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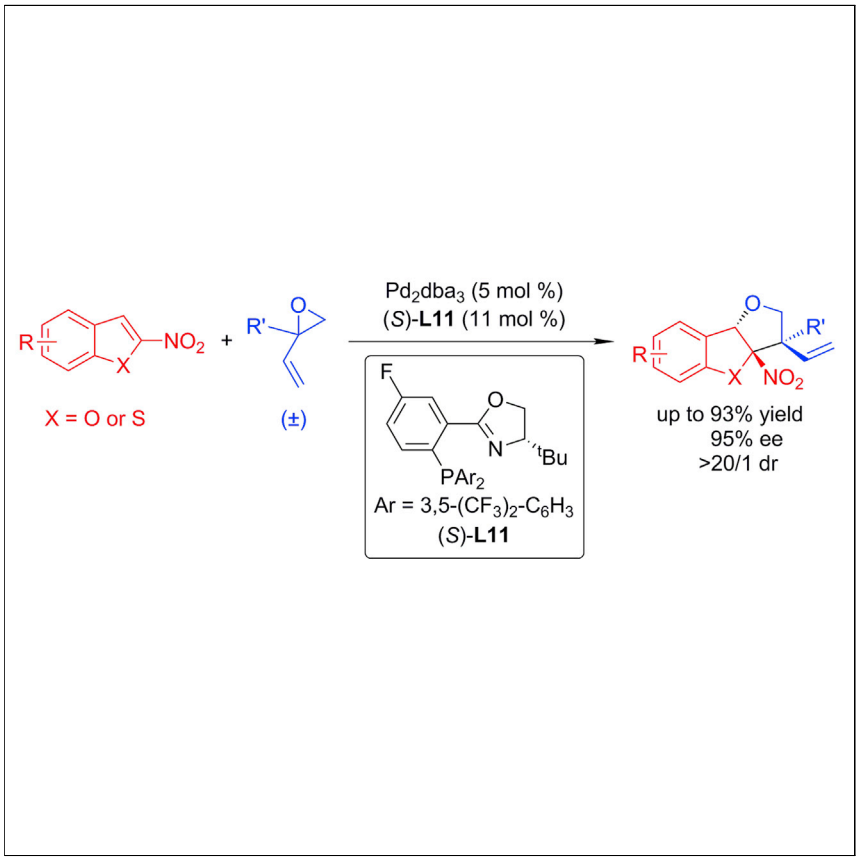
Palladium-Catalyzed Highly Stereoselective Dearomative [3 + 2] Cycloaddition of Nitrobenzofurans



You and colleagues have developed a method for the straightforward construction of tetrahydrofurobenzofurans, core structures of a series of natural products and biologically active compounds, via palladium-catalyzed dearomative [3 + 2] cycloaddition reactions. Good to excellent diastereo- and enantioselectivities with broad substrate scope and high functional-group compatibility were enabled via fine-tuning of chiral PHOX ligands. In addition, this method could also provide dearomatized products with vicinal chiral quaternary carbon centers, a general challenge in synthetic chemistry.

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HIGHLIGHTS

High diastereo- and enantioselectivity enabled by a fine-tuned palladium catalyst

Direct construction of tetrahydrofurobenzofurans via dearomatization reactions

Straightforward construction of vicinal chiral quaternary carbon centers

Cheng et al., Chem 3, 428–436
September 14, 2017
http://dx.doi.org/10.1016/j.chempr.2017.06.015

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Palladium-Catalyzed Highly Stereoselective Dearomative [3 + 2] Cycloaddition of Nitrobenzofurans

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SUMMARY

Stereoselective construction of highly functionalized heterocyclic molecules is an ongoing concern for the chemical community. Among the various strategies developed with this goal, catalytic asymmetric dearomatization, an attractive method for constructing cyclic molecules with multiple stereocenters from readily available aromatic compounds, has received extensive attention in recent years. Here, we report a highly stereoselective construction of tetrahydrofurobenzofurans and tetrahydrofurobenzothiophenes via palladium-catalyzed dearomative [3 + 2] cycloaddition of nitrobenzofurans and nitrobenzothiophenes, respectively. Good to excellent yields (63%–92%), diastereoselectivity (13/1 → >20/1 dr), and enantioselectivity (75%–95% ee) were obtained, leading to products with vicinal stereogenic carbon centers. The reaction features wide substrate scope and diverse transformations of the products.

INTRODUCTION

Tetrahydrofurobenzofuran occurs as a well-known structural core for many natural products isolated from herbal plants (Figure 1).[1–5] In recent years, modification of this unique structure has been implemented to obtain more pharmaceutically relevant compounds.[6–9] However, to date, most synthetic strategies for the construction of tetrahydrofurobenzofuran, especially those bearing continuous chiral carbon stereogenic centers, have been based on stepwise ring-closing processes.[6–8] Therefore, a convenient one-step construction of this tricyclic ring system appears to be more attractive.

Palladium-catalyzed formal [3 + 2] cycloaddition reaction[10–12] between electron-deficient alkenes and epoxybutenes[13] is a powerful and atom-economic tool for the synthesis of substituted tetrahydrofurans.[14–21] Unfortunately, control of the enantioselectivity and diastereoselectivity of this kind of reaction remains challenging because of the long distance between the reactive site and the chiral catalyst in the stereoselectivity-determining transition state.[22] Limited successful examples using specific substrates have been reported.[20,23–27] To figure out a more general methodology for highly stereoselective [3 + 2] ring formation reactions is still urgent.

The catalytic asymmetric dearomatization (CADA) reaction plays a significant role in the synthesis of complex organic compounds by disruption of structurally simple arenes.[28–31] Dearomatization of electron-rich arenes such as indole, pyrrole, phenol, or naphthol usually relies on their inherent nucleophilicity.[32–55] By turning these electron-rich arenes into electrophiles, which can be done by decorating an electron-withdrawing group on the arene, novel types of reactions are expected.

The Bigger Picture

There has been an increasing demand for chiral compounds, which find wide applications in areas of biological science and pharmaceuticals because of the different performance of the two enantiomers in living organisms. Asymmetric catalysis appears to be the most productive method among chiral technologies for access to enantiopure compounds. In this regard, catalytic asymmetric dearomatization has emerged as a highly efficient strategy for the construction of complex chiral molecules from planar aromatic compounds. Tetrahydrofurobenzofurans are the core structures of many biologically active natural products and pharmaceuticals. Thus, developing a new method for the rapid construction of these structures is particularly attractive. Here, we report a highly stereoselective construction of tetrahydrofurobenzofurans via palladium-catalyzed dearomative [3 + 2] cycloaddition of nitrobenzofurans.

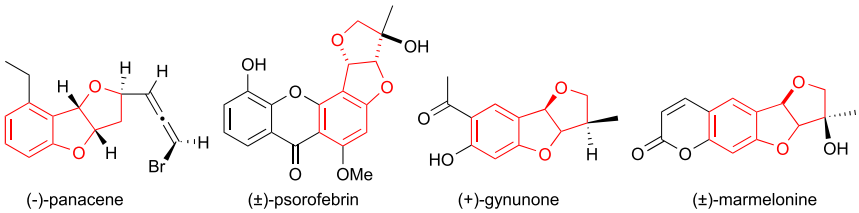

Figure 1. Selected Natural Products with the Core Structure of Tetrahydrofurobenzofuran

Interestingly, merging dearomatization of polarity-inversed benzofurans with catalytic [3 + 2] cycloaddition reaction leads to direct construction of tetrahydrofurobenzofurans. Undoubtedly, these reactions have to confront the challenge of breaking aromaticity.[56–58] Here, we report a highly stereoselective palladium-catalyzed dearomative [3 + 2] cycloaddition of nitrobenzofurans and nitrobenzothiophenes.[53,59–64]

RESULTS AND DISCUSSION

We initiated our studies with 2-nitrobenzofuran **1a** as the substrate, given the ready availability and diverse transformation of the nitro group. When **1a** was mixed with simple epoxybutene **2a** under the catalysis of chiral palladium catalyst, to our disappointment, no reaction occurred with either the Trost ligand **L1** or the Feringa ligand **L2** (Table 1, entries 1 and 2). Then we turned our attention to phosphinooxazoline (PHOX) ligands, another type of ligand often used in asymmetric allylic substitution reactions.[65–67] Gratifyingly, when **L3** was used, dearomatized product **3aa** was obtained with moderate results (65% yield, 5.9/1 dr, 53% ee; Table 1, entry 3). To realize full conversion of substrate **1a**, we screened several additives and found Cs_2CO_3 to be the best (see Table 1, entry 4, and Table S1 for details). Further screening of the conditions proved that this reaction should be performed in toluene at room temperature, although only moderate selectivity was obtained (see Table 1, entry 5, and Table S1 for details).

Next, we focused on screening PHOX ligands with different skeletons or substituents (see Tables 1 and S2 for all details).[68–74] Although comparable reactivity and enantioselectivity were obtained for **L3** and **L4**, planar chirality on the ligands had a detrimental influence on diastereoselectivity (Table 1, entries 5 and 6). After investigation of the substituents on the oxazoline ring, we found that the *tert*-butyl group on the chiral center of the ligands had the highest dr value, albeit with moderate enantioselectivity (Table 1, entries 6–8). Next, the chemical environment around the phosphine center was adjusted via modification of the phenyl rings (**L7**–**L12**). These results showed that more electron-withdrawing and sterically bulky groups on the phenyl ring resulted in better enantioselectivity (Table 1, entries 9–14). We noted that a severely electron-deficient phosphine center might cause weak binding to palladium, leading to low conversion of substrate **1a** (Table 1, entry 14). Finally, ligand **L11** was found to be the best.

With the optimized reaction conditions (5 mol % Pd_2dba_3, 11 mol % (*S*)-**L11**, 1 equiv of **1a**, 2 equiv of **2a**, 1 equiv of Cs_2CO_3 in toluene [0.1 M] at room temperature) in hand, we further explored the scope of the substrate. To our delight, nitrobenzofurans with different steric and electronic constraints underwent dearomatization smoothly (Table 2; see also Figures S1–S79 and S106–S124). For instance, substrates bearing varied substituents at the 5 position (Me, MeO, ^{t}Bu, Ph, F, Cl, Br, CO_2Me, NO_2) provided **3ba**–**3ja** with good yields (73%–93%) and excellent diastereoselectivity (>20/1 dr) and enantioselectivity (87%–94% ee) (Table 2, entries 2–10). Notably,

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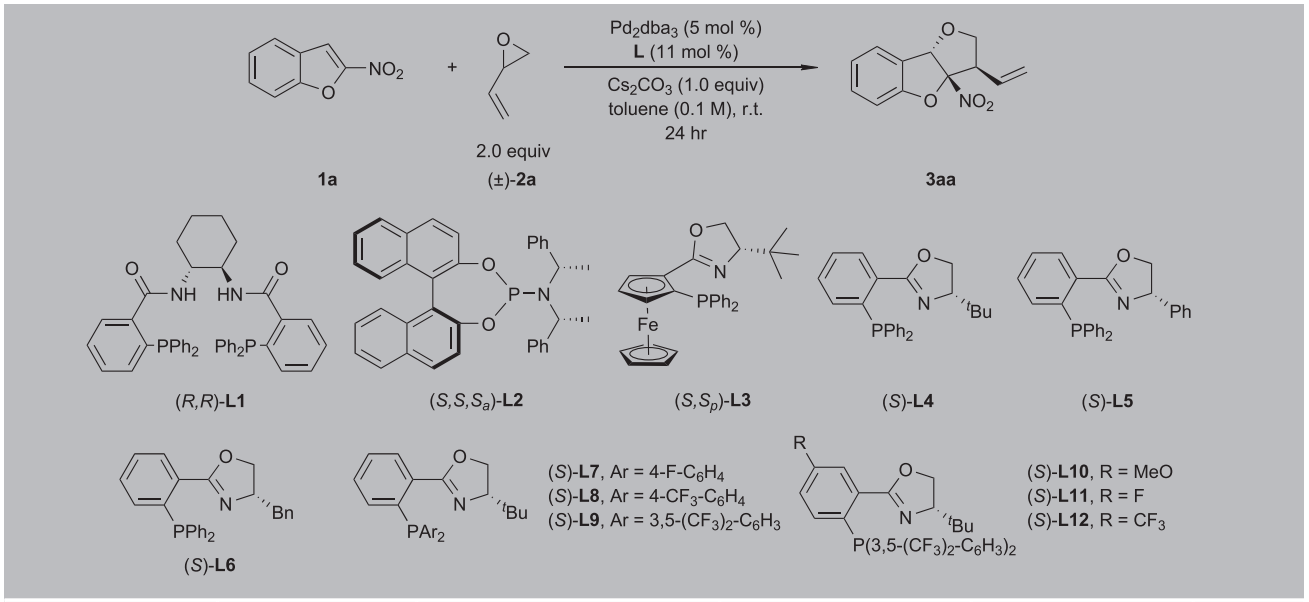
http://dx.doi.org/10.1016/j.chempr.2017.06.015

Table 1. Ligand Investigation for Dearomatization of Nitrobenzofuran 1a



Entry	L	Conversion (%)[a]	Yield (%)[b]	dr[a]	ee (%)[c]
1[d]	L1	<5	0	ND	ND
2[d]	L2[e]	<5	0	ND	ND
3[d]	L3	78	65	5.9/1	53
4[f]	L3	>95	73	6.7/1	62
5	L3	>95	78	6.9/1	62
6	L4	>95	83	18.8/1	68
7	L5	>95	42	9.1/1	33
8	L6	>95	82	11.1/1	60
9	L7	>95	87	14.0/1	72
10	L8	>95	87	>20/1	77
11	L9	>95	75	18.0/1	84
12	L10	>95	80	14.2/1	84
13	L11	>95	82	>20/1	85
14	L12	>95	50	>20/1	86

Reaction conditions: 5 mol % Pd_2dba_3, 11 mol % **L**, 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 0.1 mmol of Cs_2CO_3 in toluene (1 mL) in a sealed tube at room temperature. ND, not detected. See also Tables S1 and S2.

[a]Determined by ^1H NMR of the crude reaction mixture with CH_2Br_2 as internal standard.

[b]Isolated yield of **3aa** with both diastereoisomers.

[c]Determined by high-performance liquid chromatography (HPLC) analysis of the major diastereoisomer.

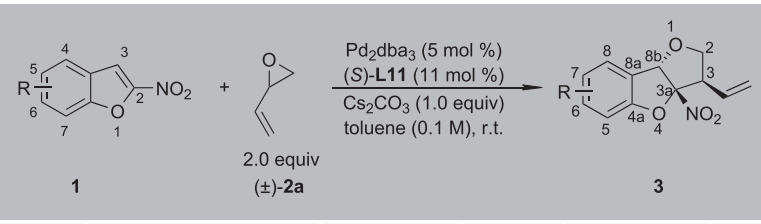
[d]Conducted at 50°C without Cs_2CO_3.

[e]22 mol % **L2** was used.

[f]Conducted at 50°C.

1i with an ester group and **1j** with a nitro group were tolerated, indicating a broad scope of this reaction. Furthermore, benzofurans with substituent at the 6 or 7 position bearing groups with varied electronic properties (6-MeO, 6-Br, 6-Ph, 6-phenylethynyl, 7-MeO, 7-Me, 7-allyl) were converted successfully in good to excellent yields and selectivity (Table 2, entries 11–17). Alkene and alkyne were also integrated under these reaction conditions (Table 2, entries 14 and 17). To our surprise, most halides (Table 2, entries 6–8, 12, and 18–19), and the even more reactive

Table 2. Substrate Scope of Nitrobenzofuran



Entry	1 (R)	Time (hr)	3	Yield (%)[a]	ee (%)[b]
1	**1a** (H)	24	**3aa**	82 (75)[c]	85 (85)[c]
2	**1b** (5-Me)	32	**3ba**	80	93
3	**1c** (5-MeO)	20	**3ca**	74	92
4	**1d** (5-^{t}Bu)	32	**3da**	73	94
5	**1e** (5-Ph)	24	**3ea**	74	94
6	**1f** (5-F)	20	**3fa**	82	90
7	**1g** (5-Cl)	30	**3ga**	84	90
8	**1h** (5-Br)	7	**3ha**	79	92
9	**1i** (5-CO_2Me)	7	**3ia**	93	88
10	**1j** (5-NO_2)	12	**3ja**	82	87
11[d]	**1k** (6-MeO)	48	**3ka**	63	86
12[e]	**1l** (6-Br)	7	**3la**	90	83
13	**1m** (6-Ph)	20	**3ma**	83	82
14	**1n** (6-phenylethynyl)	4	**3na**	92	85
15	**1o** (7-MeO)	24	**3oa**	85	91
16	**1p** (7-Me)	32	**3pa**	79	87
17	**1q** (7-allyl)	12	**3qa**	79	91
18[f]	**1r** (4-F)	20	**3ra**	88	75
19	**1s** (5,7-Cl_2)	4	**3sa**	85	92

Reaction conditions: 5 mol % Pd_2dba_3, 11 mol % (*S*)-**L11**, 0.2 mmol of **1**, 0.4 mmol of **2a**, and 0.2 mmol of Cs_2CO_3 in toluene (2 mL) in a sealed tube at room temperature. All dr > 20/1 except where otherwise noted.

[a]Isolated yield of **3** with both diastereoisomers.

[b]Determined by HPLC analysis of the major diastereoisomer.

[c]2 mmol of **1a** was used.

[d]dr = 14/1.

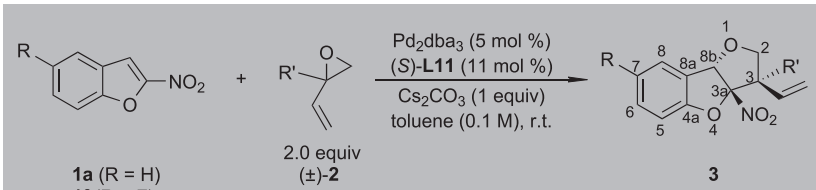
[e]dr = 16/1.

[f]dr = 13/1.

bromide group, survived under this palladium-catalyzed process, which might be attributed to the electronic deficiency of the metal center, although 4-F-substituted benzofuran **1r** displayed moderate selective control. In addition, the absolute configuration of **3fa** was determined as 3*R*,3a*S*,8b*S* by X-ray crystallographic analysis of a single crystal of the enantiopure sample (see also Figure S136).

We also applied this reaction to different substituted vinyl epoxides to further demonstrate the generality of this method (Table 3; see also Figures S84–S97 and S127–S132). Interestingly, compared with 2-vinyl-oxirane **2a**, various substituted vinyl-oxirane substrates showed better selectivity (>20/1 dr, 85%–95% ee). Methyl, phenyl, and substituted phenyl groups with various electronic properties were all endured, resulting in products bearing vicinal quaternary carbon centers. At the same time, the absolute configuration of **3fb** was determined as 3*R*,3a*S*,8b*S* by

Table 3. Substrate Scope of Substituted Epoxybutene



Entry	2 (R′)	Time (hr)	3	Yield (%)[a]	ee (%)[b]
1	**2a** (H)	24	**3aa**	82	85
2	**2b** (Me)	24	**3ab**	74	87
3	**2c** (Ph)	18	**3ac**	77	92
4	**2d** (4-F-C_6H_4)	12	**3ad**	91	94
5	**2e** (4-Ph-C_6H_4)	20	**3ae**	61	95
6	**2f** (3-MeO-C_6H_4)	24	**3af**	70	93
7[c]	**2b** (Me)	18	**3fb**	92	85

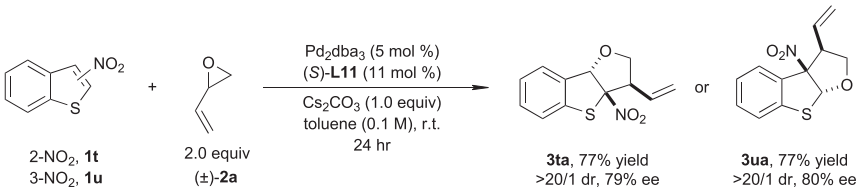
Reaction conditions: 5 mol % Pd_2dba_3, 11 mol % (*S*)-**L11**, 0.2 mmol of **1a**, 0.4 mmol of **2**, and 0.2 mmol of Cs_2CO_3 in toluene (2 mL) in a sealed tube at room temperature.
[a]Isolated yield of **3** with both diastereoisomers.
[b]Determined by HPLC analysis of the major diastereoisomer.
[c]0.2 mmol of **1f** was used.

X-ray crystallographic analysis of a single crystal of the enantiopure sample (see also Figure S137).

Interestingly, this method could be extended to the dearomatization of nitrobenzothiophene without any modification of the reaction conditions (Scheme 1; see also Figures S80–S83, S125, and S126). Both 2-nitrobenzothiophene and 3-nitrobenzothiophene underwent the [3 + 2] dearomative cycloaddition with vinyl-oxirane **2a** smoothly in reasonable yields, and diastereo- and enantioselectivity despite the presence of a sulfur atom, a potentially harmful ligating center for many metals.[75]

To our delight, when 2 mmol of **1a** was used in this reaction, 75% yield of **3aa** was obtained without erosion of the enantiomeric excess value (Table 2, entry 1). Furthermore, several transformations of the products were carried out to show the potential application of this method. When product **3aa** was used under the conditions of the cross-metathesis process with methyl acrylate, **4** was isolated in 88% yield and 82% ee (Scheme 2, equation 1; see also Figures S98, S99, and S133). The nitro group could be easily eliminated through radical reduction by Bu_3SnH in 1 hr (Scheme 2, equation 2; see also Figures S100, S101, and S134). In addition, the bromide group in **3ha** could be readily transformed into an aryl group via the Suzuki-Miyaura cross-coupling reaction; no stereocenters were influenced (Scheme 2, equation 3; see also Figures S102, S103, and S135).

A plausible catalytic cycle was proposed for this highly stereoselective dearomatization reaction (Scheme 3A). Coordination and oxidative addition of a palladium catalyst to the epoxybutene **2a** lead to ring-opened intermediate **B**. A catalyst-controlled dearomative addition of the alcohol anion with a pending π-allylpalladium complex to substrate **1a** could deliver **C**. The following quick cyclization affords the desired product **3aa**. A plausible model for the stereocontrol of the cycloaddition process was also postulated according to the report by Kollmar et al.[76,77] (Scheme 3B). The reaction occurs in the smallest sector divided according to the steric effect of



Scheme 1. Dearomatization of Nitrobenzothiophenes

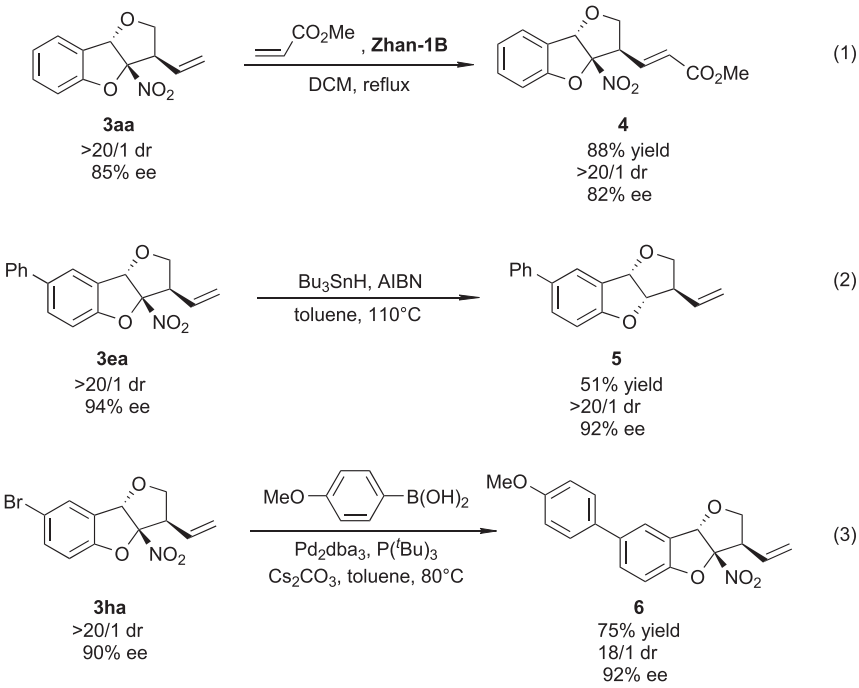
the PHOX ligand. The configuration of the resulting product was in accordance with that of the major product.

In summary, we have developed a method for the synthesis of tetrahydrofurobenzofurans with high stereoselectivity by dearomatization of nitrobenzofurans via palladium-catalyzed asymmetric formal [3 + 2] cycloaddition reaction. Fine-tuning of the electronic and steric characteristic of PHOX ligands contributed crucially to the success of this reaction. The wide scope for both substrates and easily transformable functional groups on the products make this methodology potentially useful for organic synthesis and medicinal chemistry. Further investigation of the mechanistic details and application of this method to other heteroarenes for the construction of different kinds of interesting fused-ring systems are ongoing in our lab.

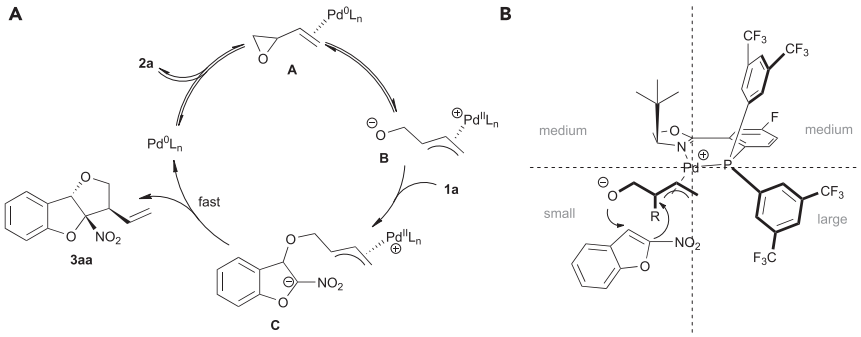
EXPERIMENTAL PROCEDURES

Representative Procedure for Catalytic Asymmetric Dearomatization of Nitrobenzofurans and Characterization of the Products

A flame-dried sealed tube was cooled to room temperature and filled with argon. To this flask were added Pd_2dba_3 (9.2 mg, 0.01 mmol, 5 mol %), (*S*)-**L11** (14.9 mg, 11 mol %), and toluene (1 mL). The mixture was stirred at room temperature for 30 min before the addition of **1a** (0.2 mmol, 1.0 equiv), Cs_2CO_3 (0.2 mmol, 1.0 equiv),



Scheme 2. Transformations of Products



Scheme 3. Mechanistic Proposal

A plausible catalytic cycle (A) and a model for the stereocontrol of the cycloaddition process (B).

2a (0.4 mmol, 2.0 equiv), and toluene (1 mL). The reaction was sealed with a Teflon plug and stirred at room temperature. After completion (monitored by thin-layer chromatography), the mixture was filtered through celite. The solution was concentrated by rotary evaporation. The diastereomeric ratio was determined by ^{1}H NMR of the crude reaction mixture. Then the residue was purified by silica gel column chromatography (PE/EtOAc = 50/1) to afford the desired product **3aa**. Pale-yellow solid, m.p. = 56.1°C–57.6°C, 38.0 mg, 82% yield, >20/1 dr, 85% ee (Agilent 1260 Infinity Analytical SFC system Daicel Chiralcel OJ-H [0.46 × 15 cm], CO_2/2-propanol = 95/5, v = 1.3 mL min^{-1}, λ = 214 nm, t(major) = min, t(minor) = min), $[\alpha]_D^{25}$ = −44.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 7.2, 0.4 Hz, 1H), 7.39 (td, J = 8.0, 1.2 Hz, 1H), 7.10 (td, J = 7.6, 0.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 5.98 (s, 1H), 5.77 (ddd, J = 16.8, 10.0, 8.4 Hz, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.8 Hz, 1H), 4.18–4.10 (m, 2H), 3.37 (dd, J = 14.8, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 131.9, 129.6, 126.2, 125.3, 123.7, 123.3, 122.2, 111.2, 87.9, 73.0, 55.4. IR (thin film): ν_{max} (cm^{-1}) = 2998, 2958, 2926, 2897, 2873, 1618, 1596, 1561, 1466, 1368, 1354, 1328, 1284, 1235, 1210, 1187, 1144, 1118, 1090, 1050, 1011, 937, 818, 792, 753, 728, 713, 684. HRMS (EI) calcd for $C_{12}H_{11}NO_4$ $[M]^+$: 233.0688; found: 233.0685.

ACCESSION NUMBERS

The structures of products **3fa** and **3fb** in this article have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC: 1552486 and 1552485, respectively.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 137 figures, 4 tables, and 2 data files and can be found with this article online at http://dx.doi.org/10.1016/j.chempr.2017.06.015.

AUTHOR CONTRIBUTIONS

Methodology, Q.C. and S.-L.Y.; Investigation, Q.C., H.-J.Z., and W.-J.Y.; Writing – Original Draft, Q.C.; Writing – Review & Editing, S.-L.Y.; Supervision, S.-L.Y.

ACKNOWLEDGMENTS

We thank the National Basic Research Program of China from the Ministry of Science and Technology (2015CB856600 and 2016YFA0202900), the National Natural Science Foundation of China (21332009 and 21421091), and the Chinese Academy of Sciences (XDB20000000 and QYZDY-SSW-SLH012) for generous financial support.

Received: April 18, 2017
Revised: June 9, 2017
Accepted: June 21, 2017
Published: September 14, 2017

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