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Desymmetrization of cyclic olefins *via* asymmetric Heck reaction and hydroarylation†

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Sijia Liu and Jianrong (Steve) Zhou*

An asymmetric Heck reaction allows desymmetrization of substituted cyclic olefins in high dr and ee. A bisphosphine oxide is uniquely stereoselective for this purpose. Desymmetrization of bicyclic olefins *via* hydroarylation can also be realized in high ee.

Asymmetric, intermolecular Heck reaction was first reported by Hayashi *et al.* in 1991, which was performed between aryl triflates and 2,3-dihydrofuran.[1] Since then, the reaction has been tested using numerous phosphorus ligands,[2] most of which are bisphosphines, mixed oxazoline–phosphines and bisphosphites.[3] Although excellent ee was realized with simple olefins such as cyclopentene and 2,3-dihydrofuran, structural diversity of asymmetric Heck products remained rather low, as compared to the intramolecular versions.[4] Recently, Sigman *et al.* reported the asymmetric Heck–Matsuda reaction between *acyclic* olefins bearing alcohol groups and aryldiazonium salts and provided arylated ketones and aldehydes in good ee.[5] Herein, we report desymmetrization of both monocyclic and bicyclic olefins that formed more than one stereocenter in high ee and excellent dr (Fig. 1).

We first attempted a model reaction between *p*-acetylphenyl triflate and a substituted cyclopentene to seek a stereoselective palladium catalyst.[6] The family of bisphosphine oxides, which we used for asymmetric Heck reaction of simple cyclic olefins, gave very promising results (Fig. 1).[7] For example, (*R*)-BINAP(O) gave predominantly the *trans* isomer with 84% ee.[8] The ratio of the amount of the *trans* isomer to the sum of two minor isomers, or the *s* ratio, was determined to be 4 : 1 by GC. The *trans* configuration of the major isomer was established using X-ray diffractional analysis of one product derivative.

In the model reaction, we found that 1,1′-spirobiindane-7,7′-bisphosphine oxide or SDP(O) led to 90% ee and an *s* ratio of 26 : 1. If *P*-phenyl groups in SDP(O) were changed to *m*-xylyl, the selectivity was improved to 97% ee. Notably, (*R*)-BINAP(O) and (*R*)-SDP(O) are technically pseudoenantiomers and they gave opposite enantiomers as major Heck products.

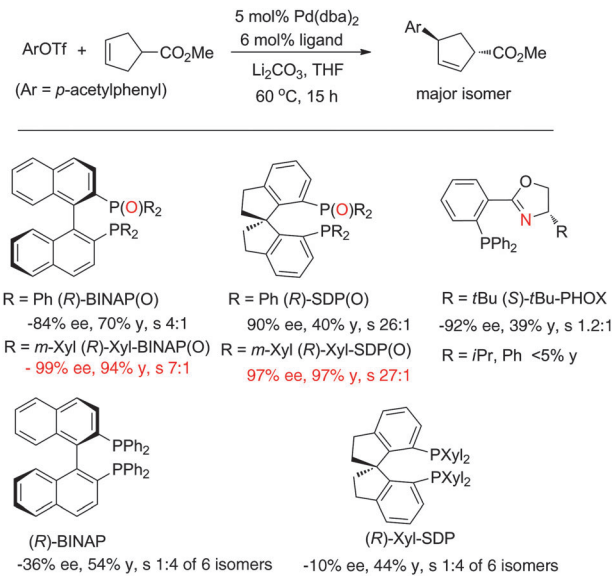

Fig. 1 Catalyst discovery for a model Heck reaction.

In comparison, when bisphosphine ligands, (*R*)-BINAP and (*R*)-Xyl-SDP were used, the *trans* isomer was formed in poor ee and as the minor isomer in a complex mixture of six isomers (judged by GC). In addition, when *t*Bu-PHOX was used, the *trans* isomer was produced together with four isomers and the *s* value was only 1.2 : 1. The other two PHOX ligands showed very poor activity.

During our condition optimization, we found that several bases worked well, including iPr_2NEt, 2,6-lutidine, Li_2CO_3 and LiOAc. Trialkylamine Et_3N, however, led to about 20% reduction of ArOTf to arene, *via* donation of hydride to cationic arylpalladium species.[9] With respect to the choice of solvents, excellent ee was obtained in THF, dioxane and toluene.

In terms of the scope of olefins, various substituted cyclopentenes reacted selectively to furnish the *trans* isomers (Fig. 2). Esters, nitriles and free alcohols can be present on the olefins. However, if the R group on the olefin was benzyl, no insertion occurred.

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore. E-mail: jrzhou@ntu.edu.sg; Fax: +65 67911961

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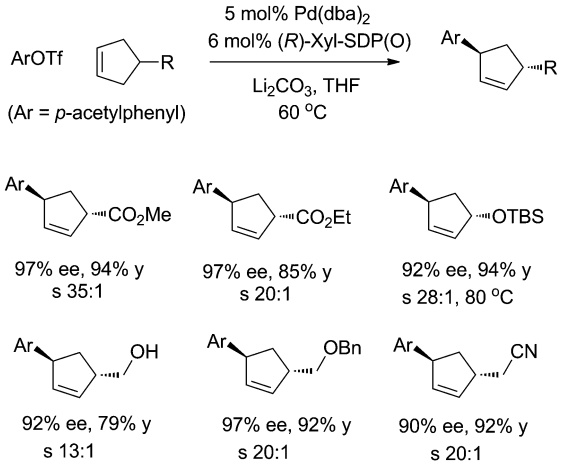

Fig. 2 Examples of cyclic olefins in Heck reaction.

A wide array of aryl triflates coupled well with a model cyclopentene (Fig. 3). On the aryl rings, both electronic perturbation and *ortho*-substituents can be present. Many polar groups such as esters, ketones and aldehydes were tolerated. Some heteroaryl triflates based on indoles and benzothiazole also reacted efficiently in good ee. One example of alkenyl triflate was included to show the scope beyond aryl ones.

Stereoselective olefin manipulation of asymmetric Heck products was performed, such as dihydroxylation, epoxidation and cyclopropanation (Fig. 4).[10] The relative configuration of the cyclopropane and epoxide derivatives was established by nOe analysis. Notably, cyclopropanation occurred almost exclusively *syn* to the siloxy group, presumably due to pre-coordination of siloxy oxygen to organozinc reagents. The *cis*-dihydroxylation

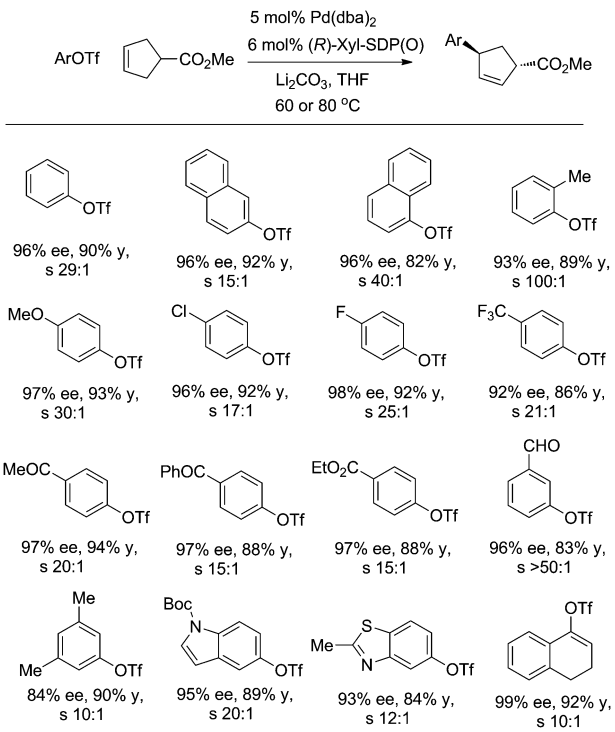

Fig. 3 Examples of aryl and vinyl triflates in Heck reaction.

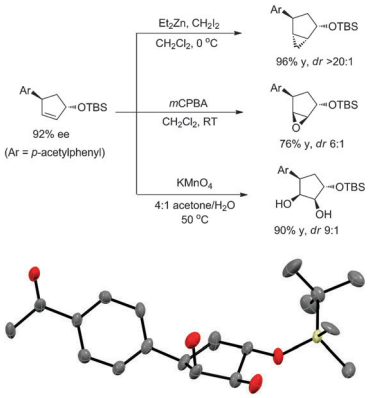

Fig. 4 Top: derivatization of one Heck product. Bottom: ORTEP diagram of a diol derivative with 50% thermal ellipsoid and hydrogen atoms omitted for clarity.

took place predominantly *anti* to the siloxy group to avoid steric repulsion. The relative configuration in the diol derivative was established using X-ray crystallography.

The Xyl-SDP(O) catalyst can be applied to asymmetric hydroarylation of bicyclic olefins (Fig. 5). Sodium formate served as the hydride donor. Excellent ee was obtained in all cases, which was not seen previously in Pd-catalyzed hydroarylations.[11] In reactions of norbornadiene, no double hydroarylation was observed. The coupling of benzonorbornadiene also proceeded smoothly.

The new hydroarylation method can find use in asymmetric synthesis of epibatidine, an alkaloid possessing potent analgesic properties.[12] Another target is an orally available therapeutic agent for the treatment of osteoporosis.[13] Only recently, Rh-catalyzed hydroarylation between azacyclic olefins and arylboronic acids gave high ee.[14] Hartwig *et al.* also reported iridium-catalyzed hydroheteroarylation of norbornene in >90% ee *via* selective CH activation of some heteroarenes.[15]

The absolute configuration of one product, *exo*-2-phenylnorbornane was determined to be 2*R*, by comparison with reported optical rotation.[16] This assignment is consistent with 5*S* configuration of the major Heck isomers in Fig. 2 *via* aryl insertion at the less hindered face of cyclopentenes.

In conclusion, we realized the Heck reaction of substituted cyclopentenes that gave almost exclusively *trans* isomers and

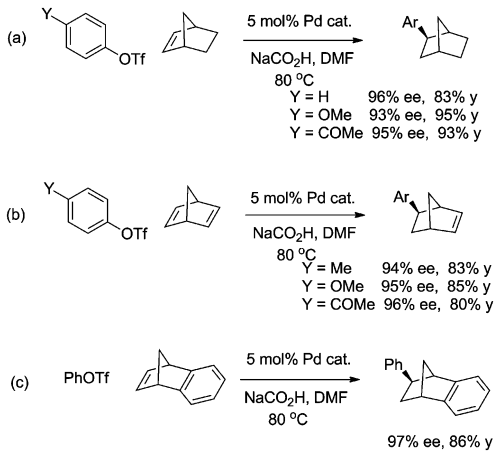

Fig. 5 Asymmetric hydroarylation of bicyclic olefins using (*R*)-Xyl-SDP(O) ligand.

established two stereocenters in high ee. Other catalysts failed to give this kind of selectivity. Applications to hydroarylation of bicyclic olefins also led to high ee, which was not seen previously in Pd catalysis.

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