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Pd-Catalyzed Enantioselective Hydroalkoxylation of Alkoxyallenes with Phenol for Construction of Acyclic *O,O*-Acetals

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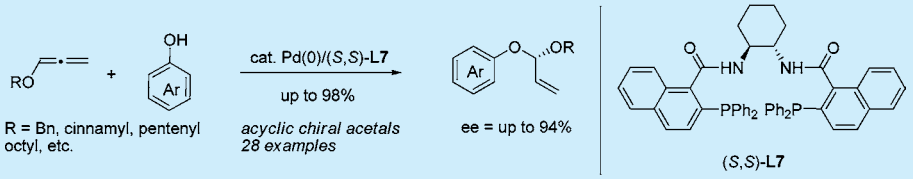
Supporting Information



ABSTRACT: Palladium-catalyzed asymmetric intermolecular hydroalkoxylation of allenes has been developed by using phenol as a pronucleophile. Acyclic *O,O*-acetals were obtained in high yields (up to 98%) with good to excellent enantiomeric excesses (up to 94% ee).

Enantiopure cyclic and acyclic *O,O*-acetals (Figure 1) represent a class of important scaffolds in many natural products and bioactive compounds,[1] such as carbohydrates, spiroketal polyketides, and chromene acetals derivatives.[2] These compounds are also useful intermediates for asymmetric transformations.[3] Therefore, development of efficient methods to generate stereodefined *O,O*-acetals are highly desired. Over the past decades, methods have been mainly focused on substrate- or auxiliary-directed stereoinduction.[4] Until recently, List and co-workers have disclosed a new and efficient organocatalytic strategy (CPAs catalysis) for the synthesis of cyclic *O,O*-acetals.[5] However, this method is unsuitable for the synthesis of acyclic *O,O*-acetals, due to the product's inherent instability in acidic conditions.[4a] Enzymatic resolutions and metal-catalyzed desymmetrizations (ring closing metathesis) are options, but a special substrate's skeleton is required.[6]

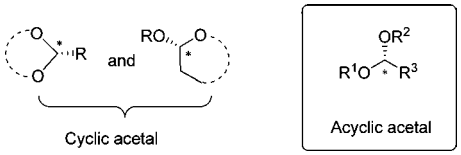


Figure 1. Enantiopure *O,O*-acetals scaffolds.

Transition-metal-catalyzed enantioselective hydrofunctionalization of allenes[7] represents an atom economic strategy for generating stereogenic C−O bonds. Particularly, chiral Au-biphophine or Au-phosphate,[8] Ag-phosphate,[9] and Rh-biphosphine[10] complexes are effective catalysts for the transformations of allenes into allylic ethers or esters in excellent regio- and enantioselectivities. Our recent research interest is focused on asymmetric metal catalysis, and we assumed that an asymmetric metal-catalyzed intermolecular O−H addition to alkoxyallenes (hydroalkoxylation) under mild condition might allow the access to acyclic *O,O*-acetals. Lately, Rhee reported a Pd-catalyzed intermolecular enantioseletive hydroalkoxylation[11] of alkoxyallenes with alcohols.[12] In this letter, we present an enantioselective hydroalkoxylation of alkoxyallenes using phenols as pronucleophiles[13] to furnish acyclic *O,O*-acetals in high yields and with good to excellent enantioselectivities.

In recent years, we developed a class of chiral sulfinylphophine ligands[14] and employed them in palladium-catalyzed reactions.[15] These ligands would be expected to work well in this title reaction.[16] The initial test was performed in the presence of 2 mol % of $\{Pd_2(dba)_3{\cdot}CHCl_3\}$, 5 mol % of ligand, 2.0 equiv of Et_3N, and dicholoroethane (DCE) as solvent. Unfortunatetly, the desired product **3a** was obtained with good yields but poor enantioselectivities (<15%) when using sulfinylphosphine **L2** and **L3** as ligands (Table 1, entries 1−3). So we turn our attention to commercially available ligands, such as **BINAP** and Trost ligands (**L5**, **L6**, and **L7**) (Table 1, entries 4−7). To our delight, (*S,S*)-DACH-naphthyl Trost ligand **L7** proved to be the right ligand to examine; the product **3a** was afforded with a 98% yield and 90% ee. 1,4-Dioxane was tested and proved to be the optimal solvent (97% yield and 92% ee) (Table 1, entry 10). Other reaction conditions such as the base and reaction temperature were also evaluated (see Supporting Information), and under the optimal reaction conditions (4 mol % of Pd(0) loading, 5 mol % of (*S,S*)-DACH-naphthyl Trost ligand **L7**, 100 mg of 4 Å molecule sieves, at 15 °C), the product **3a** was obtained with a 98% yield and 93% ee. As we expected, the use of an enantiomeric ligand afforded the enantiomeric product (Table 1, entry 12).

The substrate scope of enantioselective hydroalkoxylation was surveyed with a number of phenol derivatives (Scheme 1).

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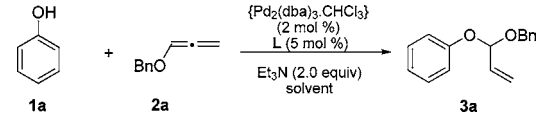
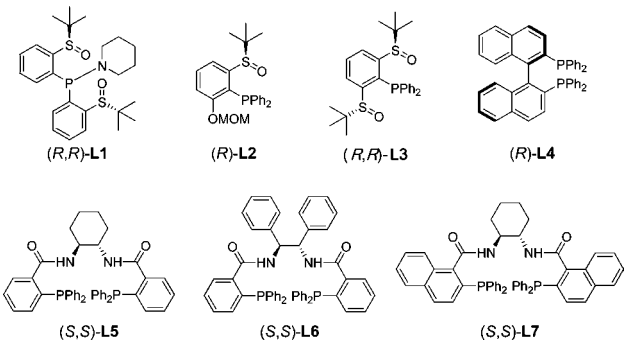
Table 1. Pd-Catalyzed Enantioselective Hydroalkoxylation of Benzyloxyallene 2a with Phenol 1a[a]



1a 2a 3a

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	(*R*,*R*)-**L1**	DCE	74	−13
2	(*R*)-**L2**	DCE	80	−7
3	(*R*,*R*)-**L3**	DCE	85	9
4	(*R*)-**L4**	DCE	94	11
5	(*S*,*S*)-**L5**	DCE	81	60
6	(*S*,*S*)-**L6**	DCE	83	74
7	(*S*,*S*)-**L7**	DCE	98	90
8	(*S*,*S*)-**L7**	THF	97	83
9	(*S*,*S*)-**L7**	toluene	94	83
10	(*S*,*S*)-**L7**	1,4-dioxane	97	92
11[d]	(*S*,*S*)-**L7**	1,4-dioxane	98	93
12[d]	(*R*,*R*)-**L7**	1,4-dioxane	96	−93

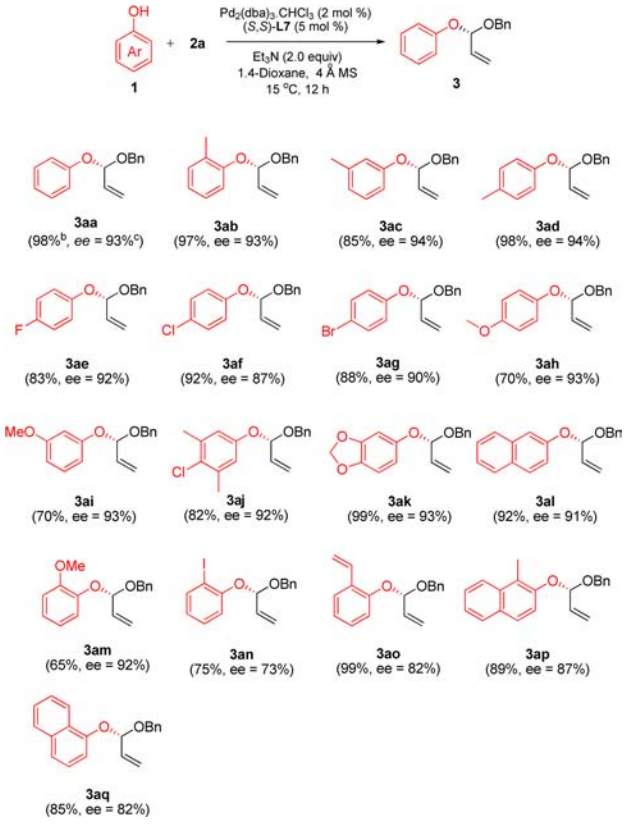
[a]Reaction condition: 2 mol % $\{Pd_2(dba)_3{\cdot}CHCl_3\}$, 5 mol % of ligand, 0.2 mmol of **1a**, and 0.3 mmol of **2a**, 200 mol % of Et_3N in 2.0 mL of solvent at rt for 12 h. [b]Isolated yields. [c]Determined by HPLC analysis. [d]At 15 °C and in the presence of 100 mg of 4 Å molecule sieves.



In all cases, the allene is in excess and phenol is totally converted to the product. A wide range of *p*-substituted (products **3ad**−**3ah**) and *m*-substituted phenols (products **3ac** and **3ai**) reacted with **2a** with good to excellent enantioselection (87−94%). Sterically hindered phenols (products **3ab**, **3am**−**3ap**) are also quite reactive, and adducts showed slightly low ee's (73−93%). Notably, multisubstituted phenols also reacted well to furnish **3aj** (82% yield and 92% ee) and **3ak** (99% yield and 94% ee). Except for phenol, the strategy enables the incorporation of 1-naphthol (product **3aq**) or 2-naphthol (product **3al**) in nonracemic *O*,*O*-acetals.

The scope of alkoxyallene was also examined (Figure 2). A number of benzyloxyallene's analogues (products **3ba**−**3ha**) reacted well with phenol in good yields (62−98%) and excellent enantiomeric excesses (90−94%). The enantioselective hydroalkoxylation of cyclohexylmethyl-, cinnamyl-, and octyl-oxyallenes also proceeded smoothly to provide **3ia**−**3ka** (60−83% yields and 90% ee's). Comparatively, **3la** was obtained with a moderate enantiomeric excess (80%), probably due to interference of competitive coordination of the substrate's terminal olefinic group to LPd-H species. All acyclic allylic *O*,*O*-acetals were thermodynamically stable. Their absolute configuration was confirmed through transformation of **3ha** to **4**,[17] the structure of the latter evidenced by X-ray diffraction analysis (eq 1, Scheme 2).

Scheme 1. Scope of Phenols[a]



[a]Conditions: 2 mol % of $\{Pd_2(dba)_3{\cdot}CHCl_3\}$, 5 mol % of (*S*,*S*)-**L7**, 0.2 mmol of **1a**, and 0.3 mmol of **2a**, 200 mol % of Et_3N, 100 mg of 4 Å MS in 2.0 mL of 1,4-dioxane at 15 °C for 12 h. [b]Isolated yields. [c]Determined by HPLC analysis.

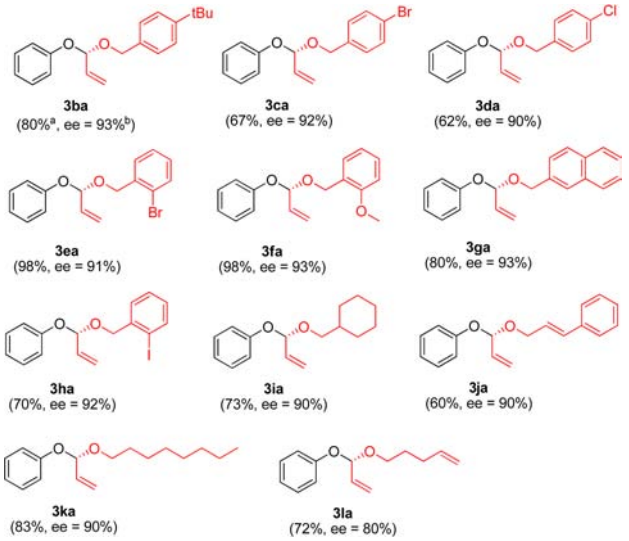


Figure 2. Scope of alkoxyallenes. Conditions: 2 mol % of $\{Pd_2(dba)_3{\cdot}CHCl_3\}$, 5 mol % of (*S*,*S*)-**L7**, 0.2 mmol of **1a**, and 0.3 mmol of **2a**, 200 mol % of Et_3N, 100 mg of 4 Å MS in 2.0 mL of 1,4-dioxane at 15 °C for 12 h. [a] Isolated yield. [b] Determined by HPLC analysis.

The proposed mechanism, as shown in Scheme 3, commences with the oxidative addition of **L**Pd(0) **I** to the phenol to generate **L**Pd−H species **II**.[18] The following hydropalladation of allene via a transition state **III** kinetically

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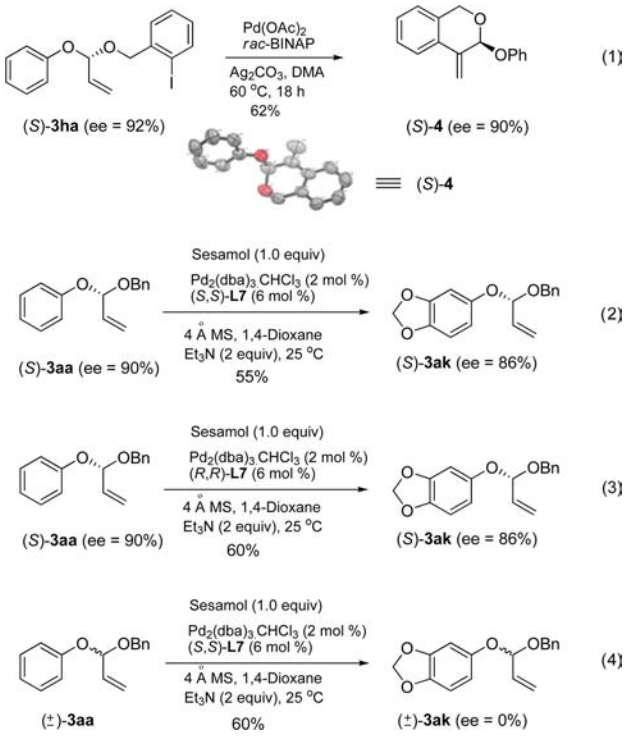
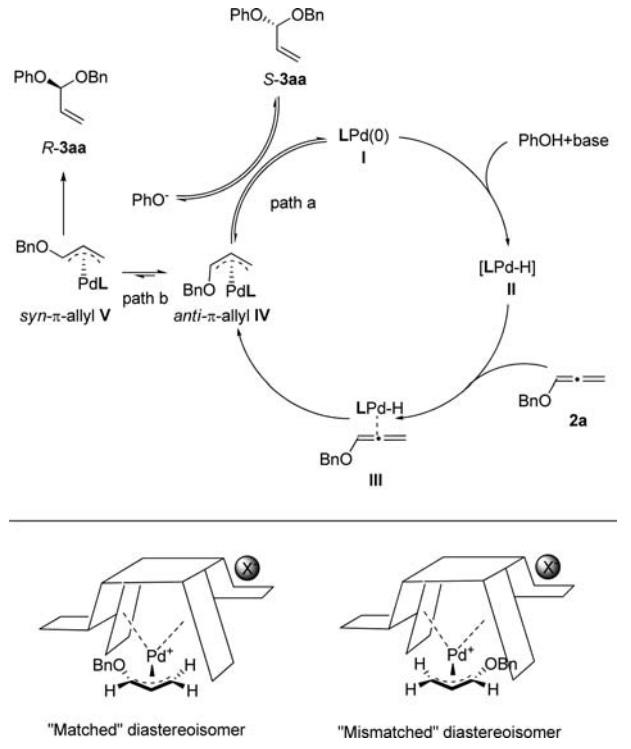
Scheme 2



Scheme 3. Possible Mechanism and Selectivity with the Use of (*S*,*S*)-L7



forms the *anti*-π-allyl intermediate **IV** that is prone to generate *syn*-π-allyl intermediate **V**. In this work, the ligand (*S*,*S*)-**L7** induces (*S*)-**3**, which implies that outer-sphere addition of a phenolic anion to the "matched" diastereoisomer[12e] of **IV** (a cartoon model shown in Scheme 3) dominates the catalytic cycle (Scheme 3, path a). Additionally, controlling experiments in Scheme 2, eqs 2−4 strongly suggest that the phenolic addition to allylpalldium complex **IV** is not the enantiodiscriminating step but reversible. In these experiments, configurationally retentive substitution (probably via double reversed pattern) of the enantioenriched or racemic phenol adduct **3aa** by sesamol was observed using an enantiomer of chiral **L7**, precluding dynamic kinetic resolution or transformation. So, the chemical outcome of hydroalkoxylation might be controlled by the addition step of **L**Pd−H **II** to allene **2a**.

In conclusion, we realized a palladium catalyzed highly enantioselective hydroalkoxylation. The catalytic process involved the hydropalladation of alkoxyallene and subsequent allyl substitution using phenol as a pronucleophile, and the desired acyclic *O*,*O*-acetals were obtained with high yields (up to 98%) and high enantioselectivities (up to 94% ee). The strategy provides a concise route for access to anomeric acyclic *O*,*O*-acetals that promises application in asymmetric synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data, and crystallographic data (CIF). 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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