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# Design and Synthesis of Planar-Chiral Oxazole−Pyridine *N,N*-Ligands: Application in Palladium-Catalyzed Asymmetric Acetoxylative Cyclization

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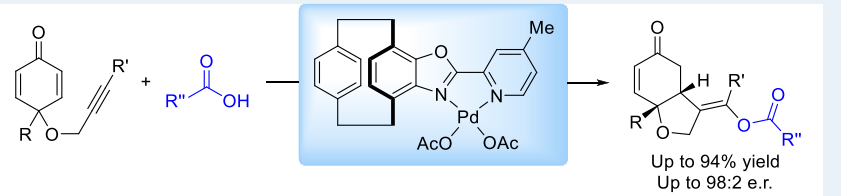


- *Newly designed planar-chiral oxazole-pyridine ligands*
- *Broad scope of carboxylic acids*
- *First highly enantioselective acetoxylative cyclization of alkyne-tethered cyclohexadienones*

**ABSTRACT:** The development of chiral ligands to fine-tune the stereocontrol has been recognized as a crucial pillar of asymmetric catalysis. In contrast to the well-developed chiral pyridine−pyridine-type and pyridine−oxazoline-type ligands, chiral oxazole−pyridine-type ligands have rarely been exploited. In this study, a class of [2.2]paracyclophane-based planar-chiral oxazole−pyridine *N,N*-ligands have been designed and synthesized. These ligands presented a superior performance in the enantioselective palladium-catalyzed asymmetric acetoxylative cyclization of alkyne-tethered cyclohexadienones, providing the chiral *cis*-hydrobenzofurans that belong to bioactive molecules with potent NF-κB inhibition in broad substrate scope. These results demonstrated the promising potential of the chiral oxazole−pyridine ligands as an efficient type of *N,N*-ligand scaffold.

**KEYWORDS:** *oxazole−pyridine ligands, planar chirality, cis-hydrobenzofurans, acetoxylative cyclization, asymmetric catalysis*



Asymmetric transition-metal catalysis stands at the forefront of modern synthetic chemistry and has been a powerful approach to the preparation of enantiomerically pure molecules.[1] The development of novel chiral ligands to tune the reactivities and stereoselectivities has been a key aspect in asymmetric catalysis.[2] Owing to easy modification and high stability, chiral nitrogen-containing ligands have held a prominent position in modern reactions.[2a,3] Among them, chiral *N,N*-ligands containing a pyridine moiety constitute one of the most widely exploited ligands.[2a,3a−d] To date, chiral pyridine-containing *N,N*-ligands mainly involve chiral pyridine−pyridine-type ligands and chiral pyridine−oxazoline-type ligands (Scheme 1a). In 1984, Botteghi and co-workers developed chiral monoalkyl-substituted 2,2′-bipyridine ligands.[4] Inspired by this pioneering research, a diverse range of pyridine−pyridine-type ligands, including central chiral bipyridine ligands,[5] axially chiral bipyridine ligands,[6] and planar chiral bipyridine ligands,[7] have been successfully developed in the last four decades. Since the first design of chiral pyridine−oxazoline ligands by Brunner's group in 1986,[8] myriad variants of pyridine−oxazoline-type ligands and structurally related pyridine−oxazoline-type ligands have been designed and been widely prevalent for utilization in asymmetric catalysis.[3d,9−16] Despite the enormous progress in the development of chiral *N,N*-ligands containing a pyridine moiety, the chiral coordinating groups mostly concentrate on the chiral pyridine moiety and the chiral oxazoline moiety. Among the various types of aza-heterocycle coordinating moieties, oxazoles have been a pivotal class of coordinating moieties and oxazole−pyridine-type ligands have been applied to some transition-metal-catalyzed reactions.[17]

To the best of our knowledge, chiral oxazole−pyridine-type ligands have been unknown. The major challenge is the difficulty of introducing the chiral element into the oxazole−pyridine skeleton (Scheme 1a).

The electronic properties of coordinating groups in ligands can obviously influence the reactions. The nitrogen atom of the benzoxazole moiety is relatively electron-poor in comparison with the nitrogen atom of the oxazoline moiety and approximately equal to the nitrogen atom of the pyridine

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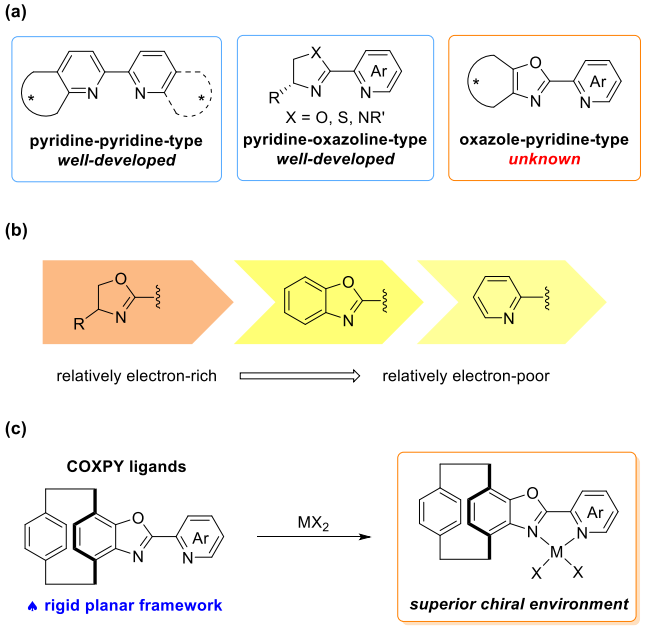
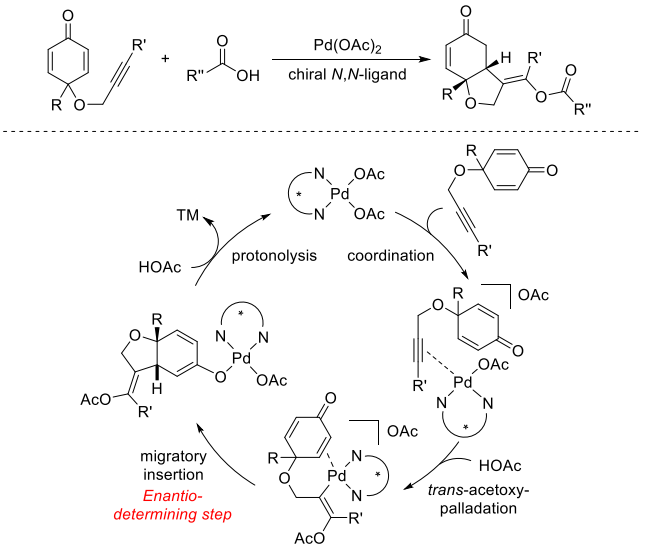
**Scheme 1. Design of Planar-Chiral Oxazole−Pyridine *N,N*-Ligands; (a) Chiral *N,N*-Ligands Containing a Pyridine Moiety; (b) Electronic Properties of Nitrogen Atoms in Aza-Heterocycles; (c) Design of Planar-Chiral Oxazole−Pyridine *N,N*-Ligands**




**Scheme 2. Palladium-Catalyzed Asymmetric Acetoxylative Cyclization of Alkyne-Tethered Cyclohexadienones**




| Group | Ligand | Carboxylic Acids | E.r. |
|---|---|---|---|
| Harned | Pyox<br>isoPINDY | HOAc | Up to 54:46<br>Up to 81:19 |
| This work | COXPY | Alkyl and aromatic carboxylic acids | Up to 98:2 |

moiety (Scheme 1b).[17a,18] Owing to the unique electronic nature of the benzoxazole moiety, the development of chiral oxazole−pyridine-type ligands is essentially desirable. Chiral [2.2]paracyclophane has emerged as a privileged type of planar chiral framework and has become a significant toolbox in asymmetric catalysis.[19] Stimulated by the inherent structural features of the [2.2]paracyclophane backbone, we envisaged developing a new type of planar-chiral oxazole−pyridine ligands (abbreviated as COXPY) by displacing the phenyl group of the benzoxazole moiety with a [2.2]paracyclophane backbone to introduce the planar chirality (Scheme 1c). These COXPY ligands have the following advantages: (1) rigid structure and high steric hindrance could form the superior chiral environment; (2) the steric and electronic properties may be fine-tuned by the structure of the pyridine moiety.

Optically active *cis*-hydrobenzofurans are ubiquitous structural motifs in natural products and bioactive molecules.[20] Transition-metal-catalyzed enantioselective cascade reactions of alkyne-tethered cyclohexadienones have been useful and provided access to the rapid construction of structurally diverse chiral *cis*-hydrobenzofurans and considerable attention has been paid to them.[21] In 2013, Harned's group identified an elegant palladium-catalyzed asymmetric acetoxylative cyclization of alkyne-tethered cyclohexadienones, providing the chiral *cis*-hydrobenzofuran products,[22] which exhibit the activity against the NF-κB signaling pathway.[20f] However, this protocol had substantial limitations: low to moderate enantioselectivities were obtained using the chiral pyridine−oxazoline-type ligand (Pyox) and the chiral pyridine−pyridine-type ligand (isoPINDY), the enantioselectivity was remarkably sensitive to structural changes of substrates, and only acetic acid was used as both the reactant and the solvent (Scheme 2). Mechanistically, this asymmetric acetoxylative cyclization involved coordination of the substrate to chiral electrophilic Pd(II) catalyst activating the alkyne for *trans*-acetoxypalladation, migratory insertion of the intramolecular double bond, which could be an enantio-determining step, followed by protonolysis to give the chiral product and regenerate the catalyst (Scheme 2).[23] The limitations might be mainly attributed to inferior induction of chirality and relatively low reactivity of palladium catalysts (more electron-rich *N,N*-ligands decrease the electrophilicity). Considering the advantages of the [2.2]paracyclophane-based planar-chiral oxazole−pyridine ligand, we envisioned the application of this ligand to resolve the dilemma. The relatively electron-poor ligand would enhance the reactivity of the chiral palladium(II) catalyst and promote the activation of the alkyne. Moreover, the rigid structure and high steric hindrance of the [2.2]-paracyclophane backbone could facilitate the stereocontrol. Herein, we reported the design and synthesis of novel planar-chiral oxazole−pyridine ligands enabled Pd-catalyzed acetoxylative cyclization of alkyne-tethered cyclohexadienones to afford biologically active *cis*-hydrobenzofurans with high yields and excellent enantioselectivities (Scheme 2), as well as broad substrate scope of carboxylic acids including drug-derived carboxylic acids.

The synthetic approach to chiral COXPY ligands was illustrated in Scheme 3a. A series of diverse COXPY ligands **L1**−**8** were conveniently synthesized from the known chiral ($R_p$)-4-hydroxy-5-amino[2.2]-paracyclophane **1** through two approaches with moderate to good yields. One is condensation reaction with readily available methyl picolinimidate derivatives. The other is the synthesis of the amide with 3-methylpicolinic acid and *p*-toluenesulfonic acid-promoted cyclization (see the Supporting Information for details). To clarify the features of chiral COXPY ligands, the complex (**L4**)Pd(OAc)$_2$ was synthesized and determined by X-ray diffraction analysis.[24] In view of the standard errors in the bond lengths from the crystal structure itself, the difference in length between Pd−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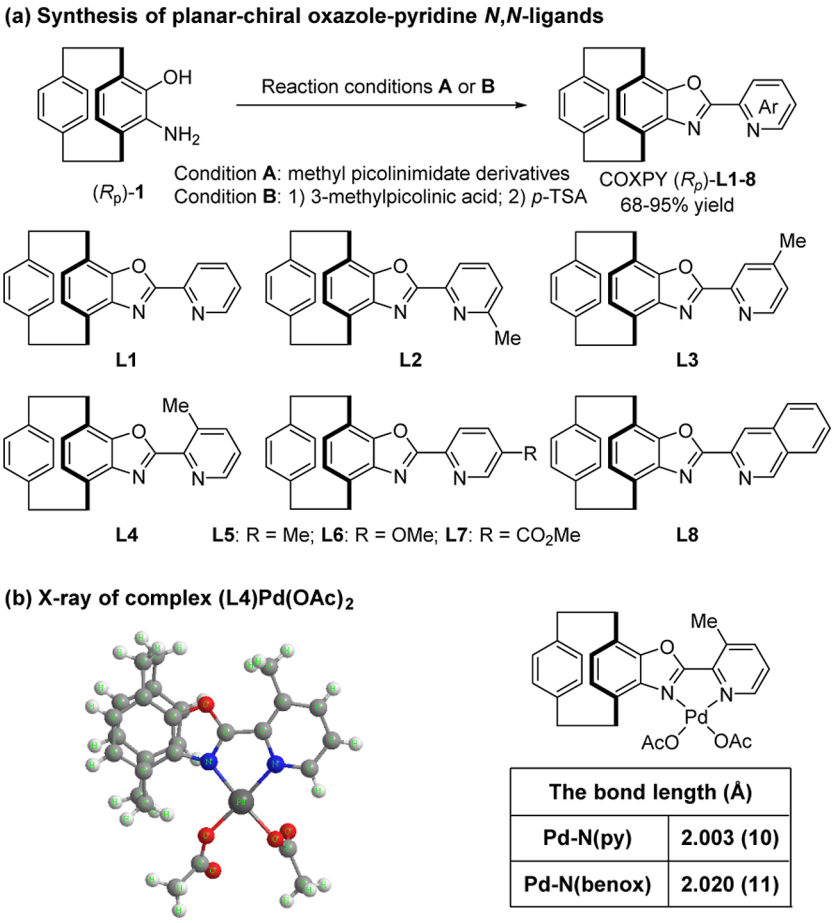
**Scheme 3. Synthesis of Planar-Chiral Oxazole−Pyridine *N*,*N*-Ligands and X-ray of Complex (L4)Pd(OAc)$_2$; (a) Synthesis of Planar-Chiral Oxazole−Pyridine *N*,*N*-Ligands; (b) X-ray of Complex (L4)Pd(OAc)$_2$**




| The bond length (Å) | |
|---|---|
| Pd-N(py) | 2.003 (10) |
| Pd-N(benox) | 2.020 (11) |

N(benzoxazole) bond and Pd−N(pyridine) bond is almost negligible (Scheme 3b), which is consistent with Scheme 1b. This suggests that nitrogen atoms of the two moieties are relatively electron-poor compared with the nitrogen atom of the oxazoline moiety and the interaction between the COXPY ligand and the palladium center is relatively weak. Hence, the palladium(II) catalyst should be more electrophilic for promoting the activation of the alkyne and *trans*-acetoxypalladation step.

With COXPY ligands in hand, we commenced our studies on palladium-catalyzed asymmetric acetoxylative cyclization of alkyne-tethered cyclohexadienones. The original experiment utilized the cyclohexadienone **1a** bearing a phenyl substituent at the terminal of the alkyne and acetic acid **2a** (17 equiv) at 60 °C in the presence of COXPY ($R_p$)-**L1** as the ligand and toluene as the solvent. Satisfyingly, the *cis*-hydrobenzofuran **3aa** was obtained with 95:5 e.r. and 70% yield (Table 1, entry 1). However, palladium black was observed during the reaction. We proposed that the formation of palladium black could be inhibited, and the yield could be further improved under an oxidative atmosphere. Therefore, the effect of oxidants was examined. Notably, the oxidant *p*-benzoquinone (BQ) could effectively elevate the yield to 88%, with the enantioselectivity maintained (entry 5).

Subsequently, the investigation of solvents indicated that *tert*-butyl methyl ether ($^t$BME) could improve the enantiomer ratio to 96:4, regrettably reducing the yield to 76% (entry 9). To gain a satisfactory yield and enantiomer ratio at the same time, the mixed solvent of toluene and $^t$BME was utilized. To our delight, the product **3aa** was produced with 87% yield and 95.5:4.5 e.r. when toluene/$^t$BME was used as the mixed solvent in a volume ratio of 1:1 (entry 10). Next, we evaluated the influence of the amount of **2a** on the reaction. It was found that increasing the amount of acetic acid **2a** would diminish the enantioselectivity of **3aa** (entry 11). Nevertheless, when **2a** was reduced to 12 equiv, the yield was lower (entry 12). Consequently, 17 equiv of **2a** proved to be the best choice. Finally, COXPY ligands with different steric and electronic properties, axially chiral bipyridine ligand **C3-ACBP**,[6a] and commercially available pyridine−oxazoline ligand $^i$**Pr-Pyox** were examined. The methyl group at the C4- or C5-position of the pyridine ring only caused slight variations in yield (entries 14 and 16). The ligand ($R_p$)-**L7** bearing an electron-withdrawing group on the pyridine moiety was detrimental to the yield of **3aa** (entry 18). Using **C3-ACBP** or $^i$**Pr-Pyox** as the chiral ligand, incomplete conversion of the cyclohexadienone **1a** was observed when the reaction time was the same as other ligands (22 h). The product **3aa** was prepared in moderate yield and enantiomer ratio with **C3-ACBP** ligand. However, $^i$**Pr-Pyox** ligand gave the desired product with poor results, which was due to inferior induction of chirality and relatively low reactivity of the palladium catalyst. It turned out that ($R_p$)-**L3** was the best in overall terms (entry 14). High enantioselectivity and isolated yield of **3aa** (0.20 mmol) were achieved (entry 22). Therefore, the optimal reaction conditions were established: using Pd-


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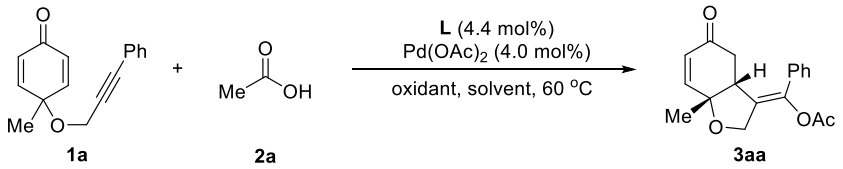
**Table 1. Conditions Optimization**[a]




| entry | oxidant | solvent | L | yield (%)[b] | e.r.[c] |
|---|---|---|---|---|---|
| 1 | | Tol. | **L1** | 70 | 95:5 |
| 2[d] | $O_2$ | Tol. | **L1** | 73 | 95:5 |
| 3[d,e] | $O_2$/$Cu(OTf)_2$ | Tol. | **L1** | 17 | 40.5:59.5 |
| 4 | AgOAc | Tol | **L1** | 58 | 92.5:7.5 |
| 5 | BQ | Tol | **L1** | 88 | 94.5:5.5 |
| 6 | BQ | DCE | **L1** | 80 | 86.5:13.5 |
| 7 | BQ | EA | **L1** | 83 | 95:5 |
| 8 | BQ | THF | **L1** | 65 | 96:4 |
| 9 | BQ | $^t$BME | **L1** | 76 | 96:4 |
| 10[f] | BQ | Tol./$^t$BME | **L1** | 87 | 95.5:4.5 |
| 11[f,g] | BQ | Tol./$^t$BME | **L1** | 91 | 86:14 |
| 12[f,h] | BQ | Tol./$^t$BME | **L1** | 71 | 95.5:4.5 |
| 13[f] | BQ | Tol./$^t$BME | **L2** | complex | |
| 14[f] | BQ | Tol./$^t$BME | **L3** | 93 | 95.5:4.5 |
| 15[f] | BQ | Tol./$^t$BME | **L4** | 92 | 90.5:9.5 |
| 16[f] | BQ | Tol./$^t$BME | **L5** | 86 | 95.5:4.5 |
| 17[f] | BQ | Tol./$^t$BME | **L6** | 84 | 94.5:5.5 |
| 18[f] | BQ | Tol./$^t$BME | **L7** | 47 | 96:4 |
| 19[f] | BQ | Tol./$^t$BME | **L8** | 91 | 95:5 |
| 20[f,i] | BQ | Tol./$^t$BME | **C3-ACBP** | 59 | 80:20 |
| 21[f,j] | BQ | Tol./$^t$BME | **$^i$Pr-Pyox** | 28 | 60.5:39.5 |
| 22[f,k] | BQ | Tol./$^t$BME | **L3** | 89 (84)[l] | 95.5:4.5 |

[a]Reaction conditions: **1a** (0.10 mmol), acetic acid **2a** (0.1 mL, 1.7 mmol), $Pd(OAc)_2$ (4.0 mol %), **L** (4.4 mol %), oxidant (30 mol %), solvent (0.9 mL), 60 °C, 22−27 h. [b]Yield was measured by analysis of $^1$H NMR spectra, using 1,3,5-trimethoxy-benzene as the internal standard. [c]Determined by chiral HPLC. [d]$O_2$ (1 atm). [e]$Cu(OTf)_2$ (4.0 mol %), **L1** (8.8 mol %). [f]Tol./$^t$BME (1:1). [g]Acetic acid **2a** (0.5 mL, 8.5 mmol), Tol./$^t$BME (0.25 mL/0.25 mL). [h]Acetic acid **2a** (69 $\mu$L, 1.2 mmol), Tol./$^t$BME (0.5 mL/0.5 mL). [i]($R_a$,*S*,*S*)-**C3-ACBP** (4.4 mol %). [j](*S*)-$^i$**Pr-Pyox** (4.4 mol %). [k]The reaction with 0.20 mmol scale. [l]Isolated yield.

$(OAc)_2$/COXPY ($R_p$)-**L3** as the catalyst, BQ as the oxidant, and toluene/$^t$BME (1:1) as the solvent to perform the reaction at 60 °C.

With the optimized conditions in hand, the substrate scope of alkyne-tethered cyclohexadienones **1** was investigated. As summarized in Scheme 4, *ortho*-, *meta*-, and *para*-substituted aromatic rings could be successfully applied to the reaction and provide the *cis*-hydrobenzofurans **3** with good to excellent enantiomer ratios (**3ba**−**3da**). A myriad of electron-donating or electron-withdrawing functional groups at the *para* position of the phenyl ring were accommodated (**3ea**−**3ia**), whereas the reactivities were low for **3ha** and **3ia** bearing electron-withdrawing groups under the standard conditions. Pleasingly, increasing the catalyst loading, the yields were dramatically improved. More importantly, the heteroaryl-substituted alkyne-tethered cyclohexadienone **1k** was suitable for the reaction to afford the desired product **3ka** in 86% yield with 91.5:8.5 e.r. Afterward, various substituents at the prochiral quaternary carbon center of substrates, such as ethyl (**1l**), *n*-propyl (**1m**), *iso*-propyl (**1n**), benzyl (**1p**), and phenyl (**1q**) were well compatible with the reaction conditions. Cyclohexadienones bearing the phenyl at the prochiral quaternary carbon center **1r**−**1t** were also suitable reaction partners, furnishing the corresponding products **3ra**−**3ta** in excellent yields and enantiomer ratios. Of note is that 3,5-dimethylphenyl-substituted alkynes delivered the desired products **3ua** and **3va** in good yields with excellent enantioselectivities. The absolute configuration of **3ga** was assigned as (3a*R*,7a*R*) by X-ray diffraction analysis (see the Supporting Information for details).[25]

To further evaluate the generality and universality of current ligands COXPY enabled asymmetric acetoxylative cyclization, we switched our attention to the scope of carboxylic acids. A plethora of carboxylic acids **2** were favorable cyclization reaction partners, providing the target products with excellent enantioselectivities. The cyclization reaction employing propionic acid **2b** delivered the product **3tb** as a single regioisomer in 80% yield with 97.5:2.5 e.r. Moreover, the secondary alkyl carboxylic acid **2c** proved to be compatible with the reaction, furnishing the product **3tc** in moderate yield and excellent e.r. The reaction could also be extended to aromatic carboxylic acids. For alkyl-substituted alkyne-tethered cyclohexadienones **1w** and **1x**, the asymmetric acetoxylative cyclization conducted smoothly with benzoic acid **2d**. However, when the trimethylsilyl group was substituted on the terminal of the alkyne, the reaction was disordered, and the reaction system was complicated. Notably, some drug-derived aromatic carboxylic acids such as aspirin and probenecid performed successfully, delivering the target products **3tf** and **3tg** in good yields (78 and 92%, respectively) with excellent enantiomer ratios (97:3 e.r.).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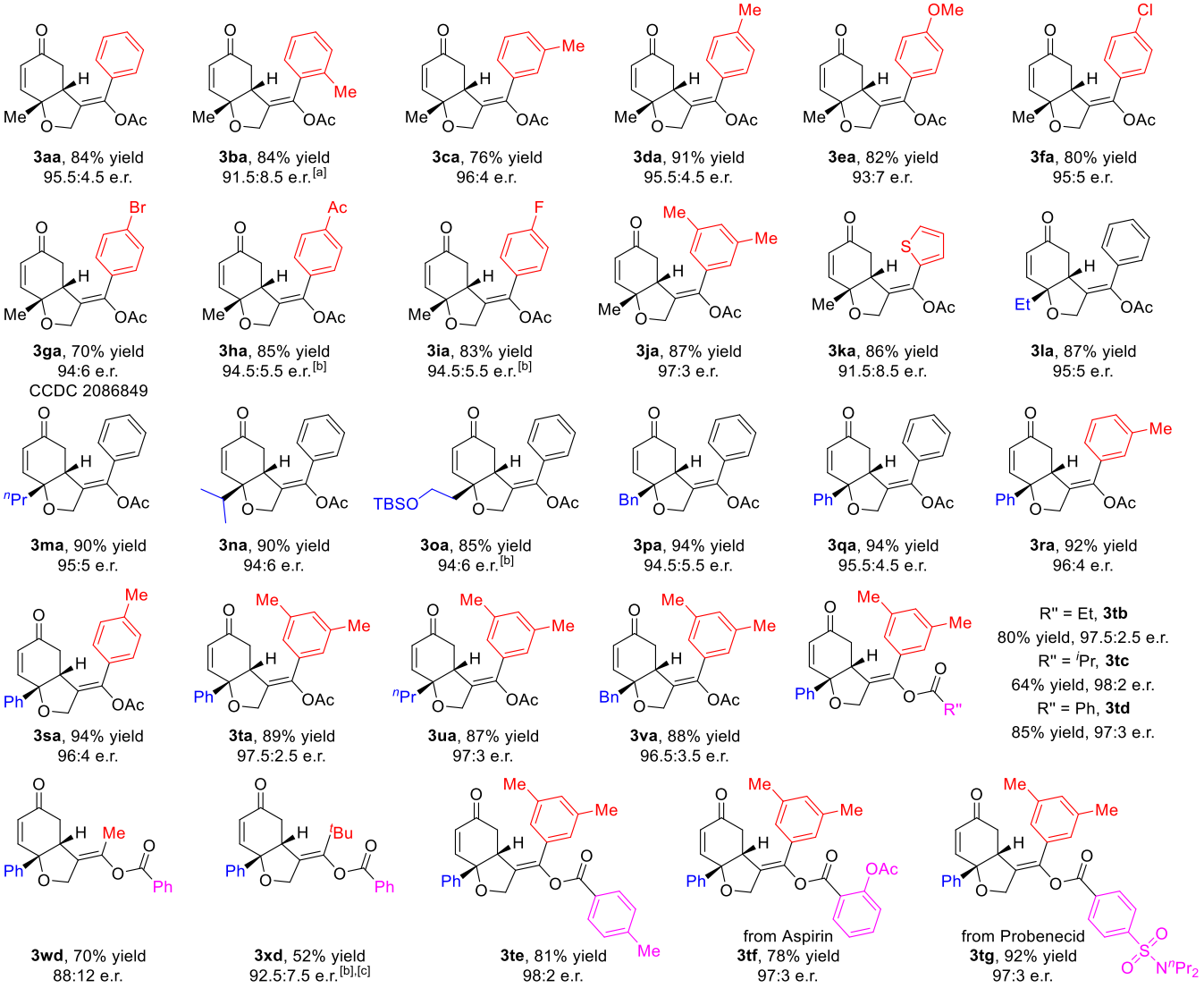
**Scheme 4. Substrate Scope: Alkyne-Tethered Cyclohexadienones 1 and Carboxylic Acids 2**[a]




[a]Reaction conditions for *cis*-hydrobenzofurans **3aa**−**3va**: alkyne-tethered cyclohexadienones **1** (0.20 mmol), acetic acid **2a** (0.2 mL, 3.4 mmol), $Pd(OAc)_2$ (4.0 mol %), ($R_p$)-**L3** (4.4 mol %), BQ (30 mol %), toluene/$^t$BME (0.9 mL/0.9 mL), 60 °C, 22−30 h. Reaction conditions for *cis*-hydrobenzofurans **3tb**−**3tg**: alkyne-tethered cyclohexadienones **1** (0.20 mmol), carboxylic acids **2** (2.0 mmol), $Pd(OAc)_2$ (4.0 mol %), ($R_p$)-**L3** (4.4 mol %), BQ (30 mol %), toluene/$^t$BME (1.0 mL/1.0 mL), 60 °C, 22−50 h. [a] Toluene (1.8 mL). [b] $Pd(OAc)_2$ (8.0 mol %), ($R_p$)-**L3** (8.8 mol %). [c] 80 °C.

To further demonstrate the potential utility of this asymmetric acetoxylative cyclization reaction, the 1.5 mmol scale reaction of **1a** was conducted under the standard conditions, and the excellent yield (85%) and enantiomer ratio (95.5:4.5) were retained (Scheme 5a). Afterward, we performed diverse transformations with the chiral *cis*-hydrobenzofurans **3aa** and **3oa**. Selective hydrogenation of the *α*,*β*-unsaturated carbon−carbon double bond of **3aa** by Pd/C proceeded smoothly, affording the reductive product **4** in 81% yield with 95.5:4.5 e.r. The alcohol **5** was obtained in 86% yield with 10:1 dr under Luche reduction conditions. Recognizing that the enol acetate can be readily converted to the ketone, **3aa** was treated with potassium carbonate in methanol and water, conferring the product **6** in 84% yield with 25:1 dr (Scheme 5b). The absolute configuration of the diketone **6** was assigned as (3*R*,3a*R*,7a*R*) by X-ray diffraction analysis (see the Supporting Information for details).[26] As for the product **3oa**, the TBS group could be removed by tetrabutylammonium fluoride under acidic conditions, and an intramolecular oxa-Michael addition reaction occurred to provide the tricyclic skeleton **7** in 86% yield with 93.5:6.5 e.r. Whereafter, the double bond of **7** was cleft by ozonolysis to give the desirable chiral product **8** in moderate yield without loss of optical purity (Scheme 5c), which is the architecture unit of incarviditone.[20b,e]

Density functional theory calculations were performed to elucidate the reaction mechanism and the origin of enantioselectivity in palladium-catalyzed asymmetric acetoxylative cyclization. The reaction of the cyclohexadienone **1a** with acetic acid **2a** catalyzed by $Pd(OAc)_2$/COXPY ($R_p$)-**L3** was adopted as the model reaction for the mechanistic study (see Supporting Information for computational details). As depicted in Figure 1a, starting from the Pd(II)−acetate complex (**Int0**), the coordination of **1a** forms a more stable species **Int1** (−4.3 kcal/mol) with the alkyne on the *cis* position to the benzoxazole moiety. **Int1** undergoes *trans*-



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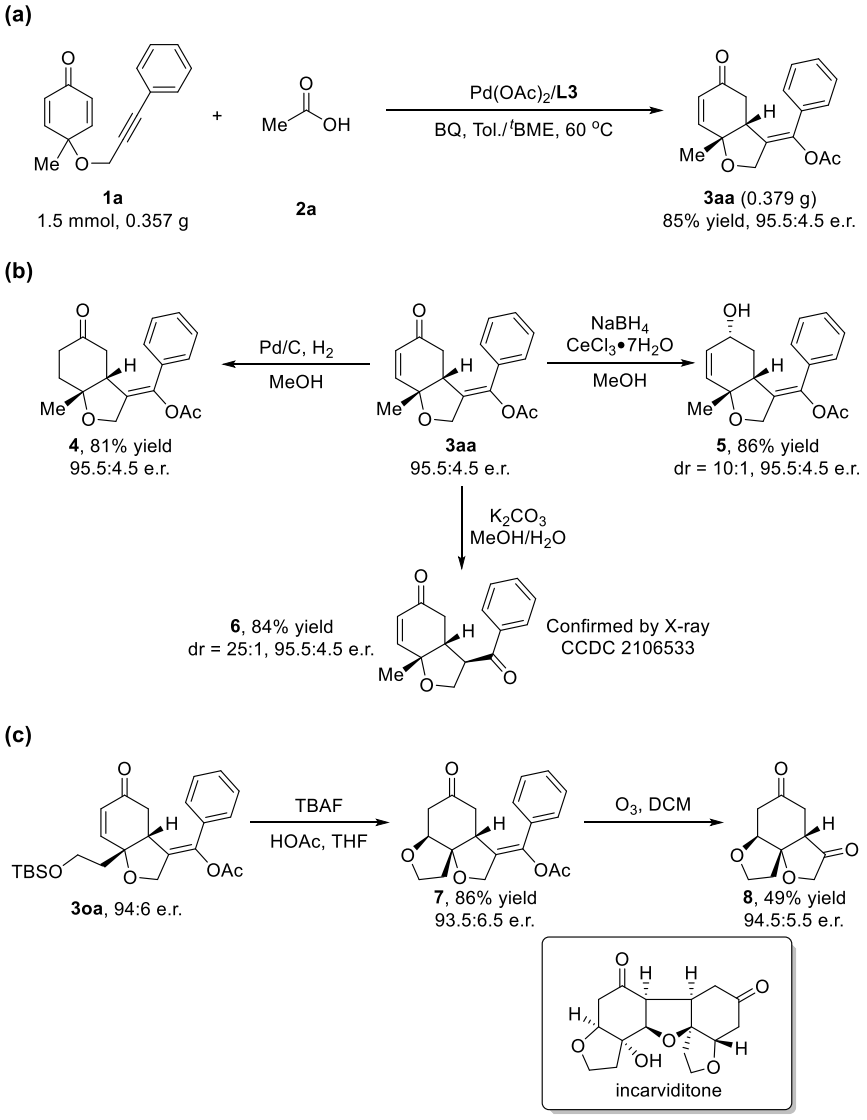
**Scheme 5. Experiment at 1.5 mmol Scale and Synthetic Transformations; (a) 1.5 mmol Scale Experiment; (b) Transformations of the Chiral *cis*-Hydrobenzofuran 3aa; (c) Transformation of the Chiral *cis*-Hydrobenzofuran 3oa**




acetoxypalladation with acetic acid **2a** *via* **TS1** with a barrier of 9.9 kcal/mol relative to **Int1** to afford the vinyl-palladium intermediate **Int2** (−9.8 kcal/mol). After the decoordination of acetic acid **2a**, two diastereomeric transition states (**TS2-*RR*** and **TS2-*SS***) were located for the stereoselective cyclohexadienone insertion into the Pd−C bond, leading to the major and minor configurations, respectively. The calculated results suggest that **TS2-*RR*** is lower in energy than **TS2-*SS*** by 1.2 kcal/mol ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol). A comparison of the optimized structures (Figure 1b) shows that the slightly higher energy of **TS2-*SS*** is presumably due to the steric repulsion between the vinylic phenyl group of the substrate and the nearby benzoxazole moiety of the ligand. Such repulsion deforms the coordination between the benzoxazole moiety and the Pd center. The dihedral angle of C1−C2−N3−Pd in **TS2-*SS*** is 23.1°, larger than that in **TS2-*RR*** (16.1°); thus, the latter possesses a smaller distortion compared with the dihedral angle of C1−C2−N3−Pd in **Int0** (4.9°). As a consequence, the unfavorable repulsive interaction exists in **TS2-*SS***, whereas no such effect is observed in **TS2-*RR***, thus favoring the formation of (3a*R*,7a*R*)-**3aa** over (3a*S*,7a*S*)-**3aa**. Subsequent $\eta^1$ to $\eta^3$ isomerization of the palladium complexes (*via* **TS3-*RR***) and protonolysis (**TS4-*RR***, Figure S5) steps were calculated to be irreversible. Meanwhile, a parallel reaction pathway involving the *trans*-acetoxypalladation occurring at the *cis* position to the pyridine moiety of the ligand contributes to the generation of (3a*R*,7a*R*)-**3aa** as well (see pathway A in Figure S6). Notably, the formation of the ion-pair [**Int0**•**AcO**$^-$] from the initial catalyst Pd(OAc)$_2$/COXPY ($R_p$)-**L3** is endergonic by 22.4 kcal/mol (see Figure S7), and for simplicity, the AcO$^-$ is omitted in the calculation of the reaction pathways.

To demonstrate the universality of COXPY ligands, we applied them to palladium-catalyzed enantioselective addition of arylboronic acids to *N*-sulfonylimines.[27] Gratifyingly, the ligand **L7** is efficient for asymmetric arylation of the aldimine **9** with arylboronic acids to deliver chiral diarylmethylamines in high yields and enantioselectivities.

Moreover, the ligand **L7** also exhibited superior performance in the asymmetric addition of the ketimine **12** with arylboronic acids at lower temperature (30 °C), giving chiral quaternary carbon-containing sulfamidates in excellent yields and enantioselectivities (Scheme 6).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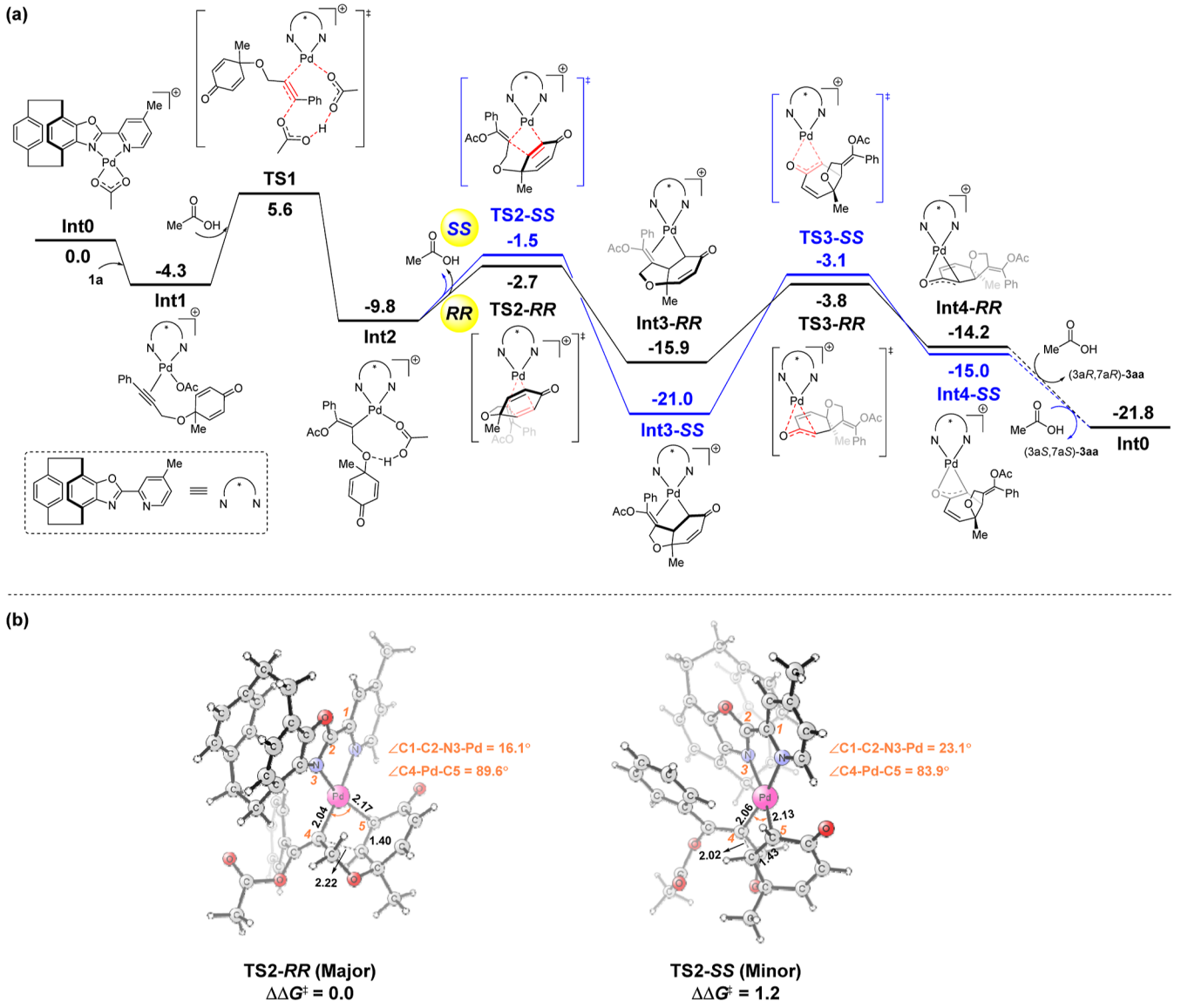
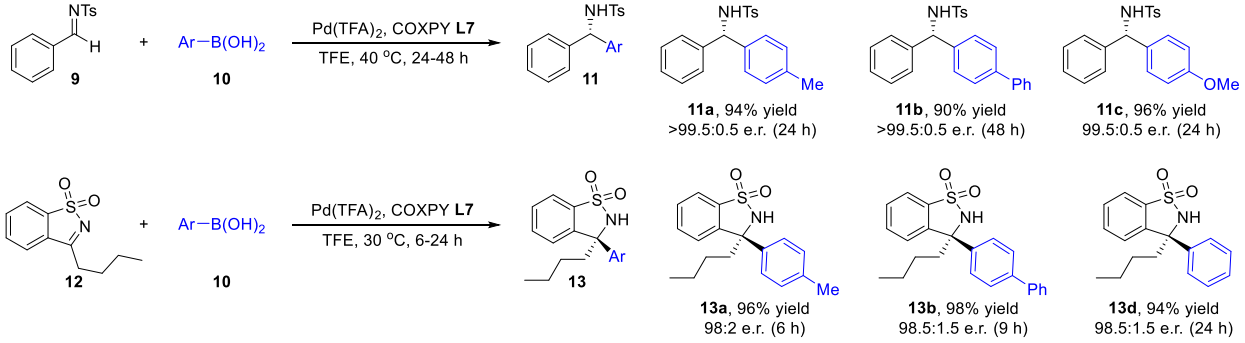



**Figure 1.** (a) Gibbs free energy profile (kcal/mol) at the SMD-B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/6-31g(d,p)-SDD(Pd) for the palladium-catalyzed asymmetric acetoxylative cyclization. (b) The optimized geometries of the transition states in the enantio-determining step.

**Scheme 6. Palladium-Catalyzed Enantioselective Addition of Arylboronic Acids to *N*-Sulfonylimines**[a]




[a]Reaction conditions: imines **9** or **12** (0.20 mmol), arylboronic acids **10** (0.30 mmol), $Pd(TFA)_2$ (5.0 mol %), ($R_p$)-**L7** (7.5 mol %), TFE (2.0 mL).

Collectively, a novel class of [2.2]paracyclophane-based planar-chiral oxazole−pyridine *N*,*N*-ligands were designed and synthesized. These ligands enabled the first highly enantioselective palladium-catalyzed acetoxylative cyclization of alkyne-tethered cyclohexadienones, providing biologically active molecules chiral *cis*-hydrobenzofurans in excellent enantiose-



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lectivities, with a broad scope of alkyne-tethered cyclohexadienones and carboxylic acids including drug-derived carboxylic acids. These results suggested the superior performance of COXPY ligands as an effective type of *N,N*-ligand scaffold in transition-metal-catalyzed asymmetric syntheses. Further studies are currently underway toward expanding the application of chiral COXPY ligands in asymmetric catalysis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c01163.

Detailed experimental procedures, characterization of new compounds, spectra, and X-ray data (PDF)

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### Notes

The authors declare no competing financial interest.

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