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Pd-Catalyzed Asymmetric Intramolecular Aryl C–O Bond Formation with SDP(O) Ligand: Enantioselective Synthesis of (2,3-Dihydrobenzo[*b*][1,4]dioxin-2-yl)methanols

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Supporting Information

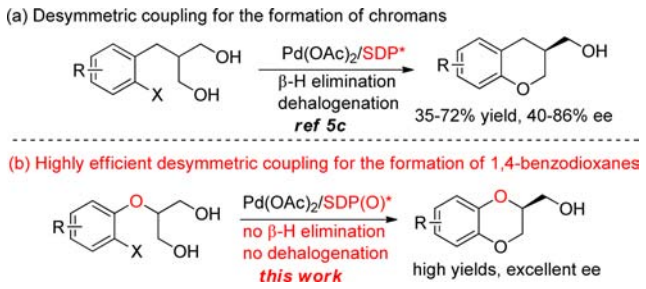
ABSTRACT: Employing a chiral spirodiphosphine monoxide ligand with 1,1′-spirobiindane backbone (SDP(O)), a desymmetrization strategy of Pd-catalyzed intramolecular asymmetric aryl C–O coupling of 2-(2-halophenoxy)-propane-1,3-diols, was developed. The SDP(O) ligand shows much better results than its SDP counterpart. The protocol provides an efficient and highly enantioselective method for the synthesis of 2-hydroxymethyl-1,4-benzodioxanes. Density functional theory studies provide a model that accounts for the origin of the enantioselectivity.

In the past few decades, there has been much progress with transition-metal-catalyzed cross-coupling reactions, and they have been widely applied in organic synthesis.[1] However, highly enantioselective cross-coupling reactions, especially aryl C–heteroatom coupling reactions, still are a significant challenge in this area, perhaps because no new stereocenters are directly involved in the bond-formation process.[2,3]

Asymmetric desymmetrization[4] is a general and powerful strategy for the enantioselective synthesis of chiral compounds. In our continuing efforts to develop transition-metal-catalyzed asymmetric aryl C–heteroatom coupling reactions,[5] we reported in 2013 a Pd-catalyzed enantioselective intramolecular aryl C–O coupling reaction[5c] based on asymmetric desymmetrization of 2-(2-haloaryl)propane-1,3-diols (Scheme 1a). However, in most cases, the desired products were obtained with only moderate enantioselectivity and in low to moderate yields due to competitive side reactions involving either *β*-hydride elimination and dehydroxylation[6] or dehalogenation.[7] Such limitations have greatly retarded the practical applications of such asymmetric C–O coupling reactions, and it is necessary to solve these problems in order to develop practically useful asymmetric O-arylation reactions.

Enantiomerically pure 2-substituted 1,4-benzodioxane structures (Figure 1) have been found to be prevalent in a variety of bioactive natural products[8] and important intermediates for various drug molecules such as the selective 5-HT1A receptor agonist MKC-242 (**1**),[9] the selective α_{1D}-adrenoceptor inhibitor WB4101 (**2**),[10] the anticonvulsant JNJ-24689112 (**3**),[11] or the antihypertensive α_{1A}-adrenoceptor blocker doxazosin (**4**).[12]

Scheme 1. *O*-Arylation Reaction via Asymmetric Desymmetrization Strategy



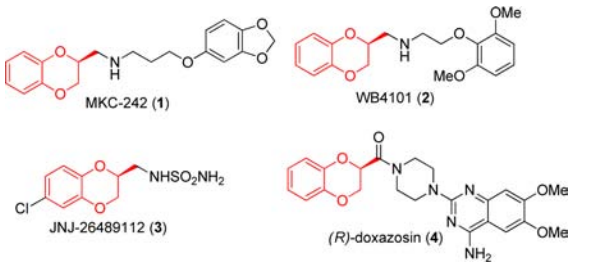


Figure 1. Some bioactive compounds with a 1,4-benzodioxane unit.

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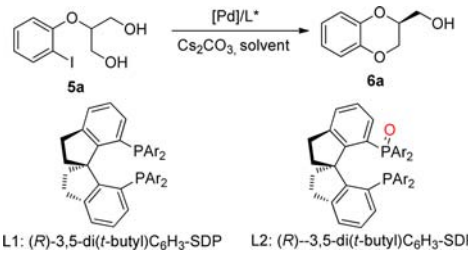
Although there are many approaches available for the synthesis of the important, enantiomerically enriched intermediate 2-(hydroxymethyl)-1,4-benzodioxane and related compounds, most of them are not straightforward and often need multiple steps.[6,13,14] We envisioned that the Pd-catalyzed desymmetric intramolecular *O*-arylation reaction may be developed as a simple and efficient method for the enantioselective formation of such structures if the problems of productivity and enantioselectivity could be resolved. Consequently, we studied enantioselective desymmetrization of 2-(2-halophenoxy)propane-1,3-diols for the synthesis of 2-(hydroxymethyl)-1,4-benzodioxanes and found that a bisphosphine monoxide ligand with a 1,1′-spirobiindane backbone (SDP(O)) was superior to the corresponding bisphosphine (SDP) ligand used in our previous study. No β-H elimination and dehalogenation side reactions were observed in the SDP(O) reaction system, and the desired products were obtained with high enantioselectivity and in excellent yields. In this paper, we report the details of this research (Scheme 1b).

Our research adopted the desymmetrization reaction of **5a** (Table 1) as a model case. Under the conditions used in our previous study, the $Pd(OAc)_2$/L1-catalyzed reaction of **5a** was performed at 90 °C in 1,4-dioxane with Cs_2CO_3 as the base. However, the reactivity of this substrate was minimal, and the desired coupling product was obtained in only 25% yield, with a recovery of more than 60% of the starting material and about 12% of dehalogenated byproduct. Moreover, the enantioselectivity was disappointing; only 60% ee was obtained (Table 1, entry 1).

Table 1. Screening Reaction Conditions[a]



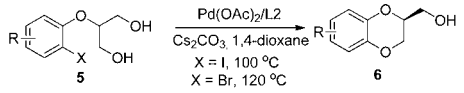
entry	[Pd]/L*	solvent	base	yield[b] (%)	ee[c] (%)
1	$Pd(OAc)_2$/L1	1,4-dioxane	Cs_2CO_3	25	60
2	$Pd(OAc)_2$/L2	1,4-dioxane	Cs_2CO_3	85	96
3	$Pd(OAc)_2$/L2	1,4-dioxane	K_3PO_4	76	96
4	$Pd(OAc)_2$/L2	1,4-dioxane	K_2CO_3	13	96
5	$Pd(OAc)_2$/L2	1,4-dioxane	KOAc	12	96
6	$Pd(OAc)_2$/L2	THF	Cs_2CO_3	12	45
7	$Pd(OAc)_2$/L2	DMF	Cs_2CO_3	73	92
8	$Pd(OAc)_2$/L2	toluene	Cs_2CO_3	10	84
9	$PdCl_2$/L2	1,4-dioxane	Cs_2CO_3	86	95
10	$Pd(CN)_2Cl_2$/L2	1,4-dioxane	Cs_2CO_3	85	96
11[d]	**$Pd(OAc)_2$/L2**	**1,4-dioxane**	**Cs_2CO_3**	**96**	**96**

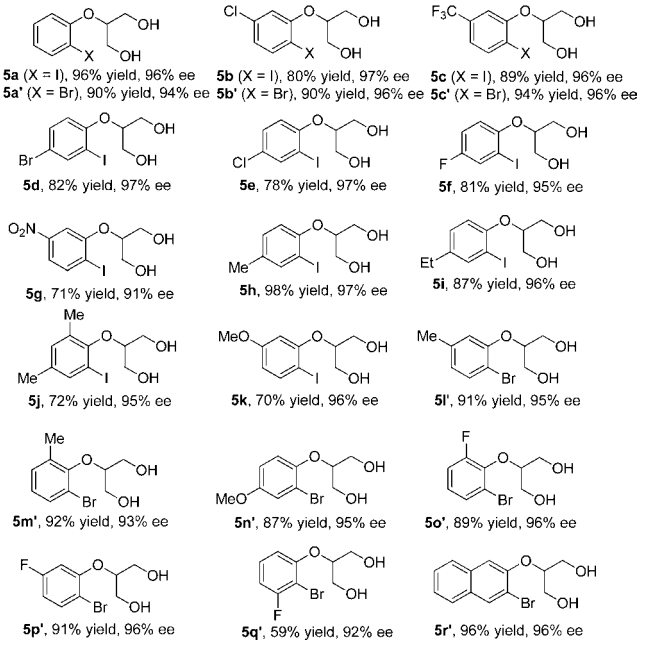
[a]Reagents and reaction conditions: **1a** (0.25 mmol, 1.0 equiv), Pd (0.0075 mmol, 3 mol %), L1 or L2 (0.0075 mmol, 3 mol %), Cs_2CO_3, (0.5 mmol, 2.0 equiv), solvent (1 mL),90 °C, 20 h. [b]Isolated yields [c]Determined by HPLC analysis (Chiracel OD-H column). [d]100 °C.

To increase the reactivity and enantioselectivity and to minimize the dehalogenation side reaction, further examination of chiral ligands was undertaken. Recently, some interesting chiral bis-phosphine monooxide ligands (BPMOs)[15] with metal catalysts have demonstrated unique properties in a variety of chemical transformations. They often markedly influence the reactivity and selectivity when compared with their phosphine counterparts, such as those in palladium-catalyzed asymmetric allylic alkylations[16] or Heck-type coupling reactions.[17,18] We tested the SDP(O) ligand (L2),[5c,19] an intermediate in the synthesis of L1, and found that it worked well in this model reaction, with both the reactivity and enantioselectivity being enhanced dramatically. The coupling product **6a** was afforded in 85% yield and 96% ee at 90 °C (Table 1, entry 2). Moreover, no dehalogenated or β-H elimination related byproducts were detected. Other solvents and bases were also screened, and the combination of 1,4-dioxane and Cs_2CO_3 seemed optimum (Table 1, entries 3−8). Different sources of palladium were also explored but had little effect on the enantioselectivity (Table 1, entries 9 and 10). Higher reaction temperatures (100 °C) accelerated the reaction and afforded the desired product in higher yield without loss of enantioselectivity (Table 1, entry 11). Comparison with reported data showed that the absolute configuration of **6a** was *S*.[20]

Having established the optimized conditions, we explored possible variations in the substrate. The results are shown in Scheme 2. A variety of aryl iodide substrates were first examined, and at 100 °C, all produced the corresponding desymmetric coupling products in high yields.[21] Enantioselectivity of >95% ee was obtained in all cases, with the exception of the nitro-substituted substrate **5g**, which afforded the desired product **6g** with 91% ee. Different aryl ring substituents, such as alkyl, methoxyl, halo, trifluoromethyl, and nitro groups, were well

Scheme 2. Scope of the Substrates[a−c]





[a]Reagents and reaction conditions: **3** (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.0075 mmol, 3 mol %), L2 (0.0075 mmol, 3 mol %), Cs_2CO_3, (0.5 mmol, 2.0 equiv), 1,4-dioxane (1 mL), for X = I, 20 h, X = Br, 40 h. [b]Isolated yields. [c]Enantiomeric excesses were determined by HPLC analysis.

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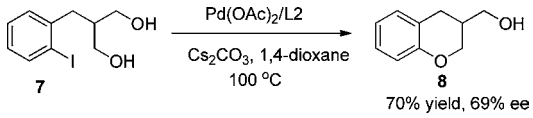
tolerated. Aryl bromides also coupled well although at a slightly elevated temperature of 120 °C and with a prolonged reaction time (40 h).

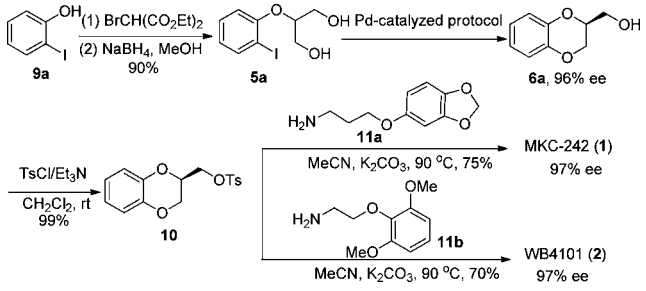
Interestingly, for substrate **7**,[5c] the Pd/SDP(O) catalytic system performed less promising than that for substrate **5**. As shown in Scheme 3, the coupling product **8** was afforded in about 70% yield and 69% ee, and about 20% of dehalogenated side product was observed.

Scheme 3. Exploration of Substrates with a Carbon Linker



To demonstrate the practical utility of this method, we undertook as examples the simple syntheses of MKC-242 (**1**) and WB4101 (**2**) (Scheme 4). With 2-iodophenol **9a** as a starting

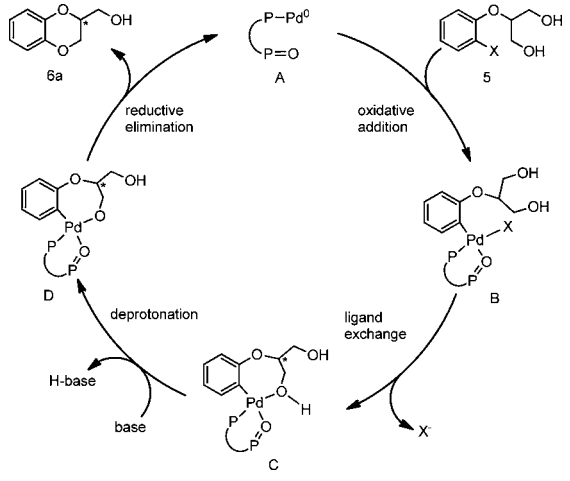
Scheme 4. Simple Synthesis of MKC-242 and WB4101



material, compound **6a** was obtained in high yield and with an excellent ee value through simple substitution/reduction and this asymmetric desymmetric coupling protocol. Further, compound **6a** was reacted with TsCl in CH_2Cl_2 according to reported methods to give the activated intermediate **10**,[13a] which was then reacted with amines **11a** and **11b** to afford high yields of the corresponding products **1** and **2**, respectively.

Scheme 5 illustrates a conventional catalytic cycle for the Pd-catalyzed aryl C−O coupling reaction.[20,22,23] We examined the crucial intermediate **C** in order to reveal the origin of the high enantioselectivity.[24] Twelve conformations of complex **C** have

Scheme 5. Plausible Catalytic Cycle



been optimized with density functional theory (DFT).[25] The most stable conformer which leads to *S* product and a schematic model are presented in Figure 2. Unlike SDP, which adopts a *C*2

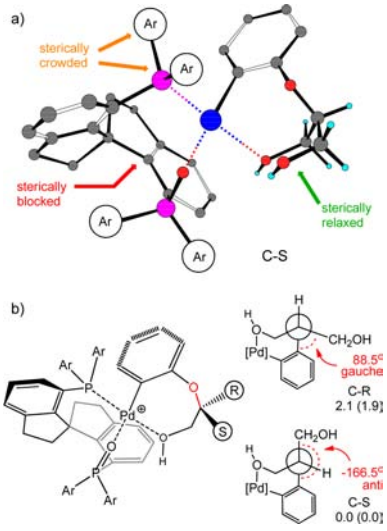


Figure 2. (a) Most stable conformers of **C** leading to *S* products. (b) Schematic presentation of boat conformers. Relative energies and free energies (in parentheses) (kcal/mol).

symmetry, SDP(O) exhibits an asymmetric chiral environment. The spiro-backbone constrains the bidentate coordination in a rigid 9-membered ring. As a result of the coordination with the oxygen, the spirobiindane backbone at the phosphine oxide is forced to tile toward the Pd and block the space below the Pd coordination plane. Because the binding of phosphine oxide is weaker than the phosphine, the arene substrate prefers the *cis* position of the phosphine, avoiding a strong *trans*-influence. Due to the blocking of the spirobiindane backbone and the hindrance from the phenyl groups of the phosphine, the tether of the arene substrate is oriented upward. One hydroxyl group binds with Pd to form a seven-membered ring via coordination/deprotonation. The enantioseletivity is determined by the position of the other $-CH_2OH$.

Both of the seven-membered rings in **C-S** and **C-R** adopt a boat conformation with the arene and a CH_2 puckering downward. The $-CH_2OH$ group in **C-R** endures a repulsive interaction with the arene group, while the $-CH_2OH$ in **C-S** is directed toward an uncumbered space. The effect can be clearly visualized by the Newman projection. The dihedral angles θ, defined by $C_{prochiral}-O$, in **C-S** and **C-R** are −166.5° and 88.5°, indicating anti and gauche conformations, respectively. Due to the short C−O bond length,[26] the gauche C−O−C−C conformation is much less stable than the anti conformation, as indicated by the calculated energetic preference of **C-S** over **C-R**. The computational result is consistent with the experiment and provides a model to rationalize the origin of the excellent enantioselectivity.

In summary, we have established a palladium-catalyzed highly enantioselective intramolecular *O*-arylation for the formation of important (2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methanols based on an asymmetric desymmetrization strategy. In this process, the SDP(O) ligand is the key to both high yields and excellent enantioselectivity. The results of this method are superior to those obtained with the analogous phosphine. The method was highlighted by the simple synthesis of biologically

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important agents. Further exploration and application of this method in organic synthesis are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data, including ^{1}H and ^{13}C NMR for all new compounds, and chiral HPLC spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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