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Communication

Palladium/TY-Phos-Catalyzed Asymmetric Heck/Tsuji–Trost Reaction of *o*-Bromophenols with 1,3-Dienes

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ABSTRACT: 2,3-Dihydrobenzofurans are crucial building blocks in the synthesis of natural products and pharmaceutical molecules. However, their asymmetric synthesis has been a long-standing formidable challenge so far. In this work, we developed a highly enantioselective Pd/TY-Phos-catalyzed Heck/Tsuji–Trost reaction of *o*-bromophenols with various 1,3-dienes, allowing expedient access to chiral substituted 2,3-dihydrobenzofurans. This reaction features excellent regio- and enantiocontrol, high functional group tolerance, and easy scalability. More importantly, the demonstration of this method as a highly valuable tool for the construction of optically pure natural products (*R*)-tremetone and fomannoxin is highlighted.

Optically pure α-alkenyl-substituted 2,3-dihydrobenzofurans are key structural motifs spread across medicinally relevant natural products and synthetic pharmaceuticals,[1] such as 2-rotenone, remirol, isoangenomalin, megapodiol, angenomalin, phenostereum A, and fomannoxin (Figure 1).[2] Because

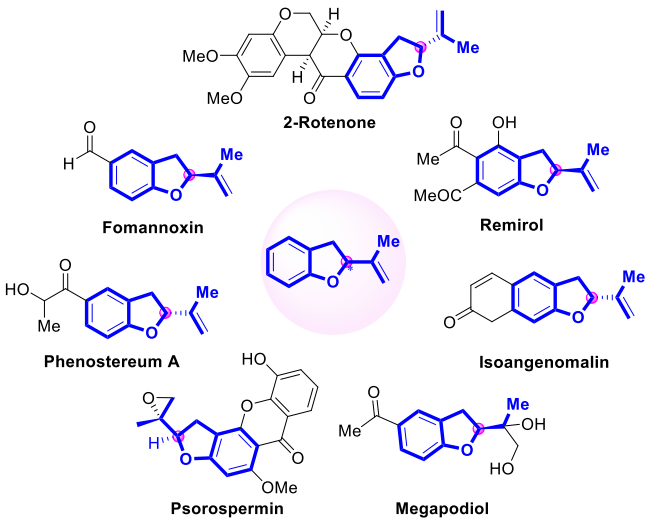

Figure 1. Representative examples of biologically active α-alkenyl-substituted 2,3-dihydrobenzofurans.

the alkenyl moiety can be transformed into a wide range of functionalities, α-alkenyl-substituted 2,3-dihydrobenzofurans are widely recognized as the most useful units among α-substituted 2,3-dihydrobenzofuran derivatives. During the last two decades, several elegant and efficient strategies for the asymmetric construction of α-substituted 2,3-dihydrobenzofurans have been reported. In 2012, Glorius[3] successfully applied a chiral ruthenium NHC complex for the asymmetric synthesis of valuable 2,3-dihydrobenzofurans. Hintermann[4] and Li[5] achieved a metal-catalyzed asymmetric intramolecular hydroxidation reaction to construct chiral α-substituted 2,3-dihydrobenzofurans. In 2021, Liu's group[6] obtained chiral α-substituted 2,3-dihydrobenzofurans via an oxidative kinetic resolution. Despite much great progress in this field, to the best of our knowledge, very few strategies for chiral α-alkenyl-2,3-dihydrobenzofurans have been reported so far. Therefore, the development of highly efficient methods leading to chiral α-alkenyl-substituted 2,3-dihydrobenzofurans is still a very challenging task and highly desirable.

In 1990s, the groups of Dieck[7] and Larock[8] independently pioneered an ideal method to access a wide range of heterocycles via the palladium-catalyzed tandem Heck/Tsuji–Trost reaction.[9] Larock and co-workers[10] further used their approach to develop cascade syntheses of 2,3-dihydrobenzofuran products in moderate yields. Despite the importance of this versatile methodology, the asymmetric version of this chemistry has not been realized well until now, with only sporadic reports concerning enantioselective tandem Heck/Tsuji–Trost reactions for the synthesis of indolines, isochromans, and indoles in the last three decades. In 2007, Schmalz and Koning[11] realized the palladium-catalyzed intramolecular asymmetric allylation of multistep-synthesized substrates (Scheme 1a), delivering chiral α-alkenyl-substituted 2,3-dihydrobenzofurans with high ee but with only two examples. Two years later, Kitamura and co-workers[12] reported a single example of Ru-catalyzed intramolecular asymmetric dehydrative cyclization (Scheme 1b). In 2021, Yi and co-workers[13] developed the redox-neutral Rh(III)-catalyzed C–H activation/[3 + 2] annulation of *N*-phenoxyacetamides with 1,3-dienes for direct construction of the 2,3-dihydrobenzofuran framework with up to 62% *ee* (Scheme 1c). To date, the highly

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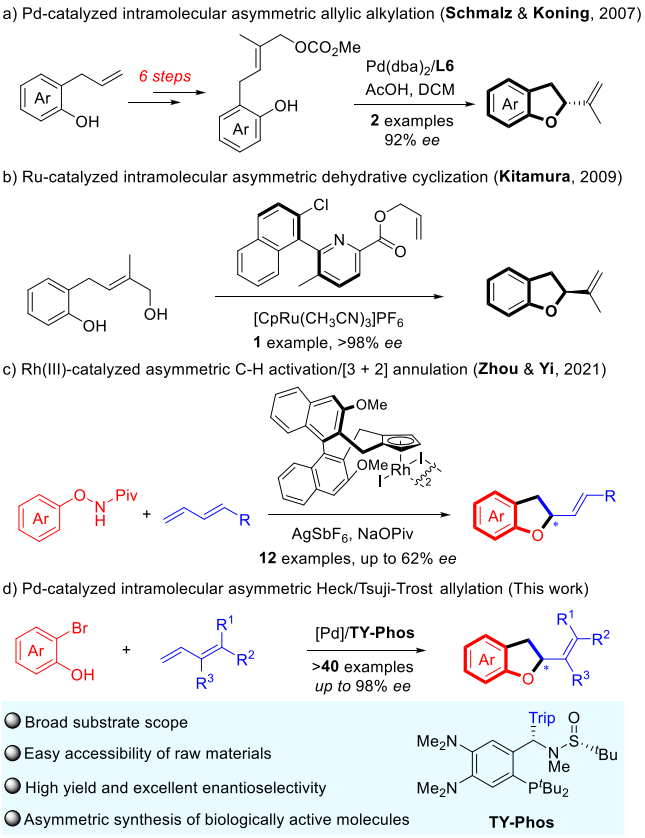
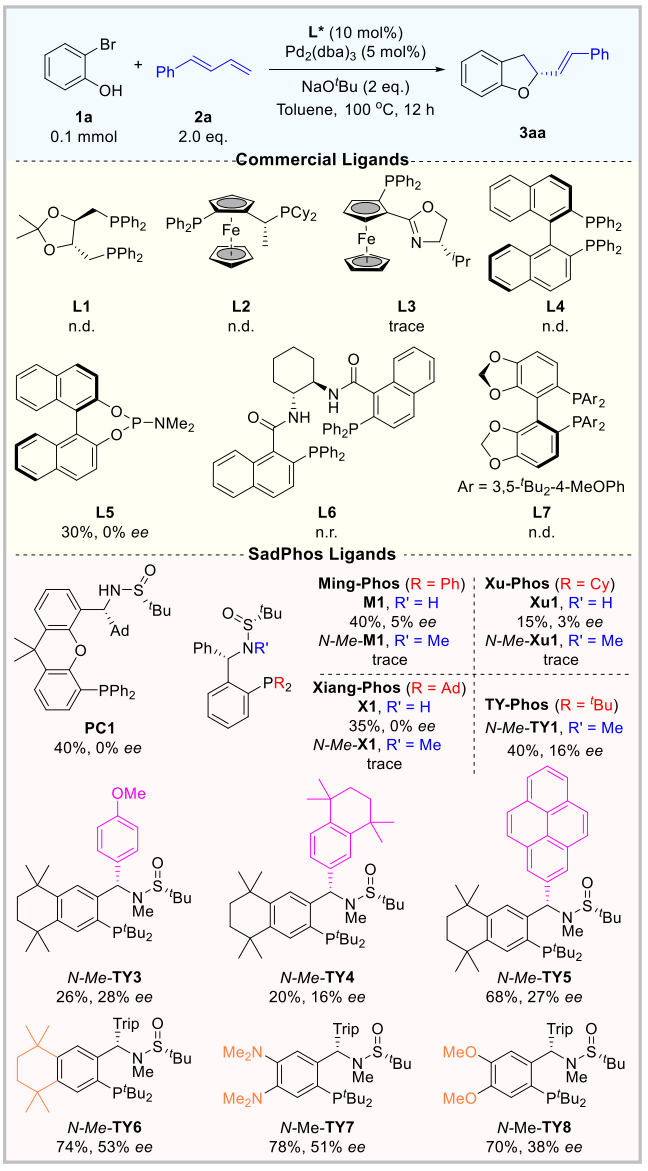
Scheme 1. Transition-Metal-Catalyzed Enantioselective Syntheses of Chiral α-Alkenyl-Substituted 2,3-Dihydrobenzofurans



Scheme 2. Screening of Commercial Ligands and Optimization of the TY-Phos Ligands



enantioselective synthesis of 2,3-dihydrobenzofurans has remained a realistic challenge. The challenging part of the asymmetric version is finding ideal ligands for the Heck reaction and subsequent asymmetric Tsuji−Trost reaction. In connection with our interest in the exploration of asymmetric tandem Heck/Tsuji−Trost[14] and intermolecular carbo-hetero-functionalization,[15] herein we describe a Pd-catalyzed enantioselective synthesis of substituted 2,3-dihydrobenzofurans from 1,3-dienes and 2-bromophenols using the new electron-rich ligand **TY-Phos** bearing an *N*-Me group, which was finally identified after systematic fine-tuning and is responsible for the reactivity and enantioselectivity (Scheme 1d).

Initially, we employed 2-bromophenol and (*E*)-1-phenylbutadiene as model substrates to investigate various chiral ligands (Scheme 2), bases, palladium sources, solvents, and temperatures. First, we screened the commercially available ligands **L1**−**L7**. Most of them could not deliver the desired product, and only ligand **L5** was able to produce the racemic product in 30% yield. Afterward, we checked the efficiency of a series of **Sadphos** ligands that we developed. Using **Ming-Phos**,[16] **Xu-Phos**,[14a,17] **Xiang-Phos**,[15,18] or **PC-Phos**[14b,19] as the chiral ligand did not furnish satisfactory results. When **TY-Phos**[20] was tested, to our delight, *N*-Me-**TY6** favored the production of **3aa** in 74% yield with 53% *ee*. Later on, we modified the ligand *N*-Me-**TY6** and discovered *N*-Me-**TY7**, which was able to achieve a higher yield (78%). Accordingly, we selected N-Me-**TY7** as the ligand to screen other conditions (see the Supporting Information (SI) for details). Eventually, the optimal conditions for the reaction were identified as *o*-bromophenol (1 equiv), (*E*)-1-phenylbutadiene (3 equiv), PhONa (2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mol%), *N*-Me-**TY7** (12 mol%), and DCM as the solvent at 40 °C.

Under the optimal conditions, the product **3aa** was obtained in 96% yield with 92% *ee* (Table 1). Subsequently, the substituent effect on the aryl groups of 1,3-dienes was investigated. It was found that the desired products **3ab**−**3al** were efficiently synthesized in 44−99% yield with 88−95% *ee*, regardless of the electronic nature or position of the substituent on the aryl group. Disubstituted and trisubstituted aryl groups were also well-tolerated, and the corresponding products **3am** and **3an** were obtained in good yields with excellent *ee* values. A thien-2-yl-substituted 1,3-diene was also a suitable substrate in this reaction to produce the product **3o** in 96% yield with 92% *ee*. Next, the multisubstituted 1,3-dienes (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene and (*E*)-penta-2,4-dien-2-ylbenzene were applicable to the reaction, furnishing the corresponding products **3ap** and **3aq**. Moreover, asymmetric reactions were also pursued for some unactivated

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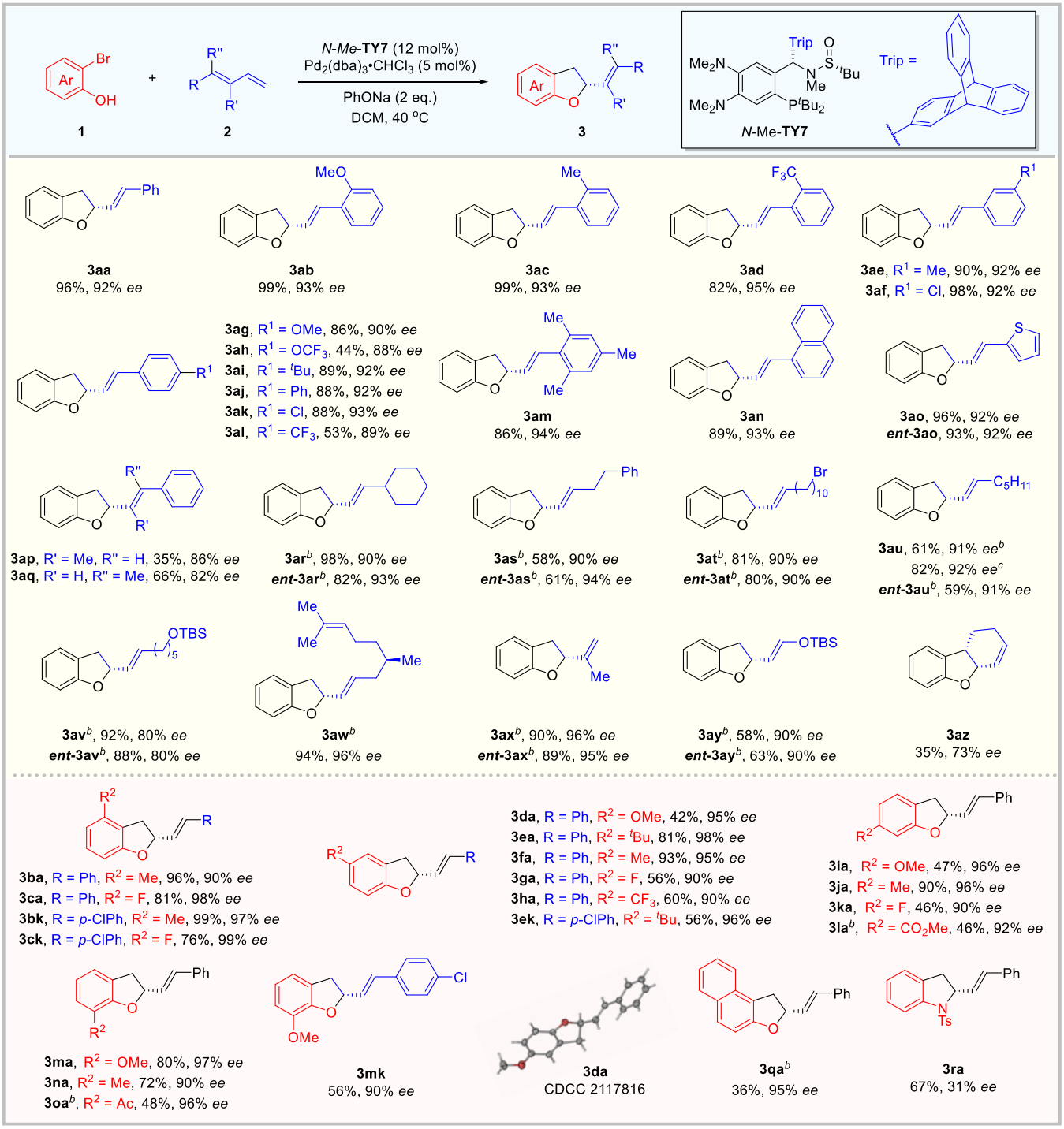
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Scope of the Reaction with Respect to Substituted *o*-Bromophenol and 1,3-Dienes[a]



[a]The reactions were performed with substituted *o*-bromophenol **1** (0.3 mmol), 1,3-dienes **2** (3 equiv), PhONa (2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mol %), *N*-Me-**TY7** (12 mol %), and DCM (1.5 mL) at 40 °C under N_2 for 48 h. The products *ent*-**3** were obtained by using *ent*-*N*-Me-**TY7**. [b]$Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), *N*-Me-**TY7** (15 mol %). [c]1,3-Diene **2** (9 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), *N*-Me-**TY7** (20 mol %).

1,3-dienes, which delivered very satisfactory outcomes. Nevertheless, the racemic reaction does not work well with the use of an achiral ligand, and thus, we synthesized the enantiomer of the *N*-Me-**TY7** ligand and subjected it to the reaction instead of *N*-Me-**TY7** to produce the enantiomer of the product and then determined the *ee*. The alkyl-chain-substituted 1,3-dienes reacted smoothly, furnishing the products **3ar**−**3av** in moderate to high yields with remarkable *ee*. It was noteworthy that increasing the amount of 1,3-diene and chiral ligand could improve the efficiency of this transformation and increase the yield of **3au** to 82%. The 1,3-diene synthesized from citronellal was compatible, producing the desired product **3aw** in 94% yield with 96% *ee*. To our delight, **3ax** and *ent*-**3ax,** which are key intermediates for natural products and pharmaceutical molecules, could be efficiently synthesized from the reaction of *o*-bromophenol and the feedstock isoprene. In addition, the

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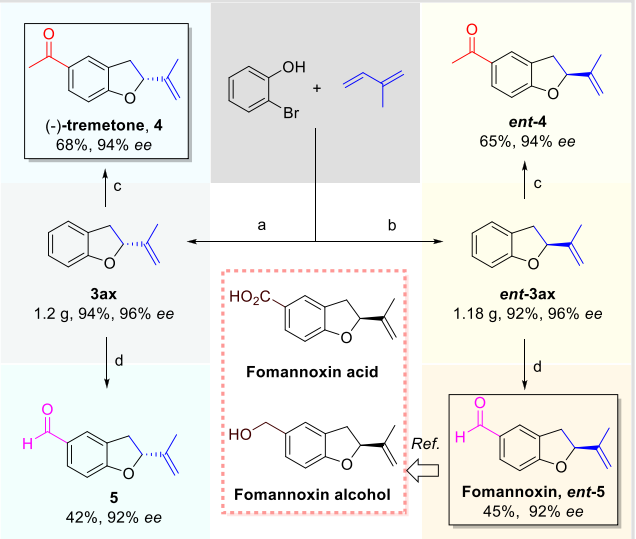
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

diene with an OTBS substituent was also compatible and furnished the target products **3ay** and *ent*-**3ay** in moderate yields with excellent *ee* values with the use of the chiral ligand and its enantiomer. 1,3-Cyclohexadiene was also examined to obtain the target product **3az** in 35% yield with 73% *ee*. We then investigated the substituents on the aromatic ring of *o*-bromophenol. An electron-donating group (OMe), neutral electron groups (^{t}Bu, Me), and halogen groups (F, Cl, CF_3) on the phenyl ring could all drive the reaction to form the desired products in moderate to high yields with excellent *ee* values. It is noteworthy that the electronic nature of the substituent had a significant effect on the efficiency of the reaction. Introducing electron-withdrawing groups (Ac, CO_2Me) resulted in lower reactivity, but after increasing the amount of palladium, ligand, and 1,3-diene and prolonging the reaction time, the reaction was also able to take place to afford the target products in moderate yields with high *ee* values (**3la**, **3oa**). Furthermore, 1-bromonaphthalen-2-ol also reacted smoothly to give the target product **3qa** with excellent *ee*. It is not surprising that the products **3bk**, **3ck**, **3ek**, and **3mk** could be obtained in 56−99% yield with 89−99% *ee* from the corresponding starting materials. *N*-Tosyl-*o*-bromoaniline could be successfully reacted to give **3ra** in moderate yield but with a relatively low *ee* value. Additionally, the absolute configuration of **3da** was determined by X-ray diffraction analysis (see the SI for details).

To demonstrate the practicality of our approach, the gram-scale syntheses of the isomeric pair **3ax** and *ent*-**3ax** were realized in the presence of 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.5 mol % *N*-Me-**TY7** with the use of 4 mL of isoprene in 2 mL of DCM (Figure 2). Some further synthetic transformations of **3ax** and *ent*-**3ax** were then carried out, providing the natural product (−)-tremetone **4** and its enantiomer *ent*-**4** in moderate yields with 94% *ee* at room temperature using acetic anhydride and trifluoromethanesulfonic acid as solvents. The natural product fomannoxin (*ent*-**5**) and **5** were both obtained with 92% *ee* in the case of $SnCl_4$ and dichloro(methoxy)methane.



[a]$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), (*S*,R_s)-*N*-Me-**TY7** (10 mol%), PhONa, DCM, 40 °C, 72 h; [b]$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), (*R*,S_s)-*N*-Me-**TY7** (10 mol%), PhONa, DCM, 40 °C, 72 h; [c]Ac_2O (2 equiv), CF_3CO_2H (1 mL), r.t., 1.5 h; [d]Sn_4Cl (1.5 equiv), Cl_2CHOCH_3 (2 equiv), DCM (1 mL), 0 °C, 2 h.

Figure 2. Gram scale and application transformations.

As the key intermediate, *ent*-**5** can easily be converted to other natural products in one or two steps.[1]

To gain insights into the effect of *E*/*Z* diene geometric isomers on the steric control of the reaction, several control experiments were then carried out (Figure 3; for more details, see the SI). It was found that treating (*E*)-diene (*E*)-**2a** under the standard conditions led to (*E*)-**3aa** as the sole product in 96% yield with 92% *ee* (Figure 3a). However, when the (*Z*)-diene (*Z*)-**2a** was used in place of (*E*)-**2a**, (*Z*)-**3aa** was obtained in 32% yield with 84% *ee* along with the formation of *ent*-(*E*)-**3aa** in 24% yield with only 12% *ee* (Figure 3b). In order to explore the possibility of the isomerization of the (*Z*)-diene to the (*E*)-diene during the reaction, two parallel reactions were performed with or without base under the standard conditions in the absence of 2-bromophenol (Figure 3c). Using NaOPh as the base or not, we did not observe isomerization of the (*Z*)-diene to the (*E*)-diene, which indicated that the hypothesis of the olefin isomerization during the reaction could be excluded.

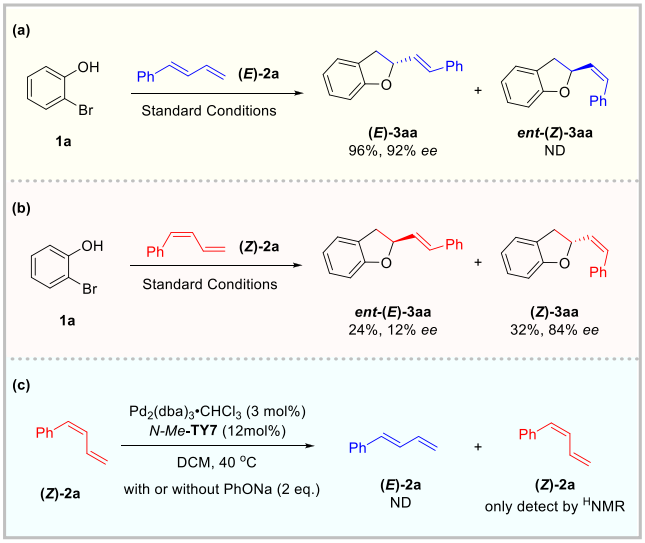


Figure 3. Control experiments.

In conclusion, we have developed a highly enantioselective Pd-catalyzed Heck/Tsuji−Trost reaction by using an accessible synthesis of chiral *N*-Me-**TY7**, which provides an efficient method for the synthesis of 2,3-dihydrobenzofuran compounds. The synthetic transformation of the products was also exhibited. The strategy provides an efficient way to approach the synthesis of valuable chiral 2,3-dihydrobenzofuran structures, which are potentially valuable for organic synthesis and medicinal chemistry. Computational studies to elucidate the stereocontrolling elements of this catalyst−ligand combination are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c12752.

Experimental procedures, compound characterization data, NMR spectra, and chiral HPLC chromatograms (PDF)

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Accession Codes

CCDC 2117816 and 2117960 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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