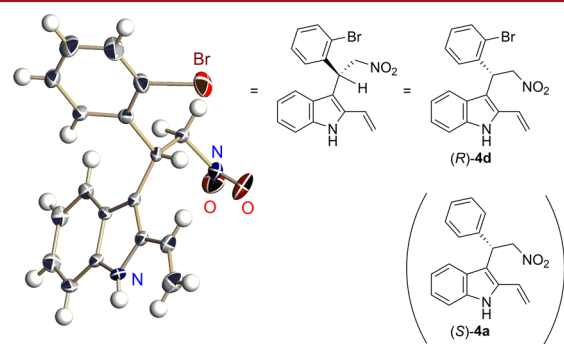


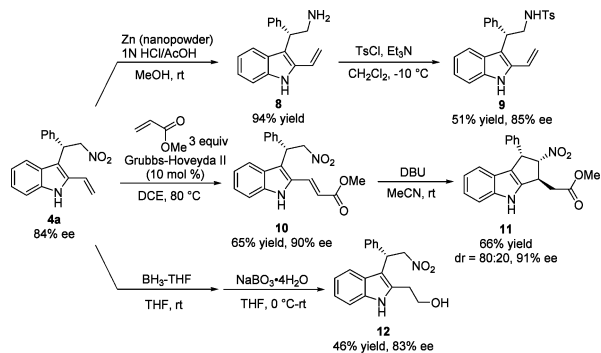
Figure 1. X-ray crystallographic analysis of 4d.

It should be noted that the use of (*S,S*)-PyBidine gives (*S*)-enriched **4a** due to the prioritization rule, when the indoles attack from the *re*-face of nitroalkenes.

The synthetic utility of the chiral 2-vinylindoles is shown in Scheme 3. The nitro group of **4a** was successfully reduced using a zinc nanopowder to give chiral tryptamine derivative **8**, and the amine **8** was tosylated to give **9** while maintaining the 2-vinyl functionality.

The vinyl group could be exchanged for other olefin substituents using a Grubbs–Hoveyda II catalyst. From the metathesis adduct **10** obtained from methyl acrylate, an intramolecular nitro-Michael reaction proceeded by DBU to give the carbocycle **11** in a diastereoselective manner (d.r. = 80:20).

## Scheme 3. Transformations of Chiral 2-Vinylindole 4a



The stereochemistry of the major isomer of **11** was determined by the X-ray crystallographic analysis (Figure 2). The vinyl group

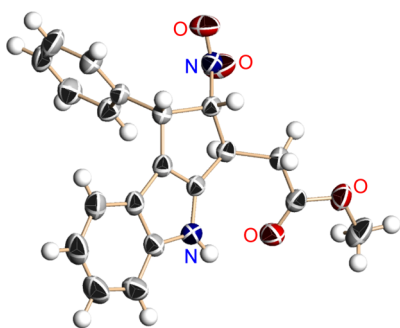
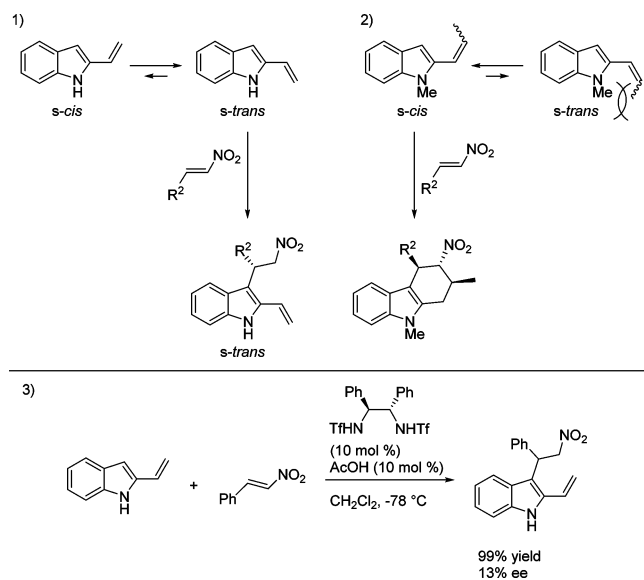


Figure 2. X-ray crystallographic analysis for major isomer of **11**.

## Scheme 4. Reaction Pathway for (1) Friedel–Crafts Reaction and (2) [4 + 2]-Cycloaddition



of **4a** could also be converted to a hydroxyl alkyl substituent by hydroboration **12**. The optical purity of indoles was retained in all of the transformations shown in Scheme 3.

The reason for the success of the catalyst in the Friedel–Crafts reaction, but not in the cyclization reaction, is unlikely to be simply the mild Lewis acidity of the PyBidine–Ni(OTf)<sub>2</sub> catalyst. The reaction course is explained by X-ray structure of **4d**, in which the vinyl group at the 2-position and the C2–C3 double bond are in the *s-trans* configuration. An *s-trans*

2-vinyl indole does not easily undergo [4 + 2]-cycloaddition (Scheme 4(1)). In Xiao's work<sup>3a</sup> on [4 + 2]-cycloaddition using 2-vinyl indoles, steric repulsion between the methyl substituent on the nitrogen and the alkene substituent at the 2-position deflects the equilibrium toward the *s-cis* form, allowing the [4 + 2]-cycloaddition reaction to proceed (Scheme 4(2)). When the reaction of 2-vinylindole **1a** with nitrostyrene **2a** was examined using Xiao's catalyst, only the Friedel–Crafts product **4a** was generated (Scheme 4(3)), which strongly suggested this scenario.

In conclusion, the chiral bis(imidazolidine)pyridine (PyBidine)–Ni(OTf)<sub>2</sub> complex is the first general catalyst for asymmetric Friedel–Crafts reactions of 2-vinylindoles with nitroalkenes. Because various chemical transformations of the 2-vinyl functionality are possible, the chiral 2-vinyl indoles are expected to be useful chiral scaffolds for diverse possibilities in organic synthesis.

## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03584.

General procedure, synthetic and analytical data, <sup>1</sup>H and <sup>13</sup>C NMR, HPLC data (PDF)

Crystallographic data (CIF, CIF)

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## Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Books and reviews for indole alkaloids: (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Alkaloids: Chemical and Biological Perspectives*, Vol. 13; Elsevier: New York, 1999; pp 163–236. (b) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (c) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Alvarez, M. *Chem. - Eur. J.* **2011**, *17*, 1388.
- (2) Bartoli, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449; Update: *Chem. Soc. Rev.* **2015**, *44*, 742.
- (3) Cycloaddition using 2-alkenyl indoles: (a) Wang, X.-F.; Chen, J.-R.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 1140. (b) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327. (c) Tan, F.; Li, F.; Zhang, X.-X.; Wang, X.-F.; Cheng, H.-G.; Chen, J.-R.; Xiao, W.-J. *Tetrahedron* **2011**, *67*, 446. (d) Tan, F.; Xiao, C.; Cheng, H.-G.; Wu, W.; Ding, K.-R.; Xiao, W.-J. *Chem. - Asian J.* **2012**, *7*, 493. (e) Pirovano, V.; Dell'Acqua, M.; Facchetti, D.; Nava, D.; Rizzato, S.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2013**, *2013*, 6267. (f) Tian, X.; Hofmann, N.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2997. (g) Talukdar, R.;

Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954. (h) Wang, Y.; Tu, M.-S.; Yin, L.; Sun, M.; Shi, F. *J. Org. Chem.* **2015**, *80*, 3223.

(4) Other cyclization using 2-alkenyl indoles: Wang, L.; Guo, W.; Zhang, X.-X.; Xia, X.-D.; Xiao, W.-J. *Org. Lett.* **2012**, *14*, 740.

(5) Cycloaddition using 3-alkenyl indoles as an enophile: (a) Tan, B.; Hernandez-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354. (b) Liu, Y.; Nappi, M.; Escudero-Adan, E.; Melchiorre, C. P. *Org. Lett.* **2012**, *14*, 1310. (c) Xiao, Y.-C.; Yue, C.-Z.; Chen, P.-Q.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 3208. (d) Zheng, H.; He, P.; Liu, Y.; Zhang, Y.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2014**, *50*, 8794. (e) Cowell, J.; Harrington, R. W.; Probert, M. R.; Hall, M. J. *Tetrahedron: Asymmetry* **2015**, *26*, 1189. (f) Wang, Y.; Zhang, P.; Liu, Y.; Xia, F.; Zhang, J. *Chem. Sci.* **2015**, *6*, 5564. (g) Zheng, H.; Liu, X.; Xu, C.; Xia, Y.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 10958. (h) Sun, X.-X.; Zhang, H.-H.; Li, G.-H.; Meng, L.; Shi, F. *Chem. Commun.* **2016**, *52*, 2968.

(6) Cycloaddition using 3-alkenyl indoles as a dienophile: Mao, Z.; Lin, A.; Shi, Y.; Mao, H.; Li, W.; Cheng, Y.; Zhu, C. *J. Org. Chem.* **2013**, *78*, 10233.

(7) Cycloaddition using 4-alkenyl indoles: Romanini, S.; Galletti, E.; Caruana, L.; Mazzanti, A.; Himo, F.; Santoro, S.; Fochi, M.; Bernardi, L. *Chem. - Eur. J.* **2015**, *21*, 17578.

(8) Cycloaddition using 7-alkenyl indoles: Shi, F.; Zhang, H.-H.; Sun, X.-X.; Liang, J.; Fan, T.; Tu, S.-J. *Chem. - Eur. J.* **2015**, *21*, 3465.

(9) Synthesis of chiral 2-alkenyl indoles: Liu, Q.-J.; Yan, W.-G.; Wang, L.; Zhang, X. P.; Tang, Y. *Org. Lett.* **2015**, *17*, 4014.

(10) Our efforts on catalytic asymmetric Friedel–Crafts reaction of indoles with nitroalkenes: (a) Arai, T.; Yokoyama, N.; Yanagisawa, A. *Chem. - Eur. J.* **2008**, *14*, 2052. (b) Arai, T.; Yokoyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4989. (c) Yokoyama, N.; Arai, T. *Chem. Commun.* **2009**, 3285. (d) Arai, T.; Awata, A.; Wasai, M.; Yokoyama, N.; Masu, H. *J. Org. Chem.* **2011**, *76*, 5450. (e) Arai, T.; Yamamoto, Y.; Awata, A.; Kamiya, K.; Ishibashi, M.; Arai, M. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2486. (f) Sato, T.; Arai, T. *Synlett* **2014**, *25*, 349.

(11) Catalytic asymmetric Friedel–Crafts reaction of indoles with nitroalkenes from the other groups: (a) Bandini, M.; Garelli, A.; Rovinetti, M.; Tommasi, S.; Umani-Ronchi, A. *Chirality* **2005**, *17*, 522. (b) Jia, Y.-X.; Zhu, S.-F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75. (c) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115. (d) Yuan, Z.-L.; Lei, Z.-Y.; Shi, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1339. (e) Lin, S.-Z.; You, T.-P. *Tetrahedron* **2009**, *65*, 1010. (f) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2010**, *352*, 1113. (g) Liu, H.; Du, D.-M. *Eur. J. Org. Chem.* **2010**, *2010*, 2121. (h) McKeon, S. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2011**, *2011*, 7107. (i) Peng, J.; Du, D.-M. *Eur. J. Org. Chem.* **2012**, *2012*, 4042. (j) Jia, Y.; Yang, W.; Du, D.-M. *Org. Biomol. Chem.* **2012**, *10*, 4739. (k) Li, C.; Liu, F.-L.; Zou, Y.-Q.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Synthesis* **2013**, *45*, 601. (l) Singh, P. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 1127. (m) Sui, Y.; Liu, L.; Zhao, J.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron* **2007**, *63*, 5173. (n) Wu, J.; Li, X.; Wu, F.; Wan, B. *Org. Lett.* **2011**, *13*, 4834. (o) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983. (p) Hao, X.-Q.; Xu, Y.-X.; Yang, M.-J.; Wang, Li.; Niu, J.-L.; Gong, J.-F.; Song, M.-P. *Organometallics* **2012**, *31*, 835. (q) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566. (r) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (s) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (t) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464. (u) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016. (v) Lin, J.-H.; Xiao, J.-C. *Eur. J. Org. Chem.* **2011**, *2011*, 4536. (w) Tang, H.-Y.; Zhang, Z.-B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 2038.

(12) Reviews of the catalytic asymmetric Friedel–Crafts reaction: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (c) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (d) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (e) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (f) Zeng, M.; You, S.-L. *Synlett* **2010**, *2010*,

1289. (g) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, *2010*, 2635.

(13) (a) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338. (b) Arai, T.; Ogino, Y. *Molecules* **2012**, *17*, 6170. (c) Arai, T.; Mishiro, A.; Matsumura, E.; Awata, A.; Shirasugi, M. *Chem. - Eur. J.* **2012**, *18*, 11219. (d) Arai, T.; Kajikawa, S.; Matsumura, E. *Synlett* **2013**, *24*, 2045. (e) Arai, T.; Matsumura, E. *Synlett* **2014**, *25*, 1776. (f) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768. (g) Awata, A.; Arai, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 10462. (h) Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watabe, M.; Yamanaka, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 1595. (i) Arai, T.; Tsuchiya, K.; Matsumura, E. *Org. Lett.* **2015**, *17*, 2416. (j) Sato, T.; Miyazaki, T.; Arai, T. *J. Org. Chem.* **2015**, *80*, 10346.