

# Palladium-Catalyzed, Asymmetric Mizoroki–Heck Reaction of Benzylic Electrophiles Using Phosphoramidites as Chiral Ligands

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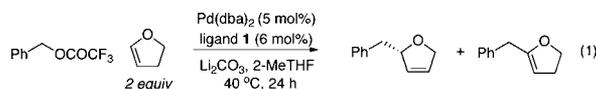
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**S** Supporting Information

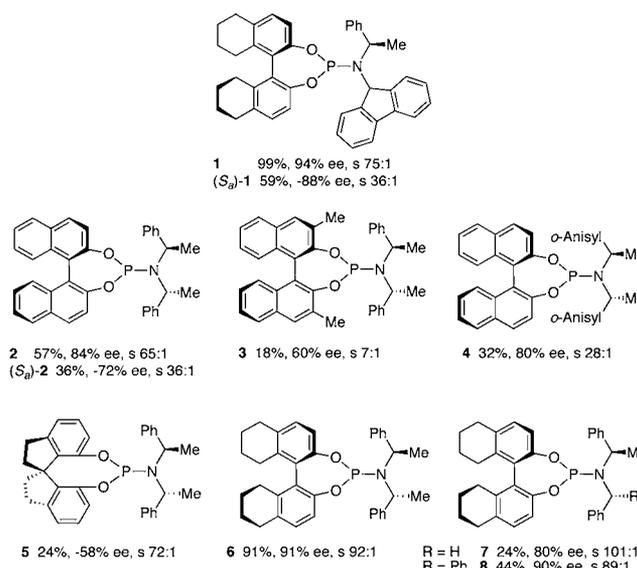
**ABSTRACT:** We report herein the first examples of asymmetric Mizoroki–Heck reactions using benzyl electrophiles. A new phosphoramidite was identified to be an effective chiral ligand in the palladium-catalyzed reaction. The reaction is compatible with polar functional groups and can be readily scaled up. Several cyclic olefins worked well as olefin components. Thirty-one examples are included.

The Mizoroki–Heck reaction usually refers to Pd-catalyzed C–C bond formation between olefins and organic (pseudo)halides. Today, it has become a powerful tool in synthesis and is commonly used in making of natural products, drugs, and functional materials.<sup>1</sup> In the past two decades, asymmetric variants have also been extensively studied and they have been employed in synthesis of many bioactive natural products.<sup>2</sup>

Compared to aryl and vinyl electrophiles, the benzylic type is less extensively studied in Heck reaction.<sup>3–5</sup> The reactions of benzyl electrophiles are often associated with slow oxidative addition of unactivated benzyl electrophiles<sup>6</sup> and slow olefin insertion into the Pd–benzyl bond.<sup>7</sup> In addition, benzyl electrophiles often produce a mixture of Heck products due to double bond migration. Herein, we report the first examples of asymmetric Heck reaction of benzylic electrophiles. In the presence of a phosphoramidite ligand **1**, the reaction of benzyl trifluoroacetate and 2,3-dihydrofuran gave 2-benzyl-2,5-dihydrofuran as major product in good yield and excellent stereoselectivity (eq 1).<sup>8</sup>



Initially, we tried many chiral monophosphines and bisphosphines as ligands in the Pd-catalyzed model reaction (eq 1), but they all failed to give any desired product. Probably, phosphines can directly undergo nucleophilic substitution with reactive benzyl halides and esters. Later, we found that Feringa ligand **2** gave promising results, 84% ee and 65:1 selectivity between two olefinic isomers.<sup>9</sup> The minor isomer from the reaction was identified to be 5-benzyl-2,3-dihydrofuran. Figure 1 shows a sample of phosphoramidites that we have examined. Modifications of ligand **2**, however, did not lead to improvement. Examples of modifications include (a) inversion of axial



**Figure 1.** Performance of phosphoramidite ligands in a model Heck reaction (eq 1). The selectivity “s” refers to ratio of two olefinic isomers.

chirality in the binaphthyl backbone as in (*S<sub>a</sub>*)-**2**, (b) introduction of methyl group on the binaphthyl skeleton (**3**), (c) use of *o*-anisyl groups in the dialkylamino moiety (**4**), and (d) use of a spiro–bisindane skeleton (**5**).

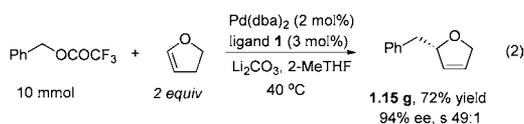
Later, we found that partial saturation of the binaphthyl backbone of ligand **2** provided more encouraging results (Figure 1). Ligand **6** gave 91% ee and 91% yield. Next, we attempted to replace one of *N*- $\alpha$ -phenylethyl groups in **6**. A smaller benzyl (**7**) or a larger benzhydryl (**8**) did not lead to better selectivity. Eventually, incorporation of a fluorenyl group (**1**) gave satisfactory results with 94% ee and high olefins selectivity between two isomers (75:1). Ligand (*S<sub>a</sub>*)-**1** contains inverted axial chirality. It not only led to slightly lower ee, but also inversion of configuration in the product. A similar trend was also noticed when results from ligands **2** and (*S<sub>a</sub>*)-**2** were compared. Thus, the diolates of the phosphoramidites are the main structural element of the chiral ligands that contribute to the asymmetric induction.

Some observations from condition optimization are worth commenting. First, the amount of the olefin can be reduced to

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The absolute configuration of the product was assigned to be (S), by comparison with reported values of optical rotation.<sup>13</sup> This Heck product can be quickly transformed to adenophostin A analogues, which can mimic inositol 1,4,5-trisphosphate to stimulate Ca<sup>2+</sup> release.<sup>14</sup>

In summary, we have realized the first examples of asymmetric Heck reaction of benzylic electrophiles. Several cyclic olefins can react efficiently as olefin components. The ee's of isolated Heck products were usually >90% and double bond migration in the immediate Heck products was kept at very low levels. The method is compatible with polar groups such as aldehyde, ester, and nitro groups. We are currently conducting mechanistic studies to understand the origin of the stereoselectivity. Exploration of asymmetric Heck reactions using other unconventional electrophiles is ongoing.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Experimental procedures for synthesis of benzylic esters and chiral phosphoramidite ligands and asymmetric Heck reactions; characterization of new ligands and Heck products (NMR, MS, and chiral HPLC analysis). 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.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

- Reviews: (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (d) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 217–316. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (f) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433. (g) *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: New York, 2009. (h) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101.
- Reviews: (a) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (c) McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122. (d) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (e) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.
- Examples: (a) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (b) Fabre, J.-L.; Julia, M.; Mansour, B.; Saussine, L. *J. Organomet. Chem.* **1979**, *177*, 221. (c) Wu, G. Z.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507. (d) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725. (e) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1995**, 245. (f) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F.

*J. Am. Chem. Soc.* **2011**, *133*, 19020. (g) Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703.

(4) Ru-catalyzed benzylation of olefins using aliphatic and benzylic alcohols: Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613.

(5) Examples of Heck reaction of alkyl electrophiles: (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. (b) Rauf, W.; Brown, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4228. (c) Bloome, K. S.; McMahan, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (d) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253. (e) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068. (f) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125.

(6) Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, *33*, 348.

(7) Narahashi, H.; Shimizu, I.; Yamamoto, A. *J. Organomet. Chem.* **2008**, *693*, 283.

(8) Oxidative addition of benzyl trifluoroacetates to Pd(0) complexes: Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799.

(9) Reviews: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486. (c) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

(10) A recent example of Pd-hydride catalyzed isomerization of olefins: Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998.

(11) (a) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. *Chem.—Eur. J.* **2011**, *17*, S921. (b) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4419. (c) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076.

(12) Schwardt, O.; Veith, U.; Gaspard, C.; Jäger, V. *Synthesis* **1999**, 1473.

(13) (a) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096. (b) Boisvert, L.; Beaumier, F.; Spino, C. *Can. J. Chem.* **2006**, *84*, 1290.

(14) Mochizuki, T.; Kondo, Y.; Abe, H.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Paul, M.; Potter, B. V. L.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2006**, *49*, 5750.