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Palladium(II)-Catalyzed Asymmetric Coupling of Allylic Alcohols and Vinyl Ethers: Insight into the Palladium and Copper Bimetallic Catalyst

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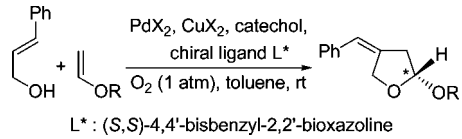
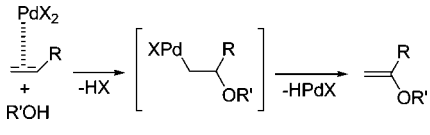


The use of PdX_2, CuX_2 (X = OAc, $OCOCF_3$, or Cl), and catechol together with (*S*,*S*)-4,4′-bisbenzyl-2,2′-bioxazoline under O_2 induces the asymmetric coupling of cinnamyl alcohols and vinyl ethers to give (*R*)-(+)-2-alkoxy-4-benzylidenetetrahydrofurans in 40−53% ee (79% yield). The present study provides implications for the so-called Wacker catalyst of PdX_2 and CuX_2, in terms of that the anionic ligands (X) of Pd and Cu interchange between two metals.

Introduction

The palladium(II)-catalyzed reaction of alkenes with O-atom nucleophiles, the so-called Wacker-type reaction, is undoubtedly a powerful tool for synthesizing a wide range of O-atom-containing functionalized compounds. A number of review articles[1] highlights fascinating developments based on this reaction. As illustrated in Scheme 1, the reaction proceeds via nucleophilic attack of ROH toward alkenes coordinated to PdX_2, the process of which is referred to as oxypalladation. The resulting σ-alkyl palladium(II) intermediate undergoes XPdH elimination to afford products oxidatively. The fate of XPdH species formed is crucial for the catalysis associated with the function of stoichiometric oxidants, which are required for this type of reaction, such as O_2 with or without CuX_2, or *p*-benzoquinone. Although recent intensive studies have disclosed the behavior of XPdH and O_2,[2] little concern has been paid into the role of CuX_2, which is a standard cocatalyst in Wacker-type oxidations.[3,4] Asymmetric versions of the Wacker-type reaction have also attracted interests in terms of developing selective oxidative reactions. Since we reported the first asymmetric, intramolecular Wacker-type oxidation in 1978 (Scheme 2),[5] several groups have made advances in its utility for synthesizing optically active O-atom-containing heterocycles in high ee.[6] For the asymmetric reactions, *p*-benzoquinones are frequently employed as the stoichiometric oxidant,[7] but it is rare to use O_2 as the oxidant with the CuX_2 cocatalyst.[6b,8]

SCHEME 1



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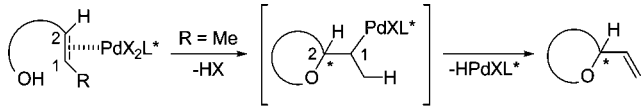
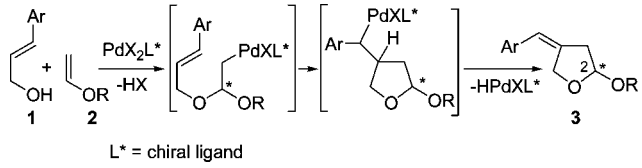
SCHEME 2



In addition, fundamental information is lacking on the intermolecular Wacker-type reaction where the enantioface of prochiral alkenes is intermolecularly differentiated by Pd(II).[9] This is because the usual reaction shown in Scheme 1 results in no asymmetry in products. However, depending on substrate structures, the pathway could be modified to induce chirality in the products. Scheme 3 is one such reaction. Thus, when

SCHEME 3[a]



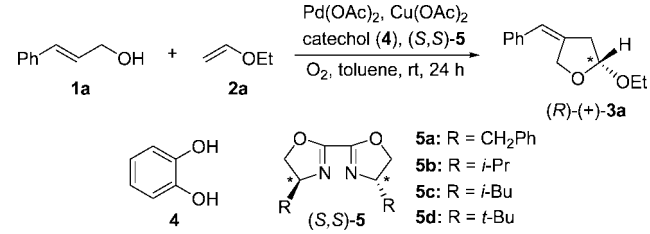
[a] A catalyst system in the present study is composed of Pd(II), Cu(II), catechol, L*, and O_2.

cinnamyl alcohols **1** are used as nucleophiles toward vinyl ethers **2**, the resulting intermolecular oxypalladation adducts undergo cyclization to give 2-alkoxy-4-benzylidenetetrahydrofurans **3** bearing chirality at the 2-position. Reported herein is the first asymmetric coupling of cinnamyl alcohols **1** and vinyl ethers **2** as an intermolecular Wacker-type oxidation. Our previous studies on the original reaction[10] developed by Oshima and Uchimoto,[11] revealed that the catalysis by $Pd(OAc)_2$ and $Cu(OAc)_2$ under O_2 is remarkably enhanced by utilizing catechol as an additive. On the basis of this fact, we have aimed to shed further light on the function of PdX_2 and CuX_2 as well as to elucidate fundamental characteristics of the asymmetric reaction shown in Scheme 3. In this study, the value of the percentage of ee obtained, albeit not higher, was used as a clue to understanding the behavior of the palladium(II) catalyst. Results of the present study provide intriguing implications on the role of the CuX_2 cocatalyst which remains uncertain in this type of reactions.

Results and Discussion

Shown in Scheme 4 is the asymmetric reaction of (*E*)-cinnamyl alcohol (**1a**) and ethyl vinyl ether (**2a**) with a catalyst system of $Pd(OAc)_2$, $Cu(OAc)_2$, catechol (**4**), and (*S*,*S*)-bisoxazolines (**5**) under O_2 (balloon). Representative results are given in Table 1. As reported previously, the catalytic efficiency of $Pd(OAc)_2$ and $Cu(OAc)_2$ in a nonasymmetric reaction was enhanced by using catechol (**4**) as an additive (Table 1, entries

SCHEME 4



1 and 2).[10b] This was also the case for the present asymmetric reaction. Thus, in the presence of catechol (**4**) (Pd/Cu/**4**/**5a** = 1/1/2/2), the reaction gave (*R*)-(+)-**3a** in 40% ee and 71% yield (24 h) (entry 3),[12] but the absence of catechol (**4**) decreased the product yield only to 26% (entry 4). In addition, the enantioselectivity was also greatly lowered to 29% ee. This

TABLE 1. Study for the Catalyst Composition in Enantioselective Coupling of Cinnamyl Alcohol (1a) and Ethyl Vinyl Ether (2a)[a]

						3a	
entry	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (mol %)	**4** (mol %)	(*S*,*S*)-**5a** (mol %)	solvent	yield (%)[b]	ee (%)[c]
1	5	5	10		MeCN[d]	82 (42)[e]	
2	5	5			MeCN[d]	38 (15)[e]	
3	5	5	10	10	toluene	71	40
4	5	5		10	toluene	26	29
5	5	5		20	toluene	18	38
6	5		10	10	toluene	17[f]	39
7	5			10	toluene	13[f]	39

[a] **1a** (1 mmol), **2a** (4 mmol), toluene (2.5 mL), O_2 (1 atm), rt, 24 h. [b] Isolated yield. [c] Measured by chiral HPLC. [d] MeCN (1.0 mL), 3 h. [e] Toluene as the solvent, 24 h. [f] NMR yield.

decrease in percentage of ee could be interpreted as follows: When catechol is absent, the ligand **5a** is able to coordinate to $Cu(OAc)_2$ as well as $Pd(OAc)_2$;[13] that is, coordination of **5a** to $Pd(OAc)_2$ is interfered by $Cu(OAc)_2$, lowering the percentage of ee.[14] In other words, catechol greatly prefers to combine with $Cu(OAc)_2$. Therefore, when catechol is present, coordination

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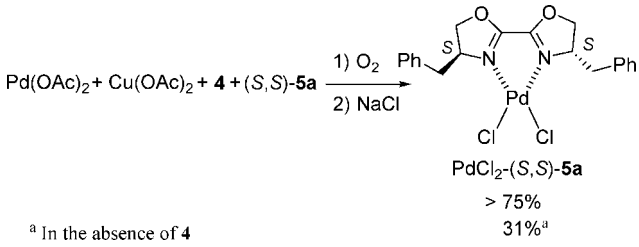
(12) The percentage of ee was determined by HPLC using an analytical column packed with cellulose tribenzoate coated on silica gel (250 mm × 4.6 mm, *i*-PrOH/*n*-hexane = 1/19, 0.5 mL/min, 258 nm). The optical rotation of **3a** obtained was $[\alpha]_D^{25} = +64.2°$ (*c* 0.335, $CHCl_3$), and thus the maximum rotation of **3a** is calculated to be 160.5 ($CHCl_3$).

(13) Chiral bis(oxazoline) ligands can coordinate to Cu, Pd, and other metals; see ref 15.

(14) When the amount of **5a** was increased to 4 equiv per Pd, the percentage of ee was not decreased (entry 5, Table 1). This must be due to the coordination of **5a** to $Pd(OAc)_2$ sufficiently taking place even in the absence of catechol, thereby not lowering the percentage of ee.

of **5a** takes place prevailingly on the side of $Pd(OAc)_2$. This interpretation is likely supported by preferential isolation (>75% yield) of $PdCl_2$-(*S*,*S*)-**5a** complex (Scheme 5) from a solution of $Pd(OAc)_2$, $Cu(OAc)_2$, catechol (**4**), and **5a** (1/1/1/1) in toluene which was stirred for 1 h under O_2 (balloon) and then treated with a saturated NaCl solution. In the absence of catechol, this complex was only isolated in 31% yield, probably because coordination of **5a** to $Cu(OAc)_2$ concurrently takes place.

SCHEME 5



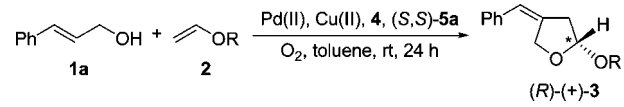
The results in Table 1 provide further implications on the role of catechol in the catalyst system: (1) Without $Cu(OAc)_2$ but in the presence of catechol (**4**), the enantioselectivity was not lowered (39% ee) from 40% (entries 6 and 3), but the yield of **3a** was remarkably decreased (17%). This means that $Cu(OAc)_2$ does not affect the enantioselectivity, and that the reactivity of catalyst is enhanced by a combination of catechol and $Cu(OAc)_2$. (2) In the absence of both $Cu(OAc)_2$ and catechol, the enantioselectivity was again not lowered (39% ee) (entry 7), but the yield of **3a** was only 13%. Thus, it can be said that the enantioselectivity is exerted by a combination of $Pd(OAc)_2$ and **5a**, and that the reactivity is dependent on the assembly of $Cu(OAc)_2$ and catechol.

After surveying the amounts of **4** and **5a** used per Pd and Cu, we have decided a combination of Pd/Cu/**4**/**5a** = 1/1/2/2 to be suitable for the catalysis, and it has been used as a standard in the present study. The detail of our survey was given in the Supporting Information. In the present asymmetric reaction, toluene proved to be superior (Table 1, entry 3). Results using other solvents such as benzene, THF, methylene chloride, and 1,2-dichloroethane are also given as Supporting Information. The use of acetonitrile, which was a good solvent for the nonasymmetric version, results in only 9% ee of **3a** in 59% yield under the standard condition. The chiral coordination environment of the catalyst is probably compromised by preferential coordination of acetonitrile to Pd(II), significantly reducing the percentage of ee.

The use of simple chiral bisoxazolines **5**[15] bearing other substituents R at the 4,4′-position (Scheme 4), instead of R = CH_2Ph (**5a**), afforded no good results for percentage of ee. For example, under the standard conditions, the product **3a** was formed in 85% yield and 32% ee with (*S*,*S*)-**5b** (R = *i*-Pr), 85% yield and 32% ee with (*S*,*S*)-**5c** (R = *i*-Bu), 29% yield and 1% ee with (*S*,*S*)-**5d** (R = *t*-Bu), and 52% yield and 1% ee with (*R*,*R*)-**5e** (R = Ph), respectively.

As shown in Table 2, the percentage of ee was also not improved by changing the alkyl side chain of OR in vinyl ethers **2** with ethyl,

TABLE 2. Change of Enantioselectivity with Changing Substituent (R) of Vinyl Ether 2[a]



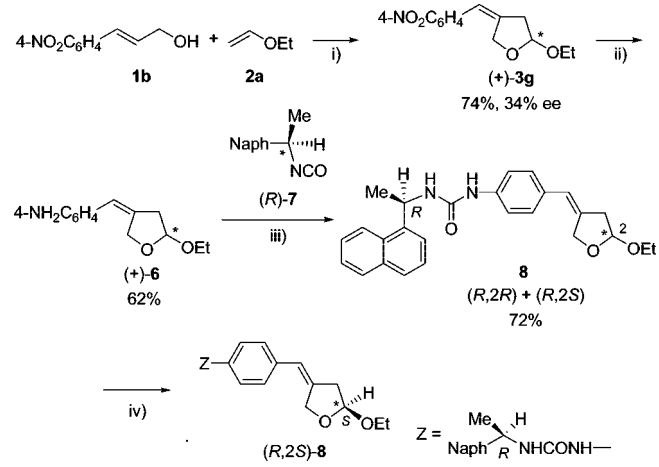
entry	OR, **2**	R	product, **3**	yield (%)[b]	ee (%)[c]
1	**2a**	Et	**3a**	71[d]	40
2	**2b**	Propyl	**3b**	67	35
3	**2c**	*n*-Bu	**3c**	86	53
4	**2d**	*n*-Hexyl	**3d**	41	34
5	**2e**	*n*-Octyl	**3e**	69	47
6	**2f**	Benzyl	**3f**	60	46

[a] **1a** (1 mmol), **2** (4 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (5 mol %), catechol (**4**) (10 mol %), (*S*,*S*)-**5a** (10 mol %), toluene (2.5 mL), O_2 (1 atm). [b] NMR yield. [c] Measured by chiral HPLC. [d] Isolated yield.

propyl, butyl, hexyl, and octyl.[16] Of those, butyl vinyl ether afforded **3c** (R = *n*-Bu) in 53% ee, which was the highest value in the present study. The value itself is not necessarily high in current outstanding advances in this field, but it is ranked higher among the asymmetric Wacker-type oxidations using copper salts as the cocatalyst.[9a] The effect of bulky side chains of OR, such as a *tert*- and *sec*-butyl group, on enantioselectivity was not examined, because of inaccessibility for preparing such vinyl ethers. This subject remains to be studied in the future.

The (+)-enantiomer of **3a** (R = Et) obtained as the major product (Scheme 4) was assigned as the (*R*) configuration by the following experiments (Scheme 6). Thus, 4-nitrocinnamyl

SCHEME 6[a]



[a] (i) **1b** (2 mmol), **2a** (8 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (10 mol %), catechol (**4**) (20 mol %), (*S*,*S*)-**5a** (20 mol %), toluene (5.0 mL), rt, 28 h. (ii) (+)-**3g** (0.5 mmol), $NH_2NH_2 \cdot H_2O$ (4 equiv), $FeCl_3$ (0.5 equiv), active-carbon (7 equiv per $FeCl_3$), 2.5 mL each of THF and EtOH, 70 °C, 2 h. (iii) (+)-**6** (0.23 mmol), (*R*)-**7** (0.23 mmol), THF (0.9 mL), rt, 21 h. (iv) Crystallization from $MeO(CH_2)_2OMe$-*i*Pr_2O for X-ray analysis.

alcohol (**1b**) was first reacted with ethyl vinyl ether (**2a**) using (*S*,*S*)-**5a**. The resulting (*Z*)-(+)-4-(4-nitrobenzylidene)-2-ethoxytetrahydrofuran (**3g**) (74% yield, 34% ee)[17] was converted into the corresponding 4-aminobenzylidene derivative **6** ($FeCl_3$, $NH_2NH_2 \cdot H_2O$). Treatment of **6** with commercially available (*R*)-

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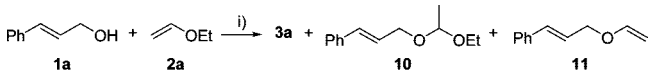
(17) The optical rotation of each enantiomer **3g** being collected repeatedly by semi-preparative HPLC was $[\alpha]_D^{25} = +142°$ (*c* 1.01, $CHCl_3$) and $-142°$ (*c* 1.01, $CHCl_3$) for (+)-**3g** and (−)-**3g**, respectively.

(−)-(1-isocyanatoethyl)naphthalene (**7**) gave urea **8** as a 65:35 mixture of two diastereomers, from which a single crystal suitable for X-ray analysis was obtained upon crystallization from 1,2-dimethoxyethane and diisopropyl ether. The ORTEP drawing, which is given as Supporting Information, indicates that its structure has a (*R*,2*S*) configuration. The crystal used for X-ray analysis was, unexpectedly, found to be the minor diastereomer of **8** by HPLC and NMR (also see the Supporting Information). Therefore, the absolute configuration of (+)-**3a** obtained as the major enantiomer in Scheme 4 was assigned as (*R*).

Following the survey of fundamental characteristics, we next examined the effect of anionic ligands (X) of Pd(II) or Cu(II) on the reaction of **1a** and **2a**. As shown in entry 1 of Table 3,

TABLE 3. Effect of Anionic Ligands of Pd(II) and Cu(II) on the Reaction of Cinnamyl Alcohol (1a) and Ethyl Vinyl Ether (2a)[a]



i) catalyst system: Pd(II), Cu(II), **4**, and (*S*,*S*)-**5a**

							3a	
entry	Pd(II)	Cu(II)	L*	base	**10** yield (%)[b]	**11** yield (%)[b]	yield (%)[b]	ee (%)[c]
1	$Pd(OAc)_2$	$Cu(TFA)_2$	(*S*,*S*)-**5a**		11		65	35
2	$Pd(TFA)_2$	$Cu(OAc)_2$	(*S*,*S*)-**5a**		10		57	41
3	$Pd(OAc)_2$	$Cu(TFA)_2$			18	11	9	
4	$Pd(TFA)_2$	$Cu(OAc)_2$			7	14	6	
5	$Pd(OAc)_2$	$CuCl_2$	(*S*,*S*)-**5a**		11	12	9	26
6	$PdCl_2$	$Cu(OAc)_2$	(*S*,*S*)-**5a**		3	5	3	28
7	$Pd(OAc)_2$	$Cu(TFA)_2$	(*S*,*S*)-**5a**	NEt_3			64	37
8	$Pd(TFA)_2$	$Cu(OAc)_2$	(*S*,*S*)-**5a**	NEt_3			79	43
9	$Pd(OAc)_2$	$Cu(TFA)_2$		NEt_3			51	
10	$Pd(TFA)_2$	$Cu(OAc)_2$		NEt_3			67	
11	$PdCl_2$	$Cu(OAc)_2$	(*S*,*S*)-**5a**	NEt_3			10	29
12	$Pd(TFA)_2$	$Cu(TFA)_2$	(*S*,*S*)-**5a**		31		31	8

[a] **1a** (1 mmol), **2a** (4 mmol), Pd(II) (5 mol %), Cu(II) (5 mol %), catechol (**4**) (10 mol %), L* = (*S*,*S*)-**5a** (10 mol %), NEt_3 (10 mol %), toluene (2.5 mL), rt, 24 h. [b] NMR yield. [c] Measured by chiral HPLC.

the use of $Pd(OAc)_2$ and $Cu(TFA)_2$ with **4** and (*S*,*S*)-**5a** gave **3a** in 65% yield (35% ee) along with byproduct **10** (11%), an addition product of **1a** to **2a**. When the anionic ligands were reversed, the use of $Pd(TFA)_2$ and $Cu(OAc)_2$ also gave **3a** and **10** in similar yields as above (entry 2). When (*S*,*S*)-**5a** was not used, an additional byproduct **11**, besides **10**, was formed in both systems (entries 3 and 4). The byproduct **11** corresponds to ether exchange in the alkoxy moiety of vinyl ether **2a** with **1a**. Here again, the product distributions are closely similar between these two systems. The similarity in the product distribution was also observed between the $Pd(OAc)_2$−$CuCl_2$ and $PdCl_2$−$Cu(OAc)_2$ system (entries 5 and 6).[18] In all cases, the presence of NEt_3 completely inhibits the formation of **10** and **11** without substantially changing the product yields and percentage of ee (entries 7 and 8). Not only NEt_3 but also a variety of bases including inorganic bases can suppress the formation of **10** and/or **11** as shown in Table 4. The effectiveness of base appears to be dependent on their pK_a values.

The original reaction using $Pd(OAc)_2$−$Cu(OAc)_2$ gave no byproduct **10** (Table 1, entry 3). This reaction undoubtedly produces CH_3COOH in the stage of oxypalladation leading to **9** (Scheme 7). In contrast, a combination of $Pd(TFA)_2$ and $Cu(TFA)_2$, which produces CF_3COOH, gave a higher yield of

(18) Detailed results using $PdCl_2$ as the catalyst are given in the Supporting Information.

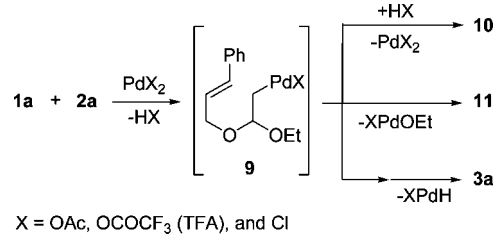
TABLE 4. Effect of the Base on the Reaction of Cinnamyl Alcohol (1a) and Ethyl Vinyl Ether (2a) Using $Pd(TFA)_2$−$Cu(OAc)_2$ as a Catalyst[a]

			3a		
entry	base	**10** yield (%)[b]	yield (%)[b]	ee (%)[c]	pK_a
1		10	57	41	
2	pyridine	5	46	7	5.33
3	2,4,6-tri*tert*-butylpyridine	5	52	31	7.02
4	NEt_3	0	79	43	10.87
5	$(i\text{-Pr})_2NEt$	0	80	41	11.26
6	proton sponge	0	78	40	12.50
7	DBU	0	80	41	13.47
8	$Ca(OH)_2$	0	63	43	
9	Na_2CO_3	0	60	39	10.33
10	Cs_2CO_3	0	44	47	10.33

[a] **1a** (1 mmol), **2a** (4 mmol), $Pd(TFA)_2$ (5 mol %), $Cu(OAc)_2$ (5 mol %), catechol (10 mol %), (*S*,*S*)-**5a** (10 mol %), base (10 mol %), toluene (2.5 mL), rt, 24 h. [b] NMR yield. [c] Measured by chiral HPLC.

10 (31%) with **3a** (31% yield, 8% ee) (Table 3, entry 12). Thus, a stronger acid such as CF_3COOH may cleave the Pd−C bond of intermediate **9** (Scheme 7) to afford **10**. Alternatively, **10** may be formed by simple addition of **1a** to **2a** catalyzed by a stronger acid.[19] The formation of **11** is explained by either Pd(II)- or acid-catalyzed Pd−OEt elimination from **9**, because such a process has been precedent.[20]

SCHEME 7

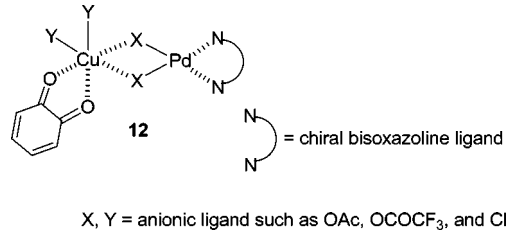


The similarity in the product distribution observed in Table 3 suggests that an anionic ligand of Pd is exchangeable with that of Cu and vice versa. If in the $Pd(OAc)_2$−$Cu(TFA)_2$ system, the OAc ligand of Pd is not exchanged with the TFA ligand of Cu, the oxypalladation occurs only with $Pd(OAc)_2$ to produce only CH_3COOH. Therefore, no formation of **10** is expected, but this is not the case (Table 3, entry 1). Accordingly, it can be said that the OAc ligand of Pd is replaced by TFA on Cu to produce CF_3COOH in the stage of oxypalladation. In the $Pd(TFA)_2$−$Cu(OAc)_2$ system, the anionic ligands of Pd and Cu are also exchangeable with each other, thereby resulting in the product distribution similar to that in $Pd(OAc)_2$−$Cu(TFA)_2$ (Table 3, entries 1 and 2).

In the present catalyst system, the chiral ligand **5a** must preferentially coordinate to Pd(II), because a higher yield of Pd(II) complex bearing **5a** was able to be isolated from a solution of $Pd(OAc)_2$, $Cu(OAc)_2$, **4**, and **5a** (1/1/1/1) in toluene (Scheme 5). Although the reactivity of the catalyst is effected by a combination of catechol and $Cu(OAc)_2$, catechol may be acting as *o*-quinone, because it is readily oxidized into *o*-quinone upon treatment with O_2 in the presence of the $Pd(OAc)_2$−$Cu(OAc)_2$ catalyst, as reported previously.[10b] On the basis of these considerations, we propose a simplified model of the catalyst assembly such as **12** in which

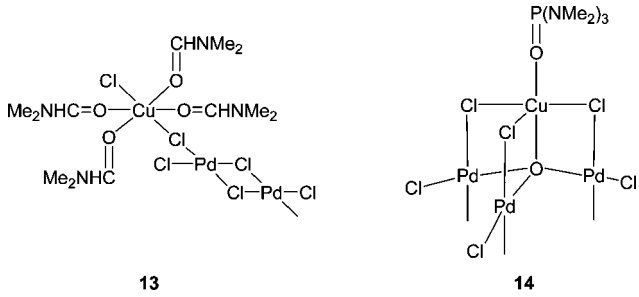
(19) In fact, when a solution of **1a** (1 mmol) in toluene (1.5 mL) was treated with **2a** (4 mmol) in the presence of CF_3COOH (0.05 mmol) in 1,2-dichloroethane (1.0 mL) for 24 h at room temperature, it gave **10** in 56% yield (NMR).

(20) For β-heteroatom elimination, see: Zhao, H.; Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 812–819.



X, Y = anionic ligand such as OAc, $OCOCF_3$, and Cl

FIGURE 1. Simplified representation for the anion exchange in the $Pd(OAc)_2-Cu(TFA)_2$ catalyst.



13 14

FIGURE 2. Examples of Pd−Cu bimetallic complexes.

o-quinone is incorporated to Cu(II) as the ligand (Figure 1).[21] The representation of Pd−Cu bimetallic complex-bearing anionic bridge is based on our previous studies[3] for isolation of bimetallic complexes such as **13** and **14**, where Cl acts as the bridge ligand between Pd and Cu (Figure 2). These complexes **13** and **14** are readily formed in the reaction of $PdCl_2$ and $CuCl_2$ with DMF[3a] or with HMPA and O_2.[3b] Since $Pd(OAc)_2$ itself exists as a trimeric complex bearing OAc bridges,[22] it is not unreasonable to postulate such OAc bridging. In bimetallic complexes **12**, the anionic ligands (X, Y) of OAc and TFA can be exchangeable with each other, resulting in the similarity of product distribution.

So far, several studies have outlined that the catalysis in this type of reaction is initiated by XPdH species which reacts with O_2 to give XPdOOH species. Alternatively, the XPdH species is converted into Pd(0) and HX, and the resulting Pd(0) reacts with O_2 to give η^2-peroxoPd(II) species from which XPdOOH species is formed by the action of HX. In either case, the XPdOOH species acts as the catalyst.[2,23−25] The catalysis of the present reaction must be also exerted by the XPdOOH species derived from XPdH formed during the reaction.[26] The species is likely bimetallic with copper. Further study is obviously necessary to address the catalysis and mechanistic questions including the stereochemistry for the present oxypalladation (syn or anti addition) and the enantioface-differentiation process.

Conclusions

In conclusion, we presented fundamental data for the first asymmetric coupling of cinnamyl alcohols and vinyl ethers using (*S*,*S*)-4,4′-benzylbisoxazoline with the so-called Wacker catalyst of PdX_2 and CuX_2 under O_2, in which the catalytic activity is enhanced by addition of catechol to the catalyst system. The present study provided the following insights into the PdX_2-CuX_2 catalyst. (1) The catalysis must be of Pd−Cu bimetallic form with anionic bridging ligands, in which the anionic ligands are interchangeable between two metals. (2) The enantioselectivity is exerted by $Pd(OAc)_2$ and a chiral ligand such as **5a**, whereas the reactivity is dependent on the assembly of $Cu(OAc)_2$ and catechol.

Experimental Section

General methods and the X-ray crystallographic study are described in the Supporting Information.

Representative Procedures for Asymmetric Coupling. (a) (*Z*)-4-Benzylidene-2-ethoxytetrahydrofuran (3a). $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), catechol (**4**) (11.0 mg, 0.1 mmol), and (*S*,*S*)-4,4′-bisbenzyl-2,2′-bioxazoline (**5a**) (32.0 mg, 0.1 mmol) were dissolved in toluene (1.5 mL) in a 25 mL side-armed round-bottomed flask under O_2 (balloon), and the reaction mixture was stirred for 30 min at room temperature. Ethyl vinyl ether (**2a**) (288 mg, 4.0 mmol) was added to the flask, and a solution of (*E*)-3-phenyl-2-propen-1-ol (**1a**) (134 mg, 1.0 mmol) in toluene (1.0 mL) was then added. After the reaction mixture was stirred for 24 h at room temperature, the mixture was filtered through a Florisil column (10 mm × 80 mm, 3 g, EtOAc/*n*-hexane = 1/20, $R_f = 0.62$), and the solvent was evaporated under reduced pressure to give **3a** in nearly pure form. Purification by thin-layer chromatography on silica gel gave **3a** in 71% isolated yield (145 mg, 0.71 mmol) as a colorless oil. The enantiomer excess (40% ee) was determined by HPLC analysis (*i*-PrOH/*n*-hexane = 1/19, 0.5 mL/min, 258 nm). Bp (bulb-to-bulb): 105−108 °C (15 mmHg). FTIR (neat, cm^{-1}): 3053, 3025, 1739, 1598, 1184, 1095, 1032, 997. GCMS: *m/e* 204 (M^+). ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, $J = 7.2$ Hz, 3H), 2.72 (dm, $J = 16.4$ Hz, 1H), 2.94 (ddddd, $J = 16.4$, 5.2, 2.4, 2.4, 2.4 Hz, 1H), 3.51 (dq, $J = 9.6$, 7.2 Hz, 1H), 3.77 (dq, $J = 9.6$, 7.2 Hz, 1H), 4.70 (ddd, $J = 2.4$, 2.4, 1.6 Hz, 1H), 5.23 (d, $J = 4.4$ Hz, 1H), 6.43 (br s, 1H), 7.13 (d, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.34 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.2, 41.2, 62.6, 67.9, 102.0, 121.6, 126.4, 127.8, 128.4, 137.4, 139.1. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.42; H, 7.89. Found: C, 76.32; H, 7.49.

(b) (*Z*)-4-Benzylidene-2-*n*-butoxytetrahydrofuran (3c). $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), catechol (**4**) (11.0 mg, 0.1 mmol), and (*S*,*S*)-4,4′-bisbenzyl-2,2′-bioxazoline (**5a**) (32.0 mg, 0.1 mmol) were dissolved in toluene (1.5 mL) in a 25 mL side-armed round-bottomed flask under O_2 (balloon), and the mixture was stirred for 30 min at room temperature. *n*-Butyl vinyl ether (**2c**) (401 mg, 4.0 mmol) was added to the flask, and a solution of (*E*)-3-phenyl-2-propen-1-ol (**1a**) (134 mg, 1.0 mmol) in toluene (1.0 mL) was then added. After the reaction mixture was stirred for 24 h at room temperature, the mixture was filtered through a Florisil column (10 mm × 80 mm, 3 g, EtOAc/*n*-hexane = 1/20, $R_f = 0.67$), and the solvent was evaporated under reduced pressure to give **3c** in pure form as a colorless oil. The yield was determined to be 86% (161 mg, 0.86 mmol) by NMR (terephthalaldehyde as an internal standard). The enantiomer excess (53% ee) was determined by HPLC analysis (*i*-PrOH/*n*-hexane = 1/19, 0.5 mL/min, 258 nm). Bp (bulb-to-bulb): 115−117 °C (15 mmHg). FTIR (neat, cm^{-1}): 3026, 2930, 2870, 1599, 1492, 1449, 1423, 1345, 1180, 1097, 1038, 925, 840, 749, 695. GCMS: *m/e* 232 (M^+). ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.6$ Hz, 3H), 1.32−1.41 (m, 2H), 1.54−1.60 (m, 2H), 2.72 (dm, $J = 16.4$ Hz,

(21) For an example of copper−quinone complexes, see: Rall, J.; Kalm, W. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 2905–2908.

(22) Skapski, A. C.; Smart, M. L. *Chem. Commun.* **1970**, 658–659.

(23) For representative references on the behavior of XPdH and O_2, see ref 2 and also: (a) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615. (b) Keith, J. M.; Muller, R. P.; Kemp, R. A.; Goldberg, K. I.; Goddard, W. A., III; Oxgaard, J. *Inorg. Chem.* **2006**, *45*, 9631–9633. (c) Keith, J. M.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 13172–13179. (d) Privalov, T.; Linde, C.; Zetterberg, K.; Moberg, C. *Organometallics* **2005**, *24*, 885–893.

(24) For isolation of PdOOH species, see: (a) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904–2907. (b) Konnick, M. M.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212–10213. (c) Denney, M. C.; Smythe, N. A.; Cetto, K. L.; Kemp, R. A.; Goldberg, K. I. *J. Am. Chem. Soc.* **2006**, *128*, 2508–2509.

(25) Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816.

(26) In the present reaction, the presence of base entirely suppressed the formation of byproducts **10** and **11** possibly formed by the action of acid HX (X = $OCOCF_3$ or Cl) (Tables 3 and 4). If this means that the acid (HX) generated during the reaction is completely captured by base, the XPdOOH species could not be formed by η^2-peroxoPd(II) species and HX (for such an argument, see ref 25).

1H), 2.93 (ddddd, J = 16.4, 5.2, 2.8, 2.8, 2.8 Hz, 1H), 3.45 (dt, J = 9.6, 6.8 Hz, 1H), 3.72 (dt, J = 9.6, 6.8 Hz, 1H), 4.70 (ddd, J = 2.0, 2.0, 2.0 Hz, 2H), 5.22 (d, J = 5.2 Hz, 1H), 6.43 (br s, 1H), 7.14 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8, 19.3, 31.7, 41.1, 67.0, 67.9, 102.2, 121.5, 126.4, 127.8, 128.4, 137.4, 139.1. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.53; H, 8.62.

(c) (*Z*)-4-(4-Nitrobenzylidene)-2-ethoxytetrahydrofuran (3g). $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), $Cu(OAc)_2$ (18.2 mg, 0.1 mmol), catechol (**4**) (22.0 mg, 0.2 mmol), and (*S*,*S*)-4,4′-bisbenzyl-2,2′-bioxazoline (**5a**) (64.0 mg, 0.2 mmol) were dissolved in toluene (4.0 mL) in a 25 mL side-armed round-bottomed flask under O_2 (balloon), and the mixture was stirred for 30 min at room temperature. Ethyl vinyl ether (**2a**) (577 mg, 8.0 mmol) was added to the flask, and a solution of (*E*)-3-(4-nitrophenyl)-2-propen-1-ol (**1b**) (358 mg, 2.0 mmol) in toluene (1.0 mL) was then added. After the reaction mixture was stirred for 24 h at room temperature, the mixture was filtered through a Florisil column (15 mm × 60 mm, 5 g, EtOAc). Evaporation of the solvent under reduced pressure gave **3g** in a solid state. The pure product **3g** was obtained by column chromatography (100−200 mesh silica gel, EtOAc/*n*-hexane = 1/4) in 74% yield (367 mg, 0.74 mmol) as a brown solid. The enantiomer excess (34% ee) was determined by HPLC analysis (*i*-PrOH/*n*-hexane = 1/9, 2.0 mL/min, 258 nm). Mp: 75−76 °C. FTIR (Nujol, cm^{-1}): 2927, 1652, 1592, 1513, 1099, 1049, 996. GCMS: *m*/*e* 249 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 2.77 (d, J = 16.8 Hz, 1H), 2.98 (ddddd, J = 16.9, 5.2, 2.4, 2.4, 2.4 Hz, 1H), 3.52 (dq, J = 9.7, 7.2 Hz, 1H), 3.78 (dq, J = 9.7, 7.2 Hz, 1H), 4.71 (ddd, J = 2.4, 2.4, 1.6 Hz, 2H), 5.26 (d, J = 5.2 Hz, 1H), 6.51 (br s, 1H), 7.20 (d, J = 8.9 Hz, 2H), 8.19 (d, J = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.1, 41.6, 62.8, 67.8, 101.9, 120.0, 123.9, 128.2, 143.4, 143.7, 145.0. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.38; H, 6.05; N, 5.50.

Synthesis of (*Z*)-4-(4-Aminobenzylidene)-2-ethoxytetrahydrofuran (6). 3g (125 mg, 0.5 mmol), $FeCl_3$ (40.6 mg, 0.25 mmol), and active-C (284 mg, 7 equiv per $FeCl_3$) were dissolved in THF (2.5 mL) and EtOH (2.5 mL) in a 25 mL side-armed round-bottomed flask. Hydrazine monohydrate (0.1 mL, 2 mmol) was added to the mixture at 70 °C with stirring. After stirring for 2 h at 70 °C, the reaction mixture was filtered through filter paper, and the solvent was evaporated under reduced pressure. The resulting mixture was diluted by adding ethyl acetate (30 mL), washed with water (2 × 20 mL) and brine (30 mL), and dried ($MgSO_4$). Removal of the solvent gave pure **6** in 62% NMR yield (68.2 mg, 0.62 mmol, terephthalaldehyde as an internal standard) as a brown solid. Mp: 44−45 °C. FTIR (KBr, cm^{-1}): 3449, 3356, 3218, 2979, 2933, 1627, 1606, 1516, 1459, 1422, 1374, 1348, 1291, 1182, 1114, 1091, 1052, 1035, 995, 912, 865, 851, 570, 528, 419. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.2 Hz, 3H), 2.67 (dm, J = 16.4 Hz, 1H), 2.90 (ddddd, J = 16.0, 5.2, 2.4, 2.4, 2.4 Hz, 1H), 3.50 (dq, J = 9.6, 7.2 Hz, 1H), 3.76 (dq, J = 9.6, 7.2 Hz, 1H), 4.64−4.66 (m, 2H), 5.21 (d, J = 4.4 Hz, 1H), 6.31 (br s, 1H), 6.65 (dm, J = 8.4 Hz, 2H), 6.94 (dm, J = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.2, 41.0, 62.6, 68.0, 102.0, 115.0, 121.3, 128.3, 129.0, 135.0, 144.9. HRMS (EI): calcd for $M^+ - C_2H_5O$ ($C_{13}H_{17}NO_2$), 174.0913; found, 174.0900.

Synthesis of (*Z*)-4-(4-*N*-(*R*)-(1-Naphthylethyl)ureylene)benzylidene-2-ethoxytetrahydrofuran (8). The amine **6** (50 mg, 0.23 mmol) was dissolved in THF (0.9 mL) in a 25 mL side-armed round-bottomed flask, and the reaction mixture was stirred at room temperature. Isocyanic acid (*R*)-(−)-(1-isocyanatoethyl)naphthalene (**7**) (0.04 mL, 0.23 mmol) was added to the flask, and the reaction mixture was stirred for 21 h at room temperature. *N*,*N*-Dimethyl-1,3-propanediamine (0.01 mL, 0.08 mmol) was then added to the flask, and the mixture was stirred for 30 min. After the reaction mixture was evaporated under reduced pressure, the resulting mixture was diluted by adding 30 mL of chloroform, washed with 3% citric acid (2 × 20 mL) and brine (30 mL), and dried ($MgSO_4$). Removal of the solvent gave a mixture of (*R*,2*R*)- and (*R*,2*S*)-**8** in 72% NMR yield (0.72 mmol, terephthalaldehyde as an internal standard). Further purification was made by column chromatography on silica gel (EtOAc/*n*-hexane = 1/1) to give a mixture of (*R*,2*R*)- and (*R*,2*S*)-**8** in 66% yield (56.3 mg, 0.66 mmol) as a powder. The diastereomer excess was determined by HPLC analysis (*i*-PrOH/*n*-hexane = 1/9, 3.0 mL/min, 300 nm) to be 30% de (65/35). FTIR (KBr, cm^{-1}): 3735, 3324, 3048, 2974, 2926, 2369, 1637, 1588, 1545, 1454, 1415, 1373, 1341, 1316, 1231, 1184, 1097, 1051, 1031, 998, 926, 780, 655, 614, 527, 444. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3.9H), 1.20 (t, J = 7.2 Hz, 2.1H), 1.71 (d, J = 6.8 Hz, 6H), 2.66 (dm, J = 16.4 Hz, 0.7 H), 2.68 (dm, J = 16.4 Hz, 1.3H), 2.91 (dm, J = 16.4 Hz, 2H), 3.45 (dq, J = 9.6, 7.2 Hz, 2H), 3.76 (dq, J = 9.6, 7.2 Hz, 2H), 4.60−4.68 (m, 4H), 4.87 (d, J = 7.2 Hz, 2H), 5.21 (d, J = 5.2 Hz, 0.7H), 5.22 (d, J = 5.2 Hz, 1.3H), 5.76−5.86 (m, 2H), 6.08 (s, 2H), 6.35 (br s, 2H), 7.02 (dm, J = 8.8 Hz, 2H), 7.19 (dm, J = 8.4 Hz, 2H), 7.44−7.61 (m, 4H), 7.82 (d, J = 8.4 Hz, 1H), 7.89 (dm, J = 7.6 Hz, 1H), 8.19 (d, J = 8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.2, 21.7, 35.8, 41.0, 41.1, 46.0, 62.6, 67.9, 102.0, 106.1, 120.4, 120.5, 120.9, 122.5, 123.2, 125.3, 125.9, 126.6, 128.3, 128.6, 128.8, 130.9, 133.0, 134.0, 136.7, 137.9, 138.6, 154.5. HRMS (EI): calcd for $C_{26}H_{28}N_2O_3$, 416.2100 (M^+); found, 416.2107. When the resulting powder was treated with ethyl acetate, yellow−orange material was dissolved into the ethyl acetate solution. The remaining powder was white. A portion of the white powder (10.3 mg) was dissolved into 1,2-dimethoxyethane in a sample tube. The tube was placed in a bottle containing diisopropyl ether overnight in the refrigerator, and then the mixture stood at room temperature. As the result, colorless single crystals (mp: 189−192 °C) were obtained, which was found to be (*R*,2*S*)-**8** by X-ray analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3H), 1.70 (d, J = 7.2 Hz, 3H), 2.68 (dm, J = 16.8 Hz, 1H), 2.90 (dm, J = 16.8 Hz, 1H), 3.49 (dq, J = 9.6, 7.2 Hz, 1H), 3.76 (dq, J = 10.0, 7.2 Hz, 1H), 4.62−4.65 (m, 2H), 4.86 (d, J = 7.6 Hz, 1H), 5.21 (d, J = 4.8 Hz, 1H), 5.76−5.84 (m, 1H), 6.07 (s, 1H), 6.34 (br s, 1H), 7.01 (dm, J = 8.4 Hz, 2H), 7.18 (dm, J = 8.8 Hz, 2H), 7.44−7.59 (m, 4H), 7.81 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H).

Isolation of $PdCl_2$-(*S*,*S*)-5a Complex from a Catalyst Solution. $Pd(OAc)_2$ (67.4 mg, 0.3 mmol), $Cu(OAc)_2$ (54.5 mg, 0.3 mmol), catechol (**4**) (33.0 mg, 0.3 mmol), and (*S*,*S*)-4,4′-bisbenzyl-2,2′-bioxazoline (**5a**) (96.1 mg, 0.3 mmol) were dissolved in toluene (9.0 mL) in a 25 mL side-armed round-bottomed flask under O_2 (balloon), and the reaction mixture was stirred for 1 h at room temperature. The solution was diluted with CH_2Cl_2 and washed with a saturated NaCl solution (50 mL). The organic layer was collected, dried over MS3Å powder, filtered, and concentrated under reduced pressure. The resulting black powder was dissolved into the least amount of CH_2Cl_2. The solution was passed through a Florisil column (10 mm × 40 mm, 1.5 g, CH_2Cl_2), and evaporation of the solvent gave a $PdCl_2$-(*S*,*S*)-**5a** complex as a nearly pure form in 74% NMR yield (terephthalaldehyde as an internal standard) (109.8 mg, 0.22 mmol) as a brown solid. Mp: 257−258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (dm, J = 13.6 Hz, 2H), 3.63 (dm, J = 13.6 Hz, 2H), 4.69−4.82 (m, 6H), 7.24−7.40 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 29.7, 39.4, 64.1, 127.5, 129.0, 129.7, 134.5, 159.8. Anal. Calcd for $C_{20}H_{20}N_2O_2PdCl_2$: C, 48.26; H, 4.05; N, 5.62. Found: C, 48.58; H, 4.08; N, 5.66. In the absence of catechol, the same complex was obtained only in 31% NMR yield.

Supporting Information Available: Detailed experimental procedures and characterization data for all reported new compounds and X-ray crystallographic data for single diastereomer (*R*,2*S*)-**8**. ^{1}H and ^{13}C NMR spectra for all reported new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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