

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

Zhigang Yang and Jianrong (Steve) Zhou*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

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.

➡ he 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.¹ In the past two decades, asymmetric variants have also been extensively studied and they have been employed in synthesis of many bioactive natural products.²

Compared to aryl and vinyl electrophiles, the benzylic type is less extensively studied in Heck reaction.³⁻⁵ The reactions of benzyl electrophiles are often associated with slow oxidative addition of unactivated benzyl electrophiles⁶ and slow olefin insertion into the Pd-benzyl bond.⁷ 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).⁸



Initially, we tried many chiral monophosphines and bisphosphines as ligands in the Pd-catalzyed model reaction (eq 1), but they all failed to give any desired product. Probably, phosphines can directly undergo nucleophilic subtitution 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.⁹ 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_a) -2, (b) introduction of methyl group on the binaphthyl skeleton (3), (c) use of *o*-anisyl groups in the dialkylamine 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- α -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_a) -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_a) -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

Received: April 28, 2012

1.2 equiv and a similar result was observed. Second, the choice of base was important. Li_2CO_3 proved to be the optimal to deprotonate the palladium hydride and thus minimize olefin isomerization in the immediate Heck product.¹⁰ Comparably good results were also obtained when trialkylamine bases such as triethylamine and Hünig base were used. Third, in terms of choice of solvents, many ethereal solvents worked well and gave similarly good results (>90% conversion and 94% ee after 14 h at 40 °C), including 2-methyltetrahydrofuran (2-MeTHF), THF, dioxane, glyme, and diglyme. In less polar solvents such as diethyl ether, TBME, and toluene, the turnover was lower. DMSO and DMA inhibited the catalysis, probably due to strong coordination of the solvents to the Pd–benzyl species.

After condition optimization, we have explored the scope of benzylic electrophiles, using 2,3-dihydrofuran as model olefin (Figure 2). A few observations are noteworthy. (a) The Pd/



Figure 2. Heck reaction of 2,3-dihydrofuran.

ligand 1 catalyst can tolerate sensitive groups such as aldehyde and nitro groups. (b) Both electron-donating and electronwithdrawing groups can be present on the aryl ring. (c) *Ortho*substituents can also be present. (d) When an *o*-vinyl group was present in the benzyl ester, no insertion of the Pd–alkyl intermediate into the vinyl group was observed. (e) Some heteroaryl derivatives of thiophene and furan also worked well. Pyridine-containing substrates inhibited the catalysis, due to strong binding of pyridine nitrogen to the palladium center. (f) 1-Naphthylmethyl trifluoroacetate reacted much slower than the benzyl ester. (g) Secondary electrophiles such as α phenylethyl and benzhydryl trifluoroacetates did not react. (h) Benzyl electrophiles carrying other leaving groups, such as Br, Cl, OTs, OMs, OCO₂Et, OBz, and even OAc, did not react. In all cases, <5% conversion was observed at 40 °C.

We have examined other olefins in the new Heck reaction. To our surprise, electron-deficient 2,5-dihydrofuran provided 2benzyl-2,5-dihydrofurans as major products (Figure 3). Analysis of the reaction mixture at partial conversion revealed that a fraction of 2,5-dihydrofuran isomerized to 2,3-dihydrofuran. The latter is an electron-rich olefin and is responsible for the formation of all isolated Heck products. In classic Heck reactions involving cationic Pd-aryl species, electron-rich olefins proved to be more reactive than electron-deficient olefins. Thus, this observation suggested that in our Heck reaction, cationic Pd-benzyl species, instead of neutral



Figure 3. Heck reaction of 2,5-dihydrofuran.

ones, are involved. This explains observed inhibition of catalysis by strongly coordinating solvents and substrates. After olefin insertion and β hydride elimination, the resulting Pd hydride species should also be cationic.

We found that another electron-rich olefin, N-Boc-2,3pyrroline, also reacted well as olefin component (Figure 4).



Figure 4. Heck reaction of N-Boc-2,3-pyrroline.

Both electron-donating methoxy and electron-withdrawing ester groups can be present on the benzyl electrophiles. The Heck reaction of *p*-methoxybenzyl trifluoroacetate quickly provided a key intermediate in asymmetric synthesis of (+)-anisomycin, an antiprotozoal and antifungal antibiotic.¹¹ In addition, this method can produce anisomycin analogues, some of which showed antitumor activity.¹²

In reactions of cyclopentene, the desired products were also obtained in high stereoselectivity and little double bond migration was detected in the immediate Heck product (Figure 5). The reactions of cycloheptene, however, only led to ca. 60% ee. Cyclohexene did not react, because in the twisted half-chair conformation axial hydrogens hinder binding of either face of the olefin to Pd.

We have scaled up an asymmetric Heck reaction to 10 mmol scale and the catalyst loading can be reduced to 2 mol % (eq 2). The desired product was obtained in good yield and 94% ee.



Figure 5. Heck reaction of cyclopentene.



The absolute configuration of the product was assigned to be (S), by comparison with reported values of optical rotation.¹³ This Heck product can be quickly transformed to adenophostin A analogues, which can mimic inositol 1,4,5-trisphosphate to stimulate Ca²⁺ release.¹⁴

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.

AUTHOR INFORMATION

Corresponding Author

jrzhou@ntu.edu.sg

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Singapore National Research Foundation (NRF-RF2008-10) and Nanyang Technological University for financial support. We thank Johnson Matthey for a gift of palladium salts.

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.

(2) 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.

(3) 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.; McMahen, 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, 5921. (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.